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[Diagnostic Test Accuracy Review]

Menopausal status, ultrasound and biomarker tests in combination for the diagnosis of ovarian cancer in symptomatic women

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ABSTRACT

Background

Ovarian cancer (OC) has the highest case fatality rate of all gynaecological cancers. Diagnostic delays are caused by non-specific symptoms. Existing systematic reviews have not comprehensively covered tests in current practice, not estimated accuracy separately in pre- and postmenopausal women, or used inappropriate meta-analytic methods.

Objectives

To establish the accuracy of combinations of menopausal status, ultrasound scan (USS) and biomarkers for the diagnosis of ovarian cancer in pre- and postmenopausal women and compare the accuracy of different test combinations.

Search methods

We searched CENTRAL, MEDLINE (Ovid), Embase (Ovid), five other databases and three trial registries from 1991 to 2015 and MEDLINE (Ovid) and Embase (Ovid) form June 2015 to June 2019. We also searched conference proceedings from the European Society of Gynaecological Oncology, International Gynecologic Cancer Society, American Society of Clinical Oncology and Society of Gynecologic Oncology, ZETOC and Conference Proceedings Citation Index (Web of Knowledge). We searched reference lists of included studies and published systematic reviews.

Selection criteria

We included cross-sectional diagnostic test accuracy studies evaluating single tests or comparing two or more tests, randomised trials comparing two or more tests, and studies validating multivariable models for the diagnosis of OC investigating test combinations, compared with a reference standard of histological confirmation or clinical follow-up in women with a pelvic mass (detected clinically or through USS) suspicious for OC.

Data collection and analysis

Two review authors independently extracted data and assessed quality using QUADAS-2. We used the bivariate hierarchical model to indirectly compare tests at commonly reported thresholds in pre- and postmenopausal women separately. We indirectly compared tests across all thresholds and estimated sensitivity at fixed specificities of 80% and 90% by fitting hierarchical summary receiver operating characteristic (HSROC) models in pre- and postmenopausal women separately.

Main results

We included 59 studies (32,059 women, 9545 cases of OC). Two tests evaluated the accuracy of a combination of menopausal status and USS findings (IOTA Logistic Regression Model 2 (LR2) and the Assessment of Different NEoplasias in the adneXa model (ADNEX)); one test evaluated the accuracy of a combination of menopausal status, USS findings and serum biomarker CA125 (Risk of Malignancy Index (RMI)); and one test evaluated the accuracy of a combination of menopausal status and two serum biomarkers (CA125 and HE4) (Risk of Ovarian Malignancy Algorithm (ROMA)). Most studies were at high or unclear risk of bias in participant, reference standard, and flow and timing domains. All studies were in hospital settings. Prevalence was 16% (RMI, ROMA), 22% (LR2) and 27% (ADNEX) in premenopausal women and 38% (RMI), 45% (ROMA), 52% (LR2) and 55% (ADNEX) in postmenopausal women. The prevalence of OC in the studies was considerably higher than would be expected in symptomatic women presenting in community-based settings, or in women referred from the community to hospital with a suspicion of OC. Studies were at high or unclear applicability because presenting features were not reported, or USS was performed by experienced ultrasonographers for RMI, LR2 and ADNEX.

The higher sensitivity and lower specificity observed in postmenopausal compared to premenopausal women across all index tests and at all thresholds may reflect highly selected patient cohorts in the included studies.

In premenopausal women, ROMA at a threshold of 13.1 (± 2), LR2 at a threshold to achieve a post-test probability of OC of 10% and ADNEX (post-test probability 10%) demonstrated a higher sensitivity (ROMA: 77.4%, 95% CI 72.7% to 81.5%; LR2: 83.3%, 95% CI 74.7% to 89.5%; ADNEX: 95.5%, 95% CI 91.0% to 97.8%) compared to RMI (57.2%, 95% CI 50.3% to 63.8%). The specificity of ROMA and ADNEX were lower in premenopausal women (ROMA: 84.3%, 95% CI 81.2% to 87.0%; ADNEX: 77.8%, 95% CI 67.4% to 85.5%) compared to RMI 92.5% (95% CI 90.3% to 94.2%). The specificity of LR2 was comparable to RMI (90.4%, 95% CI 84.6% to 94.1%).

In postmenopausal women, ROMA at a threshold of 27.7 (± 2), LR2 (post-test probability 10%) and ADNEX (post-test probability 10%) demonstrated a higher sensitivity (ROMA: 90.3%, 95% CI 87.5% to 92.6%; LR2: 94.8%, 95% CI 92.3% to 96.6%; ADNEX: 97.6%, 95% CI 95.6% to 98.7%) compared to RMI (78.4%, 95% CI 74.6% to 81.7%). Specificity of ROMA at a threshold of 27.7 (± 2) (81.5, 95% CI 76.5% to 85.5%) was comparable to RMI (85.4%, 95% CI 82.0% to 88.2%), whereas for LR2 (post-test probability 10%) and ADNEX (post-test probability 10%) specificity was lower (LR2: 60.6%, 95% CI 50.5% to 69.9%; ADNEX: 55.0%, 95% CI 42.8% to 66.6%).

Authors' conclusions

In specialist healthcare settings in both premenopausal and postmenopausal women, RMI has poor sensitivity. In premenopausal women, ROMA, LR2 and ADNEX offer better sensitivity (fewer missed cancers), but for ROMA and ADNEX this is off-set by a decrease in specificity and increase in false positives. In postmenopausal women, ROMA demonstrates a higher sensitivity and comparable specificity to RMI. ADNEX has the highest sensitivity in postmenopausal women, but reduced specificity. The prevalence of OC in included studies is representative of a highly selected referred population, rather than a population in whom referral is being considered. The comparative accuracy of tests observed here may not be transferable to non-specialist settings. Ultimately health systems need to balance accuracy and resource implications to identify the most suitable test.

PLAIN LANGUAGE SUMMARY

What is the accuracy of different combinations of ultrasound imaging and blood tests to diagnose ovarian cancer in women before and after the menopause?

Why is improving the diagnosis of ovarian cancer important?

Many women diagnosed with ovarian cancer (OC) die from the disease, because it has usually spread outside the tubes/ovaries at the time of diagnosis. Missing OC (a false-negative result) may need major surgery and a lower chance of survival. An incorrect diagnosis of OC (a false-positive result) may result in anxiety, unnecessary further tests and surgery.

What did we aim to do?

We aimed to find out how accurate ultrasounds and blood tests are for diagnosing OC in premenopausal women and postmenopausal women.

What did we study?

We included 59 studies that compared four tests: Risk of Malignancy Index (RMI) (ultrasound and CA125 blood test); Risk of Ovarian Malignancy Algorithm (ROMA) (CA125 and HE4 blood tests); the IOTA Logistic Regression model 2 (LR2) ultrasound and the Assessment of Different NEoplasias in the adneXa model (ADNEX) (CA125 blood test and ultrasound).

What were the main results?

Premenopausal women

The sensitivities (proportion of women *with* OC correctly identified) of ROMA (77.4%), LR2 (83.3%) and ADNEX (95.5%) are higher than RMI (57.2%).

The specificities (proportion of women *without* OC correctly identified) of ROMA (84.3%) and ADNEX (77.8%) were lower than RMI (92.5%) and LR2 (90.4%).

The results indicate that if these tests were to be used in hospital settings in a group of 1000 premenopausal women, of whom 30 (3%) actually have OC:

– for RMI 13 women, for ROMA 7 women, for LR2 5 women and for ADNEX 1 woman would have their cancer missed by the test (false-negative result);

– for RMI 73 women, for ROMA 152 women, for LR2 93 women and for ADNEX 215 women would test positive when they do not have OC (false-positive result).

Postmenopausal women

The sensitivities of ROMA (90.3%), LR2 (94.8%) and ADNEX (97.6%) are higher than RMI (78.4%).

The specificities of ROMA (81.5%) and RMI (85.4%) are higher than LR2 (60.6%) and ADNEX (55.0%).

The results of these studies indicate that if these tests were to be used in hospital settings in a group of 1000 postmenopausal women, of whom 30 (3%) actually have OC:

– for RMI 6 women, for ROMA 3 women, for LR2 2 women and for ADNEX 1 woman would have their cancer missed by the test (false-negative result);

– for RMI 142 women, for ROMA 179 women, for LR2 382 women and for ADNEX 437 women would test positive when they do not have OC (false-positive result).

How reliable are the results?

OC was diagnosed by histology (looking at surgically removed specimens under a microscope) or following up women for one year to see if they remained free of OC. In some studies, women with negative test results were not followed up for long enough to be sure a cancer had not been missed, and some studies excluded women with types of OC that are harder to diagnose. This may make tests appear more accurate than they are in practice.

Who do the results apply to?

Most studies were conducted in European hospitals in women with a confirmed pelvic mass. The occurrence of OC in included studies was much higher than seen in the community and so the accuracy of these tests may be different for women being tested in non-specialist healthcare settings.

What are the implications?

This review suggests that in both pre- and postmenopausal women referred to hospital with a pelvic mass, ADNEX appears to miss the fewest cases of OC and RMI misses the most cases of OC. RMI appears to result in the fewest incorrect diagnoses of OC and ADNEX results in the most incorrect diagnoses of OC. Incorrect diagnoses of OC, when no cancer is present (false-positive test), may result in anxiety, unnecessary further tests and surgery. When choosing which test to use, the potential for missed cancers must be balanced against unnecessary testing and surgery.

How up-to-date is this review?

The review includes studies published up to June 2019.

Summary of findings 1. Summary of findings for menopausal status, ultrasound scan and biomarker tests in pre- and postmenopausal women in secondary care (prevalence ovarian cancer 3%)

Review question	Menopausal status, ultrasound scan and biomarker tests in combination for the diagnosis of ovarian cancer in women with symptoms suspicious for ovarian cancer
Setting	Secondary care
Reference standards	Histology in women who have undergone surgery and clinical follow-up (> 6 months) in women with negative index tests results who do not undergo surgery
Study limitations	For the participant selection domain, 44/59 (75%) studies were at high or unclear risk of bias because of concerns about selective recruitment of women. 58/59 (92%) studies were at high or unclear applicability concern for the participant selection domain because study participants were not symptomatic women. For the index test domain, 9/42 (21%) of ROMA studies, 11/20 (55%) of RMI studies, 2/4 (50%) of ADNEX studies, and 5/5 (100%) of LR2 studies were at high risk of bias because of lack of blinding of the index test or for ROMA studies because of no predefined threshold. Applicability concern was high or unclear for all RMI, ADNEX and LR2 studies because ultrasound was conducted by specialist sonographers or this was unclear. For the reference standard domain, 2/59 studies were at high risk of bias because the minimum length of follow-up for index negatives was not reported or because of lack of blinding. Applicability concern was high or unclear in 50/59 (85%) studies because borderline tumours had been excluded from analysis or classification of borderline tumours for estimation of test accuracy was unclear. For the flow and timing domain, 45/59 (76%) studies were at unclear or high risk of bias because of no information about the interval between the index test and the reference standard or because not all participants receiving an index test received a reference standard.

Population	**Premenopausal women**					
Index test, threshold **Studies (participants)**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Absolute sensitivity difference (95% CI) compared to RMI**	**Absolute specificity difference (95% CI) compared to RMI**	**Consequences in a hypothetical cohort of 1000 women assuming a prevalence of 3%***	
					Number of women who would have their cancer missed (false-negatives) (95% CI)	**Number of women who would test positive when they do not have ovarian cancer (false-positives) (95% CI)**
RMI 200 17 (5233)	57.2 (50.3 to 63.8)	92.5 (90.3 to 94.2)	—	—	13 (11 to 15)	73 (56 to 94)
ROMA 13.1 (± 2)	77.4 (72.7 to 81.5)	84.3 (81.2 to 87.0)	20.2 (12.2 to 28.3);	–8.2 (–11.7 to –4.7); P < 0.0001	7 (6 to 8)	152 (126 to 182)

27 (4463)			P < 0.0001			
LR2 post-test probability ovarian cancer 10% 4 (2843)	83.3 (74.7 to 89.5)	90.4 (84.6 to 94.1)	26.2 (16.2 to 36.2); P < 0.0001	−2.1 (−7.2 to 2.9); P = 0.404	5 (3 to 8)	93 (57 to 149)
ADNEX post-test probability ovarian cancer 10% 4 (1696)	95.5 (91.0 to 97.8)	77.8 (67.4 to 85.5)	38.3 (30.9 to 45.8); P < 0.0001	−14.8 (−24.0 to −5.5); P = 0.002	1 (1 to 3)	215 (141 to 316)
Population	**Postmenopausal women**					
Index test, threshold **Studies (participants)**	**Sensitivity (95% CI)**	**Specificity** **(95% CI)**	**Absolute sensitivity difference (95% CI) compared to RMI**	**Absolute specificity difference (95% CI) compared to RMI**	**Consequences in a hypothetical cohort of 1000 women assuming a prevalence of 3%***	
					Number of women who would have their cancer missed (false-negatives) (95% CI)	**Number of women who would test positive when they do not have ovarian cancer (false-positives) (95% CI)**
RMI 200 17 (4369)	78.4 (74.6 to 81.7)	85.4 (82.0 to 88.2)	—	—	6 (5 to 8)	142 (114 to 175)
ROMA (27.7 (± 2)) 13 (2002)	90.3 (87.5 to 92.6)	81.5 (76.5 to 85.5)	11.9 (7.6 to 16.3); P < 0.0001	−3.9 (−9.4 to 1.5); P = 0.157	3 (2 to 4)	179 (141 to 228)
LR2 post-test probability ovarian cancer 10% 5 (2157)	94.8 (92.3 to 96.6)	60.6 (50.5 to 69.9)	16.4 (12.3 to 20.5); P < 0.0001	−24.8 (−35.1 to −14.5); P < 0.0001	2 (1 to 2)	382 (292 to 480)
ADNEX post-test probability ovarian cancer 10% 4 (1365)	97.6 (95.6 to 98.7)	55.0 (42.8 to 66.6)	19.2 (15.4 to 23.1); P < 0.0001	−30.4 (−42.9 to −17.9); P < 0.0001	1 (0 to 1)	437 (324 to 555)

*Estimate of disease prevalence (pretest probability) reflecting the NICE threshold for cancer referral from generalist to specialist settings in the UK (NICE 2017). Note this is considerably lower (3%) compared to the prevalence of ovarian cancer in included studies in the review (16% to 55%).
ADNEX: Assessment of Different NEoplasias in the adneXa model; CI: confidence interval; LR2: Logistic Regression model 2; RMI: Risk of Malignancy Index; ROMA: Risk of Ovarian Malignancy Algorithm.

BACKGROUND

The estimated lifetime risk of being diagnosed with ovarian cancer (OC) is 1 in 50 (2%) for females born after 1960 in the UK Office for National Statistics (ONS) (Office for National Statistics 2016; Smittenaar 2016). Increasing age is a risk factor for OC; with incidence rates highest in females between 75 and 79 years of age (Cancer Research UK 2017).

OC is the most common cause of mortality among all gynaecological cancers. In 2018, 295,414 women were diagnosed with OC and 184,799 women died worldwide (Bray 2018). The high case fatality rate is largely attributed to the advanced stage at diagnosis in most women with OC. Although overall survival is 35% at 10 years, one-year survival is only 51% in stage 4 disease, in comparison to 99% in stage 1 disease (Office for National Statistics 2016). Lack of awareness and recognition of pertinent symptoms and signs by patients and physicians is considered one of the main factors contributing to a delay in diagnosis. Diagnosis of OC is challenging because of variable presentation, the non-specific nature of symptoms (Fitch 2002), and low prevalence. The prevalence of OC in primary care has been estimated as 0.023% (Bankhead 2005; Hamilton 2009), whilst recent hospital audits suggest a prevalence of OC in secondary care of 10% (Rai 2015). The prevalence of OC in women undergoing surgery for ovarian pathology in tertiary care settings is in the region of 30% (Nunes 2014; Timmerman 2010; Timmerman 2016).

Diagnosis of OC in premenopausal women poses additional challenges. Most ovarian tumours detected in premenopausal women tend to be benign; only 1 in 1000 symptomatic ovarian cysts are malignant, increasing to 3 in 1000 at age 50 years (RCOG 2011).

Advances in surgical practice and chemotherapy in recent years have slightly improved survival, but a diagnosis of OC continues to be associated with a high mortality, largely attributed to an advanced stage at diagnosis.

Target condition being diagnosed

OC has various subtypes including, epithelial ovarian cancers (EOC), germ cell tumours, stromal cell tumours, metastatic cancers (from other primary sites) and tumours of low malignant potential (LMP) also known as borderline tumours. EOC are the most common type of OC in both pre- and postmenopausal women. More than 90% of OCs in postmenopausal women and 80% to 85% of OCs in premenopausal women are EOC; in premenopausal women, germ cell tumours account for 15% to 20% of OCs. Within the EOC group, high-grade serous carcinoma (HGSC) is the most common histological type. Other common epithelial histological types are mucinous, clear cell and endometrioid (Shepherd 2000). Morphological and genetic studies have helped to improve our understanding of ovarian carcinogenesis and tumour behaviour according to different histology types. The distal fallopian tube is the origin for serous ovarian carcinomas and ovarian clear cell cancers; the origin of endometrioid OCs has been linked to endometriosis (Wiegand 2010). A dualistic model has been proposed based on the behaviour of tumours (Shih 2004). Type 1 tumours are indolent and present at an early stage; a typical example is endometrioid cancer. Type 2 tumours are aggressive, high-grade carcinomas, most often diagnosed at an advanced stage; a typical example is high-grade serous OC. Type 1 and Type 2 tumours display markedly different and distinct genetic patterns (Cho 2009). This advancement in understanding has major research implications, especially regarding the role of biomarkers, either alone, or as part of a composite index tests, in the management of OC.

This review is concerned with primary OC of all histological types and stages, including borderline tumours. Metastatic disease (cancer found in the ovary, but originating in another organ) is outside the remit of this review.

Index test(s)

For the purpose of this review, combination tests are defined as tests which combine measures from more than one type of clinical information (e.g. age or menopausal status), biomarkers and ultrasound scan (USS) in any combination, and in any order. Table 1 provides details of index tests considered eligible for inclusion in this review.

Clinical information

The most important risk factor for OC is a family history of breast cancer or OC (American Cancer Society 2016). Approximately 15% to 20% of OC is caused by an inherited genetic mutation in genes such as *BRCA1* and *BRCA2* (Walsh 2011). For women with a *BRCA1* or *BRCA2* genetic mutation, the lifetime risk of ovarian, fallopian tube or peritoneal cancer is approximately 41% to 46% for *BRCA1* and 10% to 27% for *BRCA2* by age 70 years (Lancaster 2015). The importance of menopausal status as a risk factor for OC is a function of the increased risk of cancer associated with increasing age (Cancer Research UK 2017). Although ovarian cysts are more common in premenopausal women, due to the physiological function of the ovary, most are benign functional cysts that resolve spontaneously. Some persistent benign cysts, caused by abnormal growth of cells such as endometriosis, fibromas and cystadenomas, may require intervention, but the risk of malignancy is low at 1/1000 women compared to 3/1000 women at age 50 years (RCOG 2011).

Biochemical markers

Biochemical markers, also known as biomarkers, are substances secreted or shed by tumours into surrounding blood and body fluids and expressed in abnormal tissues. Biomarkers may be uniquely specific for some tumour subtypes, or non-specific. It has been noted that levels of some tumour markers may begin to rise as early as three years prior to diagnosis (Anderson 2009).

The most commonly used biomarker for OC is CA125, which is raised in many benign and physiological conditions (Moss 2005; Posadas 2004). CA125 operating at a threshold of 30 units/mL has a sensitivity of 81% and specificity of 75% for distinguishing benign from malignant tumours in mixed pre- and postmenopausal populations with adnexal masses (growths that occur in or near the uterus, ovaries, fallopian tubes and the connecting tissues) (Jacobs 1990). However, CA125 has a low sensitivity (50%) for early-stage OC (Jacobs 1989), and reduced specificity in premenopausal women.

The serum tumour marker Human Epididymis protein (HE4) is a glycoprotein belonging to the Whey acidic protein family (Hellstorm 2003), and was approved as a biomarker for OC by the US Food and Drug Administration (FDA) in 2008. HE4 is elevated in 8% of benign conditions compared to 29% for CA125 and hence has the potential to improve specificity especially in premenopausal

women (Moore 2012). HE4 secretion increases with age (Moore 2012), and is affected by different cellular types of OC, highest in endometrioid (100%), 93% of serous, 50% of clear cell and not elevated in mucinous types (Drapkin 2005). HE4 has similar sensitivity, but improved specificity compared to CA125 for OC, particularly in premenopausal women (Ferraro 2013; Holcomb 2011).

Ultrasound scan

USS enables visualisation of morphological details of ovarian cysts. The diagnostic potential of USS has improved with advancing technology and the availability of transvaginal ultrasound (TVS), 3D ultrasound and Doppler techniques to characterise blood flow. However, the use of ultrasound to characterise lesions is influenced by interference from surrounding tissue, variability of the macroscopic features and the subjective nature of interpretation that is operator-dependent. Various scores have been developed to make USS more objective (Geomini 2009). Morphological features, such as size, presence of bilateral lesions, presence and thickness of septum, presence of solid areas, excrescences and papillary structures within tumours, presence of metastases (spreading of a tumour to other parts of the body), presence of ascites (abnormal accumulation of fluid in the abdomen) and Doppler measurements of blood flow, have been combined in various ways.

The 'U' score records the presence of bilateral lesions, multilocularity, solid areas, metastases or ascites, where U = 0 indicates the absence of any of these features; U = 1 indicates the presence of any one of these features and U = 3 indicates the presence of two or more of these features (RCOG 2011). The U score is a component of the Risk of Malignancy Index (RMI) (see below). The International Ovarian Tumour Analysis (IOTA) proposed more-recent USS-based models as having better diagnostic accuracy in the preoperative evaluation of ovarian tumours than the U score, including the Logistic Regression model 2 (LR2) (Kaijser 2014).

Test combinations

OC is a heterogeneous tumour and consequently it is likely that a combination of tests (clinical information, USS and biomarkers) has the potential to improve diagnostic accuracy over any single test (clinical assessment, biomarker or imaging) alone. Several composite tests have subsequently been developed.

RMI is derived by multiplying the USS score (0 to 3) (1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions), menopausal status and CA125 in units per millilitre (RMI = U × M × CA125). RMI is the most widely used combination of tests. Four different versions of RMI (I to IV) have been developed, which differ in scores attributed to the result of each test component (Atkurk 2011). In addition, RMI IV includes a score for the size of the tumour. RMI I is the version currently recommended by the National Institute for Health and Care Excellence (NICE) (NICE 2011) and the Royal College of Obstetrics and Gynaecology (RCOG) (RCOG 2016), in both pre- and postmenopausal women. In this review, we included only RMI version I and use the term RMI as synonymous with RMI I.

Risk of Ovarian Malignancy Algorithm (ROMA) combines menopausal status and the biomarkers CA125 and HE4 in a multivariable model to estimate the probability (%) of malignancy in an adnexal mass. In subgroup analysis, the accuracy of ROMA was better for EOC compared to all OCs combined, in mixed populations compared to populations segregated by menopausal status (pre- or postmenopausal) and in late- compared to early-stage disease (Li 2012).

Two test combinations that integrate clinical information and USS findings to estimate the probability (%) of malignancy in an adnexal mass include the LR2 and (Assessment of Different NEoplasias in the adneXa model) ADNEX multivariable models. LR2 (superseding LR1) is a multivariable model to estimate the probability (%) of malignancy in an adnexal mass. The model combines clinical information (age) and USS findings (presence of ascites, presence of blood flow within a solid papillary projection, maximum diameter of the solid component of a mass, irregular cyst walls and the presence of acoustic shadows) (Timmerman 2010). The ADNEX multivariable model has been developed to estimate the probability of malignancy in an adnexal mass. The model combines clinical information (age, healthcare setting), USS characteristics (maximum mass diameter, proportion of solid tissue, number of papillary projections, presence of more than 10 cyst locules (cavities within an organ), acoustic shadows, presence of ascites) and CA125 levels and shows promise in the preoperative discrimination of benign, borderline, early and advanced malignancies in ovarian masses (van Calster 2014).

Clinical pathway

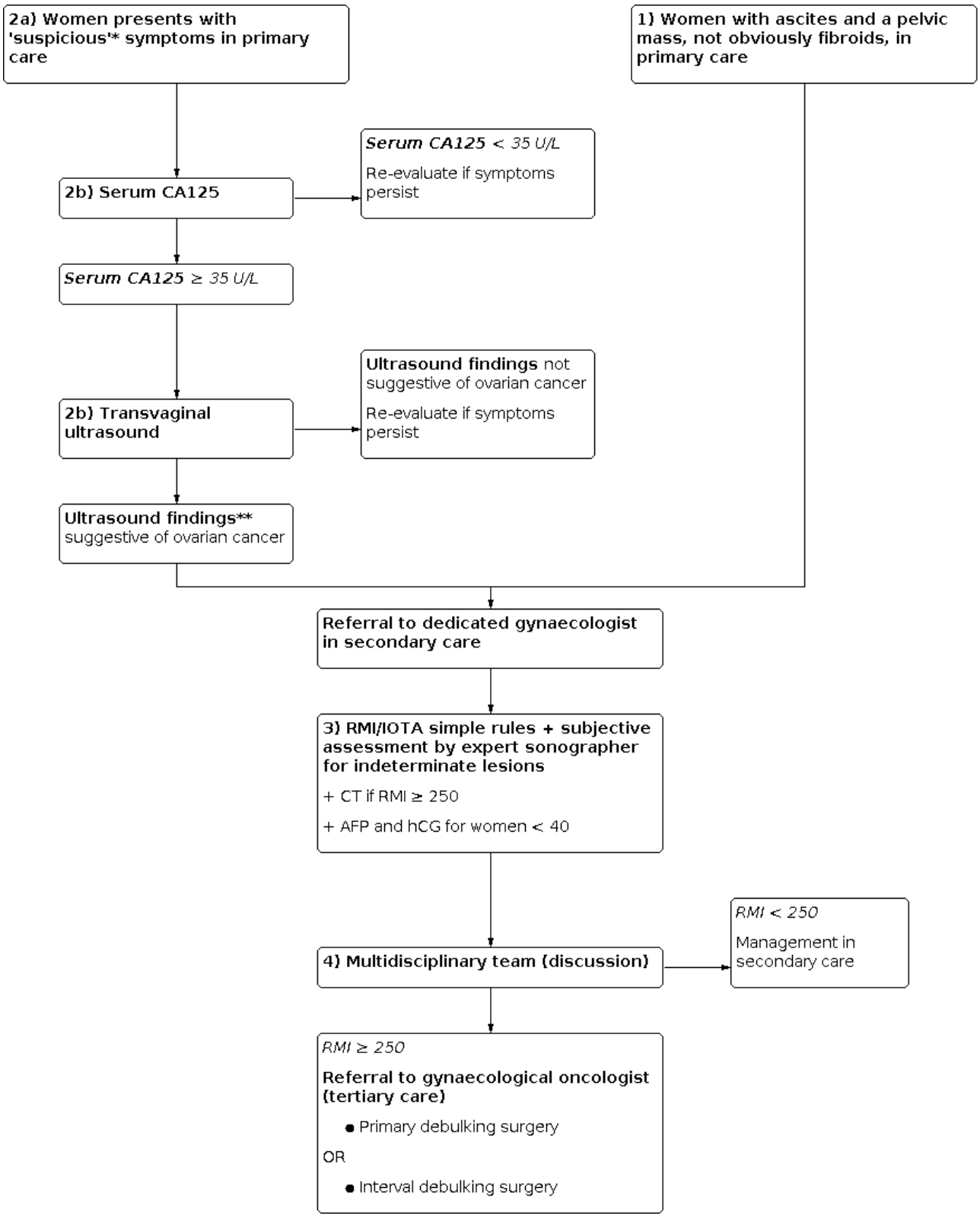
This review is concerned with women presenting with symptoms or signs (or both) in whom OC is being considered as a differential diagnosis. It is now recognised that women with OC may experience symptoms for a variable length of time prior to diagnosis (Hamilton 2009). Symptoms associated with OC include: abdominal bloating and distension; loss of appetite; early satiety; abdominal and pelvic pain; urinary urgency and frequency; vaginal and rectal bleeding; and change in bowel habit (constipation/diarrhoea).

In the UK, women with symptoms suspicious for OC may present in a generalist setting (primary care/family practice), or to hospital settings (secondary care or tertiary care (specialist gynaecological oncology units)). Symptoms should prompt investigations including the serum biomarker CA125, an USS, or both to determine whether an adnexal mass is present and the degree of suspicion for OC. It is recommended that women with a high index of suspicion for OC (a positive index test result) are referred to a gynaecological oncologist (tertiary care) for further management whereas those with a low index of suspicion for OC (a negative index test result) are referred to a designated gynaecologist in secondary care. International guidelines differ on the types of test and test positivity thresholds to used.

In the UK, NICE and RCOG recommend the following clinical pathway (NICE 2011; Figure 1).

Figure 1. UK recommended clinical pathway based on NICE and RCOG guidance *'Suspicious' symptoms: persistent (> 12 times per month) abdominal distension or bloating; early satiety/loss of appetite; urinary symptoms; abdominal or pelvic pain, weight loss; fatigue; change in bowel habit. **Ultrasound findings suggestive of ovarian cancer: laterality (any imbalance between masses observed in left compared to right ovary), multilocularity, solid areas, free fluid and distant metastasis. AFP: alpha fetoprotein; CT: computed tomography; hCG: human

chorionic gonadotrophin; IOTA: International Ovarian Tumour Analysis; NICE: National Institute for Health and Care Excellence; RCOG: Royal College of Obstetrics and Gynaecology; RMI: Risk of Malignancy Index.



- 1. Women with suspicious findings on clinical examination:

- women with ascites and a pelvic mass that is not obviously fibroids on clinical examination in a primary care setting should be immediately referred to secondary care.

- 2a. Women with suspicious symptoms:
  - women with persistent presence (more than 12 times per month) of abdominal distension or bloating, early satiety or loss of appetite, increased urinary urgency or frequency, and abdominal or pelvic pain, especially if aged over 50 years or women over 50 years presenting with unexplained weight loss, fatigue and change in bowel habit (symptoms suggestive of irritable bowel syndrome are rarely first diagnosed in women aged over 50 years).
- 2b. Women with suspicious symptoms should receive additional investigations: serum biomarker CA125 should be performed and, if 35 IU/mL or greater, a TVS scan should also be performed prior to referral to secondary care. Women with a high CA125 and presence of an adnexal mass on TVS scan should be urgently referred (within two weeks) to secondary care.
- 3. Once in secondary care, an algorithm combining menopausal status, USS features of the pelvic mass (laterality, multilocularity, solid areas, free fluid and distant metastasis) and the CA125 level is used to calculate the RMI I score. Alternatively, following referral from primary care, women may undergo USS as per IOTA criteria (RCOG 2016) TVS examination for a specific set of morphological features used to determine the malignant potential of a pelvic mass and, in the case of a mass which is indeterminate following IOTA assessment, a subjective assessment by an expert USS examiner (RCOG 2016).
- 4. Following either RMI or IOTA assessment and additional tests dictated by a woman's age (40 years or less: human chorionic gonadotrophin (hCG) and alpha fetoprotein (AFP) to detect germ cell tumours; or RMI score of 250 or greater: computed tomography (CT)), a multidisciplinary review team (MDT) is used to triage women for referral to a either a general gynaecologist (secondary care) or a gynaecological oncologist (tertiary care).

In the UK, it is estimated that 28% of women are referred via the two-week wait pathway (on the basis of symptoms and signs defined by guidelines as suspicious for cancer), 38% via general practitioner referral to gynaecologists, 26% via outpatients, 12% via other than gynaecology and 29% of women are diagnosed following an emergency presentation (Ellis-Brookes 2012). One multicentre study in the UK demonstrated variable adherence to the recent NICE guidance regarding the tests used and the impact of results on patient management (Rai 2015).

The American College of Obstetrics and Gynaecology recommends TVS as the initial test of choice if physical examination suggests the presence of an adnexal mass (ACOG 2016). Following TVS, referral to a gynaecological oncologist (tertiary care) is recommended in the presence of:

- elevated CA125 in combination with one or more of the following: a suspicious clinical history; suspicious TVS findings; elevation of other biomarkers; or
- an elevated risk score following assessment with LR2, RMI (OVA 1) or ROMA.

Referral to tertiary care is recommended for women suspected of having a germ cell tumour: elevated inhibin A/B, beta hCG, AFP, or L-lactate dehydrogenase.

No pan-European guideline for the investigation and management of suspected OC exists although variation in practice is recognised (Ledermann 2013).

Prior test(s)

As a minimum, women who are being considered for testing with the index tests because of a suspicion of OC will present with self-assessed symptoms. In addition, women may have had one or more clinical assessment (history and examination), biomarker tests and USS, depending on the point in the clinical pathway they present for testing with the index test.

Role of index test(s)

The index tests are used to decide whether women presenting with symptoms or signs (or both) suspicious for OC should receive further investigation and management in secondary care or specialist gynaecological oncology units (tertiary care).

Alternative test(s)

This review is concerned with initial investigations to diagnose OC that would be applicable in generalist and secondary-care settings. Combination tests including CT, magnetic resonance imaging (MRI), positron emission tomography (PET) and other complex imaging techniques are therefore beyond the scope of this review.

Four different versions of RMI (I to IV) have been developed (Atkurk 2011), which differ in scores attributed to the result of each test component. In addition, RMI IV includes a score for the size of the tumour. RMI I is the version currently recommended by NICE and the RCOG in both pre- and postmenopausal women and is the version of RMI that will be evaluated by this review (NICE 2011; RCOG 2016).

Rationale

The non-specific nature of symptoms associated with OC and the high prevalence of ovarian cysts of uncertain significance (30% of females with regular menstruation, 50% of females with irregular menstruation and 6% of postmenopausal females) (Duklewski 2009), continues to pose problems for early and accurate diagnosis. Combining different test types has the potential to improve accuracy over one test type used alone, but the most accurate combination of tests has yet to be determined. There is also a need to understand how test accuracy is influenced by patient characteristics so that test combinations can be appropriately targeted.

As part of a scoping review, 10 original systematic reviews were identified up to 2021 (Chacon 2019; Dodge 2012; Fakhar 2018; Geomini 2009; Kaijser 2014; Li 2012; Meys 2016; NICE 2011; Stukan 2015; Wang 2014). Six of the 10 reviews included ROMA, seven RMI and four LR2. The search date of the most recent review was 2018 (Chacon 2019). None of the reviews included ADNEX. Two reviews compared ROMA and RMI (Chacon 2019; Stukan 2015), and four compared RMI and LR2 (Dodge 2012; Kaijser 2014; Meys 2016; Stukan 2015), whilst six reviewed only single tests. Four of 10 reviews did not present results separately for pre- and

postmenopausal women. Nine of 10 reviews undertook meta-analysis, but only five used appropriate statistical methods.

OBJECTIVES

To establish the accuracy of combinations of menopausal status, ultrasound scan (USS) and biomarkers for the diagnosis of ovarian cancer in pre- and postmenopausal women and compare the accuracy of different test combinations.

Secondary objectives

We planned to investigate the following sources of heterogeneity.

Population

- Clinical setting (generalist/primary care/community/family practice) versus specialist setting (cancer unit/cancer centre/gynaecological oncology)
- Menopausal status (premenopausal versus postmenopausal)

Index tests

- Test positivity threshold
- Experience of the USS test operator (general sonographers versus specialist interest)

Target condition

- Histological subtype

Study quality

- For study participants not receiving surgery following a negative index test result (where clinical follow-up rather than histology is used as a reference standard for index test negatives): 12 months' follow-up versus less than 12 months' follow-up

METHODS

Criteria for considering studies for this review

Types of studies

We included diagnostic case-control studies (providing the control arm included women with benign ovarian pathology and these could be disaggregated from any healthy controls); diagnostic cross-sectional studies (retrospective and prospective data collection). We anticipated that in view of the low prevalence of OC, the majority of cross-sectional studies would recruit women who had already undergone the reference standard and index test results would be ascertained retrospectively. We also included studies externally validating multivariable models for the diagnosis of OC. We included comparative diagnostic test accuracy studies of any design (within-person or between-person comparisons). Studies were eligible if there were sufficient data to extract 2 × 2 tables on diagnostic test performance. We allowed inclusion of studies not providing verification of index test negatives where 2 × 2 tables could be constructed by imputation using setting-specific prevalence estimates. However, we did not identify eligible studies where index test negatives were not verified.

Participants

Women aged 18 years or older, irrespective of menopausal status. We excluded studies restricted exclusively to populations under 18. We excluded studies restricted to pregnant women, or women with a previous history of OC.

Prior tests

This review is concerned with women in whom a diagnosis of OC is suspected (i.e. women with symptoms or signs suggestive of OC). As a minimum, women should have self-referred to a healthcare professional on the basis of the presence of symptoms. Individual components of the test combinations (index tests) included in this review may be used alone in both generalist and specialist settings and so at the time women receive an index test, in addition to presentation with symptoms and signs, they may have had prior testing with one or more testing with one or more biomarkers or imaging with USS. We excluded studies explicitly describing included participants as asymptomatic, for example where the index test was being applied as a screening test, or where studies explicitly included asymptomatic participants and these could not be disaggregated from participants who were symptomatic. Where the prior presence of symptoms or signs was unclear or not reported, studies were included and this was reflected as part of the quality assessment of included studies (QUADAS-2) in the patient applicability domain.

Index tests

We included the following index tests in use in clinical practice at the time of undertaking our searches: any combination (two or more of the following test types): RMI (menopausal status, CA125 and USS examination); ROMA (menopausal status, CA125 and HE4), and the multivariable models LR2 and ADNEX (menopausal status and USS examination) (Table 1). We included studies where USS examination as part of RMI, LR2 and ADNEX was conducted by ultrasonographers with any experience: general sonographers or those with specialist training.

Target conditions

OC, all stages and types. We excluded studies where only one type of ovarian pathology was reported with the exception of EOC, as this is the most common (greater than 90% in postmenopausal women) of the OCs and is associated with the highest mortality. We excluded studies concerned exclusively with recurrent OC, OC which was metastatic from another primary cancer site, and studies where it was not possible to disaggregate participants with primary OC from metastatic or recurrent disease.

Reference standards

Histology in women who have undergone surgery and clinical follow-up in women with negative index test results (suggestive of no OC) who do not undergo surgery. For studies using clinical follow-up, the length of follow-up was considered as part of quality assessment; a minimum of one year of follow-up was considered of higher quality compared to less than one year of follow-up. We planned to investigate length of follow-up as a potential source of heterogeneity.

Search methods for identification of studies

Electronic searches

Original searches were conducted in 2015 to support a generic protocol for four separate reviews: USS, biomarkers, symptom scores and test combinations for the diagnosis of OC. With the exception of the symptom and symptom score search strategy, a

date restriction was applied (1991 onwards) to ensure applicability to current technology. For the symptom search strategy a date restriction of 2009 was applied, reflecting the existence of a comprehensive review of symptoms for the diagnosis of OC (NICE 2011). The 2015 strategies were designed to run across a range of databases: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE In Process (Ovid), Embase (Ovid), CINAHL (EBSCO), the *Cochrane Database of Systematic Reviews* (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA) and SCI Science Citation Index (ISI Web of Knowledge).

We updated the search strategy in June 2019 specifically for this test combination review. The 2019 searches were a targeted update of evidence about RMI, ROMA, LR2 and ADNEX as these test combinations had emerged in the intervening period as the main contenders for use in clinical practice. For pragmatic reasons we restricted databases to MEDLINE and MEDLINE In Process (Ovid) and Embase (Ovid) for the 2019 update, combining terms for OC with terms to capture the index tests or their components (biochemical markers, symptom scores and USS) that were used in the original 2015 searches. The 2019 search was developed iteratively and evaluated for its performance in detecting key articles already deemed eligible for inclusion post-2015. Specifically, the following changes were made between the 2015 and 2019 search strategies to reflect changes in the review scope: the 2019 search strategy additionally included terms for the index tests of current clinical interest: RMI, ROMA, LR2 and ADNEX; used a reduced range of terms used to describe symptoms and symptom scores (as symptoms are not a major component of the index tests of current interest), and used a reduced range of biomarker terms reflecting those contained in the index tests of current interest. Changes were also made to terms used to describe the target condition (OC) in line with changes in the description of OC as a disease of the adnexa, rather than being a disease of tubal or ovarian origin. The search strategy used for the original 2015 searches as well as the 2019 targeted updated search strategy are shown in Appendix 1 and Appendix 2.

No language restrictions were applied.

Searching other resources

To identify ongoing and unpublished studies, we searched the following trials registers and conference abstracts and proceedings without date restrictions as part of the 2015 search strategy: ClinicalTrials.gov, UK Clinical Research Network Study Portfolio Database (UKCRN) and WHO International Clinical Trials Registry Platform (ICTRP). We searched conference proceedings from the European Society of Gynaecological Oncology (ESGO), International Gynecologic Cancer Society (IGCS), American Society of Clinical Oncology (ASCO) and Society of Gynecologic Oncology (SGO), supplemented by searches of the ZETOC and Conference Proceedings Citation Index (Web of Knowledge). For both the 2015 and 2019 search strategies, we drew on reference lists of existing systematic reviews and guidelines identified in the electronic searches as a source of primary studies.

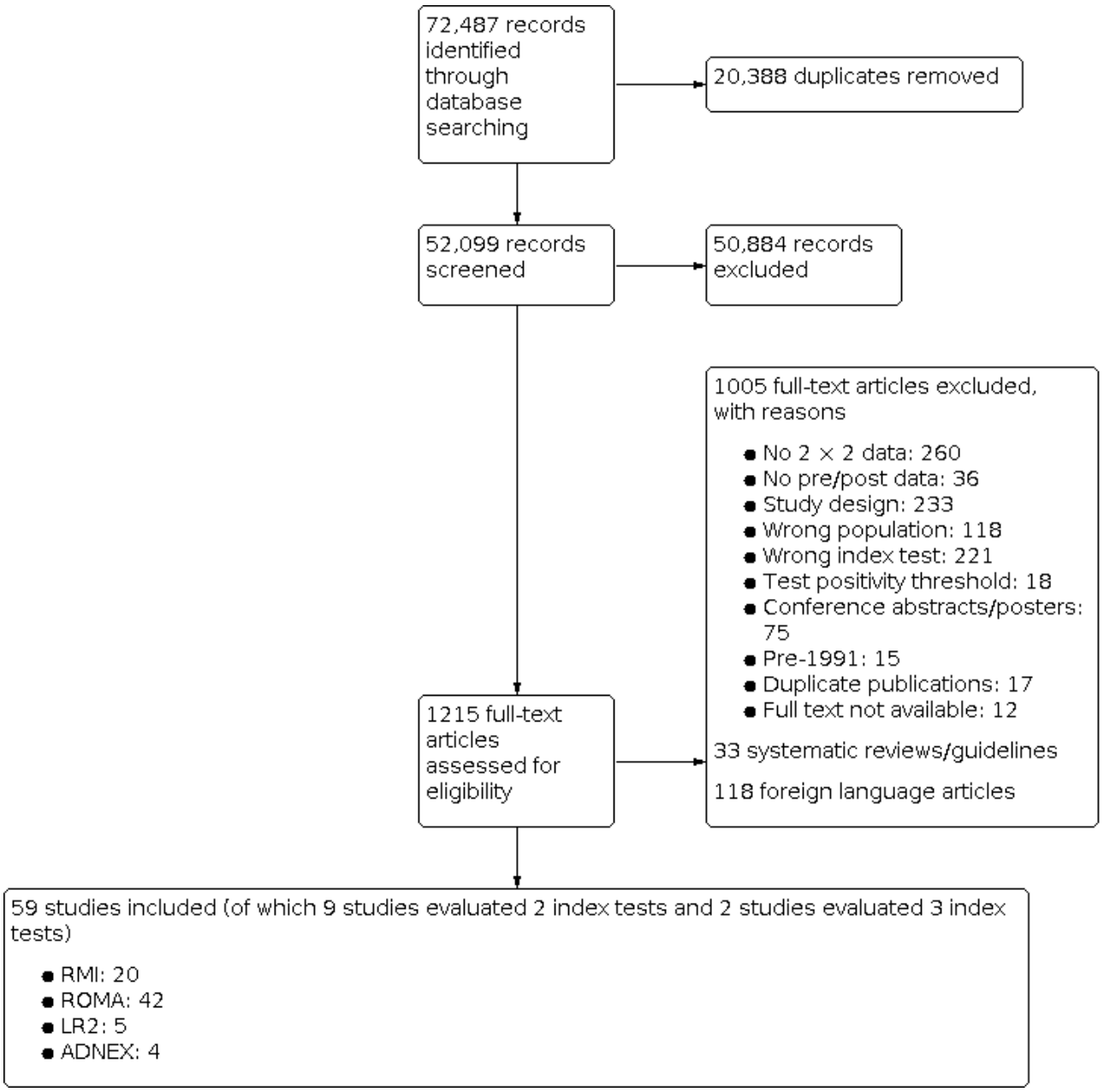
Data collection and analysis

Search results were managed in EndNote. After removal of duplicates, two review authors (from NR, RC, PSh, PSa) independently carried out study selection by reading the titles and abstracts and excluded obviously irrelevant studies at this stage. Two review authors (from NR, RC, PSh, PSa) independently read the full text of remaining studies. A third review author (CD, SS) resolved disagreements. Two review authors (NR, PSh, CD) independently extracted data into 2 × 2 tables and assessed quality. Another review author (RC or CD) double-checked characteristics of 30% of the studies. We resolved disagreements by discussion.

Selection of studies

We reviewed unique titles and abstracts against predefined selection criteria to select potentially relevant studies for full-text review. The results of the selection process and reasons for exclusion are documented and summarised using a PRISMA flow diagram (Figure 2).

Figure 2. PRISMA study flow diagram. ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression Model 2; RMI: Risk of Malignancy Index; ROMA: Risk of Ovarian Malignancy Algorithm.



Data extraction and management

We used a predefined data collection form to extract the following data into an Excel database prior to entry into Review Manager 5 (Review Manager 2014): study design; country; setting; single or multicentre; method of recruitment; reasons for exclusion; number of participants; number of women with a diagnosis of OC and borderline ovarian tumours; age; menopausal status (directly or using age over 50 years or history of previous hysterectomy as a proxy for postmenopausal status); prior tests; index tests and index test threshold(s); expertise of index test operator (for symptoms and USS); reference standard (including where relevant duration of follow-up); stage, and histological subtype of OC. Either a clinician (NR) or review author (PSh, RC, CD) extracted data to derive a 2 × 2 table for each study; either a methodologist or statistician (CD, JD, SB) checked data.

Assessment of methodological quality

Quality assessment was undertaken using the QUADAS-2 checklist tailored according to the topic and detailed in Appendix 3 (Whiting 2011).

Tailoring of QUADAS-2 to the clinical topic required consideration of the following.

Patient selection domain

Studies were considered at high risk of bias if they excluded certain types of malignant or benign pathology that is known to affect the accuracy of index tests specifically for detecting primary OC. Examples include endometriosis (which, for example, causes a raised serum CA125) and borderline ovarian tumours (which are managed surgically, similar to malignant tumours, but may result in a negative index test result). Additionally, restricting populations by age was considered to place studies at high risk of bias because an increase in age is associated with a change in disease spectrum. For example, EOC is more prevalent in older women and germ cell tumours are more prevalent in younger women. It has also been shown that index test performance differs in different histological subtypes of OC and at different stages of malignancy Kobayashi 2012).

Menopausal status is a risk factor for OC. In addition the spectrum of disease (the type and severity of OC and the range of differential diagnoses) observed in postmenopausal women are different to those of premenopausal women. For example, in premenopausal women, the normal menstrual cycle and benign pathology, such as endometriosis, can result in false-positive test results. Therefore, we considered distinguishing test performance in pre- and postmenopausal women an important feature of studies. For this reason, the quality of studies that stratified test results by menopausal status is presented separately.

The target population for this review was symptomatic women receiving index tests because of a suspicion of OC on the basis of clinical history and examination. Therefore, studies were considered of high applicability concern if women were asymptomatic, and were selected for testing with index tests in secondary or tertiary care, following prior testing with one or more biomarker or USS.

Index test domain

The review included composite index tests comprised at least two of three different test types: clinical information (menopausal status), biochemical testing and USS examination. Studies were considered at high risk of bias if the USS component of index tests was not conducted blind to the results of other index test components (biochemical markers and clinical assessment). Similarly, studies were considered at high risk of bias if the USS component of composite index tests was not conducted and interpreted blind to the disease status/reference standard result. Studies that did not prespecify the test positivity threshold were considered at high risk of bias because this usually results in over-optimistic test accuracy estimates that are not replicable outside of the study sample. For quality assessment of index tests based on multivariable models (LR2 and ADNEX), QUADAS-2 was tailored by adding items taken from the PROBAST risk of bias tool for prognostic studies (Wolf 2019). These items were whether all model components and thresholds were prespecified and whether individual test components were assessed in a similar way (e.g. in similar healthcare settings or by individuals with similar levels of expertise). Assessment of applicability of index tests comprised consideration of whether the expertise of clinicians undertaking clinical assessment and USS examination was representative of a generalist setting.

Reference standard and target condition domain

We considered histological diagnosis or clinical follow-up for a minimum of 12 months as likely to classify correctly the target condition (therefore a low risk of bias). In studies using clinical follow-up, risk of bias was considered high if follow-up was less than six months. Concerning the applicability of the target condition, as defined by the reference standard; assessments were based on how authors had dealt with borderline tumours in their analysis and the implications this had for meta-analysis. Within the constraints of a 2 × 2 table and reflecting current clinical practice, we considered that borderline tumours should be classified as malignant for the purposes of estimation of test accuracy. Thus studies reporting results allowing grouping of borderline tumours with malignant for the purpose of meta-analysis were considered of low-applicability concern.

Flow and timing domain

We considered risk of bias high if the interval between index test and reference standard application was more than three months.

Statistical analysis and data synthesis

Summary

Exploratory analyses included plotting estimates of sensitivity and specificity grouped by test threshold on Forest plots and in summary ROC (receiver operating characteristic) plots.

Analyses were conducted in Stata version SE 17.0 (StataCorp 2019) and SAS software (version 9.4) (SAS 2015). Where there were adequate data available and it was considered reasonable to pool results, we performed meta-analyses using hierarchical models using the NLMIXED procedure in SAS (SAS 2015). Where meta-analysis was not considered appropriate due to clinical or methodological heterogeneity, or in the case of fewer than three studies, we used narrative synthesis.

Estimation of the accuracy of individual index tests

Since the characteristics measured by index tests could be extracted as 2 × 2 tables reported at common index test thresholds, we used the bivariate model including random effects (Chu 2006; Reitsma 2005). To estimate average sensitivity and specificity at fixed thresholds, we performed the analysis of each index test version by first restricting to studies that reported thresholds recommended in guidelines or used in clinical practice (or both), and second to those thresholds most commonly reported across included studies. In addition, for ROMA, we included studies using thresholds ± 2 units around the most commonly reported thresholds. We excluded thresholds based on particular values of sensitivity and specificity where no threshold in terms of index test operation was reported for the values of sensitivity and specificity used. We used random-effects univariate analyses (which ignore any correlation between sensitivity and specificity) where pooling was an appropriate approach but bivariate models failed to converge.

Comparison of index tests

In order to maximise use of data across studies using different thresholds, we undertook indirect comparisons of index tests by fitting HSROC models and estimating sensitivity at fixed vales of specificity (80% and 90%), reflecting clinical consensus about an acceptable false-positive rate (RCOG 2016). To illustrate the

comparative accuracy of index tests at specific test-operating thresholds that could be applied in clinical practice, we also undertook indirect comparisons of index tests using bivariate hierarchical models.

For the HSROC analysis (Rutter 2001), we used a covariate for test type and estimated a summary ROC curve for each index test across all included thresholds. Each included study contributed one threshold to the summary ROC curve. Where an individual study reported more than one threshold, we selected the most commonly reported threshold for that index test across all included studies for the meta-analyses. The selection of one threshold per study was only necessary for ROMA studies where the threshold pairs 31.1 (± 2 units) and 27.2 (± 2 units) were the most commonly reported across studies. Summary ROC curves which have a common shape were fitted to the data. We performed estimation of differences in accuracy using the NLMIXED procedure in Statistical Analysis System (SAS 2015) and the metandi macro (Takwoingi 2010). We computed P values for the difference in accuracy for each test compared to RMI (RMI being the test combination currently in routine use in the UK in both pre- and postmenopausal women) using Wald tests. We reported the difference in sensitivities at fixed specificities of 80% and 90% for each index test version compared to RMI with 95% confidence interval (CI).

For the bivariate hierarchical analysis, we undertook a comparison of index tests at the single most commonly reported threshold across studies, including a covariate for test type. Absolute differences in sensitivity/specificity and the corresponding P values for each pair-wise test comparison were reported from the model. Bivariate models were fitted using the *meqrlogit* command in Stata. Where appropriate, models were simplified by setting near-zero variance estimates of the random effects to zero (Takwoingi 2017). In cases where both random effects were set to zero, a fixed-effect logistic regression was fitted using the *blogit* command. Absolute differences in sensitivities/specificities and P values were derived from bivariate models using the *nlcom* command in Stata. This computes point estimates and standard errors using the delta method. We used random-effects univariate analyses (which ignore any correlation between sensitivity and specificity) where pooling was considered an appropriate approach, but bivariate models failed to converge.

We translated summary estimates of sensitivity and specificity into summary estimates of the absolute numbers of true-positives, false-negatives, false-positives and true-negatives using a hypothetical population of 1000 women using an estimate of disease prevalence (pretest probability) reflecting the NICE threshold for cancer referral from generalist to specialist settings in the UK of 3% (NICE 2017).

Investigations of heterogeneity

We investigated the effect on estimates of test accuracy of menopausal status (premenopausal or postmenopausal) and of classification of histologically borderline ovarian tumours as disease positive (grouped with histologically malignant ovarian tumours) or where classification of borderline ovarian tumours was unclear or these tumour types were excluded. Grouping of histologically borderline ovarian tumours with histologically malignant ovarian tumours was considered clinically appropriate (reflecting current clinical practice) whereas exclusion of histologically borderline ovarian tumours was considered methodologically inappropriate.

We performed estimation of differences in accuracy using the NLMIXED procedure in Statistical Analysis System (SAS 2015) by including menopausal status or borderline grouping as covariates in the bivariate model. We reported differences in accuracy using the ratio of Diagnostic odds ratios with 95% CI and computed associated P values using Wald tests.

We were unable to conduct separate meta-analyses for the following planned investigations of heterogeneity because of a lack of data:

- healthcare setting: generalist setting (primary care, community care, family practice) versus specialist setting (secondary care, tertiary care (cancer unit, cancer centre));
- target condition: histological subtype: EOC versus non-EOC; high-grade serous epithelial (type II) versus other epithelial (type I); early-stage (stage I/II) versus late-stage disease (stage III/IV).

Sensitivity analyses

We did not undertake any sensitivity analyses.

Assessment of reporting bias

We did not undertake any formal assessment of reporting bias in our review due to current uncertainty about how to assess reporting bias in diagnostic test accuracy reviews, especially in the presence of heterogeneity (Deeks 2005).

RESULTS

Results of the search

The search identified 72,487 references. After removal of 20,388 duplicates, there remained 52,099 unique records. After reviewing titles and abstracts, we obtained and screened full-text copies of 1215 potentially relevant reports, of which 59 studies reporting 71 data sets were deemed eligible for inclusion. Reasons for full-text study exclusions are detailed in Figure 2 and studies are listed in Appendix 4. Forty-nine studies assessed the accuracy of a single test, whilst 10 studies included a within-person comparison of two or more index tests (Al Musalhi 2016; Anton 2012; Krascsenitis 2016; Liest 2019; Lycke 2018; Meys 2017; Niemi 2017; Richards 2015; Sayasneh 2013a; Testa 2014). Test types and thresholds were too varied to permit separate meta-analyses of direct comparison studies.

Index tests and thresholds

Of the 71 data sets (59 studies; 32,059 participants, 9545 cases of OC), 17 evaluated the accuracy of RMI at a threshold of 200 and two at a threshold of 250 (10,283 participants, 2654 cases of OC); 42 evaluated the accuracy of ROMA (13,715 unique participants, 3944 cases of OC) at threshold pairs for pre- and postmenopausal women of 7.4 (± 2) (N = 12) and 25.3 (± 2) (N = 15); 12.5 and 14.4 (N = 3), 13.1 (± 2) (N = 27) and 27.7 (± 2) (N = 13); 11.4 (N = 11) and 29.9 (N = 12); five studies evaluated the accuracy of LR2 (5000 participants, 1743 cases of OC to achieve a post-test probability of OC of 10%); and four studies evaluated the accuracy of ADNEX (3061 participants, 1204 cases of OC) to achieve a post-test probability of OC of 3%, 5%, 10% and 15% (Table 2).

Characteristics of included studies

In summary, 41 studies were conducted in Europe, 12 in the Asia-Pacific region, five in North America and one in South America. Nineteen studies were multicentre. These tests can be carried out in primary care, by dedicated gynaecologists in hospital settings (secondary care), by gynaecological oncologists in specialist units (tertiary care), or across a mixture of healthcare settings. Forty-nine studies were conducted in specialist settings (nine in mixed secondary and tertiary settings, 28 in tertiary care settings and 12 in secondary settings) and 10 studies did not report the healthcare setting.

Menopausal status and age alter the spectrum of disease (the prevalence of OC, range of histological subtypes and the range of differential diagnoses). In postmenopausal women, the prevalence of OC is higher and certain histological subtypes (EOC) are more common. In premenopausal women the prevalence of germ cell tumours is higher and the normal menstrual cycle and benign pathology such as endometriosis can result in false-positive test results. In the absence of information on menopausal status, 50 years can be used to stratify women for estimation of test accuracy to reflect this change in spectrum and risk. Across all studies reporting age (41/59 included studies), mean age varied between 37 and 65 years and age range varied between 11 and 94 years. One study restricted inclusion to premenopausal women and four studies restricted inclusion to postmenopausal women.

Testing prior to surgical investigation in this patient group in current clinical practice will have included one or more of clinical history and examination, biomarker measurement and USS. None of the studies detailed the clinical pathway of participants from presentation to the decision to test and the role of the index tests. Only three ROMA studies (Farzaneh 2014; Karlsen 2012; Ortiz-Munoz 2014), and one RMI study (Karlsen 2012) specified the presence of symptoms including 'gynaecological symptom's, pelvic pain and vaginal bleeding, pain, distension and weight loss', whilst 10 ROMA studies reported that an adnexal mass was identified following investigation with one of USS, MRI or CT.

Excluding certain tumour types changes the population spectrum as index test performance differed in different histological subtypes and at different stages of malignancy. For example, CA125 is known to have a higher sensitivity in EOC compared to other types of ovarian tumour such as stromal and germ cell tumours (Kobayashi 2012). The range of ovarian pathology reported in included studies varied. Eighteen ROMA and four RMI studies explicitly restricted inclusion to EOC, and seven ROMA studies and one RMI study explicitly excluded borderline tumours. A further 18 ROMA and three RMI studies did not report the occurrence of borderline tumours.

Characteristics of included studies are summarised in Table 3 (RMI), Table 4 (ROMA), Table 5 (LR2) and Table 6 (ADNEX).

Methodological quality of included studies

The methodological quality of all 59 included studies (71 data sets) evaluating one or more of RMI, ROMA, LR2 and ADNEX studies is summarised in Figure 3 and Figure 4. Separate figures summarise study quality by index test: RMI, ROMA, LR2 and ADNEX (Appendix 5).

Figure 3. Risk of bias and applicability concerns graph for 59 individual included studies for index tests. Review authors' judgements about each domain presented as percentages across included studies. ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROMA: Risk of Ovarian Malignancy Algorithm.

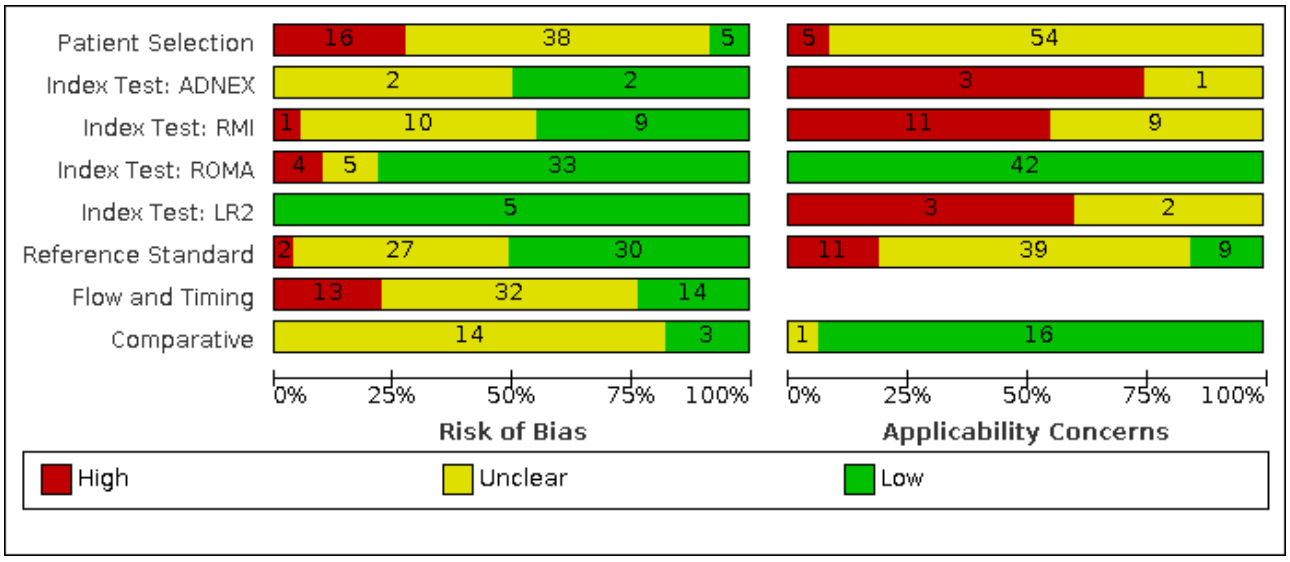


Figure 4. Risk of bias and applicability concerns figure for 59 individual included studies for index tests. Review authors' judgements about each domain for each included study. Empty cells indicate that an index test was not

evaluated by a study. ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROMA: Risk of Ovarian Malignancy Algorithm.

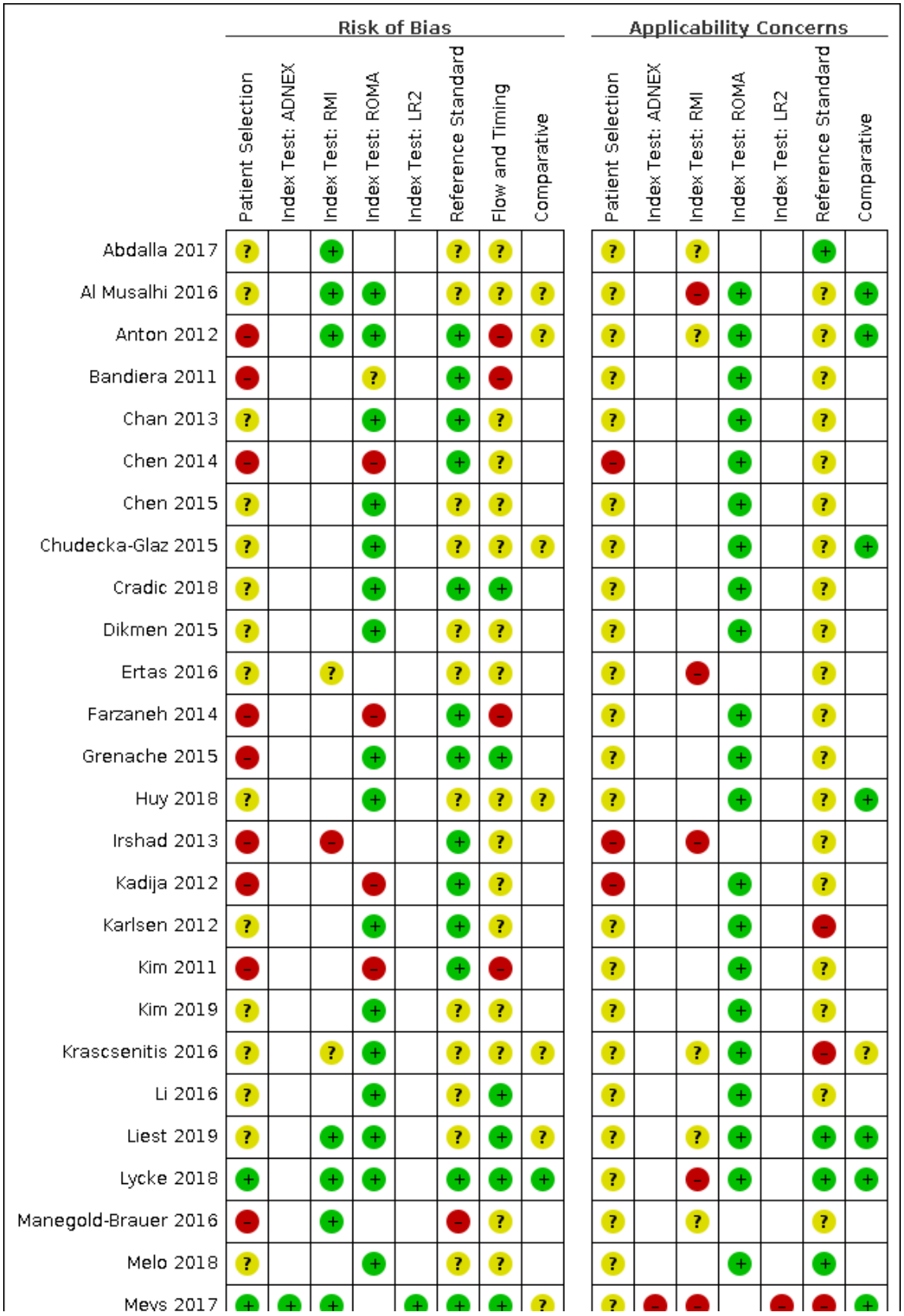


Figure 4. (Continued)

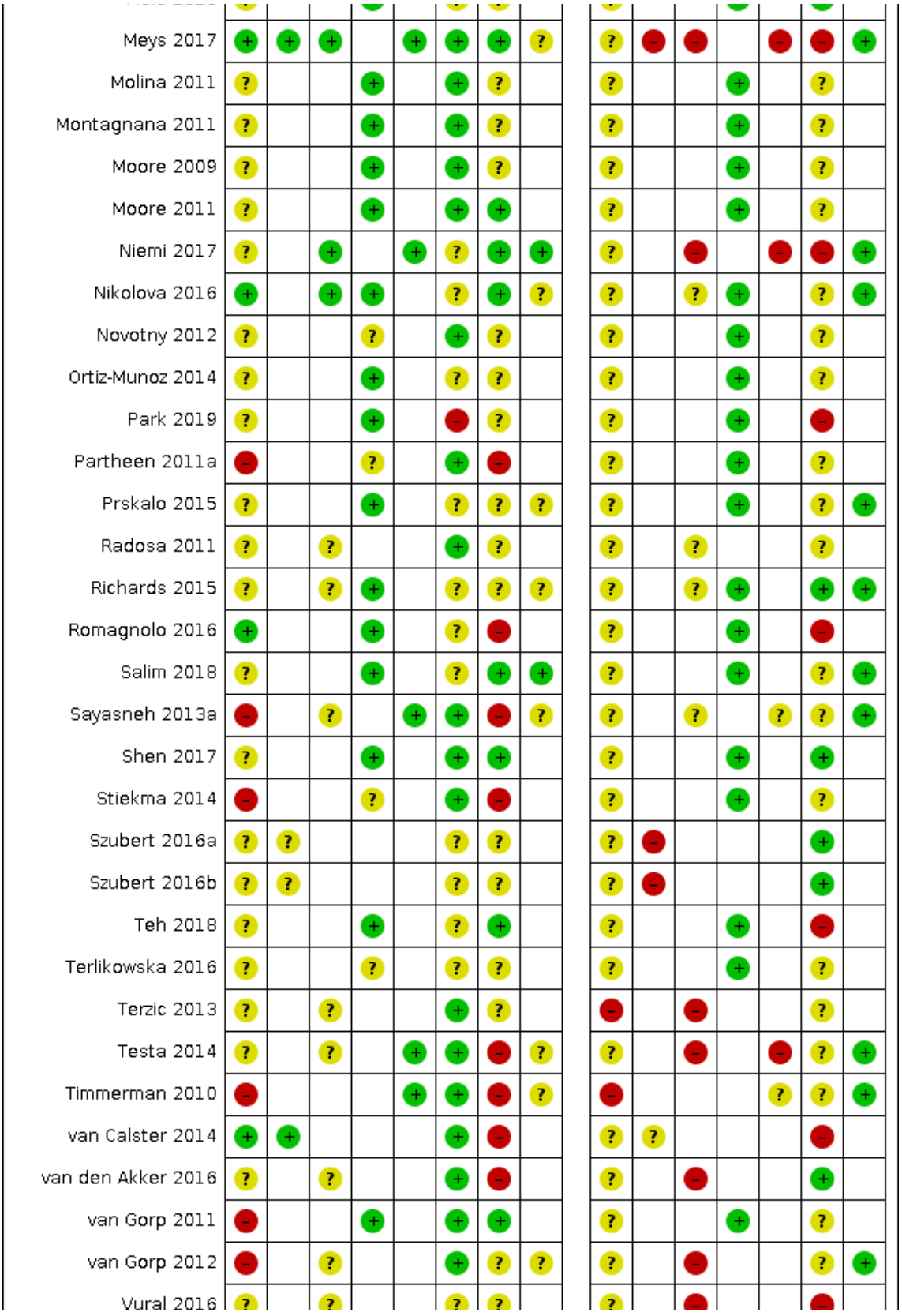
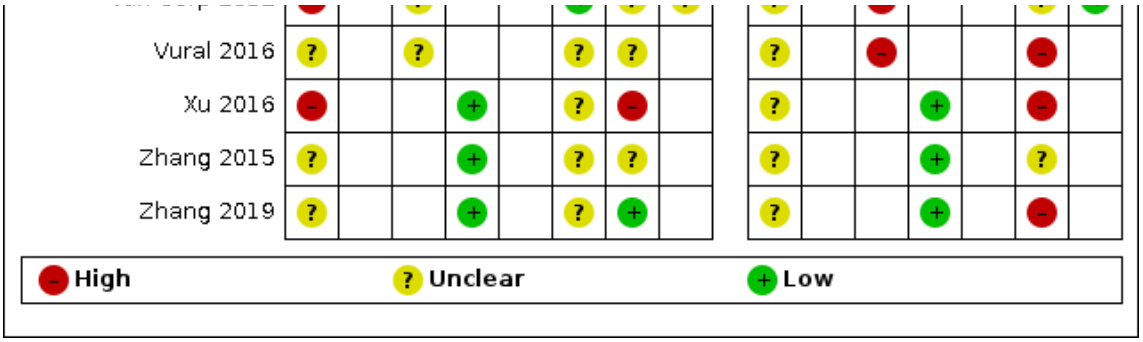


Figure 4. (Continued)



Participant selection domain

Across all included studies for the participant selection domain (Figure 3), 16/59 (27%) studies were at high risk of bias and 38/59 (64%) at unclear risk of bias. Only five studies were at low risk of bias on the basis that authors explicitly reported consecutive sampling and comprehensively listed tumour pathology identified at histology allowing a judgement to be made about selection of tumour types that might affect estimates of accuracy such as EOC and borderline tumours (Lycke 2018; Meys 2017; Nikolova 2016; Romagnolo 2016; van Calster 2014). Fifty-four of 59 (92%) studies were at high or unclear applicability concern for the participant selection domain because study participants did not obviously represent symptomatic women.

Index test domain

For the index test domain, 33/42 (79%) ROMA studies, 2/4 (50%) ADNEX studies and 9/20 (45%) RMI studies were at low risk of bias either because of the prospective nature of studies, or in the case of ROMA, the objective nature of the index test. One retrospective RMI study was at high risk of bias because RMI test results were interpreted with knowledge of the reference standard result (presence of absence of OC) (Irshad 2013). Four ROMA studies were at high risk of bias because they did not predefine the definition of the cut-off point for a positive test result (Chen 2014; Farzaneh 2014; Kadija 2012; Kim 2011). For the index test domain, applicability concern was high or unclear for all RMI, ADNEX and LR2 studies because USS was conducted by specialist sonographers or their level of specialisation was unclear.

Reference standard and target condition domain

For the reference standard domain, 30/59 (51%) studies were at low risk of bias. Twenty-seven of 59 (46%) studies were at unclear risk of bias, and two were at high risk of bias (Huy 2018; Park 2019), either because the minimum length of follow-up for index negatives was not reported at six months, or because there was concern that the reference standard outcome was ascertained with knowledge of the index test result. For the reference standard and target condition domain, applicability concern was as high or unclear in 50/59 (85%) studies because borderline tumours had been excluded from analysis or classification of borderline tumours for estimation of test accuracy was unclear.

Flow and timing domain

For the flow and timing domain, 32/59 (54%) studies were at unclear risk of bias most commonly because of no information about the interval between the index test and the reference standard. Thirteen of 59 (22%) studies were at high risk of bias because not all participants receiving an index test received a reference standard.

Findings

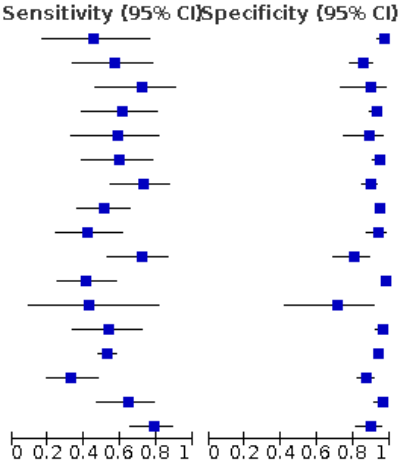
Comparison of accuracy in premenopausal and postmenopausal women

Table 2, Figure 5 (RMI), Figure 6 (ROMA), Figure 7 (LR2) and Figure 8 (ADNEX) present the accuracy of the 59 unique included studies and 71 data sets in pre- and postmenopausal women. There was a consistent difference in sensitivity (higher in postmenopausal women) and specificity (lower in postmenopausal women) across all versions of all index tests at all thresholds analysed. Subsequently, we estimated sensitivity and specificity in pre- and postmenopausal women separately.

Figure 5. Forest plot of tests: Risk of Malignancy Index I (RMI I) at thresholds of 200 and 250, separately for pre-menopausal and post-menopausal women. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

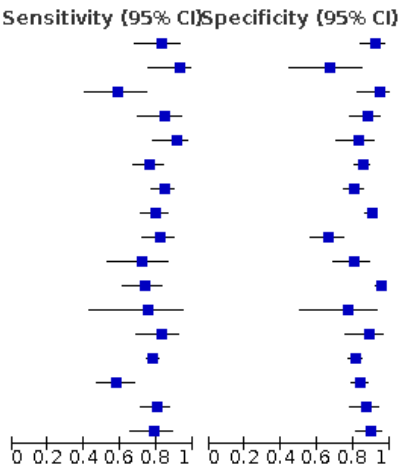
RMI I 200 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	5	6	6	178	0.45 [0.17, 0.77]	0.97 [0.93, 0.99]
Al Musalhi 2016	12	21	9	120	0.57 [0.34, 0.78]	0.85 [0.78, 0.91]
Anton 2012	13	3	5	26	0.72 [0.47, 0.90]	0.90 [0.73, 0.98]
Ertas 2016	14	20	9	248	0.61 [0.39, 0.80]	0.93 [0.89, 0.95]
Krascsenitis 2016	10	5	7	38	0.59 [0.33, 0.82]	0.88 [0.75, 0.96]
Liest 2019	16	18	11	287	0.59 [0.39, 0.78]	0.94 [0.91, 0.96]
Lycke 2018	24	24	9	206	0.73 [0.54, 0.87]	0.90 [0.85, 0.93]
Manegold-Brauer 2016	25	35	24	546	0.51 [0.36, 0.66]	0.94 [0.92, 0.96]
Meys 2017	13	6	18	91	0.42 [0.25, 0.61]	0.94 [0.87, 0.98]
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]
Radosa 2011	16	19	23	832	0.41 [0.26, 0.58]	0.98 [0.97, 0.99]
Richards 2015	3	4	4	10	0.43 [0.10, 0.82]	0.71 [0.42, 0.92]
Sayasneh 2013a	15	5	13	132	0.54 [0.34, 0.72]	0.96 [0.92, 0.99]
Testa 2014	200	59	178	917	0.53 [0.48, 0.58]	0.94 [0.92, 0.95]
van den Akker 2016	15	30	31	204	0.33 [0.20, 0.48]	0.87 [0.82, 0.91]
van Gorp 2012	25	6	14	133	0.64 [0.47, 0.79]	0.96 [0.91, 0.98]
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]



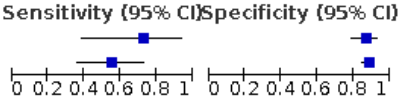
RMI I 200 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	34	6	7	70	0.83 [0.68, 0.93]	0.92 [0.84, 0.97]
Al Musalhi 2016	25	8	2	16	0.93 [0.76, 0.99]	0.67 [0.45, 0.84]
Anton 2012	21	2	15	35	0.58 [0.41, 0.74]	0.95 [0.82, 0.99]
Ertas 2016	37	9	7	64	0.84 [0.70, 0.93]	0.88 [0.78, 0.94]
Krascsenitis 2016	40	10	4	48	0.91 [0.78, 0.97]	0.83 [0.71, 0.91]
Liest 2019	89	46	28	260	0.76 [0.67, 0.83]	0.85 [0.80, 0.89]
Lycke 2018	112	42	21	173	0.84 [0.77, 0.90]	0.80 [0.75, 0.86]
Manegold-Brauer 2016	98	35	25	320	0.80 [0.71, 0.86]	0.90 [0.87, 0.93]
Meys 2017	69	39	15	75	0.82 [0.72, 0.90]	0.66 [0.56, 0.74]
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]
Radosa 2011	49	21	18	383	0.73 [0.61, 0.83]	0.95 [0.92, 0.97]
Richards 2015	9	4	3	13	0.75 [0.43, 0.95]	0.76 [0.50, 0.93]
Sayasneh 2013a	38	5	8	39	0.83 [0.69, 0.92]	0.89 [0.75, 0.96]
Testa 2014	470	85	132	362	0.78 [0.75, 0.81]	0.81 [0.77, 0.85]
van den Akker 2016	54	48	39	249	0.58 [0.47, 0.68]	0.84 [0.79, 0.88]
van Gorp 2012	89	11	22	74	0.80 [0.72, 0.87]	0.87 [0.78, 0.93]
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]



RMI I 250 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nikolova 2016	8	12	3	82	0.73 [0.39, 0.94]	0.87 [0.79, 0.93]
Terzic 2013	17	38	14	287	0.55 [0.36, 0.73]	0.88 [0.84, 0.92]



RMI I 250 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Irshad 2013	21	3	2	10	0.91 [0.72, 0.99]	0.77 [0.46, 0.95]
Terzic 2013	59	22	15	88	0.80 [0.69, 0.88]	0.80 [0.71, 0.87]

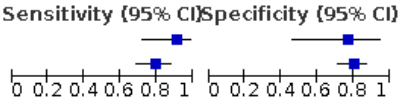
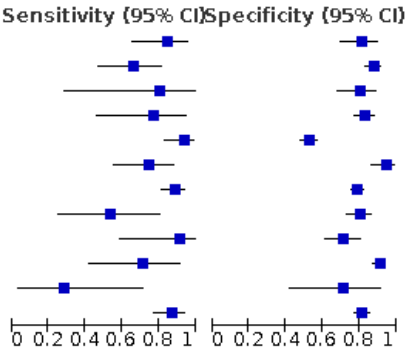


Figure 6. Forest plot of tests: Risk of Ovarian Malignancy Algorithm (ROMA) in at thresholds of 7.4 (± 2), 12.5, 13.1 (± 2), 7.4, 13.1 and 11.4 in premenopausal women, and at thresholds of 25.3 (± 2), 14.4, 27.7 (± 2), 25.3, 27.7 and 29.9 in postmenopausal women. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

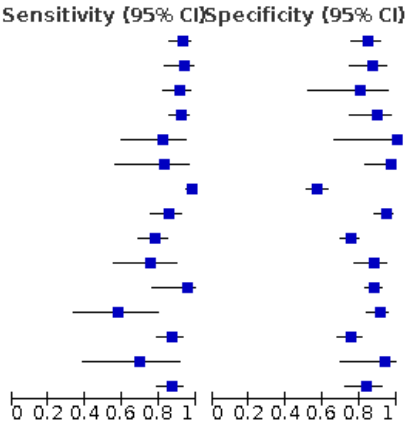
ROMA 7.4 (± 2) premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	22	13	4	56	0.85 [0.65, 0.96]	0.81 [0.70, 0.90]
Chan 2013	21	34	11	235	0.66 [0.47, 0.81]	0.87 [0.83, 0.91]
Grenache 2015	4	13	1	52	0.80 [0.28, 0.99]	0.80 [0.68, 0.89]
Huy 2018	10	37	3	180	0.77 [0.46, 0.95]	0.83 [0.77, 0.88]
Karlsen 2012	46	251	3	279	0.94 [0.83, 0.99]	0.53 [0.48, 0.57]
Kim 2011	23	4	8	67	0.74 [0.55, 0.88]	0.94 [0.86, 0.98]
Li 2016	96	136	12	501	0.89 [0.81, 0.94]	0.79 [0.75, 0.82]
Melo 2018	7	28	6	114	0.54 [0.25, 0.81]	0.80 [0.73, 0.86]
Nikolova 2016	10	27	1	67	0.91 [0.59, 1.00]	0.71 [0.61, 0.80]
Park 2019	10	29	4	282	0.71 [0.42, 0.92]	0.91 [0.87, 0.94]
Richards 2015	2	4	5	10	0.29 [0.04, 0.71]	0.71 [0.42, 0.92]
Shen 2017	60	79	9	347	0.87 [0.77, 0.94]	0.81 [0.77, 0.85]



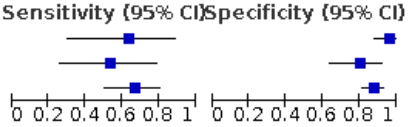
ROMA 25.3 (± 2) postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	81	15	6	81	0.93 [0.86, 0.97]	0.84 [0.76, 0.91]
Chan 2013	46	7	3	46	0.94 [0.83, 0.99]	0.87 [0.75, 0.95]
Chen 2014	63	3	6	12	0.91 [0.82, 0.97]	0.80 [0.52, 0.96]
Chudecka-Glaz 2015	114	4	10	33	0.92 [0.86, 0.96]	0.89 [0.75, 0.97]
Farzaneh 2014	18	0	4	9	0.82 [0.60, 0.95]	1.00 [0.66, 1.00]
Huy 2018	14	1	3	29	0.82 [0.57, 0.96]	0.97 [0.83, 1.00]
Karlsen 2012	198	120	5	159	0.98 [0.94, 0.99]	0.57 [0.51, 0.63]
Li 2016	70	5	12	85	0.85 [0.76, 0.92]	0.94 [0.88, 0.98]
Liest 2019	91	76	26	230	0.78 [0.69, 0.85]	0.75 [0.70, 0.80]
Melo 2018	21	8	7	56	0.75 [0.55, 0.89]	0.88 [0.77, 0.94]
Novotny 2012	20	28	1	207	0.95 [0.76, 1.00]	0.88 [0.83, 0.92]
Park 2019	11	9	8	90	0.58 [0.33, 0.80]	0.91 [0.83, 0.96]
Partheen 2011a	81	41	12	124	0.87 [0.79, 0.93]	0.75 [0.68, 0.82]
Richards 2015	9	1	4	15	0.69 [0.39, 0.91]	0.94 [0.70, 1.00]
Shen 2017	91	9	14	47	0.87 [0.79, 0.93]	0.84 [0.72, 0.92]



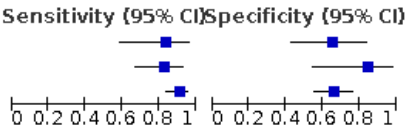
ROMA 12.5 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kadija 2012	7	2	4	54	0.64 [0.31, 0.89]	0.96 [0.88, 1.00]
Montagnana 2011	8	7	7	29	0.53 [0.27, 0.79]	0.81 [0.64, 0.92]
van Gorp 2011	28	17	14	125	0.67 [0.50, 0.80]	0.88 [0.82, 0.93]



ROMA 14.4 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kadija 2012	15	8	3	15	0.83 [0.59, 0.96]	0.65 [0.43, 0.84]
Montagnana 2011	33	2	7	11	0.82 [0.67, 0.93]	0.85 [0.55, 0.98]
van Gorp 2011	108	29	11	57	0.91 [0.84, 0.95]	0.66 [0.55, 0.76]



ROMA 13.1 (± 2) premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	11	14	10	127	0.52 [0.30, 0.74]	0.90 [0.84, 0.94]
Anton 2012	14	9	4	20	0.78 [0.52, 0.94]	0.69 [0.49, 0.85]
Chen 2014	48	16	6	38	0.89 [0.77, 0.96]	0.70 [0.56, 0.82]
Chen 2015	20	7	0	41	1.00 [0.83, 1.00]	0.85 [0.72, 0.94]
Chudecka-Glaz 2015	29	16	9	198	0.76 [0.60, 0.89]	0.93 [0.88, 0.96]
Cradic 2018	37	12	2	63	0.95 [0.83, 0.99]	0.84 [0.74, 0.91]
Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Farzaneh 2014	16	7	5	40	0.76 [0.53, 0.92]	0.85 [0.72, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]
Kadija 2012	7	2	4	54	0.64 [0.31, 0.89]	0.96 [0.88, 1.00]
Kim 2019	10	71	4	496	0.71 [0.42, 0.92]	0.87 [0.84, 0.90]
Krascsenitis 2016	12	11	5	32	0.71 [0.44, 0.90]	0.74 [0.59, 0.86]
Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]

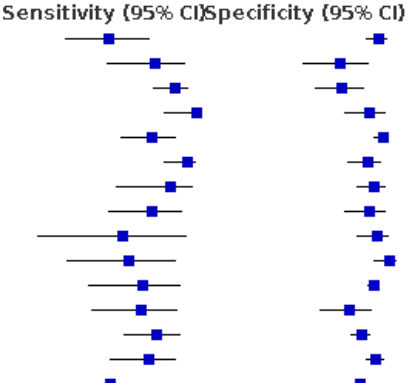
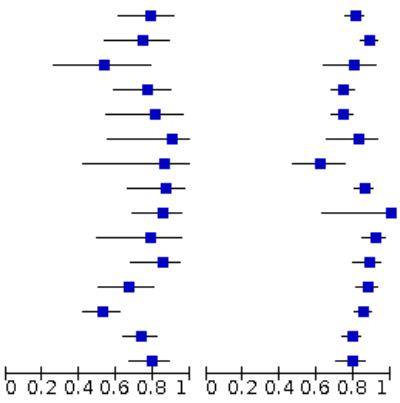


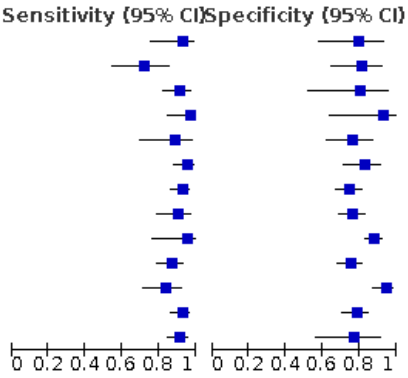
Figure 6. (Continued)

Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]
Montagnana 2011	8	7	7	29	0.53 [0.27, 0.79]	0.81 [0.64, 0.92]
Moore 2009	26	51	8	151	0.76 [0.59, 0.89]	0.75 [0.68, 0.81]
Moore 2011	13	60	3	173	0.81 [0.54, 0.96]	0.74 [0.68, 0.80]
Ortiz-Munoz 2014	9	6	1	28	0.90 [0.55, 1.00]	0.82 [0.65, 0.93]
Prskalo 2015	6	19	1	31	0.86 [0.42, 1.00]	0.62 [0.47, 0.75]
Romagnolo 2016	20	30	3	186	0.87 [0.66, 0.97]	0.86 [0.81, 0.90]
Stiekma 2014	29	0	5	8	0.85 [0.69, 0.95]	1.00 [0.63, 1.00]
Teh 2018	11	7	3	81	0.79 [0.49, 0.95]	0.92 [0.84, 0.97]
Terlikowska 2016	28	10	5	77	0.85 [0.68, 0.95]	0.89 [0.80, 0.94]
van Gorp 2011	28	17	14	125	0.67 [0.50, 0.80]	0.88 [0.82, 0.93]
Xu 2016	56	38	51	226	0.52 [0.42, 0.62]	0.86 [0.81, 0.90]
Zhang 2015	70	59	25	226	0.74 [0.64, 0.82]	0.79 [0.74, 0.84]
Zhang 2019	50	24	13	91	0.79 [0.67, 0.89]	0.79 [0.71, 0.86]



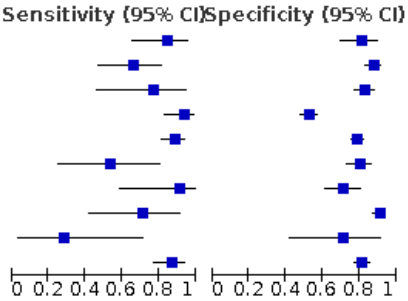
ROMA 27.7 (± 2) postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	25	5	2	19	0.93 [0.76, 0.99]	0.79 [0.58, 0.93]
Anton 2012	26	7	10	30	0.72 [0.55, 0.86]	0.81 [0.65, 0.92]
Chen 2014	63	3	6	12	0.91 [0.82, 0.97]	0.80 [0.52, 0.96]
Dikmen 2015	32	1	1	12	0.97 [0.84, 1.00]	0.92 [0.64, 1.00]
Grenache 2015	23	12	3	38	0.88 [0.70, 0.98]	0.76 [0.62, 0.87]
Molina 2011	80	10	4	49	0.95 [0.88, 0.99]	0.83 [0.71, 0.92]
Moore 2009	108	38	9	112	0.92 [0.86, 0.96]	0.75 [0.67, 0.81]
Moore 2011	46	36	5	114	0.90 [0.79, 0.97]	0.76 [0.68, 0.83]
Novotny 2012	20	28	1	207	0.95 [0.76, 1.00]	0.88 [0.83, 0.92]
Partheen 2011a	81	41	12	124	0.87 [0.79, 0.93]	0.75 [0.68, 0.82]
Romagnolo 2016	50	5	10	83	0.83 [0.71, 0.92]	0.94 [0.87, 0.98]
Salim 2018	113	30	9	108	0.93 [0.86, 0.97]	0.78 [0.70, 0.85]
Stiekma 2014	103	6	10	20	0.91 [0.84, 0.96]	0.77 [0.56, 0.91]



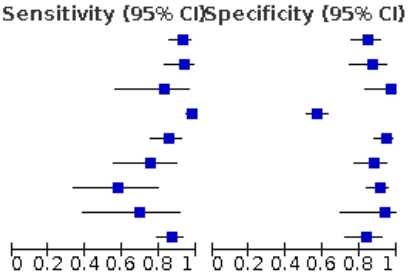
ROMA 7.4 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	22	13	4	56	0.85 [0.65, 0.96]	0.81 [0.70, 0.90]
Chan 2013	21	34	11	235	0.66 [0.47, 0.81]	0.87 [0.83, 0.91]
Huy 2018	10	37	3	180	0.77 [0.46, 0.95]	0.83 [0.77, 0.88]
Karlsen 2012	46	251	3	279	0.94 [0.83, 0.99]	0.53 [0.48, 0.57]
Li 2016	96	136	12	501	0.89 [0.81, 0.94]	0.79 [0.75, 0.82]
Melo 2018	7	28	6	114	0.54 [0.25, 0.81]	0.80 [0.73, 0.86]
Nikolova 2016	10	27	1	67	0.91 [0.59, 1.00]	0.71 [0.61, 0.80]
Park 2019	10	29	4	282	0.71 [0.42, 0.92]	0.91 [0.87, 0.94]
Richards 2015	2	4	5	10	0.29 [0.04, 0.71]	0.71 [0.42, 0.92]
Shen 2017	60	79	9	347	0.87 [0.77, 0.94]	0.81 [0.77, 0.85]



ROMA 25.3 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	81	15	6	81	0.93 [0.86, 0.97]	0.84 [0.76, 0.91]
Chan 2013	46	7	3	46	0.94 [0.83, 0.99]	0.87 [0.75, 0.95]
Huy 2018	14	1	3	29	0.82 [0.57, 0.96]	0.97 [0.83, 1.00]
Karlsen 2012	198	120	5	159	0.98 [0.94, 0.99]	0.57 [0.51, 0.63]
Li 2016	70	5	12	85	0.85 [0.76, 0.92]	0.94 [0.88, 0.98]
Melo 2018	21	8	7	56	0.75 [0.55, 0.89]	0.88 [0.77, 0.94]
Park 2019	11	9	8	90	0.58 [0.33, 0.80]	0.91 [0.83, 0.96]
Richards 2015	9	1	4	15	0.69 [0.39, 0.91]	0.94 [0.70, 1.00]
Shen 2017	91	9	14	47	0.87 [0.79, 0.93]	0.84 [0.72, 0.92]



ROMA 13.1 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	11	14	10	127	0.52 [0.30, 0.74]	0.90 [0.84, 0.94]
Anton 2012	14	9	4	20	0.78 [0.52, 0.94]	0.69 [0.49, 0.85]
Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]

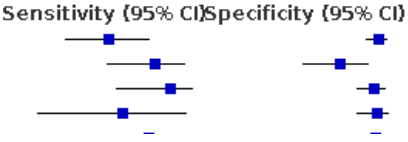
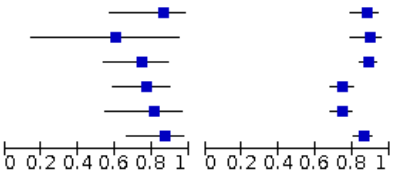


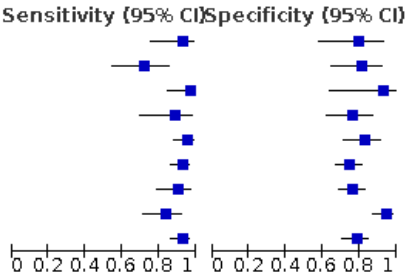
Figure 6. (Continued)

Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]
Moore 2009	26	51	8	151	0.76 [0.59, 0.89]	0.75 [0.68, 0.81]
Moore 2011	13	60	3	173	0.81 [0.54, 0.96]	0.74 [0.68, 0.80]
Romagnolo 2016	20	30	3	186	0.87 [0.66, 0.97]	0.86 [0.81, 0.90]



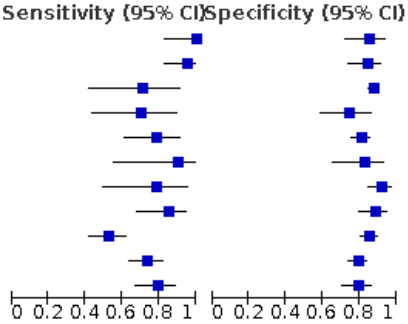
ROMA 27.7 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	25	5	2	19	0.93 [0.76, 0.99]	0.79 [0.58, 0.93]
Anton 2012	26	7	10	30	0.72 [0.55, 0.86]	0.81 [0.65, 0.92]
Dikmen 2015	32	1	1	12	0.97 [0.84, 1.00]	0.92 [0.64, 1.00]
Grenache 2015	23	12	3	38	0.88 [0.70, 0.98]	0.76 [0.62, 0.87]
Molina 2011	80	10	4	49	0.95 [0.88, 0.99]	0.83 [0.71, 0.92]
Moore 2009	108	38	9	112	0.92 [0.86, 0.96]	0.75 [0.67, 0.81]
Moore 2011	46	36	5	114	0.90 [0.79, 0.97]	0.76 [0.68, 0.83]
Romagnolo 2016	50	5	10	83	0.83 [0.71, 0.92]	0.94 [0.87, 0.98]
Salim 2018	113	30	9	108	0.93 [0.86, 0.97]	0.78 [0.70, 0.85]



ROMA 11.4 premenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2015	20	7	0	41	1.00 [0.83, 1.00]	0.85 [0.72, 0.94]
Cradic 2018	37	12	2	63	0.95 [0.83, 0.99]	0.84 [0.74, 0.91]
Kim 2019	10	71	4	496	0.71 [0.42, 0.92]	0.87 [0.84, 0.90]
Krascsenitis 2016	12	11	5	32	0.71 [0.44, 0.90]	0.74 [0.59, 0.86]
Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Ortiz-Munoz 2014	9	6	1	28	0.90 [0.55, 1.00]	0.82 [0.65, 0.93]
Teh 2018	11	7	3	81	0.79 [0.49, 0.95]	0.92 [0.84, 0.97]
Terlikowska 2016	28	10	5	77	0.85 [0.68, 0.95]	0.89 [0.80, 0.94]
Xu 2016	56	38	51	226	0.52 [0.42, 0.62]	0.86 [0.81, 0.90]
Zhang 2015	70	59	25	226	0.74 [0.64, 0.82]	0.79 [0.74, 0.84]
Zhang 2019	50	24	13	91	0.79 [0.67, 0.89]	0.79 [0.71, 0.86]



ROMA 29.9 postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2015	38	7	2	15	0.95 [0.83, 0.99]	0.68 [0.45, 0.86]
Cradic 2018	34	8	3	48	0.92 [0.78, 0.98]	0.86 [0.74, 0.94]
Kim 2019	39	17	17	178	0.70 [0.56, 0.81]	0.91 [0.86, 0.95]
Krascsenitis 2016	42	17	2	41	0.95 [0.85, 0.99]	0.71 [0.57, 0.82]
Lycke 2018	113	49	0	186	1.00 [0.97, 1.00]	0.79 [0.73, 0.84]
Ortiz-Munoz 2014	27	7	2	112	0.93 [0.77, 0.99]	0.94 [0.88, 0.98]
Prskalo 2015	61	7	5	29	0.92 [0.83, 0.97]	0.81 [0.64, 0.92]
Teh 2018	13	4	0	10	1.00 [0.75, 1.00]	0.71 [0.42, 0.92]
Terlikowska 2016	55	3	8	38	0.87 [0.77, 0.94]	0.93 [0.80, 0.98]
Xu 2016	57	1	46	46	0.55 [0.45, 0.65]	0.98 [0.89, 1.00]
Zhang 2015	154	14	15	49	0.91 [0.86, 0.95]	0.78 [0.66, 0.87]
Zhang 2019	103	5	15	55	0.87 [0.80, 0.93]	0.92 [0.82, 0.97]

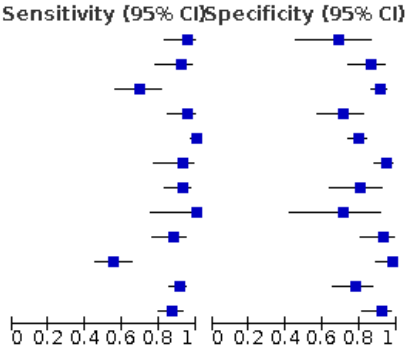


Figure 7. Forest plot of tests: Logistic Regression 2 model (LR2) separately for premenopausal and postmenopausal women. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

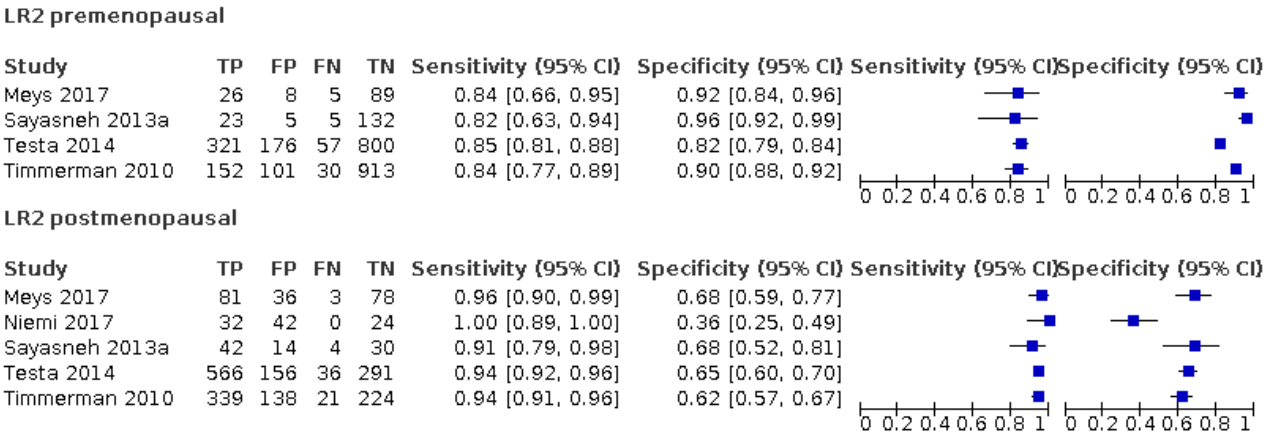
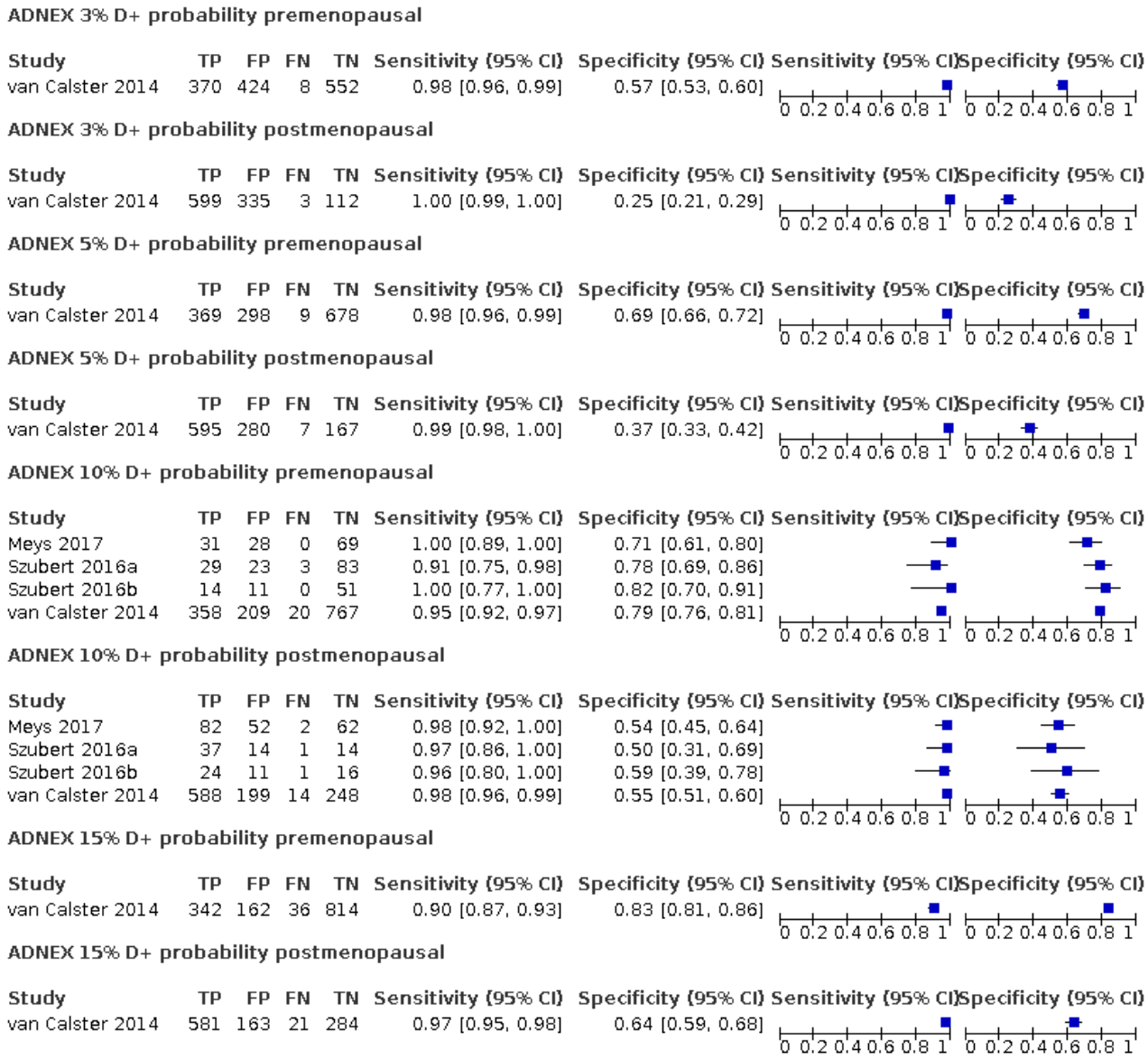


Figure 8. Forest plot of tests: Assessment of Different NEoplasias in the adneXa model (ADNEX) at thresholds of 3%, 5%, 10% and 15% disease probability separately for premenopausal and postmenopausal women. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



Test positivity threshold

ROMA and ADNEX included studies reporting accuracy across a range of test positivity thresholds. The expected trade-off between sensitivity and specificity with changes in threshold was observed; as test positivity threshold increased, sensitivity increased and specificity decreased. For ROMA, there was no evidence of a difference in accuracy at thresholds reported by included studies.

It is of note that this pattern of test performance suggests a population selected on the basis of prior testing (i.e. representative of specialist settings). At earlier points in the testing pathway for OC, it would be expected that specificity would be lower in premenopausal women compared to postmenopausal women as a result of false-positives caused by benign conditions common in premenopausal women (ovarian cysts, endometriosis) and the normal menstrual cycle.

Accuracy of RMI, ROMA, LR2 and ADNEX in premenopausal women

RMI at a threshold of 200

Based on 17 studies, including 5233 premenopausal women, of whom 851 had a diagnosis of OC, the sensitivity of RMI at a threshold of 200 was 57.1% (95% CI 50.6% to 63.4%) and the specificity was 92.5% (95% CI 90.0% to 94.4%).

RMI at a threshold of 250

Based on two studies, including 461 premenopausal women, of whom 42 had a diagnosis of OC, the sensitivity of RMI at a threshold of 250 was 59.5% (95% CI 44.3% to 73.1%) and the specificity was 88.1% (84.6% to 90.8%)

LR2 to achieve a post-test probability of ovarian cancer of 10%

Based on four studies, including 2843 premenopausal women, of whom 619 had a diagnosis of OC, the sensitivity of LR2 was 83.2% (95% CI 78.6% to 87.0%) and the specificity was 90.4% (95% CI 84.6% to 94.1%).

ROMA

For ROMA, there was no evidence of a difference in accuracy at thresholds reported by included studies. Based on the threshold pair reported by the most studies: based on 27 studies, 4463 premenopausal women, of whom 825 had a diagnosis of OC, the sensitivity of ROMA at a threshold of 13.1 ± 2 was 77.8% (95% CI 72.5% to 82.4%) and the specificity was 84.3% (95% CI 81.3% to 86.8%).

ADNEX to achieve a post-test probability of ovarian cancer of 10%

For ADNEX, accuracy was reported at a threshold to achieve a post-test probability of OC of 3% (one study), 5% (one study), 10% (four studies) and 15% (one study). Based on four studies, including 1696 premenopausal women, of whom 455 had a diagnosis of OC, the sensitivity of ADNEX to achieve a post-test probability of OC of 10% was 94.9% (95% CI 92.5% to 96.6%) and the specificity was 78.2% (95% CI 75.8% to 80.4%).

Accuracy of RMI, ROMA, LR2 and ADNEX in postmenopausal women

RMI at a threshold of 200

Based on 17 studies, including 4369 postmenopausal women, of whom 1664 had a diagnosis of OC, the sensitivity of RMI at a threshold of 200 was 78.7% (95% CI 74.3% to 82.5%) and the specificity was 85.5% (95% CI 81.3% to 88.9%).

RMI at a threshold of 250

Based on two studies, including 220 postmenopausal women, of whom 97 had a diagnosis of OC, the sensitivity of RMI at a threshold of 250 was 82.5% (95% CI 73.6% to 88.8%) and the specificity was 79.7% (95% CI 71.6% to 85.9%).

LR2 to achieve a post-test probability of ovarian cancer of 10%

Based on five studies, including 2157 postmenopausal women, of whom 1124 had a diagnosis of OC, the sensitivity of LR2 was 94.5% (95% CI 92.8% to 95.7%) and the specificity was 60.5% (95% CI 49.3% to 70.7%).

ROMA

For ROMA, there was no evidence of a difference in accuracy at thresholds reported by the included studies. Based on the threshold pair reported by the most studies: based on 13 studies, including 2002 postmenopausal women, of whom 852 had a diagnosis of OC, the sensitivity of ROMA at a threshold of 27.7 ± 2 was 90.4% (95% CI 87.4% to 92.7%) and the specificity was 81.3% (95% CI 76.9% to 85.0%).

ADNEX to achieve a post-test probability of ovarian cancer of 10%

For ADNEX, accuracy was reported at a threshold to achieve a post-test probability of OC of 3% (one study), 5% (one study), 10% (four studies) and 15% (one study). Based on four studies, including 1365 postmenopausal women, of whom 749 had a diagnosis of OC, the sensitivity of ADNEX to achieve a post-test probability of OC of 10% was 97.6% (95% CI 96.2% to 98.5%) and the specificity was 55.2% (95% CI 51.2% to 59.1%).

HSROC (between study) comparison of RMI, ROMA, LR2 and ADNEX

To maximise data for comparison, studies were included regardless of the test positivity threshold used and we undertook an indirect comparison of index (Table 7) tests by fitting HSROC curves for premenopausal women (Figure 9) and postmenopausal women (Figure 10) separately. RMI was chosen as the baseline comparator as this is the test combination currently in routine clinical use in the UK. In premenopausal women, ADNEX and LR2 but not ROMA demonstrated superior accuracy compared to RMI (relative Diagnostic Odds Ratio (rDOR): ADNEX: 4.70, 95% CI 1.45 to 15.20; P = 0.014; LR2: 2.19, 95% CI 1.18 to 4.06; P = 0.0108; ROMA: 1.19, 95% CI 0.69 to 2.07; P = 0.5202). In postmenopausal women only ROMA demonstrated superior overall accuracy compared to RMI (rDOR 1.75, 95% CI 1.23 to 2.5; P = 0.0024) (Table 7).

Figure 9. Summary ROC plot of tests (pre-menopausal women): RMI I, ROMA, LR2 and ADNEX 10% D+ probability. ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROC: receiver operating characteristic; ROMA: Risk of Ovarian Malignancy Algorithm.

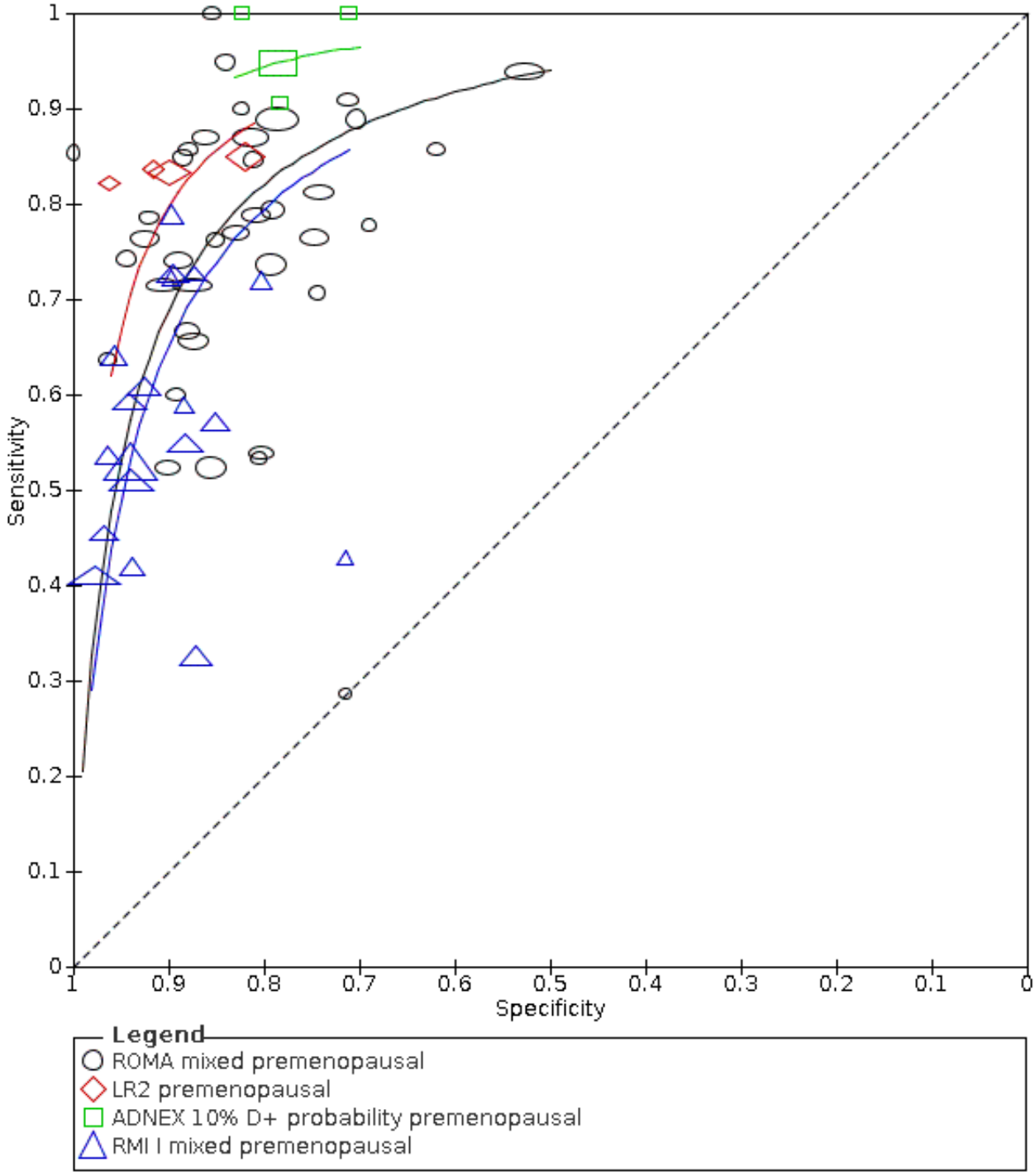
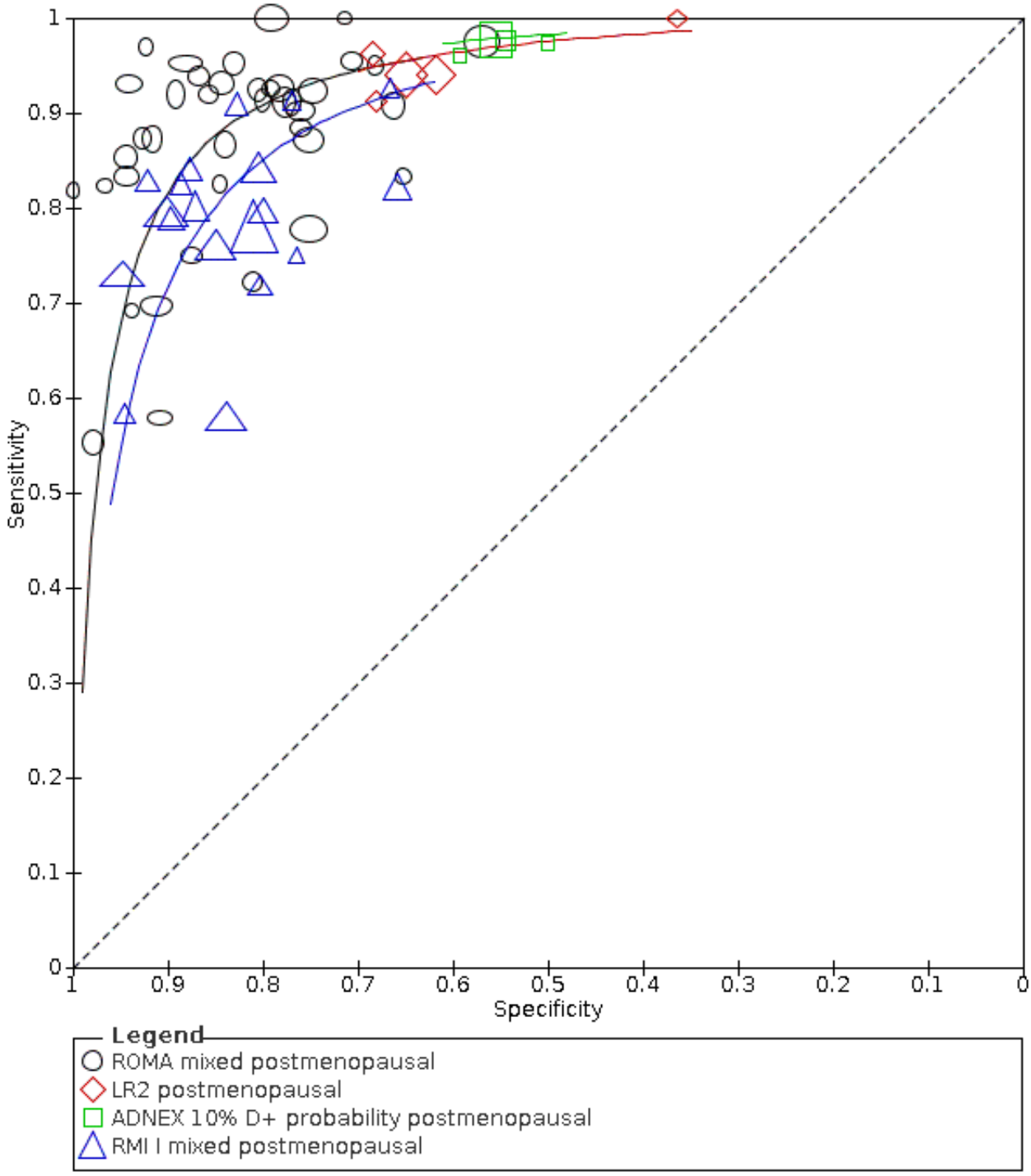


Figure 10. Summary ROC plot of tests (post-menopausal women): RMI I, ROMA, LR2 and ADNEX 10% D+ probability. ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROC: receiver operating characteristic; ROMA: Risk of Ovarian Malignancy Algorithm.



Differences in sensitivity between tests was estimated at fixed specificities of 80% and 90% (Table 7). These specificity thresholds were chosen in keeping with clinical consensus about an acceptable false-positive rate which is reflected in previous research and RCOG guidelines (RCOG 2016). It should be noted that the estimate of sensitivity for ADNEX in pre- and postmenopausal women at a fixed specificity of 90% is extrapolating beyond the data contributed by included ADNEX studies.

In premenopausal women at a fixed specificity of 80%, RMI has an estimated average sensitivity of 79.4% (95% CI 69.5% to 86.7%). The average difference in sensitivity of ROMA compared to RMI at a fixed specificity of 80% is compatible with chance (2.6% percentage points, 95% CI −5.5 to 10.7), but there was an increase in average sensitivity with LR2 and ADNEX (LR2: 9.6 percentage points higher, 95% CI 2.2 to 17.0; ADNEX: 14.9 percentage points higher, 95% CI 5.4 to 24.5).

In postmenopausal women at a fixed specificity of 80%, RMI has an average sensitivity of 85.1% (95% CI 80.9% to 88.5%). ROMA, LR2 and ADNEX demonstrated an increase in average sensitivity compared to RMI (ROMA: 5.8 percentage points, 95% CI 21.1 to 9.6; LR2: 5.7 percentage points, 95% CI 0.7 to 10.7; ADNEX: 8.3 percentage points, 95% CI 1.5 to 15.1).

Bivariate (between study) comparison of RMI, ROMA, LR2 and ADNEX

For decision-making purposes, the consequences of false-negatives (driven by sensitivity) and false-positives (driven by specificity) will not necessarily be considered equivalent and expressing accuracy in terms of overall discrimination misses this important distinction. In making recommendations for practice it is therefore useful to present test performance illustrating the trade-off between sensitivity and specificity at specific operating thresholds. Table 8 illustrates a comparison of tests at fixed thresholds in premenopausal women and Table 9 presents a comparison of tests at fixed thresholds in postmenopausal women: ROMA at a threshold of 13.1 (± 2) in premenopausal women (27/42 ROMA studies) and at a threshold of 27.7(± 2) in postmenopausal women (13/42 ROMA studies); LR2 at a post-test probability of 10% (4/4 studies in premenopausal women and 5/5 studies in postmenopausal women) and ADNEX at a post-test probability of 10% (4/4 studies in pre- and postmenopausal women) compared to RMI at a threshold of 200 (17/19 studies in pre- and postmenopausal women). For ROMA and ADNEX, the threshold pair reported by the most studies was chosen for this analysis.

Premenopausal women

In premenopausal women, RMI at a threshold of 200 (17 studies, 5233 participants, 851 cases of OC) had a sensitivity of 57.2% (95% CI 50.3 to 63.8) and a specificity of 92.5 (95% CI 90.3 to 94.2). Compared to RMI: ROMA at a threshold of 13.1 (± 2) (27 studies, 4463 participants, 825 cases of OC), demonstrated an increase in sensitivity of 20.2 percentage points (95% CI 12.2 to 28.3) but a decrease in specificity of –8.2 percentage points (95% CI –11.7 to –4.7), LR2 at a threshold to achieve a post-test probability of OC of 10% (4 studies, 2843 participants, 619 cases of OC), demonstrated an increase in sensitivity of 26.2 percentage points (95% CI 16.2 to 36.2) but with comparable specificity –2.1 percentage points (95% CI –7.2 to +2.9), ADNEX at a threshold to achieve a post-test probability of OC of 10% (4 studies, 1696 participants, 455 cases of OC), demonstrated an increase in sensitivity of 38.3 percentage points (95% CI 30.9 to 45.8) but a decrease in specificity of –14.8 percentage points (95% CI –24.0 to –5.5). In summary, in premenopausal women, ROMA, ADNEX and LR2 all demonstrated a higher sensitivity compared to RMI at a threshold of 200. In addition ADNEX appeared to demonstrate a marginally higher sensitivity compared to ROMA. LR2 had comparable specificity to RMI at a threshold of 200 whilst for ROMA and ADNEX specificity was lower.

Postmenopausal women

In postmenopausal women, RMI at a threshold of 200 (17 studies, 4369 participants, 1664 cases of OC) had a sensitivity of 78.4% (95% CI 74.6 to 81.7) and a specificity of 85.4% (95% CI 82.0 to 88.2). Compared to RMI: ROMA at a threshold of 27.7 (± 2) (13 studies, 2002 participants, 852 cases of OC), demonstrated an increase in sensitivity of 11.9 percentage points (95% CI 7.6 to 16.3) but a comparable specificity of –3.9 percentage points (95% CI –9.4 to 1.5), LR2 at a threshold to achieve a post-test probability of OC of 10% (5 studies, 2157 participants, 1124 cases of OC), demonstrated an increase in sensitivity of 16.4 percentage points (95% CI 12.3 to 20.5) but a decrease in specificity of –24.8 percentage points (95% CI –35.1 to –14.5), ADNEX at a threshold to achieve a post-test probability of OC of 10% (4 studies, 1365 participants, 749 cases of OC), demonstrated an increase in sensitivity of 19.2 percentage points (95% CI 15.4 to 23.1) but a decrease in specificity of –30.4 percentage points (95% CI –42.9 to –17.9). In summary, in postmenopausal women, ROMA, ADNEX and LR2 all demonstrated a higher sensitivity compared to RMI I at a threshold of 200. ROMA demonstrated a comparable specificity to RMI whilst for LR2 and ADNEX specificity was lower compared to RMI.

Investigation of the effect of classification of borderline tumours on estimates of test accuracy

In current clinical practice borderline ovarian tumours undergo similar surgical management to invasive malignant tumours. Included studies did not consistently include borderline ovarian tumours with malignant tumours for the purposes of estimating test accuracy. Exclusion of borderline tumours when estimating test accuracy in primary studies would be expected to result in overestimation of sensitivity, as they are a source of false-negative test results. In premenopausal women (38 ROMA studies; 19 RMI studies) and postmenopausal women (40 ROMA studies), there were sufficient data, when utilising all test positivity thresholds at a fixed specificity of 80%, to allow comparison of sensitivity estimated by studies where borderline tumours were classified as positive (grouped with malignant tumours) with studies excluding borderline tumours from analysis or where the classification of borderline tumours for analysis was unclear.

In postmenopausal women, for ROMA, there was a decrease in sensitivity of 6.4 percentage points (95% CI 1.2 to 11.5) for studies grouping borderline tumours with malignant compared to studies that excluded borderline tumours or where categorisation of borderline tumours for analysis was unclear (Table 10).

DISCUSSION

Summary of main results

To our knowledge, our systematic review is the first to compare the accuracy of ROMA, RMI and ADNEX in separately in premenopausal and postmenopausal women. Previous reviews have mostly evaluated combination tests (ROMA, RMI or LR2) in isolation and none have evaluated ADNEX. The most recent systematic review undertaking meta-analysis using hierarchical models was based on searches up to 2015 (Meys 2016). Estimates of sensitivity and specificity in premenopausal women (sensitivity 63%, specificity 93%) and postmenopausal women (sensitivity 79%, specificity 86%) were higher, but of a similar magnitude to those in this review.

Accuracy in premenopausal compared to postmenopausal women

We observed a consistent difference in sensitivity (higher in postmenopausal women) and specificity (lower in postmenopausal women) across all versions of all index tests at all thresholds analysed greater than could be expected by chance. This finding has important implications for research and practice: the utility of tests for diagnosing OC should be considered separately in premenopausal and postmenopausal women.

Comparison of the accuracy of RMI, ROMA, LR2 and ADNEX

In the UK, women with a suspected adnexal mass and with either an abnormal CA125 or USS are referred for investigation to secondary care where RMI is performed. Therefore, we investigated the performance of ROMA, LR2 and ADNEX relative to RMI. In pre- and postmenopausal women, RMI has lower sensitivity compared to ROMA, LR2 and ADNEX.

Premenopausal women

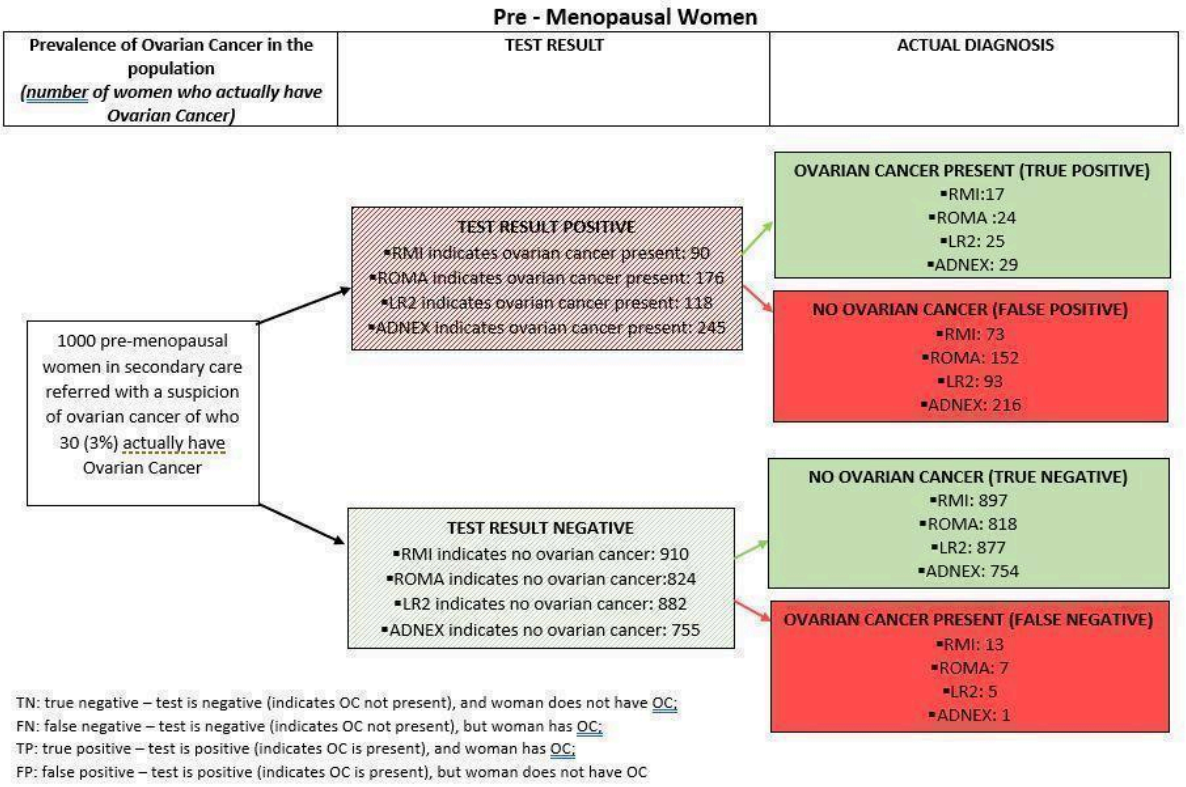
In premenopausal women, ROMA at a threshold of 13.1 (± 2), LR2 at a threshold to achieve a post-test probability of OC of 10% (post-test probability 10%) and ADNEX (post-test probability 10%) demonstrated a higher sensitivity compared to RMI (ROMA: 77.4%, 95% CI 72.7% to 81.5%; LR2: 83.3%, 95% CI 74.7% to 89.5%; ADNEX: 95.5%, 95% CI 91.0% to 97.8%; RMI: 57.2%, 95% CI 50.3% to 63.8%). The specificity of ROMA and ADNEX were lower in premenopausal women compared to RMI (ROMA: 84.3%, 95% CI 81.2% to 87.0%; ADNEX: 77.8%, 95% CI 67.4% to 85.5%; RMI: 92.5%, 95% CI 90.3% to 94.2%); the specificity of LR2 was comparable to RMI (90.4%, 95% CI 84.6% to 94.1%).

Based on our analysis, in a clinical setting with a pretest probability of OC of 3% (NICE 2017) in premenopausal women, for every 1000 premenopausal women tested:

- consequences of a positive test result:
  - an estimated 90 will have an RMI result indicating OC is present and of these 73 (81%) will not have OC;
  - an estimated 176 will have a ROMA result indicating OC is present and of these 152 (86%) will not have OC;
  - an estimated 118 will have an LR2 result indicating OC is present and of these 93 (79%) will not have OC;
  - an estimated 245 will have an ADNEX result indicating OC is present and of these 216 (88%) will not have OC;
- consequences of a negative test result:
  - of the 910 people with an RMI result indicating that OC is not present, 13 (1%) will actually have OC;
  - of the 824 people with a ROMA result indicating that OC is not present, 7 (0.8%) will actually have OC;
  - of the 882 people with an LR2 result indicating that OC is not present, 5 (0.6%) will actually have OC;
  - of the 755 people with an ADNEX result indicating that OC is not present, 1 (0.1%) will actually have OC.

See Figure 11.

Figure 11. Illustration of the consequences of testing a hypothetical cohort of premenopausal women referred from primary care (estimated prevalence of ovarian cancer 3%). ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROC: receiver operating characteristic; ROMA: Risk of Ovarian Malignancy Algorithm.



Postmenopausal women

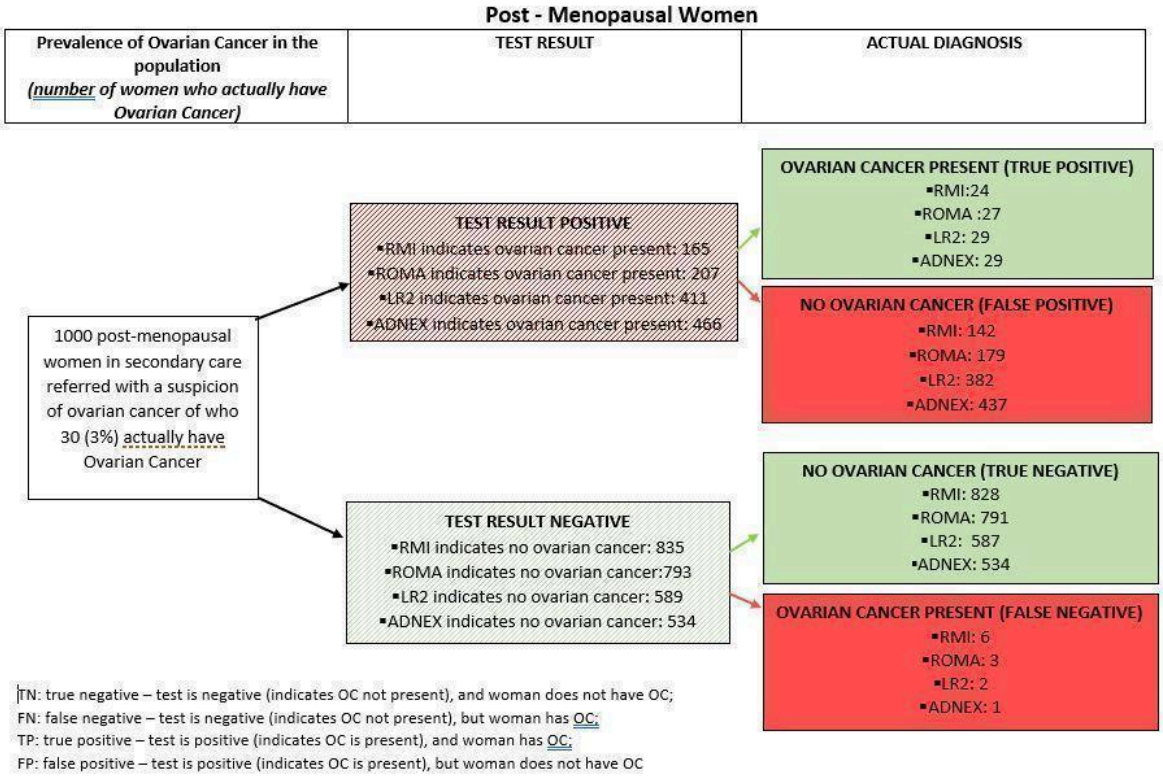
In postmenopausal women, ROMA at a threshold of 27.7 (± 2), LR2 (post-test probability 10%) and ADNEX (post-test probability 10%) demonstrated a higher sensitivity compared to RMI (ROMA: 90.3%, 95% CI 87.5% to 92.6%; LR2: 94.8%, 95% CI 92.3% to 96.6%; ADNEX: 97.6%, 95% CI 95.6% to 98.7%; RMI 78.4%, 95% CI 74.6% to 81.7%). Specificity of ROMA at a threshold of 27.7 (± 2) was comparable to RMI (ROMA: 81.5%, 95% CI 76.5% to 85.5%; RMI: 85.4%, 95% CI 82.0% to 88.2%), whereas for LR2 (post-test probability 10%) and ADNEX (post-test probability 10%), specificity was lower (LR2: 60.6%, 95% CI 50.5% to 69.9%; ADNEX: 55.0%, 95% CI 42.8% to 66.6%).

Based on our analysis, in a clinical setting with a pretest probability of OC of 3% in postmenopausal women, for every 1000 postmenopausal women tested:

- consequences of a positive test result:
  - an estimated 165 will have an RMI result indicating OC is present and of these 142 (86%) will not have OC;
  - an estimated 207 will have a ROMA result indicating OC is present and of these 179 (86%) will not have OC;
  - an estimated 411 will have an LR2 result indicating OC is present and of these 382 (93%) will not have OC;
  - an estimated 466 will have an ADNEX result indicating OC and of these 437 (94%) will not have OC;
- consequences of a negative test result:
  - of the 835 people with an RMI result indicating that OC is not present, 6 (0.7%) will actually have OC;
  - of the 793 people with a ROMA result indicating that OC is not present, 3 (0.4%) will actually have OC;
  - of the 492 people with an LR2 result indicating that OC is not present, 2 (0.4 %) will actually have OC;
  - of the 534 people with an ADNEX result indicating that OC is not present, 1 (0.1%) will actually have OC.

See Figure 12.

Figure 12. Illustration of the consequences of testing a hypothetical cohort of postmenopausal women referred from primary care (estimated prevalence of ovarian cancer 3%). ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression 2 model; RMI I: Risk of Malignancy Index I; ROC: receiver operating characteristic; ROMA: Risk of Ovarian Malignancy Algorithm.



Considerations other than accuracy when deciding on ROMA, LR2 or ADNEX as alternative tests to RMI will include the relative costs and the feasibility of introducing ROMA or ADNEX. The adoption of ROMA does not rely on availability of expertise in USS, but would require investment in laboratory facilities for processing of HE4 tests. In addition, a decision is likely to be influenced by factors such as baseline risk (prevalence) of OC, which will be dependent on healthcare setting and menopausal status, and the adverse consequences of unnecessary investigation and treatment, for example, loss of fertility.

Strengths and weaknesses of the review

Strengths

This is the first review of test combinations for the diagnosis of OC to include and compare all tests currently used in clinical practice. Although literature searches were completed in 2019, this review remains the most up-to-date comprehensive review to our knowledge. We used sensitive search strategies to capture relevant literature regardless of country of publication, publication status (published or unpublished), language or clinical setting (primary care or specialist care (secondary and tertiary). Novel features of this review include systematic investigation of the effects of menopausal status and classification of borderline tumours on estimates of test accuracy and statistical comparison of tests relevant to clinical practice at the time of writing. We attempted to mitigate against heterogeneity by attempting to restrict our analysis to primary tumours of adnexal origin and where this was not possible or unclear in studies reporting mixed primary, recurrent and metastatic disease, this was reflected in downgrading of quality assessment.

Weaknesses

Due to time and resource constraints, we were unable to consider including non-English Language studies. The impact of this omission on study findings is unknown. We acknowledge a major limitation of this review is the search date, which at the time of writing is 2.5 years old. We cannot rule out the possibility that inclusion of more-recent studies will have changed our summary estimates of accuracy for each of the four included index tests. The potential impact on estimates of test accuracy of not including more recently published studies is likely to be less for RMI (19 included studies) and ROMA (40 included studies) compared to ADNEX (four included studies) and LR2 (five included studies). LR2 has been superseded by ADNEX as the multivariable USS model of choice in clinical practice; this clinical situation is reflected by the fact that in the intervening period between our 2015 and 2019 searches, only an additional two LR2 studies were identified for inclusion in this review. In recognition of the relatively small number of ADNEX studies included in our review, we performed

a scoping search for primary studies published since our search cut-off date of June 2019. The search found three studies, two single-centre studies (Chen 2019; Nam 2021), and one multicentre study (van Calster 2014). Only one study reported sensitivity and specificity separately in pre- and postmenopausal women (Nam 2021). Sensitivity and specificity were both 83% in premenopausal women and sensitivity was 100% and specificity was 76% in postmenopausal women at a threshold to achieve a post-test probability of OC of 10%. These estimates are in line with those from studies included in this review and we consider it unlikely that inclusion of this single eligible additional ADNEX study would alter the overall conclusions of this review regarding the relative performance of tests.

We also recognise the limitation on our review methods of the pragmatic decision to reduce the number of bibliographic databases searched for the review update (between 2015 and 2019). Although we developed the 2019 search strategy iteratively, testing the sensitivity of the search strategy using articles we had already identified as potentially eligible, we cannot rule out the possibility that eligible studies may have been missed.

The major limitation of our review is deficiencies in included studies. Lack of data and poor reporting in included studies precluded quality assessment and investigation of potential important sources of heterogeneity in test accuracy estimates. These included clinical setting (primary versus specialist), target condition (primary versus recurrent and metastatic disease), and cancer histological subtype and stage. Included studies varied with respect to the range of ovarian pathology included with some restricting inclusion to EOC whilst in others metastatic disease to the ovaries could not be disaggregated from primary OC for the purposes of analysis. A lack of distinction between pre- and postmenopausal women when evaluating test accuracy continues to be a major limitation of research in this area. Thirty-seven of 59 included studies were conducted in specialist gynaecological oncology centres in women scheduled for surgery. The method of presentation of these women was documented in only four included studies.

Applicability of findings to the review question

This review aimed to answer the question of the accuracy of imaging and biomarkers for women *with symptoms suspicious for* OC. In the UK, NICE and the RCOG recommend women with suspicious symptoms presenting in primary care should receive additional investigations with biomarkers and USS to determine further management (NICE 2011; RCOG 2016). The American College of Obstetrics and Gynaecology recommends TVS as the initial test of choice *if physical examination suggests the presence of an adnexal mass* (ACOG 2016).

The presence of suspicious symptoms is therefore a trigger for further investigation. Most included studies were at high or unclear applicability to the review question on the basis that women were either asymptomatic, or it was unclear if they were symptomatic, at the point of index test use. Further, we did not identify any studies of the accuracy of test combinations to diagnose OC in a generalist setting. Most included studies had a prevalence of OC that was in keeping with tertiary hospitals. Test accuracy estimates from this review are therefore unlikely to be applicable to generalist settings, where the prevalence of OC is lower and the spectrum of the tested population more heterogeneous.

With the exception of one study (Karlsen 2012), all included women had a confirmed adnexal mass at the point of testing. Karlsen 2012 had the lowest estimated specificity (53%) and one of the highest estimates of sensitivity (94%) (Figure 6). Early in the OC testing pathway it would be expected that test specificity would be lower, particularly in premenopausal women, reflecting a more diverse population in terms of comorbidity (e.g. endometriosis and functional benign tumours), and normal physiological processes such as the menstrual cycle, which are causes of false-positive test results and a lower test specificity. Thus in generalist settings, the relationship between sensitivity and specificity and menopausal status observed in this review may be reversed. The implication is that estimates of the accuracy of index tests in this review are likely to be applicable to women selected on the basis of prior tests in specialist settings (secondary and tertiary care), but are unlikely to be applicable to women without a confirmed adnexal mass (i.e. in primary care settings).

All studies of index tests with an USS component (RMI, LR2 and ADNEX) were at high or unclear risk of bias in the index test domain on the basis that sonographers were specialists or their level of skill was not reported. Therefore, we cannot assume that the performance of RMI, LR2 or ADNEX could be replicated by non-specialist sonographers as would be the case for investigations initiated in primary care or secondary care settings.

A further concern regarding the applicability of this review's findings is that in most studies, borderline tumours were either excluded or it was unclear how they were classified for estimation of test accuracy (excluded, classified as malignant or classified as benign). Borderline ovarian tumours account for an estimated 15% of ovarian tumours (Skirnisdottir 2008). In current clinical practice, borderline ovarian tumours undergo similar surgical management to invasive malignant tumours. We observed a decrease in sensitivity of 6.4 percentage points (95% CI 1.2 to 11.5) in ROMA studies of postmenopausal women grouping borderline tumours with malignant compared to studies where borderline tumours were excluded, or where categorisation of borderline tumours for analysis was unclear (Table 10). Exclusion of borderline tumours in studies in this review is therefore likely to have resulted in overestimation of sensitivity.

AUTHORS' CONCLUSIONS

Implications for practice

This review has demonstrated that menopausal status is associated with changes in disease spectrum, which is reflected in differences in test performance for women presenting with an adnexal mass. The implications of this finding for practice is that the utility of tests for diagnosing ovarian cancer (OC) should be considered separately in premenopausal and postmenopausal women.

Furthermore, current guidelines recommending the Risk of Malignancy Index (RMI) as a diagnostic or triage test in pre- and postmenopausal women in secondary care settings should be reviewed.

The Logistic Regression Model 2 (LR2) has been superseded by the Assessment of Different NEoplasias in the adneXa model (ADNEX) in clinical practice. The strength with which we can draw conclusions about the relative accuracy of Risk of Ovarian Malignancy Algorithm (ROMA) or ADNEX, as replacements to RMI, is undermined by

the relatively small number of included ADNEX studies. However, our scoping for more-recent ADNEX studies resulted in accuracy estimates within the range of present included studies. In spite of relatively wide confidence intervals for estimates of accuracy for ADNEX, we can still conclude that:

- for premenopausal women presenting to specialist settings with an adnexal mass suspicious for OC, ROMA and ADNEX both offer higher sensitivities compared to RMI, but at the expense of a decrease in specificity;
- for postmenopausal women, ROMA and ADNEX both offer higher sensitivities compared to RMI, but at the expense of a decrease in specificity for ADNEX.

The decision about which test (ROMA or ADNEX) should replace RMI will depend in part on how healthcare systems view the trade-off between sensitivity (false-negative diagnoses) and specificity (false-positive diagnoses). Inclusion of a larger number of ADNEX studies will improve precision and may reveal a distinction between the specificity of ADNEX and ROMA in premenopausal women.

The choice of which combination test (ROMA or ADNEX) should replace RMI in practice in secondary care will also require consideration of the relative costs and the feasibility of introducing the test. ADNEX offers a polynomial probability of histology, which is valuable information for counselling patients on treatment options. However, implementing tests based on USS models will require training in specialist USS skills and quality assurance processes, similar to those introduced for nuchal scans in early pregnancy. Implementing USS through dedicated 'pelvic mass clinics' may represent a method for achieving this. Implementing testing with ROMA will require investment in laboratory processes.

The implications of our findings for women presenting in generalist settings, and early in the diagnostic pathway in secondary care, is less clear. Participants in included studies had a confirmed adnexal mass and the presence of symptoms at the time of testing was mostly not reported. Prevalence of OC in premenopausal women in included studies was upwards of 9% and in postmenopausal women 40%. Included participants are therefore likely to represent a highly selected referred population, rather than a population in whom referral is being considered. The comparative accuracy of tests observed here may also not be stable when transferred to non-specialist settings.

Implications for research

Most studies in this review were conducted in specialist centres and the prevalence of OC in both pre- and postmenopausal women was typical of tertiary healthcare settings, ranging from 8% to 81% across included studies. No studies were identified in populations with a prevalence of OC typical of that seen at the point of first referral to hospital (e.g. rapid access clinics) or in community settings. Clinical setting has significant implications for the performance of diagnostic tests and the cost-benefit impact on a healthcare system. Research is urgently needed to evaluate tests for diagnosis of OC in community settings. Future studies performed earlier in the OC diagnostic pathway should also take care to report aspects of setting that will have a bearing on test performance such as healthcare setting (e.g. primary care or rapid access hospital clinic); presenting signs and symptoms and details of test conduct such as the skill of those eliciting symptoms; signs and conducting and interpreting imaging tests. In populations such as these that are more heterogeneous the use of rigorous clinical follow-up as a reference standard in index test negative cases should be pursued. Importantly, higher reporting standards of diagnostic test accuracy studies are required. This is a common and major limitation to systematic review of diagnostic test accuracy studies, as previously noted (Nagar 2021).

Primary studies should in future clearly report the occurrence of tumours found to be borderline at histology. Separate classification of these tumour types will ensure test accuracy research can be used flexibility, as knowledge advances about the malignant potential of such tumours and their most effective management.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abdalla 2017

Study characteristics	
Patient Sampling	Country: Poland Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: presence of fibroids > 5 cm were excluded
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: patients scheduled to undergo surgery for adnexal tumours Sample size: 312 Age range: 18–85 years

Abdalla 2017 *(Continued)*

	Mean age: not reported Percentage postmenopausal (n): 37.5% (117)
Index tests	Test: RMI Prior test: ultrasound and measurement of tumour markers CA125 and HE4 Threshold for test positivity predefined: yes Threshold for test positivity: 200 Type of ultrasound (TAS, TVS, or both): both Operator experience of sonographer (generalist, specialist or trainee): not reported Type of technology or manufacturer of biomarker test: ultrasound performed with ultrasound apparatus Philips iU22. CA125 and HE4 measured via electrochemiluminescence immunoassay performed using a Cobas 8000 e602 apparatus
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 260, borderline 7, malignant 45, metastatic and others not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			

Abdalla 2017 *(Continued)*

C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear

Abdalla 2017 *(Continued)*

DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?

Abdalla 2017 *(Continued)*

If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

Abdalla 2017 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Al Musalhi 2016

Study characteristics	
Patient Sampling	Country: Oman Centres: single Study design: within-person comparison Recruitment: prospective method of patient selection: convenience Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: patients with an ovarian mass Sample size: 213 Age range: not reported Mean age: not reported Percentage postmenopausal (n): 24% (51)
Index tests	Test: RMI I and ROMA Prior test: presume USS Threshold for test positivity predefined: yes Threshold for test positivity: ROMA: premenopausal 13.1, postmenopausal 27.7, RMI I: 200 Type of ultrasound (TAS, TVS or both): TVS Operator experience of sonographer (generalist, specialist or trainee): specialised gynaecologist
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 165, borderline 7, malignant 48, metastatic and others not reported Target condition: OC/EOC (44% EOC)
Flow and timing	

Al Musalhi 2016 *(Continued)*

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

Al Musalhi 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Al Musalhi 2016 *(Continued)*

DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Unclear	

Al Musalhi 2016 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		
Could the conduct of the comparative studies have introduced bias?		Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			Low concern

Anton 2012

Study characteristics	
Patient Sampling	Country: Brazil Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience

Anton 2012 *(Continued)*

	Inappropriate exclusions (all, stage, all age, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women referred with pelvic masses diagnosed by USS or CT or MRI undergoing surgery or image-guided biopsy when they presented with signs of carcinomatosis Sample size: 120 Age range: not reported Mean age: benign 50.7 years, BOT 56.4 years, malignant 54.7 years Median age: benign 51 years, BOT 58 years, malignant 54 years Percentage postmenopausal (n): 60.8% (73) Comments: 2 participants were excluded as 1 had leiomyoma and 1 mesothelioma instead of ovarian mass on histology
Index tests	Combination RMI, ROMA Prior test: unclear Threshold for test positivity predefined: yes ROMA, yes RMI Threshold for test positivity: ROMA premenopausal ≥ 13.1%, postmenopausal ≥ 22.7%. RMI cut-off 200 Type of ultrasound (TAS, TVS or both): mixed modalities of imaging, parameters identical to the sonographic parameters for RMI were used from the other imaging modalities. Operator experience of sonographer (generalist, specialist or trainee): unclear Type of technology or manufacturer of biomarker test: CA125 (Cobas and Roche), HE4 (EIA)
Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology: benign 66, borderline 17, malignant 30, metastatic and others 7 Staging: early not reported, late not reported
Flow and timing	
Comparative	ROMA vs RMI
Notes	
Methodological quality	

Anton 2012 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (RMI)			

Anton 2012 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	

Anton 2012 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		

Anton 2012 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		
Could the conduct of the comparative studies have introduced bias?		Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			Low concern

Bandiera 2011

Study characteristics	
Patient Sampling	Country: USA Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions: BOT excluded; non-EOC excluded Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: not reported Sample size: 278

Bandiera 2011 *(Continued)*

	Age range: 25–89 years Mean age: premenopausal: benign 41.5 years, malignant 44.7 years; postmenopausal: benign 64.0 years, malignant 66.3 years Median age: not reported Percentage postmenopausal (n): 65.8% (183) Comments: pre- and postmenopausal women were balanced in cohorts
Index tests	Combination Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 (CMIA)
Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology: benign 165, borderline excluded, malignant 113, metastatic and others excluded ? Staging: early 33, late 80, unstaged 1
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		

Bandiera 2011 *(Continued)*

B) Includes all stages and types of ovarian cancer	No	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Bandiera 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers	

Bandiera 2011 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Unclear	
Were all patients included in the analysis?	No	

Bandiera 2011 *(Continued)*

Could the patient flow have introduced bias?	High risk
DOMAIN 5: Comparative	
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Chan 2013

Study characteristics	
Patient Sampling	Country: Asia-pacific Centres: multicentre (6; Hong Kong, Japan, Korea, Taiwan, Thailand, Philippines) Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: consecutive Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women aged > 18 years with adnexal mass diagnosed by any imaging method (USS, CT or MRI) Sample size: 414 Age range: not reported Mean age: not reported Median age: not reported Percentage postmenopausal (n): 26% (108) Comments: N/A

Chan 2013 *(Continued)*

Index tests	Combination vs biomarker Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: ROMA combined 0; premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: ARCHITECT
Target condition and reference standard(s)	Only surgical patients included Histology: benign 322, borderline 16, malignant 74, metastatic and others 3 (unclear metastatic/others) Staging: early 23, late 38, unstaged 4
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			

Chan 2013 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	

Chan 2013 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Chan 2013 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		

Chan 2013 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Chen 2014

Study characteristics	
Patient Sampling	Country: China Centres: single Study design: non-comparative Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): women with non-EOC excluded
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with EOC and benign lesions Sample size: 192 Age range: not reported Mean age: not reported Median age: not reported Percentage postmenopausal (n): 43.75% (84)
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: cut-off at 75% specificity; premenopausal 12.2%, postmenopausal 25.8% Type of ultrasound (TAS, TVS, or both): N/A Operator experience of sonographer (generalist, specialist or trainee): Type of technology or manufacturer of biomarker test
Target condition and reference standard(s)	Only surgical patients included

Chen 2014 *(Continued)*

	Histology: benign 69, borderline not reported, malignant 123, metastatic and others not reported Staging: early not reported, late not reported, unstaged not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	No		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			

Chen 2014 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?

Chen 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	No	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		High risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		

Chen 2014 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Chen 2015

Study characteristics	
Patient Sampling	Country: China Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): unclear
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women with pelvic masses scheduled for surgery Sample size: 232 Age range: 17–81 years Mean age: benign 33 years, malignant 53 years Median age: not reported Percentage postmenopausal (n): not reported
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: ECLIA
Target condition and reference standard(s)	Only surgical patients included Histology: benign 70, borderline not reported, malignant 60, metastatic and others not reported Staging: early not reported, late not reported, unstaged not reported
Flow and timing	
Comparative	N/A
Notes	
Methodological quality	

Chen 2015 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (RMI)			

Chen 2015 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Chen 2015 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		

Chen 2015 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Chudecka-Glaz 2015

Study characteristics	
Patient Sampling	Country: Poland Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: consecutive Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women presenting with ovarian tumour, ovarian cyst or ascites (suspected OC) Sample size: 413

Chudecka-Glaz 2015 *(Continued)*

	Age range: OC 24–90 years; benign 18–88 years Mean age: not reported Median age: OC 59.7 years; benign 35 years Percentage postmenopausal (n): 61% (251)
Index tests	Test: ROMA and ROMA-P Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 14.1, postmenopausal 25 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: HE4: the Roche Elecsys assay on a Cobas e601 apparatus; CA125: ARCHITECT CA125 II assay on an ARCHITECT
Target condition and reference standard(s)	Only surgical patients included Histology: benign (n) 251, borderline (n) not reported, malignant (n) 162, metastatic and others not reported
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			

Chudecka-Glaz 2015 *(Continued)*

B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	

Chudecka-Glaz 2015 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Chudecka-Glaz 2015 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		
Could the conduct of the comparative studies have introduced bias?		Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			Low concern

Cradic 2018

Study characteristics	
Patient Sampling	Country: USA Centres: single

Cradic 2018 *(Continued)*

	Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: not reported; age group not stated
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with EOC or benign ovarian lesions Sample size: 207 Age range: not reported Mean age: not reported Percentage postmenopausal (n): 45% (93)
Index tests	Test: ROMA Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology: benign (n) 131, borderline (n) not reported, malignant (n) 76, metastatic and others none reported Target condition: EOC
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		

Cradic 2018 *(Continued)*

A) Includes all ages regardless of menopausal status or justify restrictions	Unclear	
B) Includes all stages and types of ovarian cancer	Unclear	
C) Includes comorbidities such as infertility and endometriosis	Unclear	
Could the selection of patients have introduced bias?		Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Cradic 2018 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes

Cradic 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	

Cradic 2018 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Dikmen 2015

Study characteristics	
Patient Sampling	Country: Turkey Centres: unclear Study design: non-comparative Recruitment: unclear Method of patient selection: unclear Inappropriate exclusions: not reported
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women were 'preoperative' Sample size: 143 Age range: not reported Mean age: benign 42 (SD 10) years, malignant 56 (SD 14) years Percentage postmenopausal (n): 32% (46)
Index tests	Test: ROMA Prior test: unclear

Dikmen 2015 *(Continued)*

	Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 13.1, postmenopausal 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: not reported; stated, "CA125 and HE4 analysed in parallel using a specific system"
Target condition and reference standard(s)	Only surgical patients included Histology (n): 100%; benign 96, borderline not reported, malignant 47, metastatic and others not reported Follow-up: none
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear

Dikmen 2015 *(Continued)*

DOMAIN 2: Index Test (ADNEX)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?

Dikmen 2015 *(Continued)*

If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Dikmen 2015 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			

Dikmen 2015 *(Continued)*

Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Ertas 2016

Study characteristics	
Patient Sampling	Country: Turkey Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with adnexal masses that underwent surgery and with complete data available Sample size: 408 Age range: 14–87 years Mean age: OC 54.4 (SD 13.6) years; benign 40.8 (SD 13.8) years Percentage postmenopausal (n): 71.4% (117)
Index tests	Test: RMI I Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist (expert radiologist) Type of technology or manufacturer of biomarker test: CA125: Architect Abbott i2000sr CMIA)): ultrasound: TVS and TAS using a Mindray DC7 ultrasound device with 5 Mhz convex abdominal and 8 Mhz vaginal probes.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 341, borderline 12, malignant 55, metastatic and others not reported
Flow and timing	

Ertas 2016 *(Continued)*

Comparative	N/A		
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

Ertas 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Ertas 2016 *(Continued)*

DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	Yes

Ertas 2016 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Farzaneh 2014

Study characteristics	
Patient Sampling	Country: Iran Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience

Farzaneh 2014 *(Continued)*

	Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): excluded non-EOC
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women with adnexal mass undergoing surgery and having attained menarche 12 months before presenting with adnexal mass Sample size: 99 Age range: 17–79 years Mean age: benign 39 years, EOC 51 years Median age: not reported Percentage postmenopausal (n): 31.3% (31)
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: best cut-off as determined by Youdon index all 18.3, premenopausal 11.5, postmenopausal 25.5 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 (Abbott), HE4 (EIA) Comments: blood samples were collected 30 minutes before the operation
Target condition and reference standard(s)	Only surgical patients included Histology: benign 56, borderline not reported, malignant 43, metastatic and others not reported Staging: early 12, late 31, unstaged 0
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Farzaneh 2014 *(Continued)*

Did the study avoid inappropriate exclusions?	No	
A) Includes all ages regardless of menopausal status or justify restrictions	Yes	
B) Includes all stages and types of ovarian cancer	No	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Farzaneh 2014 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes

Farzaneh 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		High risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	

Farzaneh 2014 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Grenache 2015

Study characteristics	
Patient Sampling	Country: USA Centres: multicentre Study design: within-person comparison Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women with abnormal adnexal mass detected on physical examination and imaging of ultrasound, CT or MRI) followed by surgery Sample size: 146 Age range: 18–89 years Mean age: 52 years Percentage postmenopausal (n): 52% (76)

Grenache 2015 *(Continued)*

	Comments: benign samples (90) were randomly collected from cohort of ICRA diagnosis of benign disease and all 6 malignant samples from the same cohort were included. Samples (50) were randomly collected from cohort of ICRA diagnosis of malignancy (25 from the confirmed benign group and 25 from the confirmed malignant group). The sampling tried to mimic prevalence of malignancy in women undergoing surgery (21%)
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: ROMA premenopausal ≥ 1.31, postmenopausal ≥ 2.77 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: MVI-Quest, HE4 and CA125 (Abbot) Comments: laboratory personnel were blinded to all clinical information. All blood samples were collected < 30 days prior to surgery except 1 (50 days)
Target condition and reference standard(s)	Only surgical patients included Histology: benign 115, borderline 7, malignant 19, metastatic and others 5 (3 mets) Staging: early 18, late 14, unstaged 4
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		

Grenache 2015 *(Continued)*

C) Includes comorbidities such as infertility and endometriosis	Yes
Could the selection of patients have introduced bias?	High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated	
B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	

Grenache 2015 *(Continued)*

A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		

Grenache 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (LR2)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			

Grenache 2015 *(Continued)*

For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Huy 2018

Study characteristics	
Patient Sampling	Country: Vietnam Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: unclear about borderline cases
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with sufficient personal information, clinical symptoms, data on serum CA125 and serum HE4 levels, and postoperative pathological findings Sample size: 277 Age range: not reported Mean age: not reported Percentage postmenopausal (n): 17% (47)
Index tests	Test: ROMA Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A

Huy 2018 *(Continued)*

	Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 measured using Elecsys 2010 system immunoassay (Elecsys, 2010) and ARCHITECT i1000SR system, respectively (ARCHITECT System User Manual, 2009).
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 247, borderline not reported, malignant 30, metastatic and others none Target condition: EOC
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			

Huy 2018 *(Continued)*

If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?

Huy 2018 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Huy 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		
Could the conduct of the comparative studies have introduced bias?		Unclear risk	

Huy 2018 *(Continued)*

Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	Low concern

Irshad 2013

Study characteristics	
Patient Sampling	Country: Pakistan Centres: single Study design: non-comparative Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): unclear (? excludes premenopausal women)
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: unclear Sample size: 36 Age range: 50–70 years Mean age: 58 (SD 5.88) years Percentage postmenopausal (n): not reported Comments: inclusion criteria not reported. Women with postmenopausal bleeding and family history of breast cancer and OC were excluded.
Index tests	Combination RMI I Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: > 250 Type of ultrasound (TAS, TVS or both): unclear Operator experience of sonographer (generalist, specialist or trainee): unclear Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology: benign 12, borderline not reported, malignant 24, metastatic and others not reported Staging: early not reported, late not reported, unstaged not reported

Irshad 2013 *(Continued)*

Flow and timing			
Comparative	N/A		
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

Irshad 2013 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	No	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		High risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Irshad 2013 *(Continued)*

DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	Yes

Irshad 2013 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Kadija 2012

Study characteristics	
Patient Sampling	Country: Serbia Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience

Kadija 2012 *(Continued)*

	Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): unclear
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women diagnosed with adnexal mass scheduled to undergo surgery Sample size: 108 Age range: not reported Mean age: not reported Median age: not reported Percentage postmenopausal (n): 40% (41) Comments: metastasis to ovaries from 4 malignancies excluded
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: premenopausal < 12.5%, postmenopausal < 14.4% Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 – Immulite 2000 (Siemens) HE4 (Fujirebio) Comments: pathologists and surgeons were blinded to the index test results.
Target condition and reference standard(s)	Only surgical patients included Histology: benign 79, borderline 5, malignant 24, metastatic and others 4 (excluded) Staging: early 9 (only invasive), late 15 (only invasive), unstaged not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		

Kadija 2012 *(Continued)*

Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Unclear	
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear	
B) Includes all stages and types of ovarian cancer	Unclear	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		High
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Kadija 2012 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	No
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes

Kadija 2012 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		High risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear

Kadija 2012 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Karlsen 2012

Study characteristics	
Patient Sampling	Country: Denmark Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): women examined as per fast track guidelines
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women admitted to surgery for pelvic mass or pelvic pain potentially caused by malignant disease or endometriosis

Karlsen 2012 *(Continued)*

	Sample size: 1218 Age range: 16–90 years Mean age: not reported Median age: 51 years Percentage postmenopausal (n): 51% (621) Comments: 69 non-OCs? metastatic
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 13.1, postmenopausal 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CMIA Comments: blood samples collected 2 weeks prior to surgery
Target condition and reference standard(s)	Only surgical patients included Histology: benign 809, borderline 79, malignant 261, metastatic and others 69 Staging: early 64 (only for EOC), late 188 (only for EOC), unstaged 0
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		

Karlsen 2012 *(Continued)*

C) Includes comorbidities such as infertility and endometriosis	Yes
Could the selection of patients have introduced bias?	Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated	
B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	

Karlsen 2012 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		

Karlsen 2012 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Kim 2011

Study characteristics	
Patient Sampling	Country: South Korea Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): only EOC included Comments (if applicable): none
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women diagnosed with adnexal mass on the first visit to the gynaecological oncology clinic and underwent surgery Sample size: 159 Age range: 14–73 years Mean age: benign 35.7 (SD 11.8) years, OC 51.7 (SD 11.7) years Median age: not reported Percentage postmenopausal (n): 68% (108) Comments: none
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: premenopausal 7.6%, postmenopausal 10.9% Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 both automated immunochemiluminescence assay
Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology: benign 81, borderline 10, malignant 68, metastatic and others 2 Staging: early 29, late 49
Flow and timing	

Kim 2011 *(Continued)*

Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	No		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

Kim 2011 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?

Kim 2011 *(Continued)*

DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	No	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		High risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	

Kim 2011 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Kim 2019

Study characteristics	
Patient Sampling	Country: Korea Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear

Kim 2019 *(Continued)*

	Inappropriate exclusions: unclear (presume BOT excluded as retrospective)
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with suspected gynaecological disease Sample size: 832 Age range: not reported Mean age: not reported Median age: benign 45.0 (IQR 36.0–51.0) years; OC: 64.0 (IQR 50.9–77.0) years Percentage postmenopausal (n): 30% (251)
Index tests	Test: ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 tests performed with a Cobas E 602 immunoassay analyser using Elecsys CA125 II and Elecsys HE4 test reagents (Roche Diagnostics GmbH, Mannheim, Germany)
Target condition and reference standard(s)	Histology: 563 (68%) Follow-up: not reported Histology (n): benign 762, borderline not reported, malignant 70, metastatic 3, others 3 stromal tumour, 3 germ cell tumour
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Kim 2019 *(Continued)*

Did the study avoid inappropriate exclusions?	Unclear	
A) Includes all ages regardless of menopausal status or justify restrictions		
B) Includes all stages and types of ovarian cancer	Unclear	
C) Includes comorbidities such as infertility and endometriosis	Unclear	
Could the selection of patients have introduced bias?		Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Kim 2019 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes

Kim 2019 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Unclear	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	

Kim 2019 *(Continued)*

Did all patients receive the same reference standard?	Unclear
Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk
DOMAIN 5: Comparative	
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Krascsenitis 2016

Study characteristics	
Patient Sampling	Country: Hungary Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: not reported
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women diagnosed with an ovarian tumour of unknown significance admitted for surgery. Sample size: 162 Age range: not reported Mean age: 55 years Percentage postmenopausal (n): 63% (102)
Index tests	Test: ROMA and RMI I Prior test: not reported

Krascsenitis 2016 *(Continued)*

	Threshold for test positivity predefined: yes Threshold for test positivity: RMI I 200; ROMA premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): not reported Operator experience of sonographer (generalist, specialist or trainee): not reported Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 101, borderline 11, malignant 34, metastatic and others 16
Flow and timing	
Comparative	RMI I vs ROMA
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			

Krascsenitis 2016 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Krascsenitis 2016 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Krascsenitis 2016 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		

Krascsenitis 2016 *(Continued)*

Could the conduct of the comparative studies have introduced bias?	Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	Unclear

Li 2016

Study characteristics	
Patient Sampling	Country: China Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women diagnosed with gynaecological diseases. Histological diagnosis verified by 2 different pathologists Sample size: 916 Age range: 18–82 years Mean age: not reported Median age: 50 years Percentage postmenopausal (n): 19% (172)
Index tests	Test: ROMA Prior test: ultrasound, CT scan, PET-CT scan or MRI histological diagnosis verified by 2 different pathologists Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: tested by the ARCHITECT CA125 II assay and ARCHITECT HE4 assay (Abbott Diagnostics, Abbott Park, IL)
Target condition and reference standard(s)	Only surgical patients included

Li 2016 *(Continued)*

	Histology (n): benign 726, borderline not reported, malignant 190, metastatic and others 0		
Flow and timing			
Comparative			
Notes			

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			

Li 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers

Li 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Li 2016 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Liest 2019

Study characteristics	
Patient Sampling	Country: Sweden Centres: multicentre

Liest 2019 *(Continued)*

	Study design: within-person comparison Recruitment: prospective Method of patient selection: convenience (enrolled by gynaecologists) Inappropriate exclusions: none reported but age group not specified
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women aged ≥ 18 years with a pelvic mass of probable ovarian origin and scheduled for surgery Sample size: 784 Age range: not reported Mean age: not reported Percentage postmenopausal (n): 81% (117)
Index tests	Test: ROMA and RMI Prior test: USS Threshold for test positivity predefined: yes Threshold for test positivity: ROMA: premenopausal 11, postmenopausal 25; RMI I 200 Type of ultrasound (TAS, TVS or both): unclear Operator experience of sonographer (generalist, specialist or trainee): unclear Type of technology or manufacturer of biomarker test: both CA125 and HE4 measured by an electrochemiluminescence immunoassay on the automated cobas e602 module (Roche Diagnostics, Mannheim, Germany)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 611, borderline not reported, malignant 144 (including borderline), metastatic and others 29 Target condition: EOC
Flow and timing	
Comparative	ROMA vs RMI
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Liest 2019 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Unclear	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Unclear	
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear	
B) Includes all stages and types of ovarian cancer	Unclear	
C) Includes comorbidities such as infertility and endometriosis	Unclear	
Could the selection of patients have introduced bias?		Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	

Liest 2019 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	

Liest 2019 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern

Liest 2019 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?		Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Lycke 2018

Study characteristics	
Patient Sampling	Country: Sweden Centres: multicentre Study design: within-person comparison Recruitment: prospective Method of patient selection: consecutive Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women aged > 18 years planned for a surgical procedure for a symptomatic or suspected malignant ovarian cyst or pelvic tumour Sample size: 638 Age range: not reported

Lycke 2018 *(Continued)*

	Mean age: benign 50.76 years, BOT 55.58 years, EOC 62.67 years Percentage postmenopausal (n): 55% (348)
Index tests	Test: ROMA and RMI I Prior test: unclear but assume history, examination and ultrasound Threshold for test positivity predefined: yes Threshold for test positivity: yes ROMA: premenopausal 11.4, postmenopausal 29.9 RMI: 200 Type of ultrasound (TAS, TVS or both): unclear Operator experience of sonographer (generalist, specialist or trainee): gynaecology specialist or trainee Type of technology or manufacturer of biomarker test: Elecsys HE4 and Elecsys CA125 II with the electrochemilluminescence (ECLIA) technique (Cobas 8000, Roche Diagnostics Scandinavia, Stockholm, Sweden)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 445, borderline 31, malignant 162, metastatic and others 0 Follow-up: none
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Low risk	

Lycke 2018 *(Continued)*

A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated	
B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes
Could the conduct or interpretation of the index test have introduced bias?	Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers	

Lycke 2018 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

Lycke 2018 *(Continued)*

DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for par-	Yes	

Lycke 2018 *(Continued)*

ticipants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Yes	
Could the conduct of the comparative studies have introduced bias?	Low risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Manegold-Brauer 2016

Study characteristics	
Patient Sampling	Country: Switzerland Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: convenience Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women who had an USS examination for an adnexal mass in a general gynaecological outpatient setting with histology and CA125 results available Sample size: 1108 Age range: not reported Mean age: not reported Median age: 48 years Percentage postmenopausal (n): 43% (478)
Index tests	Test: RMI I Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: 200 Type of ultrasound (TAS, TVS or both): not reported Operator experience of sonographer (generalist, specialist or trainee): trainee

Manegold-Brauer 2016 *(Continued)*

	Type of technology or manufacturer of biomarker test: USS performed with high-resolution machines (GE Voluson 730 Expert, GE Voulson E8, Phillips HDI 5000, Phillips IU22).
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 936, borderline 33, malignant 118, metastatic and others 17
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			

Manegold-Brauer 2016 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Manegold-Brauer 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers

Manegold-Brauer 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Melo 2018

Study characteristics	
Patient Sampling	Country: Portugal Centres: single Study design: within-person comparison Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: not reported; age group not specified
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with adnexal neoplasia submitted to surgical treatment, with a histological diagnosis and in which RO-MA had been determined Sample size: 247 Age range: not reported Mean age: not reported Percentage postmenopausal (n): 37% (92)
Index tests	Test: ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 were measured on the ARCHITECT i2000SRrVR, a fully automated immunoassay analyser (Abbott Laboratories, Abbott Park, IL)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 206, borderline 7, malignant 34, metastatic and others none reported
Flow and timing	
Comparative	
Notes	
Methodological quality	

Melo 2018 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (RMI)			

Melo 2018 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes

Melo 2018 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		

Melo 2018 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Meys 2017

Study characteristics	
Patient Sampling	Country: the Netherlands Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: consecutive Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with adnexal pathology Sample size: 326 Age range: not reported

Meys 2017 *(Continued)*

	Mean age: not reported Median age: benign 53.2 (IQR 16.1–87.2) years, malignant 67.7 (IQR 32.3–87) years Percentage postmenopausal (n): 61% (198)
Index tests	Test: ADNEX, LR2 and RMI I Prior test: not reported Threshold for test positivity predefined: Threshold for test positivity: ADNEX 10%, LR2 10%, RMI I 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): experienced gynaecologist Type of technology or manufacturer of biomarker test: transvaginal or transrectal grey-scale and colour Doppler ultrasound examination, using a Voluson E8 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine along with TAS for large mass or suspected malignancy was performed.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 211, borderline 27, malignant 115, metastatic and others 14 Target condition: OC/EOC (84% EOC)
Flow and timing	
Comparative	ADNEX vs RMI I vs LR2
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Low risk	

Meys 2017 *(Continued)*

A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (RMI)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
A) Was ultrasound performed in all patients by non-specialised sonographers			

Meys 2017 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	

Meys 2017 *(Continued)*

DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		High
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for par-		

Meys 2017 *(Continued)*

ticipants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?	Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Molina 2011

Study characteristics	
Patient Sampling	Country: Spain Centres: single Study design: within-person comparison Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): unclear
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: not reported Sample size: 396 Age range: 17–90 years Mean age: not reported Median age: benign gynaecological disease 40 (SD 0.8) years; gynaecological cancer 61 (SD 1.2) years Percentage postmenopausal (n): 34% (143) Comment: patient spectrum included OC, benign gynaecological disease (ovarian cyst, myomas, endometriosis, endometrial polyps)
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes

Molina 2011 *(Continued)*

	Threshold for test positivity: ROMA: premenopausal ≥ 13.1, post-menopausal ≥ 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CMIA
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 285 *benign gynaecological disease with 137 ovarian cysts, borderline not reported, malignant 111, metastatic and others 11 others (? Mets) Staging: early 19, late 92, unstaged 0
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			

Molina 2011 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?

Molina 2011 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Molina 2011 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			

Molina 2011 *(Continued)*

Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Montagnana 2011

Study characteristics	
Patient Sampling	Country: Italy Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions: non-EOC excluded Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women with pelvic mass scheduled to have radical surgery Sample size: 104 Age range: not reported Mean age: EOC 56.9 (SD 14.4) years, benign 42 (SD 15.5) years Median age: not reported Percentage postmenopausal (n): 51% (53) Comments: only women undergoing radical surgery were included
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal ≥ 12.5, postmenopausal ≥ 14.4 Interval between index test and reference standard: 1 day Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 (ECLIA), HE4 (RIA)

Montagnana 2011 *(Continued)*

Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology (n): benign 49, borderline – ? excluded, malignant 55, metastatic and others? excluded Staging: early 15, late 40, unstaged 0
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			

Montagnana 2011 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?

Montagnana 2011 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Montagnana 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Unclear		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			

Montagnana 2011 *(Continued)*

Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Moore 2009

Study characteristics	
Patient Sampling	Country: USA Centres: multicentre Study design: non-comparative Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women with ovarian cyst scheduled to undergo surgery Sample size: 513 Age range: 18–87 years Mean age: 54 years Median age: not reported Percentage postmenopausal (n): 29% (150) Comments: 12 centres; aged < 48 years premenopausal, aged > 55 years postmenopausal; FSH values used to categorise women into premenopausal and postmenopausal if last menstrual period was unknown
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: specificity of 75%, premenopausal ≥ 13.1%, postmenopausal ≥ 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 (Abbott), HE4 (EIA) Comments: laboratory testing was blinded to histology

Moore 2009 *(Continued)*

Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 352, borderline 22, malignant 143, metastatic and others 14 Staging: early 93 (3 BOT) (only EOC and BOT); late 93 (3 BOT) (only EOC and BOT); unstaged 14 (10 BOT) Comments: histological evaluations were blinded to laboratory testing
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			

Moore 2009 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?

Moore 2009 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Moore 2009 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?	Unclear risk	
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		

Moore 2009 *(Continued)*

Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Moore 2011

Study characteristics	
Patient Sampling	Country: USA Centres: multicentre Study design: non-comparative Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with ovarian cyst scheduled to undergo surgery Sample size: 472 Age range: 18–89 years Mean age: 50.3 years Median age: not reported Percentage postmenopausal (n): 46% (217) Comments: 13 centres, 7 general, 6 speciality; aged < 48 years premenopausal, aged > 55 years postmenopausal, aged 48–55 years FSH values used to categorise women into premenopausal and postmenopausal with unknown last menstrual period
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: specificity of 75%, premenopausal ≥ 13.1%, postmenopausal ≥ 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 (Abbott), HE4 (EIA) Comments: blood sample collected < 30 days prior to surgery
Target condition and reference standard(s)	Only surgical patients included

Moore 2011 *(Continued)*

	Histology (n): benign 383, borderline 19, malignant 68, metastatic and others 2 Staging: early 12 (only for EOC), late 34 (only for EOC), unstaged not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			

Moore 2011 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?

Moore 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		

Moore 2011 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Niemi 2017

Study characteristics	
Patient Sampling	Country: Finland Centres: single Study design: within-person comparison Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: overtly benign or malignant-looking tumours like unilocular simple ovarian cysts and tumours associated with marked ascites (depth of the greatest pool over 10 cm) were excluded
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women aged > 50 years presenting with an abnormal adnexal mass(es) Sample size: 98 Age range: 50–84 years Mean age: not reported Median age: 61 years Percentage postmenopausal (n): 100%
Index tests	Test: RMI I and LR2 Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: RMI I 200; LR2 10, 25 and 43 Type of ultrasound (TAS, TVS or both): TVS Operator experience of sonographer (generalist, specialist or trainee): experienced gynaecologist Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 66, borderline 7, malignant 23, metastatic and others 2 Target condition: OC/EOC (EOC 78%)
Flow and timing	
Comparative	RMI I vs LR2
Notes	
Methodological quality	

Niemi 2017 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (RMI)			

Niemi 2017 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Niemi 2017 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		

Niemi 2017 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Yes		
Could the conduct of the comparative studies have introduced bias?		Low risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			Low concern

Nikolova 2016

Study characteristics	
Patient Sampling	Country: Macedonia Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: consecutive Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: premenopausal women aged ≥ 18 years with USS confirming an ovarian cyst/mass and scheduled for surgical intervention

Nikolova 2016 *(Continued)*

	Sample size: 105 Age range: OC 30–50 years, benign 18–50 years Mean age: malignant 42.46 (SD 8.21) years, benign 36.90 (SD 10.12) years Percentage postmenopausal (n): 0%
Index tests	Test: ROMA and RMI I Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: ROMA premenopausal 7.4, RMI 250 Type of ultrasound (TAS, TVS or both): TVS Operator experience of sonographer (generalist, specialist or trainee): not reported Type of technology or manufacturer of biomarker test: USS was performed using a Voluson E8, 4–9 MHz RIC5-9D vaginal transducer. Sera samples were analysed using Architect CA125 II and Architect HE4 reagents on an Abbott Platform
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 94, borderline not reported, malignant 11, metastatic and others not reported Target condition: EOC only
Flow and timing	
Comparative	ROMA vs RMI I (250)
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Low risk	

Nikolova 2016 *(Continued)*

A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		

Nikolova 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern

Nikolova 2016 *(Continued)*

DOMAIN 2: Index Test (LR2)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for par-			

Nikolova 2016 *(Continued)*

ticipants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?	Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Novotny 2012

Study characteristics	
Patient Sampling	Country: Czech Republic Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: convenience Inappropriate exclusions: premenopausal women excluded Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women with pelvic abnormalities Sample size: 256 Age range: 47–93 years Mean age: benign 65.28 years, malignant 64.37 years Median age: benign 64 years, malignant 63 years Percentage postmenopausal (n): 100% (256)
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: premenopausal 26.3, postmenopausal 37.7 Type of ultrasound (TAS, TVS or both): N/A

Novotny 2012 *(Continued)*

	Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: Architect
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 256, borderline not reported, malignant 21, metastatic and others not reported Staging: early not reported, late not reported, unstaged not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			

Novotny 2012 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?

Novotny 2012 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Unclear	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Novotny 2012 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			

Novotny 2012 *(Continued)*

Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Ortiz-Munoz 2014

Study characteristics	
Patient Sampling	Country: Spain Centres: single Study design: within-person comparison Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): unclear Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with gynaecological symptoms, diagnosed with primary OC Sample size: 148 Age range: not reported Mean age: not reported Median age: benign premenopausal 39.5 (SD 8.4) years, postmenopausal 56 (SD 11.5) years; malignant premenopausal 40.5 (SD 5.8) years, postmenopausal 57 (SD 9.4) years Percentage postmenopausal (n): 70% (104)
Index tests	Combination ROMA Prior test: symptoms Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: LIA Comments: all blood tests performed 1 day prior to surgery
Target condition and reference standard(s)	22 benign cases were considered benign? on follow-up but duration of follow-up not detailed.

Ortiz-Munoz 2014 *(Continued)*

	Histology (n): benign 119, borderline not reported, malignant 29, metastatic and others not reported Staging: early 6, late 23, unstaged 0
Flow and timing	22 women diagnosed with simple ovarian cysts by TVS, unclear if they were based on follow-up, or duration of follow-up.
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			

Ortiz-Munoz 2014 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?

Ortiz-Munoz 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		

Ortiz-Munoz 2014 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Park 2019

Study characteristics	
Patient Sampling	Country: Korea Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: consecutive Inappropriate exclusions: 2 cases of non-EOC excluded from analysis
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women aged > 18 years for whom gynaecologists had requested HE4, CA125 and ROMA tests to evaluate a pelvic mass; 2 groups of participants considered: • malignant cases: 309 participants with available pathological examination reports of a biopsy • benign cases: 134 participants with imaging studies with minimum 4 weeks' follow-up and without biopsy Sample size: 433 (biopsy 309, follow-up 134) Age range: not reported Median age: EOC 52.3 (SD 6.1) years; benign 43.0 (SD 21) years, BOT 47.8 (SD 12.9) years Percentage postmenopausal (n): biopsy: 26% (81) Follow-up: minimum 28 weeks; median 29 weeks
Index tests	Test: ROMA Prior test: USS, CT or MRI Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: HE4 and CA125 measured using the ARCHITECT HE4 assay (Product Number: B2P540) and the CA125 II assay (Product Number: B2K450) (Abbott Diagnostics, Abbott Park, IL, USA).
Target condition and reference standard(s)	Histology: 309 (69%) Follow-up: 134 (31%) Duration of follow-up: median 29 weeks (minimum 4 weeks)

Park 2019 *(Continued)*

	Histology (n): benign 406, borderline 15, malignant EOC 18 (4%), non-EOC 2 (< 1%), metastatic and others 2 (< 1%)
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			

Park 2019 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers

Park 2019 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Park 2019 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Partheen 2011a

Study characteristics	
Patient Sampling	Country: Sweden Centres: single

Partheen 2011a *(Continued)*

	Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): solid and mass were excluded, non-EOC tumours were excluded.
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with complex cystic mass and suspicious of malignancy undergoing surgery Sample size: 374 Age range: not reported Mean age: not reported Median age: not reported Percentage postmenopausal (n): 73.7% (276) Comments: women aged > 56 years were considered postmenopausal; women aged < 47 to 56 years were considered menopausal if > 12 months of amenorrhoea
Index tests	Combination ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: specificity fixed at 75% premenopausal 17.3%, postmenopausal 26.0% Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): unclear Type of technology or manufacturer of biomarker test: HE4 (EIA), CA125 (Abbott)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 215, borderline 45, malignant 108, metastatic and others 6 others (? Mets) Staging: early 57, late 57, unstaged 0 Comments: women with final histology reporting the tumour was non-ovarian were excluded: BOT excluded for analysis for ROMA
Flow and timing	
Comparative	N/A
Notes	
Methodological quality	

Partheen 2011a *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (RMI)			

Partheen 2011a *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Unclear

Partheen 2011a *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Unclear	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		

Partheen 2011a *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Prskalo 2015

Study characteristics	
Patient Sampling	Country: Croatia Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: none reported
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with suspected adnexal mass on a TVS scheduled for elective surgery Sample size: 159

Prskalo 2015 *(Continued)*

	Age range: not reported Mean age: premenopausal 36.9 (SD 8.9) years, postmenopausal 60.2 (SD 9.6) years Percentage postmenopausal (n): 64% (102)
Index tests	Test: ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.7, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: HE4 and CA125 measured by electrochemiluminescence immunoassay on the Cobas e411 analyser (Hitachi, Tokyo, Japan; Roche, Mannheim, Germany)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 105, borderline 11, malignant 43, metastatic and others none
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			

Prskalo 2015 *(Continued)*

B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	

Prskalo 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		

Prskalo 2015 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes	

Prskalo 2015 *(Continued)*

For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear
Could the conduct of the comparative studies have introduced bias?	Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	Low concern

Radosa 2011

Study characteristics	
Patient Sampling	Patient sampling Country: Germany Centres: single Study design: within-person comparison Recruitment: unclear Method of patient selection: consecutive Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments: level 2 sonographers performed or supervised USS
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women with adnexal mass who subsequently underwent surgery were selected Sample size: not reported Age range: not reported Mean age: 43.3 years Median age: not reported Percentage postmenopausal (n): 32% (442) Comments: N/A
Index tests	Combination RMI Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: RMI > 200 Type of ultrasound (TAS, TVS or both): both

Radosa 2011 *(Continued)*

	Operator experience of sonographer (generalist, specialist or trainee): specialist level 2 Type of technology or manufacturer of biomarker test: CLIA
Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology (n): benign 1260, borderline 19, malignant 79, metastatic and others 4 Staging: early 11 (OC), late 68 (OC), unstaged borderline not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			

Radosa 2011 *(Continued)*

If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Radosa 2011 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?

Radosa 2011 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			

Radosa 2011 *(Continued)*

Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Richards 2015

Study characteristics	
Patient Sampling	Country: Australia Centres: single Study design: within-person comparison Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women undergoing surgery for a complex pelvic mass, presumed to be arising from the ovary Sample size: 50 Age range: not reported Mean age: not reported Median age: 60 years Percentage postmenopausal (n): 58% (29)
Index tests	Test: RMI I and ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: RMI I 200; ROMA: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): not reported Operator experience of sonographer (generalist, specialist or trainee): not reported Type of technology or manufacturer of biomarker test: the tumour markers were determined by the use of chemiluminescent enzyme immunoassay on an ARCHITECT analyser (Abbott Diagnostics, North Ryde, NSW, Australia)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 30, borderline 4, malignant 16, metastatic and others not reported Target condition: EOC

Richards 2015 *(Continued)*

Flow and timing			
Comparative	ROMA vs RMI I		
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

Richards 2015 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Richards 2015 *(Continued)*

DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	

Richards 2015 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		
Could the conduct of the comparative studies have introduced bias?		Unclear risk	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			Low concern

Romagnolo 2016

Study characteristics	
Patient Sampling	Country: Italy Centres: multicentre Study design: non-comparative Recruitment: prospective Method of patient selection: consecutive

Romagnolo 2016 *(Continued)*

	Inappropriate exclusions: non-EOC excluded
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: not reported Sample size: 387 Age range: not reported Mean age: premenopausal 37.6 (SD 8.6) years, postmenopausal 63 (SD 9.5) years Percentage postmenopausal (n): 38% (148)
Index tests	Test: ROMA Prior test: ultrasound Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 13.1, postmenopausal 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 measured by a CMIA on the automated Architect i2000SR platform (Abbott Diagnostics, Chicago, IL, USA) and HE4 by the HE4 EIA assay (Fujirebio Diagnostics AB, Gothenburg, Sweden)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 290, borderline 15, malignant 73 (EOC), 9 (non-EOC), metastatic and others 6 (not included in the analysis)
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		

Romagnolo 2016 *(Continued)*

B) Includes all stages and types of ovarian cancer	Yes	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		Low risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		

Romagnolo 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		

Romagnolo 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (LR2)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		

Romagnolo 2016 *(Continued)*

Could the patient flow have introduced bias?	High risk
DOMAIN 5: Comparative	
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Salim 2018

Study characteristics	
Patient Sampling	Country: Pakistan Centres: single Study design: non-comparative Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: postmenopausal women with ovarian mass (> 2 cm) on pelvic ultrasound examination, attending gynaecology clinics, planned for surgical intervention Sample size: 260 Age range: 40–65 years Mean age: 49.28 (SD 6.26) years Median age: 48 years Percentage postmenopausal (n): 100%
Index tests	Test: ROMA Prior test: not reported

Salim 2018 *(Continued)*

	Threshold for test positivity predefined: yes Threshold for test positivity: postmenopausal 27.7 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: serums were analysed for the quantification of CA125 and HE4 on automated immunoassay analyser, Abbot ARCHITECT i1000 by CMIA method.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 138, borderline not reported, malignant 122, metastatic and others not reported
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			

Salim 2018 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?

Salim 2018 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Salim 2018 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Yes		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Yes		

Salim 2018 *(Continued)*

Could the conduct of the comparative studies have introduced bias?	Low risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	Low concern

Sayasneh 2013a

Study characteristics	
Patient Sampling	Country: UK Centres: multicentre (3) Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: consecutive Inappropriate exclusions: none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: not reported Sample size: 255 (301 in Sayasneh 2013 secondary study) Age range: not reported Mean age: 46 years Median age: not reported Percentage postmenopausal (n): 35% (117) Comments: N/A
Index tests	Combination RMI I and LR2 Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: LR2-probability cut-off of 10% is considered malignant. RMI ≥ 200 Interval between application of index test and reference standard: < 120 days; 1 women excluded as surgery after 120 days Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): level 1 and level 2 (10 were excluded as level 3 scan) Type of technology or manufacturer of biomarker test: not reported

Sayasneh 2013a *(Continued)*

Target condition and reference standard(s)	Histology (%): 98; surgical mix but no histology in 5 cases (2 ovarian torsion and 3 tubo-ovarian abscess – abscess confirmed by microscopy culture) Follow-up: 2 of ovarian torsion after reporting were followed up Duration of follow-up: 6 months* Histology (n): benign 181, borderline 18, malignant 48, metastatic and others 8 Staging: early not reported, late not reported, unstaged not reported Comments: despite follow-up of 6 months reference standard classified as low concern as it combination of surgical visualisation and follow-up.
Flow and timing	
Comparative	LR2 vs RMI
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			

Sayasneh 2013a *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Sayasneh 2013a *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes

Sayasneh 2013a *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		High risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear		

Sayasneh 2013a *(Continued)*

Could the conduct of the comparative studies have introduced bias?	Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	Low concern

Shen 2017

Study characteristics	
Patient Sampling	Country: China Centres: multicentre Study design: non-comparative Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women aged ≥ 18 years referred to a participating centre with a pelvic mass or an ovarian cyst and planning to undergo surgery Sample size: 684 Age range: 42–82 years Mean age: 58.8 (SD 8.6) years Percentage postmenopausal (n): 25% (174)
Index tests	Test: ROMA Prior test: pelvic USS, CT, MRI and medical history (diagnosis and treatment of pelvic mass and history of renal disease) Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 7.4, postmenopausal 25.3 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125, HE4 measured using the Architect instrument and reagents (Abbott Diagnostics)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 482, borderline 18, malignant 169, metastatic 7, others 8

Shen 2017 *(Continued)*

	Target condition: EOC		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			

Shen 2017 *(Continued)*

A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers

Shen 2017 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		

Shen 2017 *(Continued)*

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Stiekma 2014

Study characteristics	
Patient Sampling	Country: the Netherlands Centres: single Study design: within-person comparison

Stiekma 2014 *(Continued)*

	Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): BOT and non-EOC excluded
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: histologically confirmed EOC or benign ovarian disease referred to the institute Sample size: 181 Age range: not reported Mean age: benign 47 years, malignant 57 years Median age: not reported Percentage postmenopausal (n): 79% (143) Comments: none
Index tests	ROMA Prior test: unclear Threshold for test positivity predefined: no Threshold for test positivity: ROMA; premenopausal 0.129, postmenopausal 0.278 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: CA125 and HE4 (both Abbott) Comments: N/A
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 34, borderline excluded, malignant 147, metastatic and others not reported Staging: early 24, late 123
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Stiekma 2014 *(Continued)*

Was a consecutive or random sample of patients enrolled?	No	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	No	
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear	
B) Includes all stages and types of ovarian cancer	No	
C) Includes comorbidities such as infertility and endometriosis	Unclear	
Could the selection of patients have introduced bias?		High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Stiekma 2014 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Unclear

Stiekma 2014 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear

Stiekma 2014 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Szubert 2016a

Study characteristics	
Patient Sampling	Country: Poland Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: (quote) "no specific exclusion criteria"
Patient characteristics and setting	Clinical setting: unclear, probably tertiary Study entry criteria: women needing surgery for an ovarian tumour Sample size: 204 Age range: 15–84 years Mean age: not reported

Szubert 2016a *(Continued)*

	Median age: 46 years Percentage postmenopausal (n): 54% (66)
Index tests	Test: ADNEX Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: 2000 IOTA criteria 10% Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: tumours evaluated using Aloka Alpha 10 with 3.75–7.5 MHz endovaginal probe and Aloka 3500 with a 7.5 MHz endovaginal probe (Hitach Aloka, Tokyo, Japan). A transabdominal probe was used in case of large tumours.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 134, borderline 12, malignant 58, metastatic and others not reported
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			

Szubert 2016a *(Continued)*

C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?	Unclear risk	
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Szubert 2016a *(Continued)*

DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?

Szubert 2016a *(Continued)*

If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

Szubert 2016a *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Szubert 2016b

Study characteristics	
Patient Sampling	Country: Spain Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: quote: "no specific exclusion criteria"
Patient characteristics and setting	Clinical setting: unclear, probably tertiary Study entry criteria: women needing surgery for an ovarian tumour Sample size: 128 Age range: 15–81 years Mean age: not reported Median age: 47 years Percentage postmenopausal (n): 42% (52)
Index tests	Test: ADNEX Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: 2000 IOTA criteria 10% Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: TVS or transrectal ultrasound using a Voluson E8 equipped with an RIC5-9MHz endovaginal probe (GE Healthcare, Milwaukee, USA). A transabdominal probe was used in case of large tumours.
Target condition and reference standard(s)	Only surgical patients included

Szubert 2016b *(Continued)*

	Histology (n): benign 89, borderline 4, malignant 35, metastatic and others none		
Flow and timing			
Comparative	N/A		
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes		

Szubert 2016b *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?	Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	High
DOMAIN 2: Index Test (RMI)	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	

Szubert 2016b *(Continued)*

A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	

Szubert 2016b *(Continued)*

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Unclear risk
DOMAIN 5: Comparative	
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Teh 2018

Study characteristics	
Patient Sampling	Country: Malaysia Centres: single Study design: non-comparative Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: low malignant potential tumours were included in the benign tumour group during analysis
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women aged ≥ 18 years with pelvic mass(es) suspected of originating in the ovary who had been scheduled for surgery or radiological-guided biopsy Sample size: 129 Age range: not reported Mean age: not reported Median age: 37 (IQR 27.5–48.5) years Percentage postmenopausal (n): 21% (27)
Index tests	Test: ROMA

Teh 2018 *(Continued)*

	Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: the serum samples were tested using the Elecsys HE4 assay (Roche Diagnostics, Mannheim, Germany) and Elecsys CA125 II assay (Roche Diagnostics, Mannheim, Germany) via electrochemiluminescence immunoassay technology.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 97, borderline 10, malignant 27, metastatic and others 3
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			

Teh 2018 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	

Teh 2018 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Teh 2018 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

Teh 2018 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Terlikowska 2016

Study characteristics	
Patient Sampling	Country: Poland Centres: multicentre Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: non-EOC excluded
Patient characteristics and setting	Clinical setting: mixed (secondary and tertiary) Study entry criteria: Caucasian women surgically treated on account of benign ovarian disease and epithelial cancer according to international treatment guidelines Sample size: 224 Age range: premenopausal 25–49 years, postmenopausal 53–74 years Mean age: not reported Median age: premenopausal 36 years, postmenopausal 63 years Percentage postmenopausal (n): 46% (104)
Index tests	Test: ROMA Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: concentrations of HE4 and CA125 were assessed with the electrochemilumi-

Terlikowska 2016 *(Continued)*

	nescence (ECLIA) technique on Cobas e411 (Roche Diagnostics, Switzerland) analyser
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 128, borderline not reported, malignant 96, metastatic and others none reported
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			

Terlikowska 2016 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?

Terlikowska 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		

Terlikowska 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Terzic 2013

Study characteristics	
Patient Sampling	Country: Serbia Centres: single Study design: non-comparative Recruitment: unclear Method of patient selection: consecutive Inappropriate exclusions (all stage, all ages, included comorbidities such as infertility or endometriosis): unclear Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: secondary Study entry criteria: women who had undergone surgery for adnexal mass Sample size: 540 Age range: 18–82 years Mean age: 53.44 (SD 16.82) Median age: not reported Percentage postmenopausal (n): 31.61% (184) Comments: 341 participants were symptomatic (benign 255, BOT 66, OC 66) but data could not be disaggregated as index test results were not given separately for test-positive and test-negative patients.
Index tests	Combination RMI I Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: > 250 Type of ultrasound (TAS, TVS or both): unclear Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 435, borderline 20, malignant 85, metastatic and others not reported Staging: early not reported, late not reported, unstaged not reported
Flow and timing	
Comparative	N/A

Terzic 2013 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Unclear		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			

Terzic 2013 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		

Terzic 2013 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	

Terzic 2013 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Testa 2014

Study characteristics	
Patient Sampling	Country: Europe Centres: multicentre; 18 centres in 6 countries (Sweden, Belgium, Italy, Poland, Spain and Czech Republic) Study design: within-person comparison Recruitment: retrospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions: none

Testa 2014 *(Continued)*

	Comment: N/A
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women presenting with adnexal mass and undergoing TVS by 1 of the principal investigators and surgery within 120 days after examination Sample size: 2403 Age range: 33–66 years Median age: benign 44 years, malignant 57 years Percentage postmenopausal (n): 44% (1049)
Index tests	Combination RMI I and LR2 Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: LR2-probability of malignancy ≥ 10%, RMI > 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: not reported CA125 results missing in 40% and multiple imputation was used to handle missing values.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 1423, borderline 153, malignant 701, metastatic and others 126 Staging: early 316, late 470, unstaged 68 + 12 mets Pathologist was blinded to the outcome of index test
Flow and timing	Interval between application of index test and reference standard: ≤ 120 days, 66 women were excluded as surgery after 120 days. 13 women were excluded because of incomplete final histology.
Comparative	RMI vs LR2
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Testa 2014 *(Continued)*

Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Yes	
A) Includes all ages regardless of menopausal status or justify restrictions	Yes	
B) Includes all stages and types of ovarian cancer	Yes	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	

Testa 2014 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

Testa 2014 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear

Testa 2014 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	No	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?		Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Timmerman 2010

Study characteristics	
Patient Sampling	Country: Europe Centres: multicentre Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions: none Comments (if applicable): 15 patients who underwent surgery > 120 days after USS examination were excluded
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with persistent adnexal mass undergoing surgery within 120 days Sample size: total 1938, 1522 women with CA125 included for RMI

Timmerman 2010 *(Continued)*

	Age range: 11–94 years Mean age: 46 years Percentage postmenopausal (n): 38% (742) Comments: 19 centres, 8 countries
Index tests	Combination RMI I and LR2 Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: LR2-probability of malignancy ≥ 10%, RMI > 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: not reported
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 542, borderline 111, malignant 373, metastatic and others 58 Staging: early 100 (BOT) + 100 (invasive), late 9 (BOT) + 232 (invasive), unstaged 2 (BOT) + 99 (invasive) Pathologist had no knowledge of the ultrasound results
Flow and timing	1501 women included for analysis for RMI; 1147 participants with CA125 results included
Comparative	RMI I vs LR2
Notes	Same cohort as Di Legge 2012 (see above). Data for RMI I extracted from Di Legge 2012.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		

Timmerman 2010 *(Continued)*

C) Includes comorbidities such as infertility and endometriosis	Yes
Could the selection of patients have introduced bias?	High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated	
B) Prior test in primary care: self-reported symptoms	
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound	
Are there concerns that the included patients and setting do not match the review question?	High
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	

Timmerman 2010 *(Continued)*

A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers

Timmerman 2010 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	No	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	No	
Could the patient flow have introduced bias?		High risk
DOMAIN 5: Comparative		

Timmerman 2010 *(Continued)*

For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?		Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

van Calster 2014

Study characteristics	
Patient Sampling	Country: Europe Centres: multicentre (19) Study design: non-comparative Recruitment: prospective cross-sectional study Method of patient selection: consecutive Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: mixed (11/19 tertiary) Study entry criteria: women with an adnexal mass on USS and selected for surgery Sample size: 2403 (2124 analysed without metastatic and borderline) Age range: not reported Mean age: not reported Median age: not reported Percentage postmenopausal (n): not reported Comments: ADNEX includes age as a variable
Index tests	Combination ADNEX Prior test: unclear

van Calster 2014 *(Continued)*

	Threshold for test positivity predefined: no Threshold for test positivity: 3%, 5%, 10% and 15% disease positive probability of malignancy Interval between application of index test and reference standard: ≤ 120 days Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): not reported Type of technology or manufacturer of biomarker test: 5 manufacturers all using OC125 Ab
Target condition and reference standard(s)	Women selected for surgery OC; secondary metastatic OC Histology (n): benign 1423, borderline 153, malignant 701, metastasis or others 126 Staging: stage I 189, Stage II-IV 521
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Low risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			

van Calster 2014 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Unclear
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ACOG)		

van Calster 2014 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?

van Calster 2014 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

van Calster 2014 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

van den Akker 2016

Study characteristics	
Patient Sampling	Only surgical patients included Histology (n): benign 128, borderline not reported, malignant 96, metastatic and others none reported
Patient characteristics and setting	Clinical setting: mixed (secondary and tertiary) Study entry criteria: women who were admitted for surgical treatment of an ovarian mass with unknown histology Sample size: 670 Age range: 13–93 years Mean age: not reported Median age: 54 years Percentage postmenopausal (n): 58% (390)
Index tests	Test: RMI I Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialist Type of technology or manufacturer of biomarker test: not reported; stated, "routine preoperative assessment included analysis of serum samples for cancer antigen 125 (CA125), and menopausal status was recorded".
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 531, borderline 46, malignant 93, metastatic and others not reported
Flow and timing	

van den Akker 2016 *(Continued)*

Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			

van den Akker 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

van den Akker 2016 *(Continued)*

DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	Yes

van den Akker 2016 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

van Gorp 2011

Study characteristics	
Patient Sampling	Country: Belgium Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: consecutive

van Gorp 2011 *(Continued)*

	Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: women diagnosed with pelvic mass undergoing surgery Sample size: 389 Age range: not reported Mean age: benign 46.3 (SD 16) years, malignant 57.8 (SD 12.6) years Median age: not reported Percentage postmenopausal (n): 41.4% (161)
Index tests	Combination Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: CA125 35 U/mL, HE4 70 pmol/L and 150 pmol/L Interval between application of index tests: < 3 months' interval Interval between application of index test and reference standard: < 3 months' interval Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: EIA
Target condition and reference standard(s)	Only surgical patients included Follow-up: none Duration of follow-up: N/A Histology (n): benign 228, borderline not reported, malignant 135, metastatic and others 26 Staging: early 51, late 80, unstaged 0
Flow and timing	
Comparative	See van Gorp 2012 below
Notes	van Gorp 2012 (see below) is a secondary publication to this study. RMI results are presented only in this publication while ROMA results are presented in both publications. Since van Gorp 2011 has a bigger cohort, results for ROMA were considered from this publication and therefore treated as a separate study.

van Gorp 2011 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			

van Gorp 2011 *(Continued)*

DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes

van Gorp 2011 *(Continued)*

If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk

van Gorp 2011 *(Continued)*

Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

van Gorp 2012

Study characteristics	
Patient Sampling	Country: Belgium Centres: single Study design: within-person comparison Recruitment: prospective cross-sectional study Method of patient selection: convenience Inappropriate exclusions (all stages, all ages, included comorbidities such as infertility or endometriosis): none Comments (if applicable): N/A
Patient characteristics and setting	Clinical setting: tertiary

van Gorp 2012 *(Continued)*

	Study entry criteria: women with a pelvic mass, scheduled for surgery Sample size: 374 Age range: not reported Mean age: benign 46.2 years (95% CI 44.1 to 48.3), malignant 57.7 years (95% CI 55.7 to 59.8) Percentage postmenopausal (n): 52.4% (196) Comments: following participants were excluded: 6 with presumed benign disease, 6 had no cyst at time of surgery, 4 with conservative management due to poor prognosis.
Index tests	Combination ROMA, RMI I Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: ROMA; premenopausal 12.5%, postmenopausal 14.4%, RMI I cut-off 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): mixed Type of technology or manufacturer of biomarker test: EIA Comments: ultrasound was performed by an experienced sonographer or supervised by an experienced sonographer; the sonographer blinded to CA125 but blinding to symptoms not given.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 224, borderline 31, malignant 94, metastatic and others 25 Staging: early 49 (only for EOC + BOT), late 72 (only for EOC + BOC), unstaged 0
Flow and timing	There was < 3 months between the blood test and reference standard but interval between ultrasound and reference standard was unclear.
Comparative	ROMA vs RMI I
Notes	This is a secondary publication to van Gorp 2011. RMI results are presented only in this publication while ROMA results are presented in both publications. Since van Gorp 2011 has bigger cohort, results for ROMA were considered from this publication and therefore treated as a separate study.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

van Gorp 2012 *(Continued)*

Was a consecutive or random sample of patients enrolled?	No	
Was a case-control design avoided?	Yes	
Did the study avoid inappropriate exclusions?	Unclear	
A) Includes all ages regardless of menopausal status or justify restrictions	Unclear	
B) Includes all stages and types of ovarian cancer	Yes	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		High risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	

van Gorp 2012 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Unclear	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High
DOMAIN 2: Index Test (ACOG)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		

van Gorp 2012 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (LR2)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 3: Reference Standard	
Is the reference standards likely to correctly classify the target condition?	Yes
Were the reference standard results interpreted without knowledge of the results of the index tests?	
Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?	
Are there concerns that the target condition as defined by the reference standard does not match the question?	Unclear

van Gorp 2012 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?	Yes	
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?	Unclear	
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	Unclear	
Could the conduct of the comparative studies have introduced bias?		Unclear risk
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		Low concern

Vural 2016

Study characteristics	
Patient Sampling	Country: Turkey Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: none
Patient characteristics and setting	Clinical setting: tertiary Study entry criteria: postmenopausal women with adnexal masses who underwent surgery Sample size: 139 Age range: 42–87 years Mean age: 61.1 (SD 8.9) years

Vural 2016 *(Continued)*

	Percentage postmenopausal (n): 100%
Index tests	Test: RMI I Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: RMI I 200 Type of ultrasound (TAS, TVS or both): both Operator experience of sonographer (generalist, specialist or trainee): specialised gynaecologist Type of technology or manufacturer of biomarker test: grey scale ultrasonographic imaging of the cases was performed by an expert radiologist via ultrasound device with five MHz convex abdominal and 8 MHz vaginal probes.
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 87, borderline 8, malignant 44, metastatic and others 11 Target condition: OC/EOC (73% EOC)
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			

Vural 2016 *(Continued)*

C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Unclear risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		High

Vural 2016 *(Continued)*

DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ROMA)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (LR2)
Were the index test results interpreted without knowledge of the results of the reference standard?

Vural 2016 *(Continued)*

If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Unclear risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

Vural 2016 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?	
Could the conduct of the comparative studies have introduced bias?	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?	

Xu 2016

Study characteristics	
Patient Sampling	Country: China Centres: single Study design: non-comparative Recruitment: retrospective Method of patient selection: unclear Inappropriate exclusions: 29 women with non-EOC excluded from analysis
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with a pelvic mass (defined as a simple, complex or solid ovarian cyst/pelvic mass) Sample size: 566 Age range: not reported Mean age: malignant 57 years, benign 42 years Percentage postmenopausal (n): 28% (166)
Index tests	Test: ROMA Prior test: not reported Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: HE4 and CA125 were determined on the Roche Cobas E170 analyser with Elecsys HE4 kits (Roche, Mannheim, Germany) and Elecsys CA125 kits (Roche, Mannheim, Germany). This assay utilises an electrochemiluminescent immunoassay method.

Xu 2016 *(Continued)*

Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 311, borderline 45, malignant 210, metastatic and others none reported
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	No		
C) Includes comorbidities such as infertility and endometriosis	Unclear		
Could the selection of patients have introduced bias?		High risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (ADNEX)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			

Xu 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (RMI)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers
Are there concerns that the index test, its conduct, or interpretation differ from the review question?
DOMAIN 2: Index Test (ACOG)
Were the index test results interpreted without knowledge of the results of the reference standard?
If a threshold was used, was it pre-specified?
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?
Could the conduct or interpretation of the index test have introduced bias?
A) Was ultrasound performed in all patients by non-specialised sonographers

Xu 2016 *(Continued)*

B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		

Xu 2016 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?			
Could the conduct of the comparative studies have introduced bias?			
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?			

Zhang 2015

Study characteristics	
Patient Sampling	Country: China Centres: multicentre

Zhang 2015 *(Continued)*

	Study design: non-comparative Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: non-EOC excluded
Patient characteristics and setting	Clinical setting: unclear Study entry criteria: women with and without pelvic mass on USS scheduled for surgery Sample size: 612 Age range: not reported Mean age: not reported Median age (25th centile, 75th centile): benign: premenopausal 41 (35, 46), postmenopausal 57 (54, 68); malignant (EOC): premenopausal 43 (38, 47), postmenopausal 59 (54, 65) Percentage postmenopausal (n): 37% (232)
Index tests	Test: ROMA Prior test: USS; adnexal lesions reported according to IOTA Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: Roche Elecsys Cobas 601 platform and the matched reagents Roche Diagnostics (Basel, Switzerland)
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 348, borderline not reported, malignant 264, metastatic and others excluded
Flow and timing	
Comparative	N/A
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Zhang 2015 *(Continued)*

Was a case-control design avoided?	Unclear	
Did the study avoid inappropriate exclusions?	Yes	
A) Includes all ages regardless of menopausal status or justify restrictions	Yes	
B) Includes all stages and types of ovarian cancer	Yes	
C) Includes comorbidities such as infertility and endometriosis	Yes	
Could the selection of patients have introduced bias?		Unclear risk
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated		
B) Prior test in primary care: self-reported symptoms		
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound		
Are there concerns that the included patients and setting do not match the review question?		Unclear
DOMAIN 2: Index Test (ADNEX)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (RMI)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Zhang 2015 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ROMA)	
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
If a threshold was used, was it pre-specified?	Yes
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes

Zhang 2015 *(Continued)*

If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 3: Reference Standard		
Is the reference standards likely to correctly classify the target condition?	Yes	
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear	
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?		
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear

Zhang 2015 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Unclear	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Unclear risk
DOMAIN 5: Comparative		
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?		
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?		
For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

Zhang 2019

Study characteristics	
Patient Sampling	Country: China Centres: single Study design: non-comparative Recruitment: prospective Method of patient selection: unclear Inappropriate exclusions: borderline excluded from analysis
Patient characteristics and setting	Clinical setting: mixed Study entry criteria: women with ovarian tumour Sample size: 373 Age range: 12–77 years Mean age: 51 years

Zhang 2019 *(Continued)*

	Percentage postmenopausal (n): 50% (185)
Index tests	Test: ROMA Prior test: unclear Threshold for test positivity predefined: yes Threshold for test positivity: premenopausal 11.4, postmenopausal 29.9 Type of ultrasound (TAS, TVS or both): N/A Operator experience of sonographer (generalist, specialist or trainee): N/A Type of technology or manufacturer of biomarker test: HE4 and CA125 serum levels were analysed by Roche cobas 60 0 0 analyser using reagents that provided by Roche (Basel, Switzerland).
Target condition and reference standard(s)	Only surgical patients included Histology (n): benign 175, borderline 17, malignant 181, metastatic 4, others 4 stromal tumour, 1 germ cell tumour
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
A) Includes all ages regardless of menopausal status or justify restrictions	Yes		
B) Includes all stages and types of ovarian cancer	Yes		
C) Includes comorbidities such as infertility and endometriosis	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
A) All patients are symptomatic or symptomatic and asymptomatic can be disaggregated			
B) Prior test in primary care: self-reported symptoms			
C) Prior test secondary care: self-reported symptoms or self-reported symptoms plus one or more biochemical markers and ultrasound			

Zhang 2019 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?	Unclear
DOMAIN 2: Index Test (ADNEX)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (RMI)	
Were the index test results interpreted without knowledge of the results of the reference standard?	
If a threshold was used, was it pre-specified?	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	
Could the conduct or interpretation of the index test have introduced bias?	
A) Was ultrasound performed in all patients by non-specialised sonographers	
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?	
DOMAIN 2: Index Test (ACOG)	

Zhang 2019 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?		
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?		
Could the conduct or interpretation of the index test have introduced bias?		
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		
DOMAIN 2: Index Test (ROMA)		
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes	
If a threshold was used, was it pre-specified?	Yes	
Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?	Yes	
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?	Yes	
Could the conduct or interpretation of the index test have introduced bias?		Low risk
A) Was ultrasound performed in all patients by non-specialised sonographers		
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers		
Are there concerns that the index test, its conduct, or interpretation differ from the review question?		Low concern
DOMAIN 2: Index Test (LR2)		
Were the index test results interpreted without knowledge of the results of the reference standard?		
If a threshold was used, was it pre-specified?		

Zhang 2019 *(Continued)*

Were all components and thresholds of composite index test (including multivariable model) prespecified before their application?			
If a composite index test was used, were components of a composite index test/model defined and assessed in a similar way (e.g. in the same healthcare setting) for all participants?			
Could the conduct or interpretation of the index test have introduced bias?			
A) Was ultrasound performed in all patients by non-specialised sonographers			
B) i. Were symptoms interpreted without the knowledge of ultrasound and biomarkers; ii: was ultrasound interpreted without the knowledge of biomarkers			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Can borderline tumours be grouped with primary ovarian cancer for the purposes of analysis?			
Are there concerns that the target condition as defined by the reference standard does not match the question?			High
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	
DOMAIN 5: Comparative			
For studies comparing two or more index tests or testing strategies in different populations, were the selection criteria for participants receiving one or other index test or testing strategy the same?			
For within-study comparisons of index tests: was the interval between application of index test less than 3 months?			

Zhang 2019 *(Continued)*

For within-study comparison of individual index tests: were index tests interpreted blind to the results of other index test results?		
Could the conduct of the comparative studies have introduced bias?		
Is there concern that included patients have been selected in a different way to participants in non-comparative studies?		

CMIA: chemiluminescent microparticle immunoassay; CT: computed tomography; EOC: epithelial ovarian cancer; MRI: magnetic resonance imaging; N/A: not applicable; OC: ovarian cancer; ROMA: Risk of Ovarian Malignancy Algorithm; RMI: Risk of Malignancy Index; SD: standard deviation; TAS: transabdominal ultrasound; TVS: transvaginal ultrasound; USS: ultrasound scan.

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

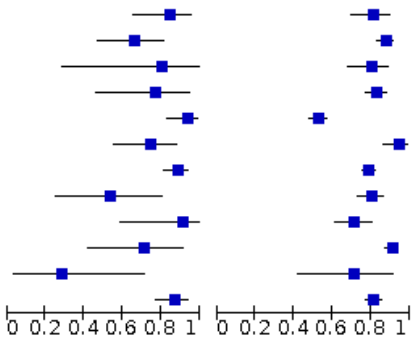
Test	No. of studies	No. of participants
1 ROMA 7.4 (± 2) premenopausal	12	3223
2 ROMA 25.3 (± 2) postmenopausal	15	2599
3 ROMA 12.5 premenopausal	3	302
4 ROMA 14.4 postmenopausal	3	299
5 ROMA 13.1 (± 2) premenopausal	27	4463
6 ROMA 27.7 (± 2) postmenopausal	13	2002
7 ROMA 7.4 premenopausal	10	3051
8 ROMA 25.3 postmenopausal	9	1386
9 ROMA 7.4/25.3 all	2	681
10 ROMA 12.5/14.4 all	3	601
11 ROMA 13.1 premenopausal	8	1353
12 ROMA 27.7 postmenopausal	9	1265
13 ROMA 13.1/27.7 all	5	1615
14 ROMA 11.4 premenopausal	11	2281
15 ROMA 29.9 postmenopausal	12	1797
18 ROMA mixed premenopausal	38	7616

Test	No. of studies	No. of participants
19 ROMA mixed postmenopausal	40	6099
20 ROMA mixed all	10	2897
21 RMI I 200 premenopausal	17	5233
22 RMI I 200 postmenopausal	17	4369
23 RMI I 200 all	5	4559
24 RMI I 250 premenopausal	2	461
25 RMI I 250 postmenopausal	2	220
26 RMI I 250 all	1	540
35 RMI mixed premenopausal	6	2990
36 RMI mixed postmenopausal	7	2099
37 RMI mixed all	6	5099
38 LR2 premenopausal	4	2843
39 LR2 postmenopausal	5	2157
40 LR2 all	3	4596
41 ADNEX 3% D+ probability all	1	2403
42 ADNEX 3% D+ probability premenopausal	1	1354
43 ADNEX 3% D+ probability postmenopausal	1	1049
44 ADNEX 5% D+ probability all	1	2403
45 ADNEX 5% D+ probability premenopausal	1	1354
46 ADNEX 5% D+ probability postmenopausal	1	1049
47 ADNEX 10% D+ probability all	1	2403
48 ADNEX 10% D+ probability premenopausal	4	1696
49 ADNEX 10% D+ probability postmenopausal	4	1365
50 ADNEX 15% D+ probability all	1	2403
51 ADNEX 15% D+ probability premenopausal	1	1354
52 ADNEX 15% D+ probability postmenopausal	1	1049
67 RMI I mixed premenopausal	19	5694
68 RMI I mixed postmenopausal	19	4589

Test 1. ROMA 7.4 (± 2) premenopausal

ROMA 7.4 (± 2) premenopausal

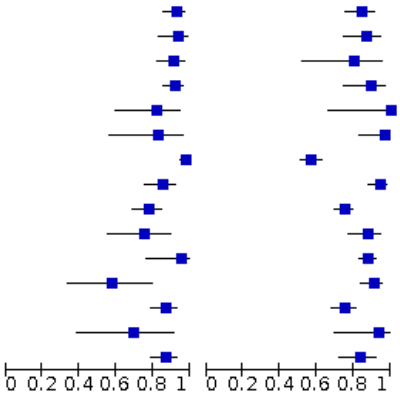
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	22	13	4	56	0.85 [0.65, 0.96]	0.81 [0.70, 0.90]		
Chan 2013	21	34	11	235	0.66 [0.47, 0.81]	0.87 [0.83, 0.91]		
Grenache 2015	4	13	1	52	0.80 [0.28, 0.99]	0.80 [0.68, 0.89]		
Huy 2018	10	37	3	180	0.77 [0.46, 0.95]	0.83 [0.77, 0.88]		
Karlsen 2012	46	251	3	279	0.94 [0.83, 0.99]	0.53 [0.48, 0.57]		
Kim 2011	23	4	8	67	0.74 [0.55, 0.88]	0.94 [0.86, 0.98]		
Li 2016	96	136	12	501	0.89 [0.81, 0.94]	0.79 [0.75, 0.82]		
Melo 2018	7	28	6	114	0.54 [0.25, 0.81]	0.80 [0.73, 0.86]		
Nikolova 2016	10	27	1	67	0.91 [0.59, 1.00]	0.71 [0.61, 0.80]		
Park 2019	10	29	4	282	0.71 [0.42, 0.92]	0.91 [0.87, 0.94]		
Richards 2015	2	4	5	10	0.29 [0.04, 0.71]	0.71 [0.42, 0.92]		
Shen 2017	60	79	9	347	0.87 [0.77, 0.94]	0.81 [0.77, 0.85]		



Test 2. ROMA 25.3 (± 2) postmenopausal

ROMA 25.3 (± 2) postmenopausal

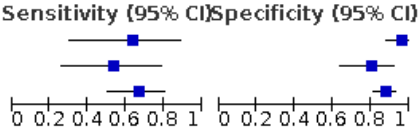
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	81	15	6	81	0.93 [0.86, 0.97]	0.84 [0.76, 0.91]		
Chan 2013	46	7	3	46	0.94 [0.83, 0.99]	0.87 [0.75, 0.95]		
Chen 2014	63	3	6	12	0.91 [0.82, 0.97]	0.80 [0.52, 0.96]		
Chudecka-Glaz 2015	114	4	10	33	0.92 [0.86, 0.96]	0.89 [0.75, 0.97]		
Farzaneh 2014	18	0	4	9	0.82 [0.60, 0.95]	1.00 [0.66, 1.00]		
Huy 2018	14	1	3	29	0.82 [0.57, 0.96]	0.97 [0.83, 1.00]		
Karlsen 2012	198	120	5	159	0.98 [0.94, 0.99]	0.57 [0.51, 0.63]		
Li 2016	70	5	12	85	0.85 [0.76, 0.92]	0.94 [0.88, 0.98]		
Liest 2019	91	76	26	230	0.78 [0.69, 0.85]	0.75 [0.70, 0.80]		
Melo 2018	21	8	7	56	0.75 [0.55, 0.89]	0.88 [0.77, 0.94]		
Novotny 2012	20	28	1	207	0.95 [0.76, 1.00]	0.88 [0.83, 0.92]		
Park 2019	11	9	8	90	0.58 [0.33, 0.80]	0.91 [0.83, 0.96]		
Partheen 2011a	81	41	12	124	0.87 [0.79, 0.93]	0.75 [0.68, 0.82]		
Richards 2015	9	1	4	15	0.69 [0.39, 0.91]	0.94 [0.70, 1.00]		
Shen 2017	91	9	14	47	0.87 [0.79, 0.93]	0.84 [0.72, 0.92]		



Test 3. ROMA 12.5 premenopausal

ROMA 12.5 premenopausal

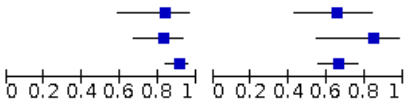
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kadija 2012	7	2	4	54	0.64 [0.31, 0.89]	0.96 [0.88, 1.00]		
Montagnana 2011	8	7	7	29	0.53 [0.27, 0.79]	0.81 [0.64, 0.92]		
van Gorp 2011	28	17	14	125	0.67 [0.50, 0.80]	0.88 [0.82, 0.93]		



Test 4. ROMA 14.4 postmenopausal

ROMA 14.4 postmenopausal

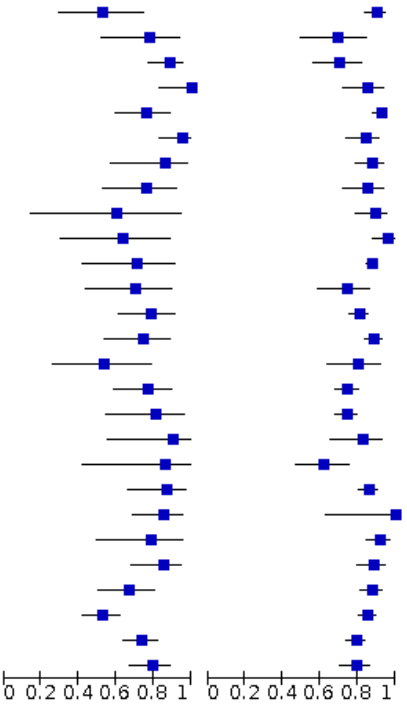
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kadija 2012	15	8	3	15	0.83 [0.59, 0.96]	0.65 [0.43, 0.84]
Montagnana 2011	33	2	7	11	0.82 [0.67, 0.93]	0.85 [0.55, 0.98]
van Gorp 2011	108	29	11	57	0.91 [0.84, 0.95]	0.66 [0.55, 0.76]



Test 5. ROMA 13.1 (± 2) premenopausal

ROMA 13.1 (± 2) premenopausal

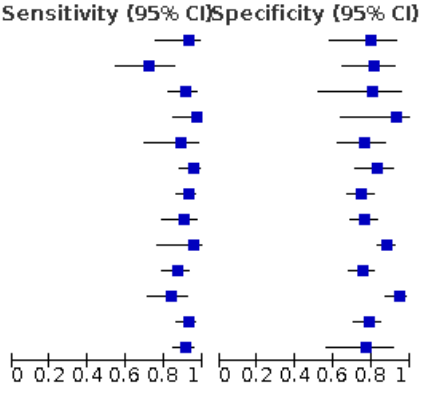
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	11	14	10	127	0.52 [0.30, 0.74]	0.90 [0.84, 0.94]
Anton 2012	14	9	4	20	0.78 [0.52, 0.94]	0.69 [0.49, 0.85]
Chen 2014	48	16	6	38	0.89 [0.77, 0.96]	0.70 [0.56, 0.82]
Chen 2015	20	7	0	41	1.00 [0.83, 1.00]	0.85 [0.72, 0.94]
Chudecka-Glaz 2015	29	16	9	198	0.76 [0.60, 0.89]	0.93 [0.88, 0.96]
Cradic 2018	37	12	2	63	0.95 [0.83, 0.99]	0.84 [0.74, 0.91]
Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Farzaneh 2014	16	7	5	40	0.76 [0.53, 0.92]	0.85 [0.72, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]
Kadija 2012	7	2	4	54	0.64 [0.31, 0.89]	0.96 [0.88, 1.00]
Kim 2019	10	71	4	496	0.71 [0.42, 0.92]	0.87 [0.84, 0.90]
Krascsenitis 2016	12	11	5	32	0.71 [0.44, 0.90]	0.74 [0.59, 0.86]
Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]
Montagnana 2011	8	7	7	29	0.53 [0.27, 0.79]	0.81 [0.64, 0.92]
Moore 2009	26	51	8	151	0.76 [0.59, 0.89]	0.75 [0.68, 0.81]
Moore 2011	13	60	3	173	0.81 [0.54, 0.96]	0.74 [0.68, 0.80]
Ortiz-Munoz 2014	9	6	1	28	0.90 [0.55, 1.00]	0.82 [0.65, 0.93]
Prskalo 2015	6	19	1	31	0.86 [0.42, 1.00]	0.62 [0.47, 0.75]
Romagnolo 2016	20	30	3	186	0.87 [0.66, 0.97]	0.86 [0.81, 0.90]
Stiekma 2014	29	0	5	8	0.85 [0.69, 0.95]	1.00 [0.63, 1.00]
Teh 2018	11	7	3	81	0.79 [0.49, 0.95]	0.92 [0.84, 0.97]
Terlikowska 2016	28	10	5	77	0.85 [0.68, 0.95]	0.89 [0.80, 0.94]
van Gorp 2011	28	17	14	125	0.67 [0.50, 0.80]	0.88 [0.82, 0.93]
Xu 2016	56	38	51	226	0.52 [0.42, 0.62]	0.86 [0.81, 0.90]
Zhang 2015	70	59	25	226	0.74 [0.64, 0.82]	0.79 [0.74, 0.84]
Zhang 2019	50	24	13	91	0.79 [0.67, 0.89]	0.79 [0.71, 0.86]



Test 6. ROMA 27.7 (± 2) postmenopausal

ROMA 27.7 (± 2) postmenopausal

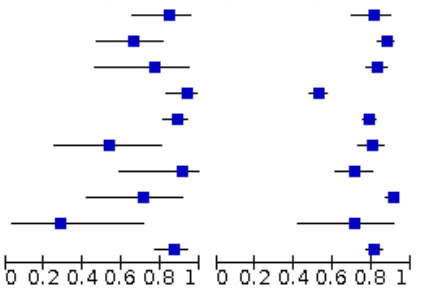
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	25	5	2	19	0.93 [0.76, 0.99]	0.79 [0.58, 0.93]
Anton 2012	26	7	10	30	0.72 [0.55, 0.86]	0.81 [0.65, 0.92]
Chen 2014	63	3	6	12	0.91 [0.82, 0.97]	0.80 [0.52, 0.96]
Dikmen 2015	32	1	1	12	0.97 [0.84, 1.00]	0.92 [0.64, 1.00]
Grenache 2015	23	12	3	38	0.88 [0.70, 0.98]	0.76 [0.62, 0.87]
Molina 2011	80	10	4	49	0.95 [0.88, 0.99]	0.83 [0.71, 0.92]
Moore 2009	108	38	9	112	0.92 [0.86, 0.96]	0.75 [0.67, 0.81]
Moore 2011	46	36	5	114	0.90 [0.79, 0.97]	0.76 [0.68, 0.83]
Novotny 2012	20	28	1	207	0.95 [0.76, 1.00]	0.88 [0.83, 0.92]
Partheen 2011a	81	41	12	124	0.87 [0.79, 0.93]	0.75 [0.68, 0.82]
Romagnolo 2016	50	5	10	83	0.83 [0.71, 0.92]	0.94 [0.87, 0.98]
Salim 2018	113	30	9	108	0.93 [0.86, 0.97]	0.78 [0.70, 0.85]
Stiekma 2014	103	6	10	20	0.91 [0.84, 0.96]	0.77 [0.56, 0.91]



Test 7. ROMA 7.4 premenopausal

ROMA 7.4 premenopausal

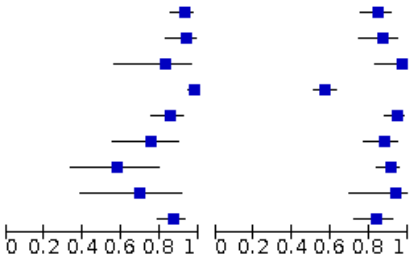
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	22	13	4	56	0.85 [0.65, 0.96]	0.81 [0.70, 0.90]		
Chan 2013	21	34	11	235	0.66 [0.47, 0.81]	0.87 [0.83, 0.91]		
Huy 2018	10	37	3	180	0.77 [0.46, 0.95]	0.83 [0.77, 0.88]		
Karlsen 2012	46	251	3	279	0.94 [0.83, 0.99]	0.53 [0.48, 0.57]		
Li 2016	96	136	12	501	0.89 [0.81, 0.94]	0.79 [0.75, 0.82]		
Melo 2018	7	28	6	114	0.54 [0.25, 0.81]	0.80 [0.73, 0.86]		
Nikolova 2016	10	27	1	67	0.91 [0.59, 1.00]	0.71 [0.61, 0.80]		
Park 2019	10	29	4	282	0.71 [0.42, 0.92]	0.91 [0.87, 0.94]		
Richards 2015	2	4	5	10	0.29 [0.04, 0.71]	0.71 [0.42, 0.92]		
Shen 2017	60	79	9	347	0.87 [0.77, 0.94]	0.81 [0.77, 0.85]		



Test 8. ROMA 25.3 postmenopausal

ROMA 25.3 postmenopausal

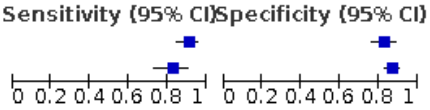
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	81	15	6	81	0.93 [0.86, 0.97]	0.84 [0.76, 0.91]		
Chan 2013	46	7	3	46	0.94 [0.83, 0.99]	0.87 [0.75, 0.95]		
Huy 2018	14	1	3	29	0.82 [0.57, 0.96]	0.97 [0.83, 1.00]		
Karlsen 2012	198	120	5	159	0.98 [0.94, 0.99]	0.57 [0.51, 0.63]		
Li 2016	70	5	12	85	0.85 [0.76, 0.92]	0.94 [0.88, 0.98]		
Melo 2018	21	8	7	56	0.75 [0.55, 0.89]	0.88 [0.77, 0.94]		
Park 2019	11	9	8	90	0.58 [0.33, 0.80]	0.91 [0.83, 0.96]		
Richards 2015	9	1	4	15	0.69 [0.39, 0.91]	0.94 [0.70, 1.00]		
Shen 2017	91	9	14	47	0.87 [0.79, 0.93]	0.84 [0.72, 0.92]		



Test 9. ROMA 7.4/25.3 all

ROMA 7.4/25.3 all

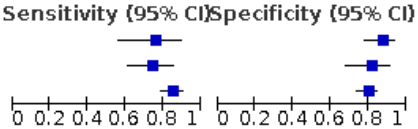
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bandiera 2011	103	28	10	137	0.91 [0.84, 0.96]	0.83 [0.76, 0.88]		
Chan 2013	67	41	14	281	0.83 [0.73, 0.90]	0.87 [0.83, 0.91]		



Test 10. ROMA 12.5/14.4 all

ROMA 12.5/14.4 all

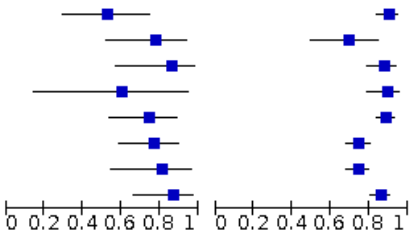
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Kadija 2012	22	10	7	69	0.76 [0.56, 0.90]	0.87 [0.78, 0.94]		
Montagnana 2011	41	9	14	40	0.75 [0.61, 0.85]	0.82 [0.68, 0.91]		
van Gorp 2011	137	46	24	182	0.85 [0.79, 0.90]	0.80 [0.74, 0.85]		



Test 11. ROMA 13.1 premenopausal

ROMA 13.1 premenopausal

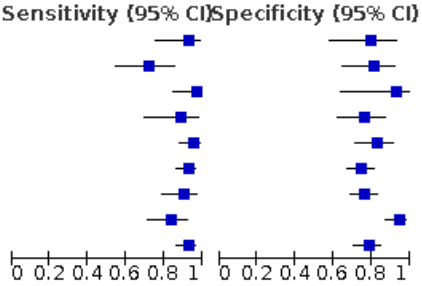
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	11	14	10	127	0.52 [0.30, 0.74]	0.90 [0.84, 0.94]
Anton 2012	14	9	4	20	0.78 [0.52, 0.94]	0.69 [0.49, 0.85]
Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]
Moore 2009	26	51	8	151	0.76 [0.59, 0.89]	0.75 [0.68, 0.81]
Moore 2011	13	60	3	173	0.81 [0.54, 0.96]	0.74 [0.68, 0.80]
Romagnolo 2016	20	30	3	186	0.87 [0.66, 0.97]	0.86 [0.81, 0.90]



Test 12. ROMA 27.7 postmenopausal

ROMA 27.7 postmenopausal

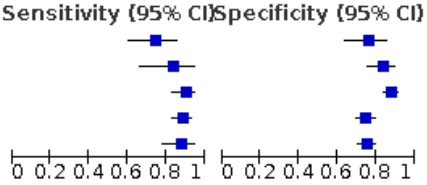
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	25	5	2	19	0.93 [0.76, 0.99]	0.79 [0.58, 0.93]
Anton 2012	26	7	10	30	0.72 [0.55, 0.86]	0.81 [0.65, 0.92]
Dikmen 2015	32	1	1	12	0.97 [0.84, 1.00]	0.92 [0.64, 1.00]
Grenache 2015	23	12	3	38	0.88 [0.70, 0.98]	0.76 [0.62, 0.87]
Molina 2011	80	10	4	49	0.95 [0.88, 0.99]	0.83 [0.71, 0.92]
Moore 2009	108	38	9	112	0.92 [0.86, 0.96]	0.75 [0.67, 0.81]
Moore 2011	46	36	5	114	0.90 [0.79, 0.97]	0.76 [0.68, 0.83]
Romagnolo 2016	50	5	10	83	0.83 [0.71, 0.92]	0.94 [0.87, 0.98]
Salim 2018	113	30	9	108	0.93 [0.86, 0.97]	0.78 [0.70, 0.85]



Test 13. ROMA 13.1/27.7 all

ROMA 13.1/27.7 all

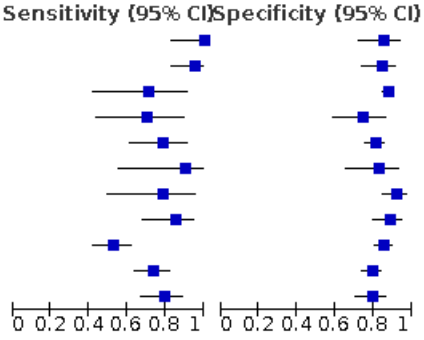
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	40	16	14	50	0.74 [0.60, 0.85]	0.76 [0.64, 0.85]
Grenache 2015	26	19	5	96	0.84 [0.66, 0.95]	0.83 [0.75, 0.90]
Molina 2011	100	35	11	250	0.90 [0.83, 0.95]	0.88 [0.83, 0.91]
Moore 2009	134	89	17	263	0.89 [0.83, 0.93]	0.75 [0.70, 0.79]
Moore 2011	59	96	8	287	0.88 [0.78, 0.95]	0.75 [0.70, 0.79]



Test 14. ROMA 11.4 premenopausal

ROMA 11.4 premenopausal

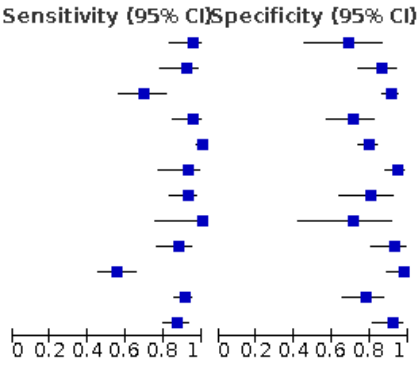
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2015	20	7	0	41	1.00 [0.83, 1.00]	0.85 [0.72, 0.94]
Cradic 2018	37	12	2	63	0.95 [0.83, 0.99]	0.84 [0.74, 0.91]
Kim 2019	10	71	4	496	0.71 [0.42, 0.92]	0.87 [0.84, 0.90]
Krascsenitis 2016	12	11	5	32	0.71 [0.44, 0.90]	0.74 [0.59, 0.86]
Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Ortiz-Munoz 2014	9	6	1	28	0.90 [0.55, 1.00]	0.82 [0.65, 0.93]
Teh 2018	11	7	3	81	0.79 [0.49, 0.95]	0.92 [0.84, 0.97]
Terlikowska 2016	28	10	5	77	0.85 [0.68, 0.95]	0.89 [0.80, 0.94]
Xu 2016	56	38	51	226	0.52 [0.42, 0.62]	0.86 [0.81, 0.90]
Zhang 2015	70	59	25	226	0.74 [0.64, 0.82]	0.79 [0.74, 0.84]
Zhang 2019	50	24	13	91	0.79 [0.67, 0.89]	0.79 [0.71, 0.86]



Test 15. ROMA 29.9 postmenopausal

ROMA 29.9 postmenopausal

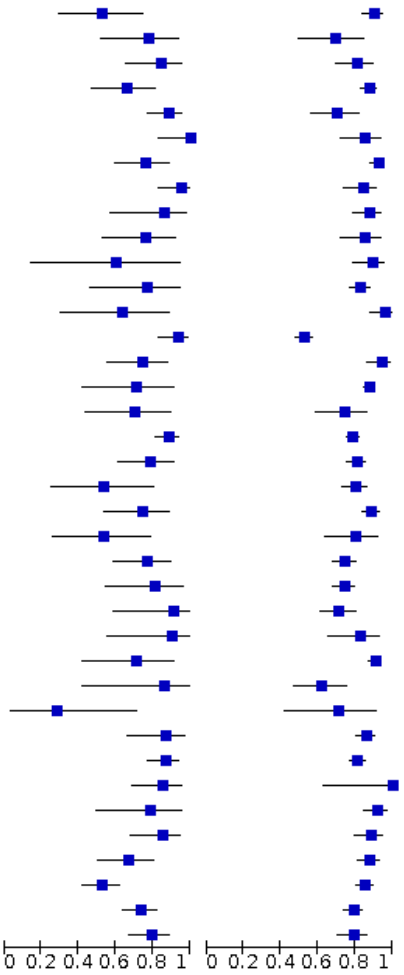
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2015	38	7	2	15	0.95 [0.83, 0.99]	0.68 [0.45, 0.86]
Cradic 2018	34	8	3	48	0.92 [0.78, 0.98]	0.86 [0.74, 0.94]
Kim 2019	39	17	17	178	0.70 [0.56, 0.81]	0.91 [0.86, 0.95]
Krascsenitis 2016	42	17	2	41	0.95 [0.85, 0.99]	0.71 [0.57, 0.82]
Lycke 2018	113	49	0	186	1.00 [0.97, 1.00]	0.79 [0.73, 0.84]
Ortiz-Munoz 2014	27	7	2	112	0.93 [0.77, 0.99]	0.94 [0.88, 0.98]
Prskalo 2015	61	7	5	29	0.92 [0.83, 0.97]	0.81 [0.64, 0.92]
Teh 2018	13	4	0	10	1.00 [0.75, 1.00]	0.71 [0.42, 0.92]
Terlikowska 2016	55	3	8	38	0.87 [0.77, 0.94]	0.93 [0.80, 0.98]
Xu 2016	57	1	46	46	0.55 [0.45, 0.65]	0.98 [0.89, 1.00]
Zhang 2015	154	14	15	49	0.91 [0.86, 0.95]	0.78 [0.66, 0.87]
Zhang 2019	103	5	15	55	0.87 [0.80, 0.93]	0.92 [0.82, 0.97]



Test 18. ROMA mixed premenopausal

ROMA mixed premenopausal

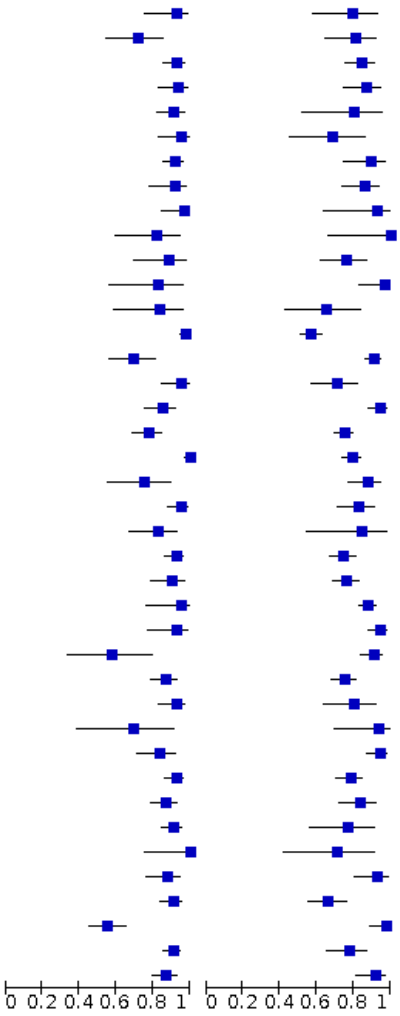
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	11	14	10	127	0.52 [0.30, 0.74]	0.90 [0.84, 0.94]
Anton 2012	14	9	4	20	0.78 [0.52, 0.94]	0.69 [0.49, 0.85]
Bandiera 2011	22	13	4	56	0.85 [0.65, 0.96]	0.81 [0.70, 0.90]
Chan 2013	21	34	11	235	0.66 [0.47, 0.81]	0.87 [0.83, 0.91]
Chen 2014	48	16	6	38	0.89 [0.77, 0.96]	0.70 [0.56, 0.82]
Chen 2015	20	7	0	41	1.00 [0.83, 1.00]	0.85 [0.72, 0.94]
Chudecka-Glaz 2015	29	16	9	198	0.76 [0.60, 0.89]	0.93 [0.88, 0.96]
Cradic 2018	37	12	2	63	0.95 [0.83, 0.99]	0.84 [0.74, 0.91]
Dikmen 2015	12	10	2	73	0.86 [0.57, 0.98]	0.88 [0.79, 0.94]
Farzaneh 2014	16	7	5	40	0.76 [0.53, 0.92]	0.85 [0.72, 0.94]
Grenache 2015	3	7	2	58	0.60 [0.15, 0.95]	0.89 [0.79, 0.96]
Huy 2018	10	37	3	180	0.77 [0.46, 0.95]	0.83 [0.77, 0.88]
Kadija 2012	7	2	4	54	0.64 [0.31, 0.89]	0.96 [0.88, 1.00]
Karlsen 2012	46	251	3	279	0.94 [0.83, 0.99]	0.53 [0.48, 0.57]
Kim 2011	23	4	8	67	0.74 [0.55, 0.88]	0.94 [0.86, 0.98]
Kim 2019	10	71	4	496	0.71 [0.42, 0.92]	0.87 [0.84, 0.90]
Krascsenitis 2016	12	11	5	32	0.71 [0.44, 0.90]	0.74 [0.59, 0.86]
Li 2016	96	136	12	501	0.89 [0.81, 0.94]	0.79 [0.75, 0.82]
Lycke 2018	26	44	7	186	0.79 [0.61, 0.91]	0.81 [0.75, 0.86]
Melo 2018	7	28	6	114	0.54 [0.25, 0.81]	0.80 [0.73, 0.86]
Molina 2011	20	25	7	201	0.74 [0.54, 0.89]	0.89 [0.84, 0.93]
Montagnana 2011	8	7	7	29	0.53 [0.27, 0.79]	0.81 [0.64, 0.92]
Moore 2009	26	51	8	151	0.76 [0.59, 0.89]	0.75 [0.68, 0.81]
Moore 2011	13	60	3	173	0.81 [0.54, 0.96]	0.74 [0.68, 0.80]
Nikolova 2016	10	27	1	67	0.91 [0.59, 1.00]	0.71 [0.61, 0.80]
Ortiz-Munoz 2014	9	6	1	28	0.90 [0.55, 1.00]	0.82 [0.65, 0.93]
Park 2019	10	29	4	282	0.71 [0.42, 0.92]	0.91 [0.87, 0.94]
Prskalo 2015	6	19	1	31	0.86 [0.42, 1.00]	0.62 [0.47, 0.75]
Richards 2015	2	4	5	10	0.29 [0.04, 0.71]	0.71 [0.42, 0.92]
Romagnolo 2016	20	30	3	186	0.87 [0.66, 0.97]	0.86 [0.81, 0.90]
Shen 2017	60	79	9	347	0.87 [0.77, 0.94]	0.81 [0.77, 0.85]
Stiekma 2014	29	0	5	8	0.85 [0.69, 0.95]	1.00 [0.63, 1.00]
Teh 2018	11	7	3	81	0.79 [0.49, 0.95]	0.92 [0.84, 0.97]
Terlikowska 2016	28	10	5	77	0.85 [0.68, 0.95]	0.89 [0.80, 0.94]
van Gorp 2011	28	17	14	125	0.67 [0.50, 0.80]	0.88 [0.82, 0.93]
Xu 2016	56	38	51	226	0.52 [0.42, 0.62]	0.86 [0.81, 0.90]
Zhang 2015	70	59	25	226	0.74 [0.64, 0.82]	0.79 [0.74, 0.84]
Zhang 2019	50	24	13	91	0.79 [0.67, 0.89]	0.79 [0.71, 0.86]



Test 19. ROMA mixed postmenopausal

ROMA mixed postmenopausal

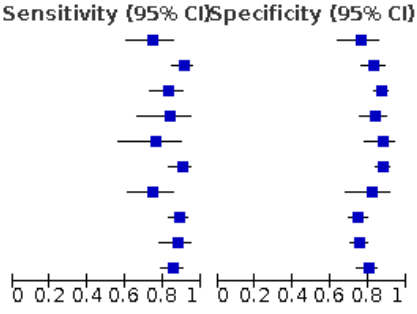
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al Musalhi 2016	25	5	2	19	0.93 [0.76, 0.99]	0.79 [0.58, 0.93]
Anton 2012	26	7	10	30	0.72 [0.55, 0.86]	0.81 [0.65, 0.92]
Bandiera 2011	81	15	6	81	0.93 [0.86, 0.97]	0.84 [0.76, 0.91]
Chan 2013	46	7	3	46	0.94 [0.83, 0.99]	0.87 [0.75, 0.95]
Chen 2014	63	3	6	12	0.91 [0.82, 0.97]	0.80 [0.52, 0.96]
Chen 2015	38	7	2	15	0.95 [0.83, 0.99]	0.68 [0.45, 0.86]
Chudecka-Glaz 2015	114	4	10	33	0.92 [0.86, 0.96]	0.89 [0.75, 0.97]
Cradic 2018	34	8	3	48	0.92 [0.78, 0.98]	0.86 [0.74, 0.94]
Dikmen 2015	32	1	1	12	0.97 [0.84, 1.00]	0.92 [0.64, 1.00]
Farzaneh 2014	18	0	4	9	0.82 [0.60, 0.95]	1.00 [0.66, 1.00]
Grenache 2015	23	12	3	38	0.88 [0.70, 0.98]	0.76 [0.62, 0.87]
Huy 2018	14	1	3	29	0.82 [0.57, 0.96]	0.97 [0.83, 1.00]
Kadija 2012	15	8	3	15	0.83 [0.59, 0.96]	0.65 [0.43, 0.84]
Karlsen 2012	198	120	5	159	0.98 [0.94, 0.99]	0.57 [0.51, 0.63]
Kim 2019	39	17	17	178	0.70 [0.56, 0.81]	0.91 [0.86, 0.95]
Krascsenitis 2016	42	17	2	41	0.95 [0.85, 0.99]	0.71 [0.57, 0.82]
Li 2016	70	5	12	85	0.85 [0.76, 0.92]	0.94 [0.88, 0.98]
Liest 2019	91	76	26	230	0.78 [0.69, 0.85]	0.75 [0.70, 0.80]
Lycke 2018	113	49	0	186	1.00 [0.97, 1.00]	0.79 [0.73, 0.84]
Melo 2018	21	8	7	56	0.75 [0.55, 0.89]	0.88 [0.77, 0.94]
Molina 2011	80	10	4	49	0.95 [0.88, 0.99]	0.83 [0.71, 0.92]
Montagnana 2011	33	2	7	11	0.82 [0.67, 0.93]	0.85 [0.55, 0.98]
Moore 2009	108	38	9	112	0.92 [0.86, 0.96]	0.75 [0.67, 0.81]
Moore 2011	46	36	5	114	0.90 [0.79, 0.97]	0.76 [0.68, 0.83]
Novotny 2012	20	28	1	207	0.95 [0.76, 1.00]	0.88 [0.83, 0.92]
Ortiz-Munoz 2014	27	7	2	112	0.93 [0.77, 0.99]	0.94 [0.88, 0.98]
Park 2019	11	9	8	90	0.58 [0.33, 0.80]	0.91 [0.83, 0.96]
Partheen 2011a	81	41	12	124	0.87 [0.79, 0.93]	0.75 [0.68, 0.82]
Prskalo 2015	61	7	5	29	0.92 [0.83, 0.97]	0.81 [0.64, 0.92]
Richards 2015	9	1	4	15	0.69 [0.39, 0.91]	0.94 [0.70, 1.00]
Romagnolo 2016	50	5	10	83	0.83 [0.71, 0.92]	0.94 [0.87, 0.98]
Salim 2018	113	30	9	108	0.93 [0.86, 0.97]	0.78 [0.70, 0.85]
Shen 2017	91	9	14	47	0.87 [0.79, 0.93]	0.84 [0.72, 0.92]
Stiekma 2014	103	6	10	20	0.91 [0.84, 0.96]	0.77 [0.56, 0.91]
Teh 2018	13	4	0	10	1.00 [0.75, 1.00]	0.71 [0.42, 0.92]
Terlikowska 2016	55	3	8	38	0.87 [0.77, 0.94]	0.93 [0.80, 0.98]
van Gorp 2011	108	29	11	57	0.91 [0.84, 0.95]	0.66 [0.55, 0.76]
Xu 2016	57	1	46	46	0.55 [0.45, 0.65]	0.98 [0.89, 1.00]
Zhang 2015	154	14	15	49	0.91 [0.86, 0.95]	0.78 [0.66, 0.87]
Zhang 2019	103	5	15	55	0.87 [0.80, 0.93]	0.92 [0.82, 0.97]



Test 20. ROMA mixed all

ROMA mixed all

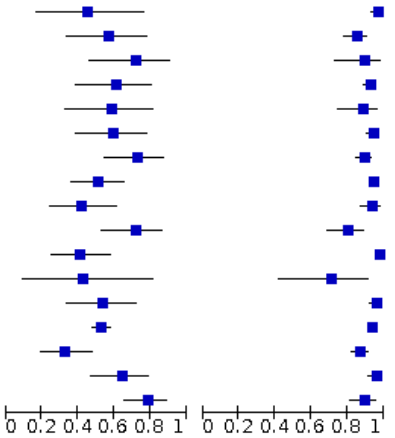
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	40	16	14	50	0.74 [0.60, 0.85]	0.76 [0.64, 0.85]
Bandiera 2011	103	28	10	137	0.91 [0.84, 0.96]	0.83 [0.76, 0.88]
Chan 2013	67	41	14	281	0.83 [0.73, 0.90]	0.87 [0.83, 0.91]
Grenache 2015	26	19	5	96	0.84 [0.66, 0.95]	0.83 [0.75, 0.90]
Kadija 2012	22	10	7	69	0.76 [0.56, 0.90]	0.87 [0.78, 0.94]
Molina 2011	100	35	11	250	0.90 [0.83, 0.95]	0.88 [0.83, 0.91]
Montagnana 2011	41	9	14	40	0.75 [0.61, 0.85]	0.82 [0.68, 0.91]
Moore 2009	134	89	17	263	0.89 [0.83, 0.93]	0.75 [0.70, 0.79]
Moore 2011	59	96	8	287	0.88 [0.78, 0.95]	0.75 [0.70, 0.79]
van Gorp 2011	137	46	24	182	0.85 [0.79, 0.90]	0.80 [0.74, 0.85]



Test 21. RMI I 200 premenopausal

RMI I 200 premenopausal

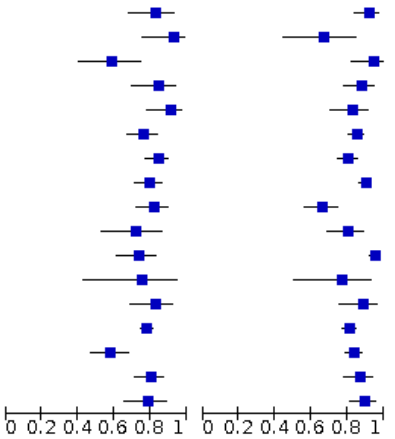
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	5	6	6	178	0.45 [0.17, 0.77]	0.97 [0.93, 0.99]		
Al Musalhi 2016	12	21	9	120	0.57 [0.34, 0.78]	0.85 [0.78, 0.91]		
Anton 2012	13	3	5	26	0.72 [0.47, 0.90]	0.90 [0.73, 0.98]		
Ertas 2016	14	20	9	248	0.61 [0.39, 0.80]	0.93 [0.89, 0.95]		
Krascsenitis 2016	10	5	7	38	0.59 [0.33, 0.82]	0.88 [0.75, 0.96]		
Liest 2019	16	18	11	287	0.59 [0.39, 0.78]	0.94 [0.91, 0.96]		
Lycke 2018	24	24	9	206	0.73 [0.54, 0.87]	0.90 [0.85, 0.93]		
Manegold-Brauer 2016	25	35	24	546	0.51 [0.36, 0.66]	0.94 [0.92, 0.96]		
Meys 2017	13	6	18	91	0.42 [0.25, 0.61]	0.94 [0.87, 0.98]		
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]		
Radosa 2011	16	19	23	832	0.41 [0.26, 0.58]	0.98 [0.97, 0.99]		
Richards 2015	3	4	4	10	0.43 [0.10, 0.82]	0.71 [0.42, 0.92]		
Sayasneh 2013a	15	5	13	132	0.54 [0.34, 0.72]	0.96 [0.92, 0.99]		
Testa 2014	200	59	178	917	0.53 [0.48, 0.58]	0.94 [0.92, 0.95]		
van den Akker 2016	15	30	31	204	0.33 [0.20, 0.48]	0.87 [0.82, 0.91]		
van Gorp 2012	25	6	14	133	0.64 [0.47, 0.79]	0.96 [0.91, 0.98]		
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]		



Test 22. RMI I 200 postmenopausal

RMI I 200 postmenopausal

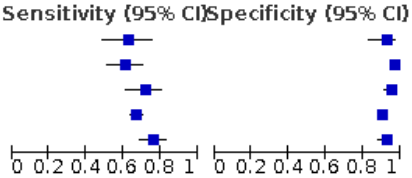
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	34	6	7	70	0.83 [0.68, 0.93]	0.92 [0.84, 0.97]		
Al Musalhi 2016	25	8	2	16	0.93 [0.76, 0.99]	0.67 [0.45, 0.84]		
Anton 2012	21	2	15	35	0.58 [0.41, 0.74]	0.95 [0.82, 0.99]		
Ertas 2016	37	9	7	64	0.84 [0.70, 0.93]	0.88 [0.78, 0.94]		
Krascsenitis 2016	40	10	4	48	0.91 [0.78, 0.97]	0.83 [0.71, 0.91]		
Liest 2019	89	46	28	260	0.76 [0.67, 0.83]	0.85 [0.80, 0.89]		
Lycke 2018	112	42	21	173	0.84 [0.77, 0.90]	0.80 [0.75, 0.86]		
Manegold-Brauer 2016	98	35	25	320	0.80 [0.71, 0.86]	0.90 [0.87, 0.93]		
Meys 2017	69	39	15	75	0.82 [0.72, 0.90]	0.66 [0.56, 0.74]		
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]		
Radosa 2011	49	21	18	383	0.73 [0.61, 0.83]	0.95 [0.92, 0.97]		
Richards 2015	9	4	3	13	0.75 [0.43, 0.95]	0.76 [0.50, 0.93]		
Sayasneh 2013a	38	5	8	39	0.83 [0.69, 0.92]	0.89 [0.75, 0.96]		
Testa 2014	470	85	132	362	0.78 [0.75, 0.81]	0.81 [0.77, 0.85]		
van den Akker 2016	54	48	39	249	0.58 [0.47, 0.68]	0.84 [0.79, 0.88]		
van Gorp 2012	89	11	22	74	0.80 [0.72, 0.87]	0.87 [0.78, 0.93]		
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]		



Test 23. RMI I 200 all

RMI I 200 all

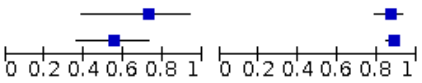
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	34	5	20	61	0.63 [0.49, 0.76]	0.92 [0.83, 0.97]		
Radosa 2011	65	40	41	1215	0.61 [0.51, 0.71]	0.97 [0.96, 0.98]		
Sayasneh 2013a	66	10	26	199	0.72 [0.61, 0.81]	0.95 [0.91, 0.98]		
Testa 2014	658	134	322	1289	0.67 [0.64, 0.70]	0.91 [0.89, 0.92]		
van Gorp 2012	114	17	36	207	0.76 [0.68, 0.83]	0.92 [0.88, 0.96]		



Test 24. RMI I 250 premenopausal

RMI I 250 premenopausal

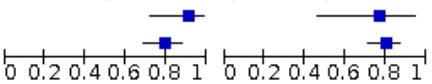
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Nikolova 2016	8	12	3	82	0.73 [0.39, 0.94]	0.87 [0.79, 0.93]		
Terzic 2013	17	38	14	287	0.55 [0.36, 0.73]	0.88 [0.84, 0.92]		



Test 25. RMI I 250 postmenopausal

RMI I 250 postmenopausal

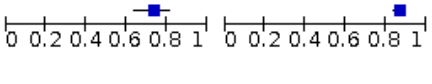
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Irshad 2013	21	3	2	10	0.91 [0.72, 0.99]	0.77 [0.46, 0.95]		
Terzic 2013	59	22	15	88	0.80 [0.69, 0.88]	0.80 [0.71, 0.87]		



Test 26. RMI I 250 all

RMI I 250 all

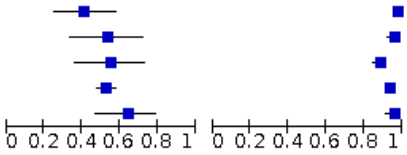
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Terzic 2013	77	57	28	378	0.73 [0.64, 0.81]	0.87 [0.83, 0.90]		



Test 35. RMI mixed premenopausal

RMI mixed premenopausal

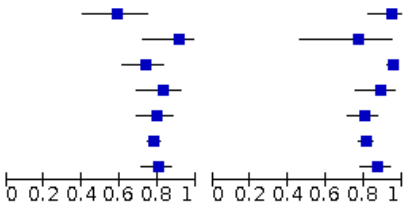
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	13	3	5	26	0.72 [0.47, 0.90]	0.90 [0.73, 0.98]		
Radosa 2011	16	19	23	832	0.41 [0.26, 0.58]	0.98 [0.97, 0.99]		
Sayasneh 2013a	15	5	13	132	0.54 [0.34, 0.72]	0.96 [0.92, 0.99]		
Terzic 2013	17	38	14	287	0.55 [0.36, 0.73]	0.88 [0.84, 0.92]		
Testa 2014	200	59	178	917	0.53 [0.48, 0.58]	0.94 [0.92, 0.95]		
van Gorp 2012	25	6	14	133	0.64 [0.47, 0.79]	0.96 [0.91, 0.98]		



Test 36. RMI mixed postmenopausal

RMI mixed postmenopausal

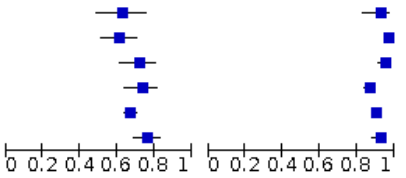
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	21	2	15	35	0.58 [0.41, 0.74]	0.95 [0.82, 0.99]		
Irshad 2013	21	3	2	10	0.91 [0.72, 0.99]	0.77 [0.46, 0.95]		
Radosa 2011	49	21	18	383	0.73 [0.61, 0.83]	0.95 [0.92, 0.97]		
Sayasneh 2013a	38	5	8	39	0.83 [0.69, 0.92]	0.89 [0.75, 0.96]		
Terzic 2013	59	22	15	88	0.80 [0.69, 0.88]	0.80 [0.71, 0.87]		
Testa 2014	470	85	132	362	0.78 [0.75, 0.81]	0.81 [0.77, 0.85]		
van Gorp 2012	89	11	22	74	0.80 [0.72, 0.87]	0.87 [0.78, 0.93]		



Test 37. RMI mixed all

RMI mixed all

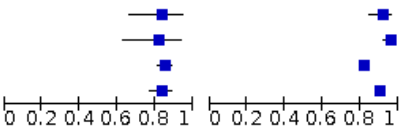
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Anton 2012	34	5	20	61	0.63 [0.49, 0.76]	0.92 [0.83, 0.97]		
Radosa 2011	65	40	41	1215	0.61 [0.51, 0.71]	0.97 [0.96, 0.98]		
Sayasneh 2013a	66	10	26	199	0.72 [0.61, 0.81]	0.95 [0.91, 0.98]		
Terzic 2013	77	57	28	378	0.73 [0.64, 0.81]	0.87 [0.83, 0.90]		
Testa 2014	658	134	322	1289	0.67 [0.64, 0.70]	0.91 [0.89, 0.92]		
van Gorp 2011	114	17	36	207	0.76 [0.68, 0.83]	0.92 [0.88, 0.96]		



Test 38. LR2 premenopausal

LR2 premenopausal

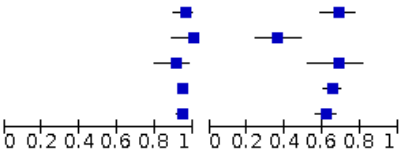
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Meys 2017	26	8	5	89	0.84 [0.66, 0.95]	0.92 [0.84, 0.96]		
Sayasneh 2013a	23	5	5	132	0.82 [0.63, 0.94]	0.96 [0.92, 0.99]		
Testa 2014	321	176	57	800	0.85 [0.81, 0.88]	0.82 [0.79, 0.84]		
Timmerman 2010	152	101	30	913	0.84 [0.77, 0.89]	0.90 [0.88, 0.92]		



Test 39. LR2 postmenopausal

LR2 postmenopausal

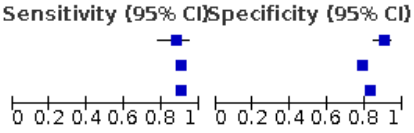
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Meys 2017	81	36	3	78	0.96 [0.90, 0.99]	0.68 [0.59, 0.77]		
Niemi 2017	32	42	0	24	1.00 [0.89, 1.00]	0.36 [0.25, 0.49]		
Sayasneh 2013a	42	14	4	30	0.91 [0.79, 0.98]	0.68 [0.52, 0.81]		
Testa 2014	566	156	36	291	0.94 [0.92, 0.96]	0.65 [0.60, 0.70]		
Timmerman 2010	339	138	21	224	0.94 [0.91, 0.96]	0.62 [0.57, 0.67]		



Test 40. LR2 all

LR2 all

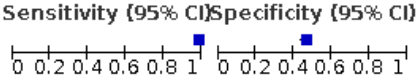
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Sayasneh 2013a	65	18	9	163	0.88 [0.78, 0.94]	0.90 [0.85, 0.94]		
Testa 2014	884	300	96	1123	0.90 [0.88, 0.92]	0.79 [0.77, 0.81]		
Timmerman 2010	490	239	52	1157	0.90 [0.88, 0.93]	0.83 [0.81, 0.85]		



Test 41. ADNEX 3% D+ probability all

ADNEX 3% D+ probability all

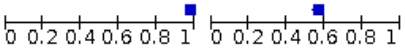
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	969	759	11	664	0.99 [0.98, 0.99]	0.47 [0.44, 0.49]		



Test 42. ADNEX 3% D+ probability premenopausal

ADNEX 3% D+ probability premenopausal

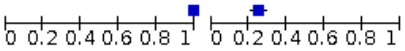
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	370	424	8	552	0.98 [0.96, 0.99]	0.57 [0.53, 0.60]		



Test 43. ADNEX 3% D+ probability postmenopausal

ADNEX 3% D+ probability postmenopausal

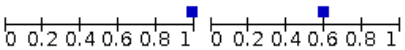
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	599	335	3	112	1.00 [0.99, 1.00]	0.25 [0.21, 0.29]		



Test 44. ADNEX 5% D+ probability all

ADNEX 5% D+ probability all

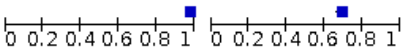
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	964	578	16	845	0.98 [0.97, 0.99]	0.59 [0.57, 0.62]		



Test 45. ADNEX 5% D+ probability premenopausal

ADNEX 5% D+ probability premenopausal

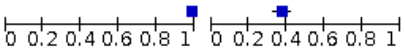
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	369	298	9	678	0.98 [0.96, 0.99]	0.69 [0.66, 0.72]		



Test 46. ADNEX 5% D+ probability postmenopausal

ADNEX 5% D+ probability postmenopausal

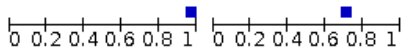
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	595	280	7	167	0.99 [0.98, 1.00]	0.37 [0.33, 0.42]		



Test 47. ADNEX 10% D+ probability all

ADNEX 10% D+ probability all

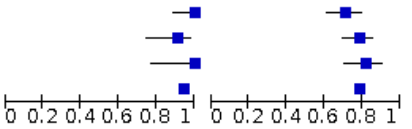
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	946	408	34	1015	0.97 [0.95, 0.98]	0.71 [0.69, 0.74]		



Test 48. ADNEX 10% D+ probability premenopausal

ADNEX 10% D+ probability premenopausal

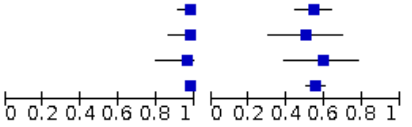
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Meys 2017	31	28	0	69	1.00 [0.89, 1.00]	0.71 [0.61, 0.80]		
Szubert 2016a	29	23	3	83	0.91 [0.75, 0.98]	0.78 [0.69, 0.86]		
Szubert 2016b	14	11	0	51	1.00 [0.77, 1.00]	0.82 [0.70, 0.91]		
van Calster 2014	358	209	20	767	0.95 [0.92, 0.97]	0.79 [0.76, 0.81]		



Test 49. ADNEX 10% D+ probability postmenopausal

ADNEX 10% D+ probability postmenopausal

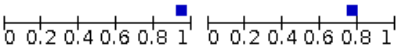
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Meys 2017	82	52	2	62	0.98 [0.92, 1.00]	0.54 [0.45, 0.64]		
Szubert 2016a	37	14	1	14	0.97 [0.86, 1.00]	0.50 [0.31, 0.69]		
Szubert 2016b	24	11	1	16	0.96 [0.80, 1.00]	0.59 [0.39, 0.78]		
van Calster 2014	588	199	14	248	0.98 [0.96, 0.99]	0.55 [0.51, 0.60]		



Test 50. ADNEX 15% D+ probability all

ADNEX 15% D+ probability all

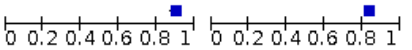
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	923	325	57	1098	0.94 [0.93, 0.96]	0.77 [0.75, 0.79]		



Test 51. ADNEX 15% D+ probability premenopausal

ADNEX 15% D+ probability premenopausal

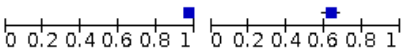
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	342	162	36	814	0.90 [0.87, 0.93]	0.83 [0.81, 0.86]		



Test 52. ADNEX 15% D+ probability postmenopausal

ADNEX 15% D+ probability postmenopausal

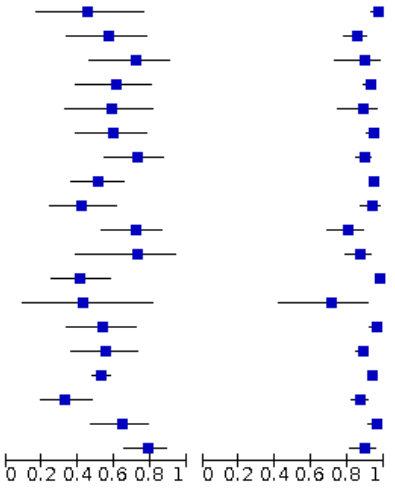
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
van Calster 2014	581	163	21	284	0.97 [0.95, 0.98]	0.64 [0.59, 0.68]		



Test 67. RMI I mixed premenopausal

RMI I mixed premenopausal

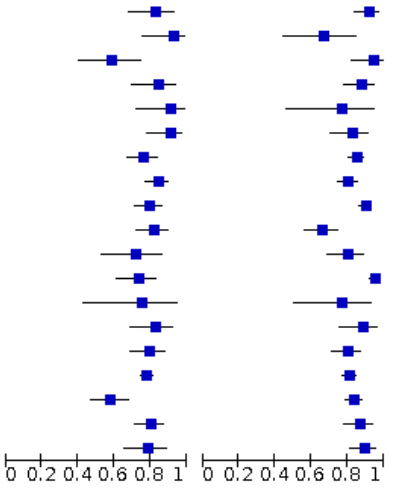
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	5	6	6	178	0.45 [0.17, 0.77]	0.97 [0.93, 0.99]
Al Musalhi 2016	12	21	9	120	0.57 [0.34, 0.78]	0.85 [0.78, 0.91]
Anton 2012	13	3	5	26	0.72 [0.47, 0.90]	0.90 [0.73, 0.98]
Ertas 2016	14	20	9	248	0.61 [0.39, 0.80]	0.93 [0.89, 0.95]
Krascsenitis 2016	10	5	7	38	0.59 [0.33, 0.82]	0.88 [0.75, 0.96]
Liest 2019	16	18	11	287	0.59 [0.39, 0.78]	0.94 [0.91, 0.96]
Lycke 2018	24	24	9	206	0.73 [0.54, 0.87]	0.90 [0.85, 0.93]
Manegold-Brauer 2016	25	35	24	546	0.51 [0.36, 0.66]	0.94 [0.92, 0.96]
Meys 2017	13	6	18	91	0.42 [0.25, 0.61]	0.94 [0.87, 0.98]
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]
Nikolova 2016	8	12	3	82	0.73 [0.39, 0.94]	0.87 [0.79, 0.93]
Radosa 2011	16	19	23	832	0.41 [0.26, 0.58]	0.98 [0.97, 0.99]
Richards 2015	3	4	4	10	0.43 [0.10, 0.82]	0.71 [0.42, 0.92]
Sayasneh 2013a	15	5	13	132	0.54 [0.34, 0.72]	0.96 [0.92, 0.99]
Terzic 2013	17	38	14	287	0.55 [0.36, 0.73]	0.88 [0.84, 0.92]
Testa 2014	200	59	178	917	0.53 [0.48, 0.58]	0.94 [0.92, 0.95]
van den Akker 2016	15	30	31	204	0.33 [0.20, 0.48]	0.87 [0.82, 0.91]
van Gorp 2012	25	6	14	133	0.64 [0.47, 0.79]	0.96 [0.91, 0.98]
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]



Test 68. RMI I mixed postmenopausal

RMI I mixed postmenopausal

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abdalla 2017	34	6	7	70	0.83 [0.68, 0.93]	0.92 [0.84, 0.97]
Al Musalhi 2016	25	8	2	16	0.93 [0.76, 0.99]	0.67 [0.45, 0.84]
Anton 2012	21	2	15	35	0.58 [0.41, 0.74]	0.95 [0.82, 0.99]
Ertas 2016	37	9	7	64	0.84 [0.70, 0.93]	0.88 [0.78, 0.94]
Irshad 2013	21	3	2	10	0.91 [0.72, 0.99]	0.77 [0.46, 0.95]
Krascsenitis 2016	40	10	4	48	0.91 [0.78, 0.97]	0.83 [0.71, 0.91]
Liest 2019	89	46	28	260	0.76 [0.67, 0.83]	0.85 [0.80, 0.89]
Lycke 2018	112	42	21	173	0.84 [0.77, 0.90]	0.80 [0.75, 0.86]
Manegold-Brauer 2016	98	35	25	320	0.80 [0.71, 0.86]	0.90 [0.87, 0.93]
Meys 2017	69	39	15	75	0.82 [0.72, 0.90]	0.66 [0.56, 0.74]
Niemi 2017	23	13	9	53	0.72 [0.53, 0.86]	0.80 [0.69, 0.89]
Radosa 2011	49	21	18	383	0.73 [0.61, 0.83]	0.95 [0.92, 0.97]
Richards 2015	9	4	3	13	0.75 [0.43, 0.95]	0.76 [0.50, 0.93]
Sayasneh 2013a	38	5	8	39	0.83 [0.69, 0.92]	0.89 [0.75, 0.96]
Terzic 2013	59	22	15	88	0.80 [0.69, 0.88]	0.80 [0.71, 0.87]
Testa 2014	470	85	132	362	0.78 [0.75, 0.81]	0.81 [0.77, 0.85]
van den Akker 2016	54	48	39	249	0.58 [0.47, 0.68]	0.84 [0.79, 0.88]
van Gorp 2012	89	11	22	74	0.80 [0.72, 0.87]	0.87 [0.78, 0.93]
Vural 2016	41	9	11	78	0.79 [0.65, 0.89]	0.90 [0.81, 0.95]



ADDITIONAL TABLES

Table 1. Details of included test combinations

Index test combination	Details	Test positivity thresholds included
RMI I *U* × *M* × CA125 Jacobs 1990	**Ultrasound (U):** (1 point for each of multilocular cysts, solid areas, metastases, ascites and bilateral lesions) where a total ultrasound point score of 0 = 0, a point score of 1 = 1, and a point score of ≥ 2 = 3 **Menopausal status (M):** premenopausal = 1 and postmenopausal = 3	200, 250

Table 1. Details of included test combinations *(Continued)*

Serum CA125: CA125 U/mL applied directly to the calculation

ROMA Bandiera 2011 Moore 2009 van Gorp 2011	**Premenopausal** PI = −12.0 + 2.38 × LN(HE4) + 0.0626 × LN(CA125) **Postmenopausal** PI = −8.09 + 1.04 × LN(HE4) + 0.732 × LN(CA125) **Predicted probability (ROMA score)** = exp(PI)/[1 + exp(PI)] × 100	Premenopausal 7.4 and postmenopausal 25.3 Premenopausal 12.5 and postmenopausal 14.4 Premenopausal 13.1 and postmenopausal 27.7 ± 2% from common (above) thresholds Premenopausal: 7.4 (5.4 to 9.4%), 12.5 (10.5 to 14.5%), 14.4 (12.4 to 16.4%) Postmenopausal: 25.3 (23.3 to 27.3%), 27.7 (25.7 to 29.7%)
LR2 Timmerman 2010	**(3)** age of the woman (in years) **(6)** presence of ascites (yes, 1; no, 0) **(7)** presence of blood flow within a solid papillary projection (yes, 1; no, 0) **(9)** maximum diameter of the solid component of the adnexal mass (expressed in millimetres, but with no increase 950 mm) **(10)** irregular internal cyst walls (yes, 1; no, 0) **(11)** presence of acoustic shadows (yes, 1; no, 0) The probability of malignancy is calculated using the formula y = 1/(1 + exp(jz)), where z = j5.3718 + 0.0354 **(3)** + 1.6159 **(6)** + 1.1768 **(7)** + 0.0697 **(9)** + 0.9586 **(10)** j 2.9486 **(11)**. The probability y is dichotomised at 0.1 to give a predictive diagnosis of cancer.	10% probability of ovarian cancer
ADNEX van Calster 2014	Age (years) Serum CA125 level (log transformed) Type of centre (oncology centres vs other hospitals) Maximum diameter of the lesion (log transformed) Proportion of solid tissue (with quadratic term) Number of papillary projections > 10 cyst locules Acoustic shadows Ascites	3%, 5%, 10% and 15% probability of ovarian cancer

ADNEX: Assessment of Different NEoplasias in the adneXa model; LR2: Logistic Regression Model 2; RMI: Risk of Malignancy Index; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 2. Summary bivariate estimates of RMI I, ROMA, LR2 and ADNEX at all thresholds in pre- and postmenopausal women

Pooled sensitivity and specificity of RMI, ROMA, ADNEX, and LR2 at thresholds reported in included studies					
Score, threshold and menopause status	**Studies**	**Participants**	**OC cases**	**Pooled sensitivity % (95% CI)**	**Pooled specificity % (95% CI)**
ROMA					
7.4 (premenopausal)	10	3051	342	80.7 (69.6 to 88.5)	80.5 (73.8 to 85.9)
25.3 (post-menopausal)	9	1386	603	86.8 (77.9 to 92.5)	87.6 (80.2 to 92.6)
11.4 (premenopausal)	11	2281	445	80.9 (71.0 to 88.0)	84.1 (81.2 to 86.7)
29.9 (post-menopausal)	12	1797	851	91.6 (84.2 to 95.7)	86.3 (80.1 to 90.7)
12.5 (premenopausal)	3	302	68	63.5 (51.0 to 74.4)	89.3 (80.8 to 94.3)
14.4 (post-menopausal)	3	299	177	88.0 (80.6 to 92.8)	68.3 (57.4 to 77.4)
13.1 (premenopausal)	8	1353	158	75.2 (67.0 to 81.9)	84.0 (78.4 to 88.3)
27.7 (post-menopausal)	9	1265	556	90.5 (86.2 to 93.6)	81.1 (75.7 to 85.5)
7.4 ± 2 (pre-menopausal)	12	3223	378	80.6 (71.5 to 87.3)	81.7 (75.7 to 86.5)
25.3 ± 2 (post-menopausal)	15	2599	1049	87.2 (81.7 to 91.3)	86.0 (80.3 to 90.3)
13.1 ± 2 (pre-menopausal)	27	4463	825	77.8 (72.5 to 82.4)	84.3 (81.3 to 86.8)
27.7 ± 2 (post-menopausal)	13	2002	852	90.4 (87.4 to 92.7)	81.3 (76.9 to 85.0)
RMI I					
200 (premenopausal)	17	5233	851	57.1 (50.6 to 63.4)	92.5 (90.0 to 94.4)
200 (postmenopausal)	17	4369	1664	78.7 (74.3 to 82.5)	85.5 (81.3 to 88.9)
Difference in sensitivity and specificity premenopausal vs postmenopausal				21.6 (13.9 to 29.2); P < 0.0001	−6.9 (−11.3 to −2.6); P = 0.002
250 (premenopausal)	2	461	42	59.5 (44.3 to 73.1)	88.1 (84.6 to 90.8)
250 (postmenopausal)	2	220	97	82.5 (73.6 to 88.8)	79.7 (71.6 to 85.9)

Table 2. Summary bivariate estimates of RMI I, ROMA, LR2 and ADNEX at all thresholds in pre- and postmenopausal women *(Continued)*

Difference in sensitivity and specificity premenopausal vs postmenopausal				23.0 (6.3 to 39.6); P = 0.007	−8.4 (−16.2 to −0.6); P = 0.034
LR2					
10 (premenopausal)	4	2843	619	83.2 (78.6 to 87.0)	90.4 (84.6 to 94.1)
10 (postmenopausal)	5	2157	1124	94.5 (92.8 to 95.7)	60.5 (49.3 to 70.7)
Difference in sensitivity and specificity premenopausal vs postmenopausal				11.2 (6.6 to 15.9); P < 0.0001	−29.9 (−41.7 to −18.0); P < 0.0001
ADNEX D+					
3 (premenopausal)	1	1354	378	97.9 (95.9 to 99.1)	56.6 (53.4 to 59.7)
3 (postmenopausal)	1	1049	602	99.5 (98.6 to 99.9)	25.1 (21.1 to 29.3)
5 (premenopausal)	1	1354	378	97.6 (95.5 to 98.9)	69.5 (66.5 to 72.3)
5 (postmenopausal)	1	1049	602	98.8 (97.6 to 99.5)	37.4 (32.9 to 42.0)
10 (premenopausal)	4	1696	455	94.9 (92.5 to 96.6)	78.2 (75.8 to 80.4)
10 (postmenopausal)	4	1365	749	97.6 (96.2 to 98.5)	55.2 (51.2 to 59.1)
Difference in sensitivity and specificity premenopausal vs postmenopausal				2.7 (0.4 to 4.9); P = 0.023	−23.0 (−27.5 to −18.4); P < 0.0001
15 (premenopausal)	1	1354	378	90.5 (87.1 to 93.2)	83.4 (80.9 to 85.7)
15 (postmenopausal)	1	1049	602	96.5 (94.7 to 97.8)	63.5 (58.9 to 68.0)

ADNEX: Assessment of Different NEoplasias in the adneXa model; CI: confidence interval; LR2: Logistic Regression model 2; OC: ovarian cancer; RMI: Risk of Malignancy Index; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 3. Study characteristics: RMI I

Author year Country	Setting	Participants characteristics	Index test threshold
Abdalla 2017 Poland	**Study criteria:** women scheduled to undergo surgery for adnexal tumours **Clinical setting:** mixed **Prior tests:** USS assessment of adnexal mass and measurement of tumour markers CA125 and HE4 within 5 days before surgical intervention **Exclusions:** presence of fibroids > 5 cm were excluded **Centre:** single	**n:** 312 **Postmenopausal n (%):** 117 (37) **Ovarian cancer n (%):** 45 (15) **Borderline n (%):** 7 (2) **Age:** range 18–85 years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes

Table 3. Study characteristics: RMI I *(Continued)*

Al Musalhi 2016 Oman	**Study criteria:** women with an ovarian mass **Clinical setting:** mixed **Prior tests:** unclear but assume USS **Exclusions:** none reported **Centre:** single	**n:** 213 **Postmenopausal n (%):** 51 (24) **Ovarian cancer n (%):** 48 (23) **Borderline n (%):** 7 (3) **Age:** not reported **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Anton 2012 Brazil	**Study criteria:** women referred with pelvic mass diagnosed by USS, CT or MRI with signs of carcinomatosis undergoing surgery or image-guided biopsy **Clinical setting:** secondary care **Prior tests:** unclear **Exclusions:** none reported **Centre:** single	**n:** 120 **Postmenopausal n (%):** 73 (60) **Ovarian cancer n(%):** 30 (25) **Borderline n (%):** 17 (14) **Mean age:** malignant 54.7 years, borderline 56.4 years, benign 50.7 years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Ertas 2016 Turkey	**Study criteria:** women with adnexal masses that underwent surgery **Clinical setting:** tertiary **Prior tests:** unclear **Exclusions:** none reported **Centre:** single	**n:** 408 **Postmenopausal n (%):** 117 (71.4) **Ovarian cancer n (%):** 55 (13) **Borderline n (%):** 12 (3) **Mean age:** benign 40.8 (SD 13.8) years, malignant 54.4 (SD 13.6) years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Irshad 2013 Pakistan	**Study criteria:** unclear (ovarian masses) **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** unclear **Centre:** single	**n:** 36 **Postmenopausal n (%):** 36 (100) **Ovarian cancer n (%)**: 24 (37) **Borderline n (%):** not reported **Mean age:** 58 years **Separated by menopausal status:** yes	**Thresholds:** 250 **Prespecified:** yes
Krascsenitis 2016 Hungary	**Study criteria:** women diagnosed with an ovarian tumour of unknown significance admitted for surgery **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 162 **Postmenopausal n (%):** 102 (63) **Ovarian cancer n (%):** 34 (21) **Borderline n (%):** 11 (7) **Mean age:** 55 years	**Threshold:** 200 **Prespecified:** yes

Table 3. Study characteristics: RMI I *(Continued)*

		Separated by menopausal status: yes	
Liest 2019 Sweden	**Study criteria:** women with a pelvic mass of probable ovarian origin and scheduled for surgery **Clinical setting:** tertiary **Prior tests:** preoperative USS **Exclusions:** none reported **Centre:** multicentre	**n:** 784 **Postmenopausal n (%):** 117 (81) **Ovarian cancer n (%):** 144 (18) (include borderline) **Borderline n (%):** not reported **Age:** not reported **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Lycke 2018 Sweden	**Study criteria:** women planned for a surgical procedure for a symptomatic/suspected malignant ovarian cyst or pelvic tumour **Clinical setting:** mixed **Prior tests:** unclear but assume history and examination, and USS from participant selection **Exclusions:** none reported **Centre:** multicentre	**n:** 638 **Postmenopausal n (%):** 348 (55) **Ovarian cancer n (%):** 162 (25) **Borderline n (%):** 31 (5) **Mean age:** benign 50.76 years, BOT 55.58 years, EOC 62.67 **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Manegold-Brauer 2016 Switzerland	**Study criteria:** women who had USS examination for an adnexal mass with histology and CA125 results available **Clinical setting:** secondary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 1108 **Postmenopausal n (%):** 478 (43) **Ovarian cancer n (%):** 118 (11) **Borderline n (%):** 33 (3) **Median age:** 48 years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Meys 2017 Netherlands	**Study criteria**: women with adnexal pathology **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 326 **Postmenopausal n (%):** 198 (61) **Ovarian cancer n (%):** 115 (35) **Borderline n (%):** 27 (8) **Median age:** benign 53.2 (IQR 16.1–87.2) years, malignant 67.7 (IQR 32.3–87) years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Niemi 2017 Finland	**Study criteria:** women aged > 50 years presenting with an abnormal adnexal mass(es) **Clinical setting:** tertiary	**n:** 98 **Postmenopausal n (%):** 98 (100) **Ovarian cancer n (%):** 23 (23)	**Threshold:** 200 **Prespecified:** yes

Table 3. Study characteristics: RMI I *(Continued)*

	Prior tests: not reported **Exclusions:** overtly benign or malignant-appearing tumours such as unilocular simple ovarian cysts and tumours associated with marked ascites (depth of the greatest pool > 10 cm) **Centre:** single	**Borderline n (%):** 7 (7) **Median age:** 61 (range 50–84) years **Separated by menopausal status:** only postmenopausal included	
Nikolova 2016 Macedonia	**Study criteria:** premenopausal women with USS confirming an ovarian cyst/mass and undergoing surgery **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** postmenopausal women **Centre:** single	**n:** 105 (analysed) **Postmenopausal n (%):** 0 **Ovarian cancer n (%):** 11 (10%) **Borderline n (%):** not reported **Mean age:** ovarian cancer 42.46 (SD 8.21) years, benign 36.90 (SD 10.12) years **Separated by menopausal status:** only premenopausal women included	**Threshold:** 250 **Prespecified:** yes
Radosa 2011 Germany	**Study criteria:** women with adnexal mass who subsequently underwent surgery were selected **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 442 **Postmenopausal n (%):** 141 (32) **Ovarian cancer n (%)**: 79 **Borderline n (%):** 19 **Mean age:** 43.3 years **Separated by menopausal status:** yes	**Thresholds:** 200 **Prespecified:** yes
Richards 2015 Australia	**Study criteria:** women who were undergoing surgery for a complex pelvic mass, presumed to be arising from the ovary **Clinical setting:** mixed **Prior tests:** unclear **Exclusions:** none reported **Centre:** single	**n:** 50 **Postmenopausal n (%):** 29 (58) **Ovarian cancer n (%):** 16 (32) **Borderline n (%):** 4 (8) **Median age:** 60 years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
Sayasneh 2013a UK	**Study criteria:** women presenting with adnexal mass and undergoing surgery within 120 days after examination **Clinical setting:** mixed **Prior test:** unclear **Exclusions:** none **Centre:** multicentre	**n:** 255 **Postmenopausal n (%):** 117 (46) **Ovarian cancer n (%)**: 48 (19) **Borderline n (%):** 18 (7) **Mean age:** 46 years **Separated by menopausal status:** yes	**Thresholds:** 200 **Prespecified:** yes

Table 3. Study characteristics: RMI I *(Continued)*

Terzic 2013 Serbia	**Study criteria:** women treated for adnexal tumours **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 689 **Postmenopausal n (%):** 138 (20) **Ovarian cancer n (%)**: 112 (16) **Borderline n (%):** 33 (5) **Mean age:** benign 42.8 years, borderline: 53.6 years, malignant 57.25 years **Separated by menopausal status:** yes	**Thresholds:** 250 **Prespecified:** yes
Testa 2014 European countries	**Study criteria:** women presenting with adnexal mass and undergoing TVS by 1 of the principal investigators and surgery within 120 days after examination **Clinical setting:** mixed **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 2403 **Postmenopausal n (%):** 1049 (44) **Ovarian cancer n (%)**: 701 (29) **Borderline n (%):** 153 (6) **Age:** not reported **Separated by menopausal status:** yes	**Thresholds:** 200 **Prespecified:** yes
van den Akker 2016 Netherlands	**Study criteria:** women admitted for surgical treatment of an ovarian mass with unknown histology **Clinical setting:** mixed **Prior tests:** not reported **Exclusions:** women with clear evidence of malignancy found before or during the surgical procedure (e.g. pleural effusions and evidence of distal organ involvement) **Centre:** multicentre	**n:** 670 **Postmenopausal n (%):** 390 (58) **Ovarian cancer n (%):** 93 (14) **Borderline n (%):** 46 (6) **Median age:** 54 years **Separated by menopausal status:** yes	**Threshold:** 200 **Prespecified:** yes
van Gorp 2012 Belgium	**Study criteria:** women with a pelvic mass, scheduled for surgery **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 374 **Postmenopausal n (%):** 196 (52) **Ovarian cancer n (%)**: 94 (25) **Borderline n (%):** 31 (8) **Mean age:** benign 46.2 years, malignant 57.7 years **Separated by menopausal status:** yes	**Thresholds:** 200 **Prespecified:** yes
Vural 2016 Turkey	**Study criteria**: postmenopausal women with adnexal masses who underwent surgery **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** premenopausal women	**n:** 139 **Postmenopausal n (%):** 139 (100) **Ovarian cancer n (%):** 44 (32) **Borderline n (%):** 8 (6)	**Threshold:** 200 **Prespecified:** yes

Table 3. Study characteristics: RMI I *(Continued)*

	Centre: single	**Mean age:** 61.1 (SD 8.9) years (range 42–87 years) **Separated by menopausal status:** yes

*Thresholds extracted for RMI I: 200 and 250.
BOT: borderline ovarian tumour; CT: computed tomography; EOC: epithelial ovarian cancer; HE4: Human Epididymis protein; IQR: interquartile range; MRI: magnetic resonance imaging; n: number of participants; RMI I: Risk of Malignancy Index I; SD: standard deviation; TVS: transvaginal ultrasound; USS: ultrasound scan.

Table 4. Study characteristics: ROMA

Author year Country	Setting	Participant characteristics	Index test threshold*
Al Musalhi 2016 Oman	**Study criteria:** women with an ovarian mass **Clinical setting:** mixed **Prior tests:** unclear but assumed USS **Exclusions:** none reported **Centre:** single	**n:** 213 **Postmenopausal n (%):** 51 (24) **Ovarian cancer n (%):** 48 (23) **Borderline n (%):** 7 (3) **Age:** not reported **Separated by menopausal status:** yes	**Threshold:** premenopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Anton 2012 Brazil	**Study criteria:** women with signs of carcinomatosis with a pelvic mass diagnosed by US, CT or MRI undergoing surgery or image-guided biopsy **Clinical setting:** secondary care **Prior tests:** not reported **Exclusions**: none reported **Centre:** single	**n:** 120 **Postmenopausal n (%):** 73 (60.8%) **Ovarian cancer n (%):** 30 (25%) **Borderline n (%):** 17 (14%) **Mean age:** malignant 54.7 years, borderline 56.4 years, benign 50.73 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Bandiera 2011 USA	**Study criteria:** not reported **Clinical setting:** tertiary care **Prior tests:** not reported **Exclusions:** non-EOC **Centre:** single	**n:** 278 **Postmenopausal n (%):** 183 (65.8) **Ovarian cancer n (%):** 113 (41) **Borderline n (%):** not reported **Mean age:** premenopausal: malignant 44.7 years, benign 41.5 years; postmenopausal: malignant 66.3 years, benign 64.0 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Chan 2013 Asia-Pacific region	**Study criteria:** women aged > 18 years diagnosed with adnexal mass diagnosed by any imaging method (US, CT or MRI)	**n:** 414 **Postmenopausal n (%):** 26 (108)	**Thresholds:** premenopausal 7.4,

Table 4. Study characteristics: ROMA *(Continued)*

	Clinical setting: unclear **Prior test:** unclear **Exclusions:** none **Centre:** multicentre	**Ovarian cancer n (%):** 74 (18) **Borderline n (%):** 16 (4) **Age mean:** not reported **Separated by menopausal status:** yes	postmenopausal 25.3 **Prespecified:** yes
Chen 2015 China	**Study criteria:** women with pelvic masses scheduled for surgery **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 130 **Postmenopausal n (%):** 62 (48) **Ovarian cancer n (%):** 60 (46) **Borderline n (%):** not reported **Median age:** benign 34 years, malignant 53 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Chen 2014 China	**Study criteria:** women with EOC and benign lesions **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** women with non-EOC **Centre:** single	**n:** 192 **Postmenopausal n (%):** 84 (44) **Ovarian cancer n (%):** 123 (64) **Borderline n (%):** not reported **Age mean:** not reported **Separated by menopausal status:** yes	**Thresholds:** premenopausal 12.2, postmenopausal 25.8 **Prespecified:** yes
Chudecka-Glaz 2015 Poland (ROMA and ROMA-P)	**Study criteria:** consecutive women who attended the hospital presenting with suspected ovarian cancer (ovarian tumour, ovarian cyst, or ascites) **Clinical setting:** tertiary **Prior test:** not reported **Exclusions:** none reported **Centre:** single	**n:** 413 **Postmenopausal (%):** 251 (61) **Ovarian cancer n (%):** 162 (39%) **Borderline n (%):** not reported **Age median:** benign 35 years, malignant 59.7 years **Separated by menopausal status:** yes	**a) ROMA** **Thresholds:** premenopausal 14.1, postmenopausal 25 **Prespecified:** yes **b) ROMA-P** **Thresholds:** determined by age group in both pre- and postmenopausal; age group included: < 20 years, 21–30 years, 31–40 years, 41–50 years, 51–60 years, 61–70 years, 71–80 years, and > 80 years **Prespecified:** no
Cradic 2018 USA	**Study criteria:** women with EOC or benign ovarian lesions **Clinical setting:** tertiary **Prior test:** not reported	**n:** 207 **Postmenopausal n (%):** 93 (45) **Ovarian cancer n (%):** 76 (37) (EOC) **Borderline n (%):** not reported	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Centre: single	**Age mean:** not reported **Separated by menopausal status:** yes	
Dikmen 2015 Turkey	**Study criteria:** women were 'preoperative' **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** none reported **Centre:** unclear	**n:** 143 **Postmenopausal n (%):** 46 (32%) **Ovarian cancer n (%):** 47 (33%) **Borderline n (%):** not reported **Age mean:** benign 42 (SD 10) years, malignant 56 (SD 14) years **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Farzaneh 2014 Iran	**Study criteria:** women with adnexal mass undergoing surgery and having attained menarche 12 months before presenting with adnexal mass **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** non-EOC **Centre:** single	**n:** 99 **Postmenopausal n (%):** 31 (31) **Ovarian cancer n (%):** 43 (43) (EOC) **Borderline n (%):** not reported **Mean age:** benign 39 years, malignant 51 years **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 11.5, postmenopausal 25.5 **Prespecified:** yes
Grenache 2015 USA	**Study criteria:** women with abnormal adnexal mass detected on physical examination and imaging Included USS, CT or MRI) followed by surgery **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** unclear **Centre:** multicentre	**n:** 146 **Postmenopausal n (%):** 76 (52) **Ovarian cancer n (%):** 19 (13) **Borderline n (%):** 7 (5) **Mean age:** 52 years **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 8.6 and 13.1, post-menopausal 27.7 **Prespecified:** yes
Huy 2018 Vietnam	**Study criteria:** women with sufficient personal information, clinical symptoms, data on serum CA125 and serum HE4 levels, and postoperative pathologic findings **Clinical setting:** mixed **Prior test:** not reported **Exclusions:** unclear borderline cases **Centre:** single	**n:** 277 **Postmenopausal n (%):** 47 (17) **Ovarian cancer n (%):** 30 (11) (EOC only) **Borderline n (%):** not reported **Age:** not reported **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Karlsen 2012 Denmark	**Study criteria:** women admitted to surgery for pelvic mass or pelvic pain potentially caused by malignant disease or endometriosis **Clinical setting:** secondary **Prior test:** unclear	**n:** 1218 **Postmenopausal n (%):** 621 (51) **Ovarian cancer n (%):** 261 (21) **Borderline n (%):** 79 (6) **Age mean:** not reported	**Thresholds:** pre-menopausal 7.4, postmenopausal 25.3 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Exclusions: none **Centre:** single	**Separated by menopausal status:** yes	
Kadija 2012 Serbia	**Study criteria:** women diagnosed with adnexal mass scheduled to undergo surgery **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 108 **Postmenopausal n (%):** 41 (38) **Ovarian cancer n (%):** 24 (22) **Borderline n (%):** 5 (5) **Age:** not reported **Separated by menopausal status:** yes	**Thresholds:** premenopausal 12.5, postmenopausal 14.4 **Prespecified:** no
Kim 2011 South Korea	**Study criteria:** women diagnosed with adnexal mass on the first visit to the gynaecological oncology clinic and underwent surgery **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** only EOC included **Centre:** single	**n:** 159 **Postmenopausal n (%):** 108 (68) **Ovarian cancer n (%):** 68 (43) **Borderline n (%):** 10 (6) **Mean age:** benign 35.7, malignant 51.7 **Separated by menopausal status:** **yes	**Threshold:** premenopausal 7.6 **Prespecified:** yes
Kim 2019 Korea	**Study criteria:** women with suspected gynaecological disease **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** unclear; presume BOT excluded as retrospective **Centre:** single	**n:** 832 **Postmenopausal n (%):** 251 (30) **Ovarian cancer n (%):** 70 (8) **Borderline n (%):** not reported **Median age:** benign 45.0 (IQR 36.0–51.0) years, malignant 64.0 (IQR 50.9–77.0) years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Krascsenitis 2016 Hungary	**Study criteria:** women diagnosed with an ovarian tumour of unknown significance admitted for surgery **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 162 **Postmenopausal n (%):** 102 (63) **Ovarian cancer n (%):** 34 (21) **Borderline n (%):** 11 (7) **Mean age:** 55 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Li 2016 **China**	**Study criteria:** women diagnosed with gynaecological diseases by US, CT scan, PET-CT scan or MRI **Clinical setting:** unclear **Prior test:** not reported **Exclusions:** none	**n:** 916 **Postmenopausal n (%):** 172 (19) **Ovarian cancer n (%):** 190 **Borderline n (%):** not reported **Median age:** 50 years (range 18–82 years)	**Thresholds:** premenopausal 7.4, postmenopausal 25.3 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Centre: single	**Separated by menopausal status:** yes	
Liest 2019 Sweden	**Study criteria:** women with a pelvic mass of probable ovarian origin and scheduled for surgery **Clinical setting:** tertiary **Prior tests:** preoperative US **Exclusions:** none reported **Centre:** multicentre	**n:** 784 **Postmenopausal n (%):** 117 (81) **Ovarian cancer n (%):** 144 (18) (EOC + borderline) **Borderline n (%):** not reported **Mean age:** not reported **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 11, postmenopausal 25 **Prespecified:** yes
Lycke 2018 Sweden	**Study criteria:** women planned for a surgical procedure for a symptomatic/suspected malignant ovarian cyst or pelvic tumour **Clinical setting:** mixed **Prior tests:** unclear but assume history and examination, and US from patient selection **Exclusions:** none **Centre:** multicentre	**n:** 638 **Postmenopausal n (%):** 348 (55) **Ovarian cancer n (%):** 162 (25) (EOC only) **Borderline n (%):** 31 (5) **Mean age:** benign 50.76 years, BOT 55.58 years, EOC 62.67 years **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Melo 2018 Portugal	**Study criteria:** women with adnexal neoplasia submitted to surgical treatment, with a histological diagnosis and in which ROMA had been determined **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** none reported but age group unclear **Centre:** single	**n:** 247 **Postmenopausal n (%):** 92 (37) **Ovarian cancer n (%):** 34 (14) **Borderline n (%):** 7 (3) **Age:** not reported **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Molina 2011 Spain	**Study criteria:** not reported **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 396 **Postmenopausal n (%):** 143 (36) **Ovarian cancer n (%):** 111 (28) **Borderline n (%):** not reported **Age:** not reported **Separated by menopausal status:** yes	**Thresholds:** pre-menopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Montagnana 2011 Italy	**Study criteria:** women with pelvic mass scheduled to have radical surgery **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** only EOC included	**n:** 104 **Postmenopausal n (%):** 53 (51) **Ovarian cancer n (%):** 55 (53) **Borderline n (%):** excluded	**Thresholds:** pre-menopausal 12.5, postmenopausal 14.4 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Centre: single	**Mean age:** malignant 56.9 years, benign 42 years **Separated by menopausal status:** yes	
Moore 2009 USA	**Study criteria:** women with ovarian cyst scheduled to undergo surgery **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** none **Centre:** multicentre	**n:** 513 **Postmenopausal n (%):** 150 (29) **Ovarian cancer n (%):** 143 (28) **Borderline n (%):** 22 (4) **Mean age:** 54 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Moore 2011 USA	**Study criteria:** women with ovarian cyst scheduled to undergo surgery **Clinical setting:** mixed **Prior test:** unclear **Exclusions:** none **Centre:** multicentre	**n:** 472 **Postmenopausal n (%):** 217 (46) **Ovarian cancer n (%):** 68 (14) **Borderline n (%):** 19 (4) **Mean age:** 50.3 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 13.1, postmenopausal 27.7 **Prespecified:** yes
Nikolova 2016 Macedonia	**Study criteria:** premenopausal women to have an USS confirming an ovarian cyst/mass and to undergo surgery **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** postmenopausal women **Centre:** single	**n:** 105 (analysed) **Postmenopausal n (%):** 0 **Ovarian cancer n (%):** 11 (10%) (EOC only) **Borderline n (%):** not reported **Mean age:** malignant 42.46 (SD 8.21) years, benign 36.90 (SD 10.12) years **Separated by menopausal status:** only premenopausal women included	**Thresholds:** premenopausal 7.4 **Prespecified:** yes
Novotny 2012 Czech Republic	**Study criteria:** women with pelvic abnormalities **Clinical setting:** secondary **Prior test:** unclear **Exclusions:** premenopausal women **Centre:** single	**n:** 256 **Postmenopausal n (%):** 256 (100) **Ovarian cancer n (%):** 21 (8) **Borderline n (%):** not reported **Mean age:** benign 65.28 years, malignant 64.37 years **Separated by menopausal status:** yes	**Thresholds:** postmenopausal 26.3 **Prespecified:** no
Ortiz-Munoz 2014 Spain	**Study criteria:** women with gynaecological symptoms, diagnosed with primary ovarian cancer **Clinical setting:** tertiary **Prior test:** symptoms	**n:** 148 **Postmenopausal n (%):** 104 (70) **Ovarian cancer n (%):** 29 (20) **Borderline n (%):** not reported	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Exclusions: none **Centre:** single	**Age:** not reported **Separated by menopausal status:** **yes	
Park 2019 Korea	**Study criteria:** women for whom gynaecologists had requested HE4, CA125 and ROMA tests to evaluate a pelvic mass **Clinical setting:** secondary **Prior test:** USS, CT or MRI **Exclusions:** 2 cases of non-EOC excluded from analysis **Centre:** single	**n:** 433 (biopsy 309; follow-up 134) **Postmenopausal n (%):** biopsy: 81 (26), follow-up: 37 (28) **Ovarian cancer n (%):** 18 (4) **Borderline n (%):** 15 (3) **Median age:** benign 43.0 (SD 21.0) years, malignant 52.3 (SD 6.1) years, BOT 47.8 (SD 12.9) years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Partheen 2011a Sweden	**Study criteria:** women with complex cystic mass and suspicious of malignancy undergoing surgery **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** solid and unilocular mass **Centre:** single	**n:** 374 **Postmenopausal n (%):** 276 (74) **Ovarian cancer n (%):** 108 (29) **Borderline n (%):** 45 (12) **Age:** not reported **Separated by menopausal status:** **yes	**Thresholds:** premenopausal 17.3, postmenopausal 26.0 **Prespecified:** yes
Prskalo 2015 Croatia	**Study criteria:** women with suspected adnexal mass on a TVS scheduled for elective surgery **Clinical setting:** mixed **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 159 **Postmenopausal n (%):** 102 (64) **Ovarian cancer n (%):** 43 (27) **Borderline n (%):** 11 (7) **Mean age:** premenopausal 36.9 (SD 8.9) years; postmenopausal 60.2 (SD 9.6) years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.7, postmenopausal 29.9 **Prespecified:** yes
Richards 2015 Australia	**Study criteria:** women who were undergoing surgery for a complex pelvic mass, presumed to be arising from the ovary **Clinical setting:** mixed **Prior tests:** unclear **Exclusions:** none reported **Centre:** single	**n:** 50 **Postmenopausal n (%):** 29 (58) **Ovarian cancer n (%):** 16 (32) (EOC only) **Borderline n (%):** 4 (8) **Median age:** 60 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Romagnolo 2016 Italy	**Study criteria:** women referred to gynaecological oncologist with a suspicious pelvic mass requiring surgery **Clinical setting:** tertiary	**n:** 387 **Postmenopausal n (%):** 148 (38)	**Thresholds:** premenopausal 13.1, postmenopausal 27.7

Table 4. Study characteristics: ROMA *(Continued)*

	Prior test: pelvic masses confirmed by USS prior to inclusion **Exclusions:** non-EOC **Centre:** multicentre	**Ovarian cancer n (%):** 73 (19) (EOC only) **Borderline n (%):** 15 (3.9) **Mean age:** premenopausal 37.6 (SD 8.6) years, postmenopausal 63 (SD 9.5) years **Separated by menopausal status:** yes	**Prespecified:** yes
Salim 2018 Pakistan	**Study criteria:** postmenopausal women with ovarian mass (> 2 cm) on pelvic ultrasound examination, attending gynaecology clinics, planned for surgical intervention **Clinical setting:** secondary **Prior test:** not reported **Exclusions:** only postmenopausal women included **Centre:** single	**n:** 260 **Postmenopausal n (%):** 260 (100) **Ovarian cancer n (%):** 122 (47) **Borderline n (%):** NR **Mean age:** 49.28 (SD 6.26) years **Separated by menopausal status:** only postmenopausal women included	**Thresholds:** postmenopausal 27.7 **Prespecified:** yes
Shen 2017 China	**Study criteria:** women referred to a participating centre with a pelvic mass or an ovarian cyst and planning to undergo surgery **Clinical setting:** mixed **Prior test:** pelvic USS, CT, MRI and the medical history (the diagnosis and treatment of pelvic mass and history of renal disease) **Exclusions:** none **Centre:** multicentre	**n:** 684 **Postmenopausal n (%):** 174 (25) **Ovarian cancer n (%):** 169 (25) (EOC + BOT) **Borderline n (%):** 18 (3) **Mean age:** 58.8 (SD 8.6) years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 7.4, postmenopausal 25.3 **Prespecified:** yes
Stiekma 2014 Netherlands	**Study criteria:** histologically confirmed EOC or benign ovarian disease referred to the institute **Clinical setting:** tertiary **Prior test:** unclear **Exclusions:** BOT **Centre:** single	**n:** 181 **Postmenopausal n (%):** 143 (79) **Ovarian cancer n (%):** 147 (81) **Borderline n (%):** excluded **Mean age:** benign 47 years, malignant 57 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 12.9, postmenopausal 27.8 **Prespecified:** yes
Teh 2018 Malaysia	**Study criteria:** women with pelvic mass(es) suspected of originating in the ovary who had been scheduled for surgery or radiological-guided biopsy **Clinical setting:** tertiary **Prior test:** not reported **Exclusions:** unclear; low malignant potential tumours were included in the benign tumour group for analysis	**n:** 129 **Postmenopausal n (%):** 27 (21) **Ovarian cancer n (%):** 27 (21) **Borderline n (%):** 10 (8) **Median age:** 37 (IQR 27.5–48.5) years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes

Table 4. Study characteristics: ROMA *(Continued)*

	Centre: single		
Terlikowska 2016 Poland	**Study criteria:** Caucasian women surgically treated on account of benign ovarian disease and epithelial cancer according to international treatment guidelines **Clinical setting:** mixed **Prior test:** not reported **Exclusions:** non-EOC **Centre:** multicentre	**n:** 224 **Postmenopausal n (%):** 104 (46) **Ovarian cancer n (%):** 96 (43) (EOC only) **Borderline n (%):** not reported **Median age:** premenopausal 36, postmenopausal 63 **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
van Gorp 2011 (van Gorp 2012 secondary publication; smaller cohort) Belgium	**Study criteria:** women diagnosed with pelvic mass undergoing surgery **Clinical setting:** unclear **Prior test:** unclear **Exclusions:** none **Centre:** single	**n:** 389 **Postmenopausal n (%):** 161 (41) **Ovarian cancer n (%):** 161 (41) **Borderline n (%):** not reported **Mean age:** benign 46.3 years, malignant 57.8 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 12.5, postmenopausal 14.4 **Prespecified:** yes
Xu 2016 China	**Study criteria:** women with a pelvic mass (defined as a simple, complex or solid ovarian cyst/pelvic mass) and healthy women from the Physical Examination Center **Clinical setting:** mixed **Prior test:** not reported **Exclusions:** non-EOC **Centre:** single	**n:** 566 **Postmenopausal n (%):** 159 (28) **Ovarian cancer n (%):** 210 (37) (EOC only) **Borderline n (%):** 45 (8) **Mean age:** benign 42 years, malignant 57 years **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Zhang 2015 China	**Study criteria:** all women scheduled for surgery, with and without pelvic mass on USS **Clinical setting:** unclear **Prior test:** USS; adnexal lesions reported according to IOTA **Exclusions:** non-EOC excluded **Centre:** multicentre	**n:** 612 **Postmenopausal n (%):** 232 (37) **Ovarian cancer n (%):** 264 (43) (EOC only) **Borderline n (%):** not reported **Median age (25th centile, 75th centile):** benign: premenopausal 41 (35, 46), postmenopausal 57 (54, 68); malignant premenopausal 43 (38, 47), postmenopausal 59 (54, 65) **Separated by menopausal status:** yes	**Thresholds:** premenopausal 11.4, postmenopausal 29.9 **Prespecified:** yes
Zhang 2019 China	**Study criteria:** women with ovarian tumour **Clinical setting:** tertiary **Prior test:** unclear	**n:** 373 **Postmenopausal n (%):** 185 (50) **Ovarian cancer n (%):** 181 (48)	**Thresholds:** premenopausal 11.4, postmenopausal 29.9

Table 4. Study characteristics: ROMA *(Continued)*

	Exclusions: borderline excluded from analysis **Centre:** single	**Borderline n (%):** 17 (5) **Mean age:** 51 years **Separated by menopausal status:** yes	**Prespecified:** yes

*ROMA thresholds most commonly reported and included: **premenopausal** 7.4 (± 2); 12.5; 13.1 (± 2); **postmenopausal** 25.3 (± 2); 14.4; 27.7 (± 2)
**Threshold for premenopausal women OR postmenopausal women reported in the study not included in analysis.
BOT: borderline ovarian tumour; CT: computed tomography; EOC: epithelial ovarian cancer; HE4: Human Epididymis protein; IQR: interquartile range; IOTA: International Ovarian Tumour Analysis; MRI: magnetic resonance imaging; n: number of participants; PET-CT: positron emission tomography–computed tomography; ROMA: Risk of Ovarian Malignancy Algorithm; ROMA-P: a modified ROMA; TVS: transvaginal ultrasound; USS: ultrasound scan.

Table 5. Study characteristics: LR2

Author year country	Setting*	Participant characteristics	Index test threshold
Meys 2017 **Netherlands**	**Study criteria**: women with adnexal pathology **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 326 **Postmenopausal n (%):** 198 (61) **Ovarian cancer n (%):** 115 (35) **Borderline n (%):** 27 (8) **Median age:** malignant 67.7 (IQR 32.3–87) years, borderline 53.2 (016.1–87.2) years **Separated by menopausal status:** yes	**Threshold:** 10% post-test probability of malignancy **Prespecified:** yes
Niemi 2017 **Finland**	**Study criteria**: women aged > 50 years presenting with an abnormal adnexal mass(es) **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** overtly benign or malignant-appearing tumours such as unilocular simple ovarian cysts and tumours associated with marked ascites (depth of the greatest pool > 10 cm) **Centre:** single	**n:** 98 **Postmenopausal n (%):** 98 (100) **Ovarian cancer n (%):** 23 (23) **Borderline n (%):** 7 (7) **Median age:** 61 (range 50–84) years **Separated by menopausal status:** only postmenopausal included	**Threshold:** 10%, 25% and 43% of post-test probability of malignancy **Prespecified:** yes
Sayasneh 2013a **Secondary study:** Sayasneh 2013 (see under Sayasneh 2013a) **UK**	**Study criteria:** women presenting with adnexal mass and undergoing surgery within 120 days after examination **Clinical setting:** mixed secondary and tertiary care **Prior tests:** not reported **Exclusions:** none reported **Centre:** multicentre	**n:** 255 **Postmenopausal n (%):** 117 (45.9) **Malignant n (%):** 48 (18.8) **Borderline n (%):** 18 (7.1) **Mean age:** 46 years **Separated by menopausal status:** yes	**Threshold:** 10% post-test probability of malignancy **Prespecified threshold:** yes

Table 5. Study characteristics: LR2 *(Continued)*

Testa 2014 **Europe**	**Study criteria:** women presenting with adnexal mass on TVS and undergoing surgery within 120 days. **Clinical setting:** mixed secondary and tertiary care **Prior tests:** not reported **Exclusions:** none reported **Centre:** multicentre	**n:** 2403 **Postmenopausal n (%):** 1049 (43.7) **Malignant n (%):** 701(18.8) **Borderline n (%):** 153 (6.4) **Median age:** malignant 57 (range 33–66) years; benign 44 (range not reported) years **Separated by menopausal status:** yes	**Threshold:** 10% post-test probability of malignancy **Prespecified threshold:** yes
Timmerman 2010 Secondary study: Di Legge 2012 **Europe**	**Study criteria:** women with persistent adnexal mass undergoing surgery within 120 days **Clinical setting:** mixed secondary and tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** multicentre	**n:** 1938 **Postmenopausal n (%):** 742 (38.0) **Malignant n (%):** 373 (19.2) **Borderline n (%):** 111 (5.7) **Mean age:** 46 years **Separated by menopausal status:** yes	**Threshold:** 10% post-test probability of malignancy **Prespecified threshold:** yes

*Setting: secondary care: dedicated gynaecologist in a general hospital; tertiary care: gynaecological oncology centre.
IQR: interquartile range; n: number of participants; TVS: transvaginal ultrasound.

Table 6. Study characteristics: ADNEX

Author year country	Setting*	Participants characteristics	Index test threshold
Meys 2017 **Netherlands**	**Study criteria**: women with adnexal pathology **Clinical setting:** tertiary **Prior tests:** not reported **Exclusions:** none reported **Centre:** single	**n:** 326 **Postmenopausal n (%):** 198 (61) **Ovarian cancer n (%):** 115 (35) **Borderline n (%):** 27 (8) **Median age:** benign 53.2 (IQR 16.1–87.2) years, malignant 67.7 (IQR 32.3–87) years **Separated by menopausal status:** yes	**Threshold:** 10% post-test probability of malignancy **Prespecified:** yes
Szubert 2016a **Poland**	**Study criteria:** women with a 'need for surgery due to an ovarian tumour' **Clinical setting:** unclear, probably tertiary **Prior test:** not reported **Exclusions:** none reported **Centre:** single	**n:** 204 **Postmenopausal n (%):** 66 (54) **Ovarian cancer n (%):** 58 (28) **Borderline n (%):** 12 (6) **Median age:** 46 **Separated by menopausal status:** yes	**Thresholds:** 2000 IOTA criteria 10% **Prespecified: y**es

Table 6. Study characteristics: ADNEX *(Continued)*

Szubert 2016b **Spain**	**Study criteria:** women with a 'need for surgery due to an ovarian tumour' **Clinical setting:** unclear, probably tertiary **Prior test:** not reported **Exclusions:** none reported **Centre:** single	**n:** 128 **Postmenopausal n (%):** 52 (42) **Ovarian cancer n (%):** 35 (27) **Borderline n (%):** 4 (3) **Median age:** 47 years **Separated by menopausal status:** yes	**Thresholds:** 2000 IOTA criteria 10% **Prespecified:** yes
van Calster 2014 **Europe**	**Study criteria:** women presenting with adnexal mass on US and selected for surgery **Clinical setting:** mixed secondary and tertiary care **Prior tests:** not reported **Exclusions:** none reported **Centre:** multicentre	**n:** 2403 **Postmenopausal n (%):** 1049 (43.7)** **Malignant n (%):** 827 (34.4) **Borderline n (%):** 153 (6.4) **Age:** not reported **Separated by menopausal status:** yes**	**Threshold:** 3, 5, 10 and 15% post-test probability of malignancy **Prespecified threshold:** yes

*Setting: secondary care: dedicated gynaecologist in a general hospital; tertiary care: gynaecological oncology centre.
**Contact with authors
IOTA: International Ovarian Tumour Analysis; IQR: interquartile range; n: number of participants.

Table 7. HSROC analysis: comparison of sensitivity at a fixed specificity of 80% and 90%: all studies, all thresholds, pre- and postmenopausal women separately

HSROC analysis: comparison of ROMA, LR2 and ADNEX compared to RMI I. Mixed test positivity threshold analysis at fixed specificities of 80% and 90%									
Test	**Studies**	**Partici-pants (OC cases)**	**Diagnostic odds ratio (95% CI)**	**Relative di-agnostic odds ratio (95% CI)**	**P value**	**Sensitivity at fixed specificity of 80%**		**Sensitivity at fixed specificity of 90%**	
						Sensitivity (95% CI)	**Difference from RMI I (95% CI)**	**Sensitivity (95% CI)**	**Difference from RMI I (95% CI)**
Premenopausal									
RMI I 200/250	19	5694 (893)	15.5 (9.0 to 26.5)	—	—	79.4 (69.5 to 86.7)	—	65.1 (57.2 to 72.2)	—
ROMA mixed	38	7616 (1198)	18.5 (14.3 to 23.9)	1.19 (0.69 to 2.07)	0.5202	82.0 (77.9 to 85.5)	2.6 (–5.5 to 10.7)	68.8 (61.8 to 75.0)	3.7 (–7.3 to 14.7)
LR2	4	2843 (619)	33.9 (21.5 to 53.3)	2.19 (1.18 to 4.06)	0.014	89.0 (83.8 to 92.7)	9.6 (2.2, 17.0)	79.7 (71.3 to 86.1)	14.6 (5.6 to 23.6)
ADNEX 10%	4	1696 (455)	72.6 (29.4 to 179.2)	4.70 (1.45 to 15.20)	0.0108	94.4 (88.3 to 7.4)	14.9 (5.4 to 24.5)	89.0 (77.6 to 95.0)	23.9 (12.0 to 35.8)
Postmenopausal									
RMI I 200/250	19	4589 (1761)	22.8 (17.3 to 30.1)	—	—	85.1 (80.9 to 88.5)	—	71.8 (65.4 to 77.4)	—
ROMA mixed	40	6099 (2746)	40.0 (31.5 to 50.8)	1.75 (1.23 to 2.50)	0.0024	90.9 (88.8 to 92.7)	5.8 (2.1 to 9.6)	81.7 (76.8 to 85.7)	9.9 (4.0 to 15.8)
LR2 10%	5	2157 (1124)	39.5 (22.6 to 69.0)	1.73 (0.97 to 3.09)	0.0622	90.8 (85.9 to 94.1)	5.7 (0.7 to 10.7)	81.5 (70.0 to 89.2)	9.7 (2.0 to 17.4)
ADNEX 10%	4	1365 (749)	56.7 (21.9 to 146.8)	2.48 (0.90 to 6.85)	0.0776	93.4 (85.9 to 97.1)	8.3 (1.5 to 15.1)	86.3 (70.2 to 94.4)	14.6 (3.4 to 25.7)

Notes to table: ADNEX 10% & LR2 10%: threshold to achieve a post-test probability of ovarian cancer of 10%. ADNEX and LR2 studies reported a range of thresholds but all included a threshold of 10%. For RMI I and ROMA studies, each included study contributed a different test positivity threshold.
ADNEX: Assessment of Different NEoplasias in the adneXa model; CI: confidence interval; HSROC: hierarchical summary receiver operating characteristic; LR2: Logistic Regression Model 2; OC: ovarian cancer; RMI I: Risk of Malignancy Index I; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 8. Bivariate comparisons of ROMA, LR2 and ADNEX compared to RMI I in premenopausal women

Bivariate model-pairwise comparisons: premenopausal women					
Absolute sensitivity difference (95% CI); P value for comparison **Absolute specificity difference (95% CI); P value for comparison**			**RMI I** **(200)**	**ROMA** **(13.1 ± 2)**	**LR2** **(10)**
		Studies (participants)	17 (5233)	27 (4463)	4 (2843)
		Sensitivity % (95% CI)	57.2 (50.3 to 63.8)	77.4 (72.7 to 81.5)	83.3 (74.7 to 89.5)
		Specificity % (95% CI)	92.5 (90.3 to 94.2)	84.3 (81.2 to 87.0)	90.4 (84.6 to 94.1)
	Studies (participants)				
ROMA (13.1 ± 2)	27 (4463)	77.4 (95% CI 72.7 to 81.5) 84.3 (95% CI 81.2 to 87.0)	20.2 (12.2 to 28.3); P < 0.0001 −8.2 (−11.7 to −4.7); P < 0.0001	—	—
LR2 (10)	4 (2843)	83.3 (95% CI 74.7 to 89.5) 90.4 (95% CI 84.6 to 94.1)	26.2 (16.2 to 36.2); P < 0.0001 −2.1 (−7.2 to 2.9); P = 0.404	6.0 (−2.6 to 14.5); P = 0.170 6.1 (0.6 to 11.5); P = 0.029	—
ADNEX (10)	4 (1696)	95.5 (95% CI 91.0 to 97.8) 77.8 (95% CI 67.4 to 85.5)	38.3 (30.9 to 45.8); P < 0.0001 −14.8 (−24.0 to −5.5); P = 0.002	18.1 (12.7 to 23.5); P = 0.0001 −6.5 (−16.0 to 3.0); P = 0.178	12.1 (4.2 to 20.1); P = 0.003 −12.6 (−22.8 to −2.4); P = 0.015

ADNEX: Assessment of Different NEoplasias in the adneXa model; CI: confidence interval; LR2: Logistic Regression Model 2; OC: ovarian cancer; RMI I: Risk of Malignancy Index I; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 9. Bivariate comparisons of ROMA, LR2 and ADNEX compared to RMI I in postmenopausal women

Bivariate model-pairwise comparisons: postmenopausal women				
Absolute sensitivity difference (95% CI); Pvalue for comparison		**RMI I** **(200)**	**ROMA** **(27.7 ± 2)**	**LR2** **(10)**

Table 9. Bivariate comparisons of ROMA, LR2 and ADNEX compared to RMI I in postmenopausal women *(Continued)*

		Studies (participants)	17 (4369)	13 (2002)	5 (2157)
		Sensitivity % (95% CI) **Specificity % (95% CI)**	78.4 (74.6 to 81.7) 85.4 (82.0 to 88.2)	90.3 (87.5 to 92.6) 81.5 (76.5 to 85.5)	94.8 (92.3 to 96.6) 60.6 (50.5 to 69.9)
	Studies (participants)				
ROMA (27.7 ± 2)	13 (2002)	90.3 (87.5 to 92.6) 81.5 (76.5 to 85.5)	11.9 (7.6 to 16.3); P < 0.0001 −3.9 (−9.4 to 1.5); P = 0.157	—	—
LR2 (10)	5 (2157)	94.8 (92.3 to 96.6) 60.6 (50.5 to 69.9)	16.4 (12.3 to 20.5); P < 0.0001 −24.8 (−35.1 to −14.5); P < 0.0001	4.5 (1.2 to 7.8); P = 0.008 −20.9 (−31.7 to −10.1); P < 0.0001	—
ADNEX (10)	4 (1365)	97.6 (95.6 to 98.7) 55.0 (42.8 to 66.6)	19.2 (15.4 to 23.1); P < 0.0001 −30.4 (−42.9 to −17.9); P < 0.0001	7.3 (4.3 to 10.2); P < 0.0001 −26.5 (−39.4 to −13.6); P < 0.0001	2.8 (0.2 to 5.3); P = 0.034 −5.6 (−21.2 to 10.0); P = 0.480

ADNEX: Assessment of Different NEoplasias in the adneXa model; CI: confidence interval; LR2: Logistic Regression Model 2; OC: ovarian cancer; RMI I: Risk of Malignancy Index I; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 10. Sensitivity analysis: borderline ovarian tumours

Sensitivity analysis:sensitivity at fixed specificities of 80% and 90% for RMI I and ROMA (all thresholds) for studies grouping borderline ovarian tumours with malignant for the estimation of test accuracy (BOT=1) compared to studies that excluded borderline tumours or where their management for the estimation of test accuracy was unclear (BOT=2/3)

Test	Studies	Participants	OC Cases	DOR (95% CI)	Relative DOR (95% CI)	P value	Sensitivity at fixed specificity of 80%		Sensitivity at fixed specificity of 90%	
							Sensitivity (95% CI)	Difference from BOT=1 (95% CI)	Sensitivity (95% CI)	Difference from BOT=1 (95% CI)
Premenopausal										
RMI I 200/250										
BOT=1	16	4861	801	11.7 (5.3 to 25.9)	—	—	74.9 (59.6 to 85.8)	—	62.2 (53.1 to 70.5)	—
BOT=2/3	3	833	92	11.5 (4.2 to 31.6)	0.98 (0.37 to 2.60)	0.9699	74.6 (55.0 to 87.6)	−0.3 (−16.1 to 15.5)	61.8 (43.3 to 77.4)	−0.4 (−20.1 to 19.4)
ROMA mixed thresholds										
BOT=1	15	2737	363	13.9 (9.0 to 21.7)	—	—	77.6 (69.1 to 84.3)	—	59.2 (47.0 to 70.3)	—
BOT=2/3	23	4879	835	22.3 (15.9 to 31.3)	1.60 (0.94 to 2.74)	0.0837	84.9 (79.7 to 89.0)	7.4 (−1.2 to 15.9)	70.2 (60.3 to 78.6)	11.1 (−1.3 to 23.5)
Postmenopausal										
ROMA mixed thresholds										
BOT=1	15	2289	882	27.4 (18.6 to 40.4)	—	—	87.7 (82.3 to 91.7)	—	72.4 (59.6 to 82.4)	—
BOT=2/3	25	3810	1864	56.3 (40.5 to 78.1)	2.06 (1.24 to 3.40)	0.0062	94.1 (91.3 to 96.0)	6.4 (1.2, 11.5)	85.4 (79.6 to 89.8)	13.0 (1.9 to 24.0)

BOT=1: borderline tumours grouped with malignant ovarian tumours for estimation of test accuracy; BOT=2/3: borderline tumours excluded, grouped with benign or management unclear for estimation of test accuracy; CI: confidence interval; DOR: diagnostic odds ratio; OC: ovarian cancer; RMI: Risk of Malignancy Index; ROMA: Risk of Ovarian Malignancy Algorithm.

Table 11. Excluded studies: no 2 × 2 table

No 2 × 2 table
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Table 11. Excluded studies: no 2 × 2 table *(Continued)*

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Table 11. Excluded studies: no 2 × 2 table *(Continued)*

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Table 12. Excluded studies: data not reported separately by menopausal status *(Continued)*

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Auekitrungreung, 2019 (not found in end note)

Table 13. Excluded studies: duplicate data reporting

Duplicate data reporting
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Table 14. Excluded studies: full text not available

Full text not available
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Table 14. Excluded studies: full text not available *(Continued)*

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Table 15. Excluded studies: index test not applicable

Index test not applicable
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Table 15. Excluded studies: index test not applicable *(Continued)*

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Table 17. Excluded studies: population not applicable *(Continued)*

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Table 18. Excluded studies: publication pre-1991

Publication pre 1991
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Table 18. Excluded studies: publication pre-1991 *(Continued)*

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Table 19. Excluded studies: study design

Study design
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Table 20. Excluded studies: test positivity threshold

Test positivity threshold
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APPENDICES

Appendix 1. Search strategies 2015

1. OVARIAN CANCER – ULTRASOUND/IOTA

Database: MEDLINE (Ovid) 1946 to April Week 3 2015

1 exp Ovarian Neoplasms/di
2 exp Adnexal Diseases/di
3 ((borderline or border line) adj4 ovar$).tw.

4 exp Fallopian Tube Neoplasms/di
5 exp Peritoneal Neoplasms/di
6 exp Pelvic Neoplasms/di
7 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 exp ultrasonography/
11 ultraso$.tw.
12 (transvagina$ adj2 sonogra$).tw.
13 or/10-12
14 9 and 13
15 limit 14 to (human and yr=1991-2015)
16 IOTA.tw.
17 International Ovarian Tumor Analysis.tw.
18 ((ovarian or epithelial or adnex$ or fallopian or peritoneal or pelvic) adj3 (model$ or regress$ or rule$ or score$ or algorithm$ or term $ or definition$ or measure$)).ti,ab.
19 or/16-18
20 9 and 19
21 limit 20 to human
22 15 or 21

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations 27 April 2015

1 ((borderline or border line) adj4 ovar$).tw.
2 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
3 ((epithelial or germ cell) adj5 ovar$).tw.
4 or/1-3
5 ultraso$.tw.
6 (transvagina$ adj2 sonogra$).tw.
7 or/5-6
8 4 and 7
9 limit 8 to yr="1991-2015"
10 IOTA.tw.
11 International Ovarian Tumor Analysis.tw.
12 ((ovarian or epithelial or adnex$ or fallopian or peritoneal or pelvic) adj3 (model$ or regress$ or rule$ or score$ or algorithm$ or term $ or definition$ or measure$)).ti,ab.
13 or/10-12
14 4 and 13
15 9 or 14

Database: Embase (Ovid) 1974 to 27 April 2015

1 ((borderline or border line) adj4 ovar$).tw.
2 uterine tube tumor/di [Diagnosis]
3 peritoneum tumor/di [Diagnosis]
4 pelvis tumor/di [Diagnosis]
5 ovary tumor/di [Diagnosis]
6 adnexa disease/di [Diagnosis]
7 ((ovar$ or adnexal or fallopian or peritoneal or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 ultraso$.tw.
11 (transvagina$ adj2 sonogra$).tw.
12 ultrasound/
13 or/10-12
14 9 and 13
15 limit 14 to (humans and yr="1991-2015")
16 IOTA.tw.
17 International Ovarian Tumor Analysis.tw.

18 ((ovarian or epithelial or adnex$ or fallopian or peritoneal or pelvic) adj3 (model$ or regress$ or rule$ or score$ or algorithm$ or term $ or definition$ or measure$)).tw.
19 or/16-18
20 9 and 19
21 15 or 20
22 limit 21 to humans

Database: Cochrane Library (Wiley) 27 April 2015 CENTRAL, CDSR Issue 4 of 12, HTA DARE Issue 2 of 4 2015

#1 borderline near/4 ovar*
#2 "border line" near/4 ovar*
#3 MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#4 MeSH descriptor: [Pelvic Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#5 MeSH descriptor: [Ovarian Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#6 MeSH descriptor: [Adnexal Diseases] explode all trees and with qualifier(s): [Diagnosis - DI]
#7 (ovar* or adnexal or fallopian or peritoneal or pelvic) near/3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumor* or tumour*)
#8 (epithelial or "germ cell") near/5 (ovar*)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 ultraso*
#11 MeSH descriptor: [Ultrasonography] explode all trees
#12 transvagina* near/2 sonogra*
#13 #10 or #11 or #12
#14 #9 and #13 Publication Year from 1991 to 2015
#15 IOTA
#16 "International Ovarian Tumor Analysis"
#17 (ovarian or epithelial or adnex* or fallopian or peritoneal or pelvic*) near/3 (model* or regress* or rule* or score* or algorithm* or term* or definition* or measure*)
#18 #15 or #16 or #17
#19 #9 and #18
#20 #14 or #19

Database: CINAHL (EBSCO) 1960 – 27 April 2015

S1 (borderline or border-line) N4 (ovar*)
S2 (MH “Fallopian Tube Diseases+/DI)
S3 (MH “Peritoneal Neoplasms+/DI)
S4 (MH “Pelvic Neoplasms/DI”)
S5 (MH “Ovarian Neoplasms+/DI”
S6 (MH “Adnexal Diseases/DI”
S7 (ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
S8 (epithelial or germ cell) N1 (ovar*)
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 “ultraso*”
S11 (MH”Ultrasonography+)
S12 transvagina* N2 sonogra*
S13 S10 or S11 or S12
S14 S9 and S13 Limiters – Publication Year: 1991 – 2015
S15 “IOTA” or “international ovarian tumor analysis”
S16 (ovarian or epithelial or adnex*) N5 (model* or regress* or rule* or score* or algorithm* or term* or definition* or measure*)
S17 S15 or S16
S18 S17 or S14

Database: Science Citation Index (Web of Science) 1900 to 23 April 2015

#1 TS=(borderline ovar* or border line ovar*)
#2 TS=((ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
#3 TS=(((epithelial or “germ cell”)) near/1 (ovar*)
#4 #3 or #2 or #1
#5 TS=ultraso*
#6 TS=(transvagina* near/2 sonogra*)

#7 TS=#5 or #6
#8 TS=IOTA
#9 TS=(ovarian or epithelial or adnex*) near/2 (model* or regress* or rule* or score* or algorithm* or term* or definition* or measure*)
#10= #8 or #9
#11 #4 and #7 Indexes= SCI-EXPANDED Timespan= 1991-2015
#12 #10 and #4 Indexes= SCI-EXPANDED Timespan= 1991-2015
#13 #11 or #12

Database: Conference Proceedings Citation Index (CPCI) (Web of Science) 1900 to 24 April 2015

As Science Citation Index above. Searched 24 April 2015

2. OVARIAN CANCER SYMPTOM SCORES

Database: MEDLINE (Ovid) 1946 to March Week 4 2015

1 exp ovarian neoplasms/di
2 exp adnexal diseases/di
3 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumor$ or tumour$)).tw.
4 ((borderline or border line) adj4 ovar$).tw.
5 exp Fallopian Tube Neoplasms/di
6 exp Peritoneal Neoplasms/di
7 exp pelvic neoplasms/di
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 exp "Signs and Symptoms"/
11 symptom$.ti,ab.
12 exp early diagnosis/ or exp Diagnosis/
13 exp "Early Detection of Cancer"/
14 (early adj (sign$ or symptom$)).tw.
15 (abdom$ adj3 (pressure or pain$ or swelling$ or hard)).tw.
16 (bowel irregularit$ or bloat$ or fullness or satiet$ or gastro$).tw.
17 (fatigue or weight loss$ or weight gain$ or constipat$ or diarrhoea or diarrhea or gas).tw.)
18 (nausea$ or indigestion).tw.
19 ((loss or lack) adj3 (energ$ or appetite$)).tw.
20 (urin$ adj3 (frequenc$ or urgenc$)).tw.
21 ((leg$ or ankle$) adj2 (swell$ or swollen)).tw.
22 ((abnormal or irrregular or postmenopausal) adj1 vaginal adj (bleed$ or discharge$)).tw.
23 (pelvic discomfort$ or pelvic pain$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
24 or/10-22
25 9 and 24
26 (index or risk$ or score$ or scoring or checklist$ or rule$ or indices or tool$ or instrument$ or survey$ or questionnaire$ or interview$).tw.
27 25 and 26
28 limit 27 to (humans and yr="2009 - 2015")

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations 20 March 2015

1 ((borderline or border line) adj4 ovar$).tw.
2 ((ovar$ or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
3 ((epithelial or germ cell) adj5 ovar$).tw.
4 or/1-3
5 (symptom$ or sign$).tw.
6 (early adj2 (sign$ or detect$ or diagnos$)).tw.
7 (abdom$ adj3 (pressure or pain$ or swelling$ or hard)).tw.
8 (bowel irregularit$ or bloat$ or fullness or satiet$ or gastro$).tw.
9 (fatigue or weight loss or weight gain$ or constipat$ or diarrhoea or diarrhea or gas).tw.
10 nausea$ or indigestion.tw.
11 ((lack or loss) adj3 (energ$ or appetite$)).tw.
12 (urin$ adj3 (frequenc$ or urgenc$)).tw.
13 ((leg$ or ankle$) adj2 (swell$ or swollen)).tw.
14 ((abnormal or irregular$ or postmenopausal) adj1 vaginal adj (bleed$ or discharge$)).tw.

15 (pelvic discomfort$ or pelvic pain$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
16 or/5-15
17 (index or risk$ or score$ or scoring or checklist$ or rule$ or indices or tool$ or instrument$ or survey$ or questionnaire$ or interview$).tw.
18 4 and 16 and 17
19 limit 18 to yr="2009 - 2015"

Database: Embase (Ovid) 1974 to 27 March 2015

1 ((ovar$ or adnexal or fallopian or peritoneal or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
2 ((epithelial or germ cell) adj ovar$).tw.
3 ((borderline or border line) adj4 ovar$).tw.
4 uterine tube tumor/di
5 peritoneum tumor/di
6 pelvis tumor/di
7 ovary tumor/di [Diagnosis]
8 adnexa disease/di
9 or/1-8
10 symptom/ or symptom$.tw.
11 early diagnosis/
12 diagnosis/
13 (early adj (sign$ or symptom$)).tw.
14 (abdom$ adj3 (pressure or pain$ or swelling$ or hard)).tw.
15 (bowel irregularit$ or bloat$ or fullness or satiet$ or gastro$).tw.
16 (fatigue or weight loss$ or weight gain$ or constipat$ or diarrhoea or diarrhea or gas).tw.
17 nausea$.mp. or indigestion.tw.
18 ((loss or lack) adj3 (energ$ or appetit$)).tw.
19 (urin$ adj3 (frequenc$ or urgenc$)).tw.
20 ((leg$ or ankle$) adj2 (swell$ or swollen)).tw.
21 ((abnormal or irregular or postmenopausal) adj1 vaginal adj (bleed$ or discharge$)).tw.
22 (pelvic discomfort$ or pelvic pain$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
23 or/10-22
24 9 and 23
25 (index or risk$ or score$ or scoring or checklist$ or rule$ or indices or tool$ or instrument$ or survey$ or questionnaire$ or interview$).tw.
26 24 and 25
27 limit 26 to (human and yr="2009 - 2015")

Database: Cochrane Library (Wiley) 23 February 2015 CENTRAL, CDSR Issue 1 of 12 HTA DARE Issue 1 of 4 2015

#1 borderline near/4 ovar*
#2 "border line" near/4 ovar*
#3 MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#4 MeSH descriptor: [Pelvic Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#5 MeSH descriptor: [Ovarian Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#6 MeSH descriptor: [Adnexal Diseases] explode all trees and with qualifier(s): [Diagnosis - DI]
#7 (ovar* or adnexal or fallopian or peritoneal or pelvic) near/3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumor* or tumour*)
#8 (epithelial or "germ cell") next (ovar*)
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Signs and Symptoms] explode all trees
#11 MeSH descriptor: [Early Diagnosis] explode all trees
#12 early near/1 (sign* or symptom*)
#13 (abdom*) near/3 (pressure* or pain* or swelling or hard)
#14 bloat* or fullness or satiet* or gastro*
#15 bowel next irregular*
#16 fatigue or "weight loss" or "weight gain" or constipat* or diarrhoea or diarrhea or gas or nausea* or indigestion
#17 (loss or lack) near/3 (appetit*)
#18 (urin*) near/3 (frequenc* or urgenc*)
#19 Leg* or ankle* near/2 (swell* or swollen)
#20 (loss or lack) near/3 (energy)
#21 (abnormal or irregular or postmenopausal) near/1 (vaginal) near/1 (bleed* or discharge*)
#22 "pelvic discomfort" or "pelvic pain" or "chest pain*" or "respirator* difficult*" or "lower back pain"
#23 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #20 or #21 or #22

#24 #9 and #23
#25 index* or risk* or score* or scoring or checklist* or rule* or indices or tool* or instrument* or survey* or questionnaire* or interview*
#26 #24 and #25 Publication Year from 2009 to 2015

Database: CINAHL (EBSCO) 1960 – 23 February 2015

S1 (borderline or border-line) N4 (ovar*)
S2 (MH "Fallopian Tube Diseases+/DI)
S3 (MH "Peritoneal Neoplasms+/DI)
S4 (MH "Pelvic Neoplasms/DI")
S5 (MH "Ovarian Neoplasms+/DI"
S6 (MH "Adnexal Diseases/DI"
S7(ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
S8 (epithelial or germ cell) N1 (ovar*)
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 (MH "Symptoms")
S11 (MH "Early Diagnosis+")
S12 (MM"Diagnosis")
S13 early warning sign*
S14 (abdom*) N5 (pressure or pain* or swelling or hard*)
S15 bowel irregularit* or bloat* or fullness or satiet* or gastro*
S16 fatigue or weight loss* or weight gain* or constipat* or diarrhoea or gas or nausea* or indigestion
S17 loss N1 appetit*
S18 Lack N1 energy
S19 urin* N3 (frequenc* or urgenc*)
S20 Leg N2 (swell* or swollen)
S21 (abnormal or irregular or postmenopausal) N1 (vaginal bleed*) or (vaginal discharge*)
S22 pelvic discomfort* or pelvic pain* or chest pain* or respirator* difficult* or lower back pain
S23 S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
S24 S9 and S23
S25 index or risk* or score* or scoring or checklist* or rule* or indices or tool or instrument* or survey* or questionnaire* or interview*
S26 S24 and S25
S27 S24 and S25 Limiters – Publication Year: 2009-2015

Science Citation Index (Web of Science) 1900 to 23 February 2015

#1 TS=(borderline ovar* or border line ovar*)
#2 TS=((ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
#3 TS=(((epithelial or "germ cell")) near/1 (ovar*)
#4 #3 or #2 or #1
#5 TS=symptom*
#6 TS="early diagnosis"
#7 TS="early warning sign*"
#8 TS=(((abdom*) near/5 (pressure* or pain* or swelling* or hard)))#9 TS=((bowel irregularit* or bloat* or fullness or satiet* or gastro*))
#10 TS=((fatigue or weight loss or weight gain or constipat* or diarrhoea or gas or nausea or indigestion))
#11 TS=((loss near/1 appetit*))
#12 TS=((lack near/1 energ*))
#13 TS=((urin*) near/3 (frequenc* or urgenc*))
#14 TS=((leg) near/2 (swell* or swollen)
#15 TS=(("pelvic discomfort" or "pelvic pain" or "chest pain" or respirator* difficult* or "lower back pain"))
#16 TS=((index or risk* or score* or scoring or checklist* or rule* or indices or tool* or instrument* or survey* or questionnaire* or interview*))
#17 #15 or #14 or #13 or #12 or #11 or #10 or #9 or #8 or #7 or #6 or #5
#18 #17 and #16 and #4 Limited: 2009-2015

Database: Conference Proceedings Citation Index (CPCI) (Web of Science) 1900 to 23 February 2015

As Science Citation Index above.

3. OVARIAN CANCER BIOMARKERS

Database: MEDLINE (Ovid) 1946 to April Week 3 2015

1 exp Ovarian Neoplasms/di
2 exp Adnexal Diseases/di
3 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
4 ((borderline or border line) adj4 ovar$).tw.
5 exp Fallopian Tube Neoplasms/di
6 exp Peritoneal Neoplasms/di
7 exp Pelvic Neoplasms/di
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 exp Tumor Markers, Biological/
11 exp Biological Markers/
12 Proteomics/
13 Genetic Markers/
14 Metabolomics/
15 multiplex$.tw.
16 multivariate.tw.
17 (CA125 or CA-125 or HE4 or OVA 1 or OVA1 or HCG or LDH or AFP).mp. or CEA.tw. [
18 CA-125 Antigen/
19 Chorionic Gonadotropin/
20 L-Lactate Dehydrogenase/
21 alpha-Fetoproteins/
22 Carcinoembryonic Antigen/
23 or/10-22
24 9 and 23
25 limit 24 to (humans and yr="1991-2015")

Database: MEDLINE (Ovid) In-Process & Other Non-Indexed Citations April 23, 2015

1 ((borderline or border line) adj4 ovar$).tw.
2 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
3 ((epithelial or germ cell) adj5 ovar$).tw.
4 or/1-3
5 ((genetic or protein$) adj1 assay$).ti,ab.
6 multiplex.ti,ab.
7 ((multivariate or multimarker$) adj2 assay$).ti,ab.
8 (biomarker$ or marker$ or metabolomic$ or proteomic$ or lipomic$ or kallikrein$ or genomic$).ti,ab.
9 (CA125 or CA-125 or HE4 or OVA1 or OVA 1 or HCG or LDH or AFP).mp. or CEA.tw.
10 CA-125 antigen.tw.
11 chorionic gonadotropin.tw.
12 L-lactate dehydrogenase.tw.
13 alpha-fetoprotein$.tw.
14 carcinoembryonic antigen$.tw.
15 or/5-14
16 4 and 15
17 limit 16 to yr="1991 - 2015"

Database: EMBASE (Ovid) 1974 to 23 April 2015

1 ((borderline or border line) adj4 ovar$).tw.
2 uterine tube tumor/di [Diagnosis]
3 peritoneum tumor/di [Diagnosis]
4 pelvis tumor/di [Diagnosis]
5 ovary tumor/di [Diagnosis]
6 adnexa disease/di [Diagnosis]
7 ((ovar$ or adnexal or fallopian or peritoneal or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 multiplex$.tw.

11 ((multivariate or multimarker$) adj2 assay$).ti,ab.
12 exp tumor marker/
13 exp biological marker/
14 exp proteomics/
15 exp genetic marker/
16 exp metabolomics/
17 (CA125 or CA-125 or HE4 or OVA1 or OVA 1 or HCG or LDH or AFP).mp. or CEA.tw.
18 or/10-17
19 9 and 18
20 limit 19 to (humans and yr="1991-2015")

Database: Cochrane Library (Wiley) 23 April 2015 CENTRAL, CDSR Issue 4 of 12 HTA, DARE, Issue 2 of 4 2015

#1 borderline near/4 ovar*
#2 border next line near/4 ovar*
#3 MeSH descriptor: [Fallopian Tube Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#4 MeSH descriptor: [Peritoneal Neoplasms] explode all trees
#5 MeSH descriptor: [Pelvic Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#6 MeSH descriptor: [Ovarian Neoplasms] explode all trees and with qualifier(s): [Diagnosis - DI]
#7 MeSH descriptor: [Adnexal Diseases] explode all trees and with qualifier(s): [Diagnosis - DI]
#8 (ovar* or adnexal or fallopian or peritoneal or pelvic) near/2 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumor* or tumour*)
#9 (epithelial or "germ cell") next (ovar*)
#10 #1 or #2 or #3 or #5 or #6 or #7 or #8 or #9
#11 biomarker*
#12 marker*
#13 metabolomics*
#14 genetic next assay*
#15 protein* next assay*
#16 proteomic*
#17 lipomic*
#18 multiplex
#19 multivariate or multimarker near/2 assay*
#20 kallikrein*
#21 genomic*
#22 MeSH descriptor: [Biological Markers] explode all trees
#23 MeSH descriptor: [Proteomics] explode all trees
#24 MeSH descriptor: [Kallikreins] explode all trees
#25 MeSH descriptor: [Genomics] explode all trees
#26 CA125 or CA-125 or HE4 or OVA 1 or OVA1 or HCG or LDH or AFP or CEA
#27 MeSH descriptor: [CA-125 Antigen] explode all trees
#28 MeSH descriptor: [Chorionic Gonadotropin] explode all trees
#29 MeSH descriptor: [alpha-Fetoproteins] explode all trees
#30 MeSH descriptor: [Carcinoembryonic Antigen] explode all trees
#31 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
#32 #10 and #31 Publication Year from 1991 to 2015

Database: CINAHL (EBSCO) 1960 to 23 April 2015

S1 (borderline or border-line) N4 (ovar*)
S2 (MH “Fallopian Tube Diseases+/DI)
S3 (MH “Peritoneal Neoplasms+/DI)
S4 (MH “Pelvic Neoplasms/DI”)
S5 (MH “Ovarian Neoplasms+/DI”
S6 (MH “Adnexal Diseases/DI”
S7(ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
S8 (epithelial or germ cell) N1 (ovar*)
S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10 multiplex
S11 (multivariate or multimarker*) N2 (assay*)
S12 (MH “Biological Markers+”)
S13 (MH “Tumor Markers, Biological+”)

S14 (MM “Proteomics”)
S15 (MM “Genetic Markers”)
S16 “metabolomic*” or CA125 or CA-125 or HE4 or OVA1 or OVA1 or HCG or LDH or AFP or CEA
S17 S10 or S11 or S12 or S13 or S14 or S15 or S16
S18 S9 and S17 Limiters – Publication Year: 1991 – 2015

Database: Science Citation Index (Web of Science) 1900 to 23 April 2015

#1 TS=(borderline ovar* or border line ovar*)
#2 TS=((ovar* or adnexal or fallopian or peritoneal or pelvic) N3 (cancer* or carcinoma* or malignan* or mass or masses or cyst or cysts or neoplasm* or tumour* or tumor*)
#3 TS=(((epithelial or “germ cell”)) near/1 (ovar*)
#4 #3 or #2 or #1
#5 TS=multiplex
#6 TS=((((multivariate or multimarker*)) near/2 (assay*)))
#7 TS=(((tumor* or tumour* or genetic*) near/2 (marker*)))
#8 TS=(metabolom* or proteiomic*) or (CA125 or CA-125 or HE4 or OVA1 or OVA 1 or HCG or LDH or AFP or CEA)
#9 TS=((((genetic* or protein*)) near/1 (assay*)))
#10 #5 or #6 or #7 or #8 or #9
#11 #4 and #10 Indexes= SCI-EXPANDED Timespan= 1991-2015

Database: Conference Proceedings Citation Index (CPCI) (Web of Science) 1900 to 24 April 2015

As Science Citation Index above. Searched 24 April 2015

Appendix 2. Search strategies 2019

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations (1946 to 21 June 2019)

1 exp Ovarian Neoplasms/di
2 exp Adnexal Diseases/di
3 ((borderline or border line) adj4 ovar$).tw.
4 exp Fallopian Tube Neoplasms/di
5 exp Peritoneal Neoplasms/di
6 exp Pelvic Neoplasms/di
7 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 exp ovarian neoplasms/
11 "Neoplasms, Glandular and Epithelial"/
12 exp ovary/
13 10 or 11 or 12
14 9 or 13 (245101)
15 exp ultrasonography/
16 ultraso$.tw.
17 (transvagina$ adj2 sonogra$).tw.
18 15 or 16 or 17
19 IOTA.tw. (2231)
20 International Ovarian Tumor Analysis.tw.
21 ((ovarian or epithelial or adnex$ or fallopian or peritoneal or pelvic) adj3 (model$ or regress$ or rule$ or score$ or algorithm$ or term $ or definition$ or measure$)).ti,ab.
22 19 or 20 or 21
23 exp Tumor Markers, Biological/
24 exp Biological Markers/
25 *Proteomics/
26 *Genetic Markers/
27 *Metabolomics/
28 multiplex$.tw.
29 multivariate.tw.
30 (CA125 or CA-125 or HE4 or OVA 1 or OVA1 or HCG or LDH or AFP).mp. or CEA.tw.
31 CA-125 Antigen/
32 Chorionic Gonadotropin/

33 L-Lactate Dehydrogenase/
34 alpha-Fetoproteins/
35 Carcinoembryonic Antigen/
36 23 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37 exp "Signs and Symptoms"/
38 exp early diagnosis/ or exp Diagnosis/
39 exp "Early Detection of Cancer"/
40 symptom$.ti,ab.
41 (early adj (sign$ or symptom$)).tw.
42 (abdom$ adj3 (pressure or pain$ or swelling$ or hard)).tw.
43 (bowel irregularit$ or bloat$ or fullness or satiet$ or gastro$).tw.
44 (fatigue or weight loss$ or weight gain$ or constipat$ or diarrhoea or diarrhea or gas).tw.
45 (nausea$ or indigestion).tw.
46 ((loss or lack) adj3 (energ$ or appetite$)).tw.
47 (urin$ adj3 (frequenc$ or urgenc$)).tw.
48 ((leg$ or ankle$) adj2 (swell$ or swollen)).tw.
49 ((abnormal or irregular or postmenopausal) adj1 vaginal adj (bleed$ or discharge$)).tw.
50 (pelvic discomfort$ or pelvic pain$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
51 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52 (index or risk$ or score$ or scoring or checklist$ or rule$ or indices or tool$ or instrument$ or survey$ or questionnaire$ or interview$).tw.
53 (LR2 or RMI or ROMA or ADNEX).mp.
54 51 and 52
55 18 or 22 or 36 or 53 or 54
56 14 and 55
57 limit 56 to (humans and yr="2015 - 2019")

Database: Embase (1974 to 21 June 2019)

1 exp Ovary cancer/di
2 exp Adnexal Diseases/di
3 ((borderline or border line) adj4 ovar$).tw.
4 exp uterine cancer/di
5 exp Peritoneum tumor/di
6 exp Pelvis tumor/di
7 ((ovar$ or adnexal or fallopian or peritoneal$ or pelvic) adj3 (cancer$ or carcinoma$ or malignan$ or mass or masses or cyst or cysts or neoplas$ or tumour$ or tumor$)).tw.
8 ((epithelial or germ cell) adj5 ovar$).tw.
9 or/1-8
10 exp ovary cancer/
11 "Neoplasms, Glandular and Epithelial"/
12 exp ovary/
13 10 or 11 or 12
14 9 or 13
15 echography/
16 ultraso$.tw.
17 (transvagina$ adj2 sonogra$).tw.
18 15 or 16 or 17
19 IOTA.tw.
20 International Ovarian Tumor Analysis.tw.
21 ((ovarian or epithelial or adnex$ or fallopian or peritoneal or pelvic) adj3 (model$ or regress$ or rule$ or score$ or algorithm$ or term $ or definition$ or measure$)).ti,ab.
22 19 or 20 or 21
23 *Biological Marker/
24 *Proteomics/
25 *Genetic Marker/
26 *Metabolomics/
27 multiplex$.tw.
28 multivariate.tw.
29 (CA125 or CA-125 or HE4 or OVA 1 or OVA1 or HCG or LDH or AFP).mp. or CEA.tw.
30 CA-125 Antigen/
31 Chorionic Gonadotropin/
32 L-Lactate Dehydrogenase/

33 alpha-Fetoproteins/
34 Carcinoembryonic Antigen/
35 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36 symptom$.ti,ab.
37 early diagnosis.tw.
38 (early adj (sign$ or symptom$)).tw.
39 (abdom$ adj3 (pressure or pain$ or swelling$ or hard)).tw.
40 (bowel irregularit$ or bloat$ or fullness or satiet$ or gastro$).tw.
41 (fatigue or weight loss$ or weight gain$ or constipat$ or diarrhoea or diarrhea or gas).tw.
42 (nausea$ or indigestion).tw.
43 ((loss or lack) adj3 (energ$ or appetite$)).tw.
44 (urin$ adj3 (frequenc$ or urgenc$)).tw.
45 ((leg$ or ankle$) adj2 (swell$ or swollen)).tw.
46 ((abnormal or irregular or postmenopausal) adj1 vaginal adj (bleed$ or discharge$)).tw.
47 (pelvic discomfort$ or pelvic pain$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
48 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49 (index or risk$ or score$ or scoring or checklist$ or rule$ or indices or tool$ or instrument$ or survey$ or questionnaire$ or interview$).tw.
50 (LR2 or RMI or ROMA or ADNEX).mp.
51 48 and 49
52 18 or 22 or 35 or 50 or 51
53 14 and 52
54 limit 53 to (human and yr="2015 - 2019")

Appendix 3. QUADAS-2

DOMAIN 1: PATIENT SELECTION

PATIENT SELECTION	
A. Risk of bias	
Describe methods of patient selection:	
a) Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear
b) Was a case-control design (using healthy controls) avoided?	Yes/No/Unclear
c) Did the study avoid inappropriate exclusions?	Yes/No/Unclear
a) include all ages and regardless of menopausal status or justify restrictions	
b) include all stages of ovarian cancer	
c) include comorbidities such as infertility and endometriosis	
Could the selection of patients have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
Low: a) and b) and c) 'YES'	
High: a) or b) or c) 'NO'	
Unclear: not 'High' and a) or b) or c) 'UNCLEAR'	

PATIENT SELECTION	
B. Concerns regarding applicability	

(Continued)

Describe included patients (prior testing, presentation, intended use of index test and setting):	
a) Are all or some patients symptomatic	Yes /No/Unclar
b) Prior tests: self-reported symptoms OR self-reported symptoms PLUS one or more of biochemical markers and ultrasound by non-specialist sonographers (in primary or secondary care)	Yes/No/Unclear
Is there concern that the included patients do not match the review question? Low: a) and b) Yes High: a) or b) No Unclear: not High and a) or b) Unclear	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 2: INDEX TEST(S)

(If more than one index test was used, please complete for each test).

INDEX TEST **A. Risk of Bias**	
Describe the index test and how it was conducted and interpreted:	
a) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	Yes / No / Unclear
b) If a threshold was used, was it pre-specified?	Yes / No / Unclear
c) Were all components and thresholds of multivariable models pre-specified before their application?	Yes / No / Unclear
d) Were all components of multivariable models defined and assessed ina similar way for all patients (eg in the same healthcare setting)?	Yes / No / Unclear
Could the conduct or interpretation of the index test have introduced bias? High: a) or b) or c) or d) No Low: a) and b) and c) and d) Yes Unclear: not 'high' and a) or b) or c) or d) Unclear	**RISK: LOW/HIGH/UNCLEAR**

INDEX TEST **B. Concerns regarding applicability**	
a) Was USS performed in all patients by non-specialised sonographers	Yes/No/Unclear

(Continued)

b) Was USS/clinical examination performed with knowledge of symptoms/signs/biomarkers	Yes/No/Unclear
Is there concern that the index test, its conduct or interpretation differ from the review question? High: a) and b) No Low: a) and b) Yes Unclear: a) or b) Unclear	**CONCERN: LOW/HIGH/UNCLEAR**

DOMAIN 3: REFERENCE STANDARD

REFERENCE STANDARD **A. Risk of bias**	
Describe the reference standard and how it was conducted and interpreted:	
a) Were the reference standard results interpreted without knowledge of the index test?	Yes/No/Unclear
b) Is the reference standard likely to correctly classify the target condition? -Index test +ve: Histology following laparoscopy or laparotomy -Index test -ve: Histology following laparoscopy or laparotomy OR clinical follow-up for = > 12 months	Yes/No/Unclear
Could the reference standard, its conduct or its interpretation have introduced bias High: a) or b) No Low: a) and b) Yes Unclear: not 'High' and a) or b) Unclear	**RISK: LOW/HIGH/UNCLEAR**

REFERENCE STANDARD **B. Concerns regarding applicability**	
Can borderline tumours be grouped with primary ovarian cancer for analysis?	Yes/No/Unclear
Can metastatic tumours be disagregated for analysis?	Yes/No/Unclear
Is there concern that the target condition as defined by the reference standard does not match the review question? High: a) and b) No Low: a) and b) Yes	**CONCERN: Yes/No/Unclear**

(Continued)

Unclear: not 'High' and a) or b) Unclear

DOMAIN 4: FLOW AND TIMING

FLOW AND TIMING	
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2 × 2 table (refer to study flow diagram):	
Describe the time interval and any interventions between index test(s) and reference standard:	
a) Was there less than 3 months' interval between application of each index test and application of the reference standard?	Yes/No/Unclear
b) Did all patients receive a reference standard?	Yes/No/Unclear
c) Did all index test -ve patients receive the same reference standard?	Yes/No/Unclear
d) Were all patients who underwent testing included in the analysis?	Yes/No/Unclear
Could the patient flow have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**
LOW: a) and b) and c) and d) – Yes	
HIGH: a) or b) or c) or d) – No	
UNCLEAR: not 'high' AND a) or b) or c) or d) – Unclear	

COMPARATIVE DOMAIN (if applicable)

COMPARATIVE DOMAIN	
A. Risk of bias	
Describe the selection process for participants to receive one or other index test or index testing strategy	
Describe the time interval and any interventions between index test(s) for within-person test comparisons	
a) *For studies comparing two or more index tests or testing strategies in **different** patient populations were the selection criteria for participants receiving one or other index test or testing strategy the same?*	*Yes/No/Unclear/NA*
b) *For within-study comparisons of index tests:* *- was the interval between application of each index test < 3 months*	*Yes/No/Unclear/NA*
c) *For within-study comparisons of individual index tests:* *- were index tests interpreted blind to the results of other index test results*	*Yes/No/Unclear/NA*
Could the conduct of the comparative study have introduced bias?	**RISK: LOW/HIGH/UNCLEAR**

(Continued)

LOW: a) OR (b) and c)) – Yes

HIGH: a) OR (b) and c)) – No

UNCLEAR: a) OR (b) or c)) – Unclear

B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that included patients have been selected in a different way to participants in non-comparative studies	**CONCERN: LOW/HIGH/UNCLEAR**

Appendix 4. Tables of excluded studies with reasons

Table 11

Table 12

Table 13

Table 14

Table 15

Table 16

Table 17

Table 18

Table 19

Table 20

Appendix 5. Quality assessment tables for studies grouped by index test

RMI Figure 13

Figure 13. Risk of bias and applicability concerns summary: Risk of Malignancy Index I. Review authors' judgements about each domain for each included study.

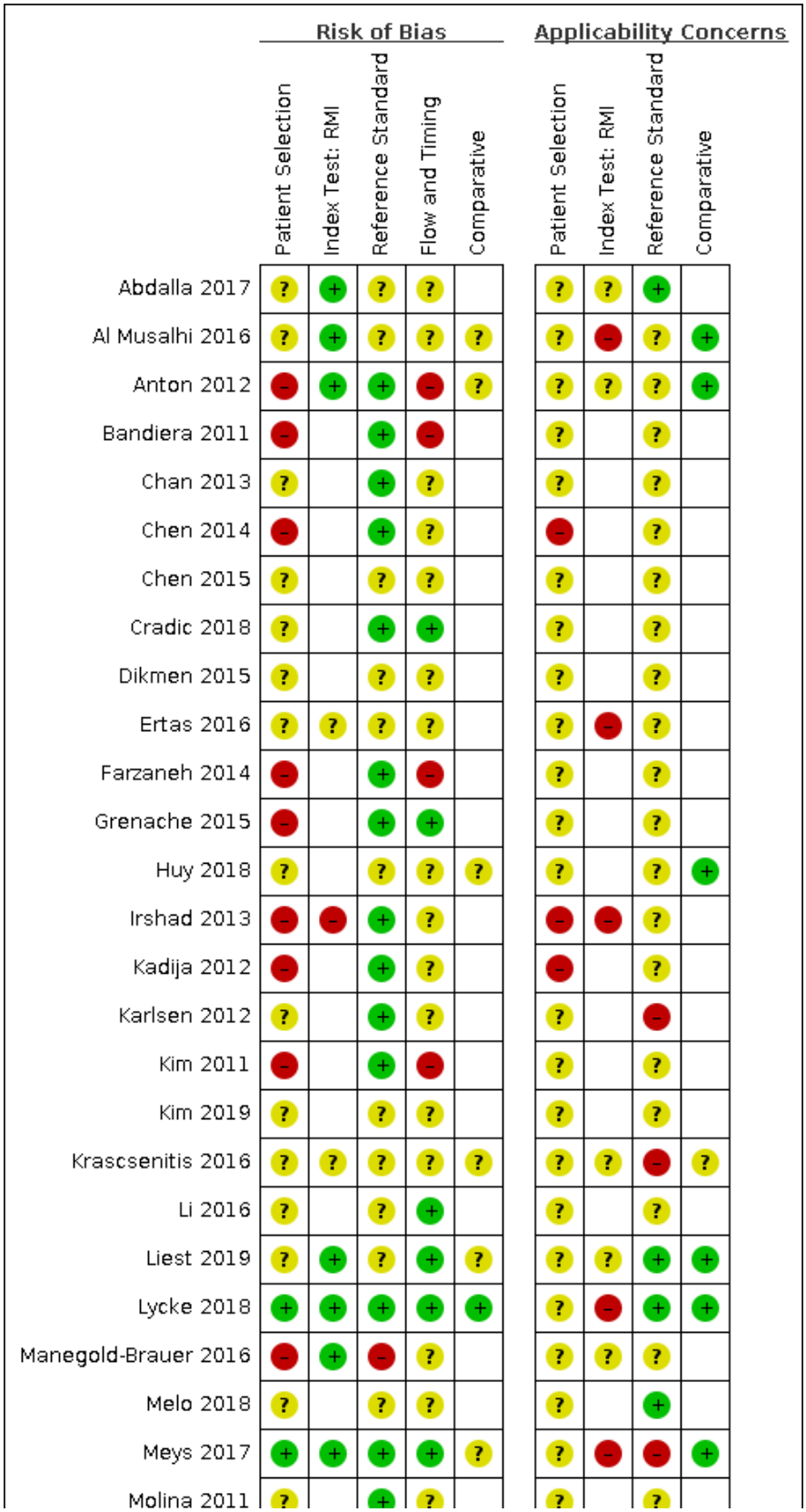


Figure 13. (Continued)

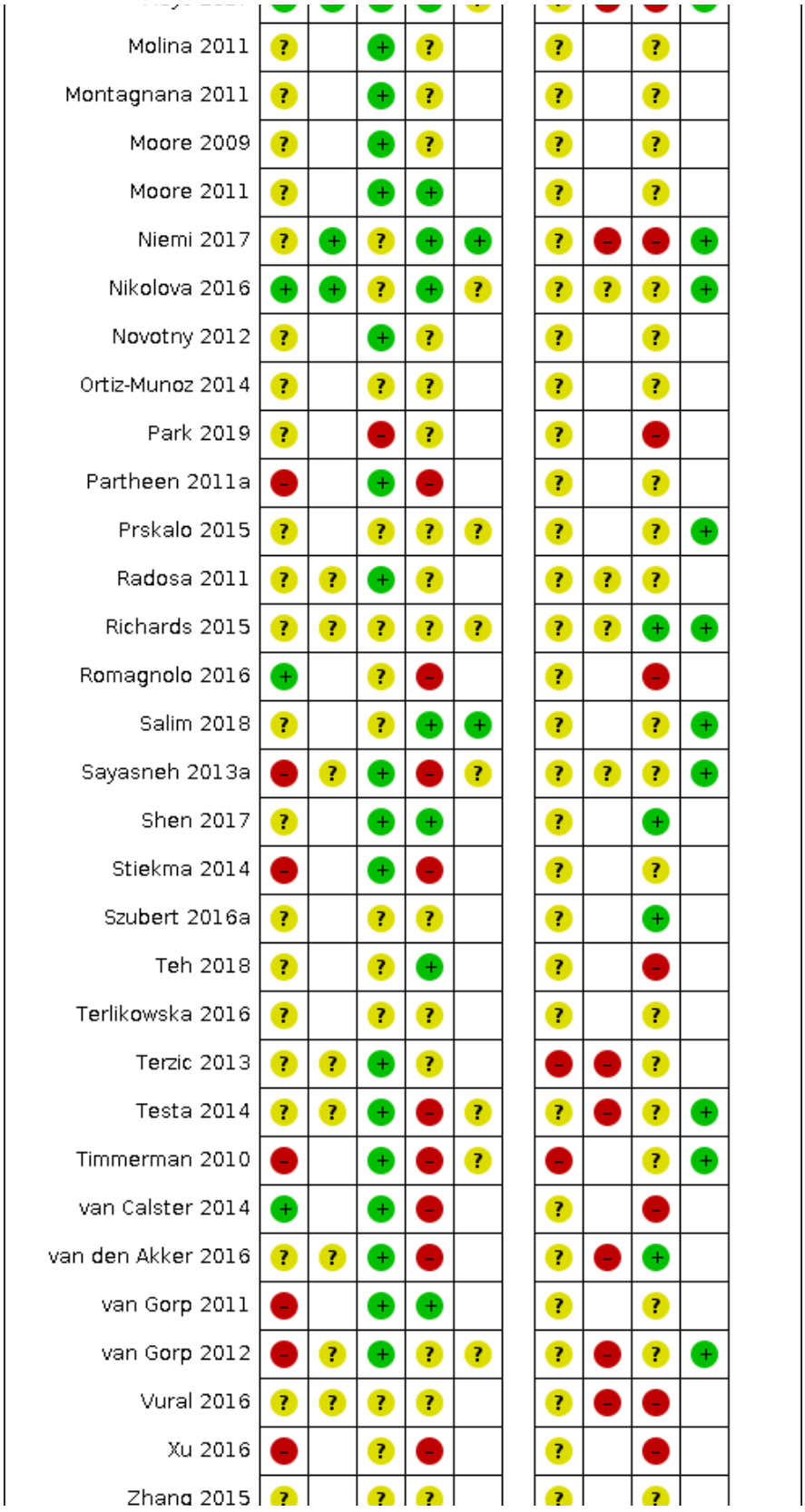
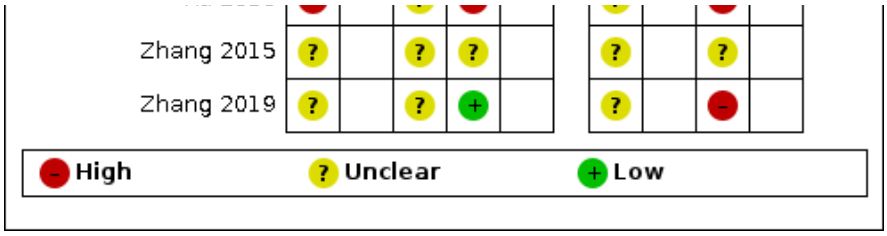


Figure 13. (Continued)



ROMA Figure 14

Figure 14. Risk of bias and applicability concerns summary: Risk of Ovarian Malignancy Algorithm. Review authors' judgements about each domain for each included study.

Figure 14. (Continued)

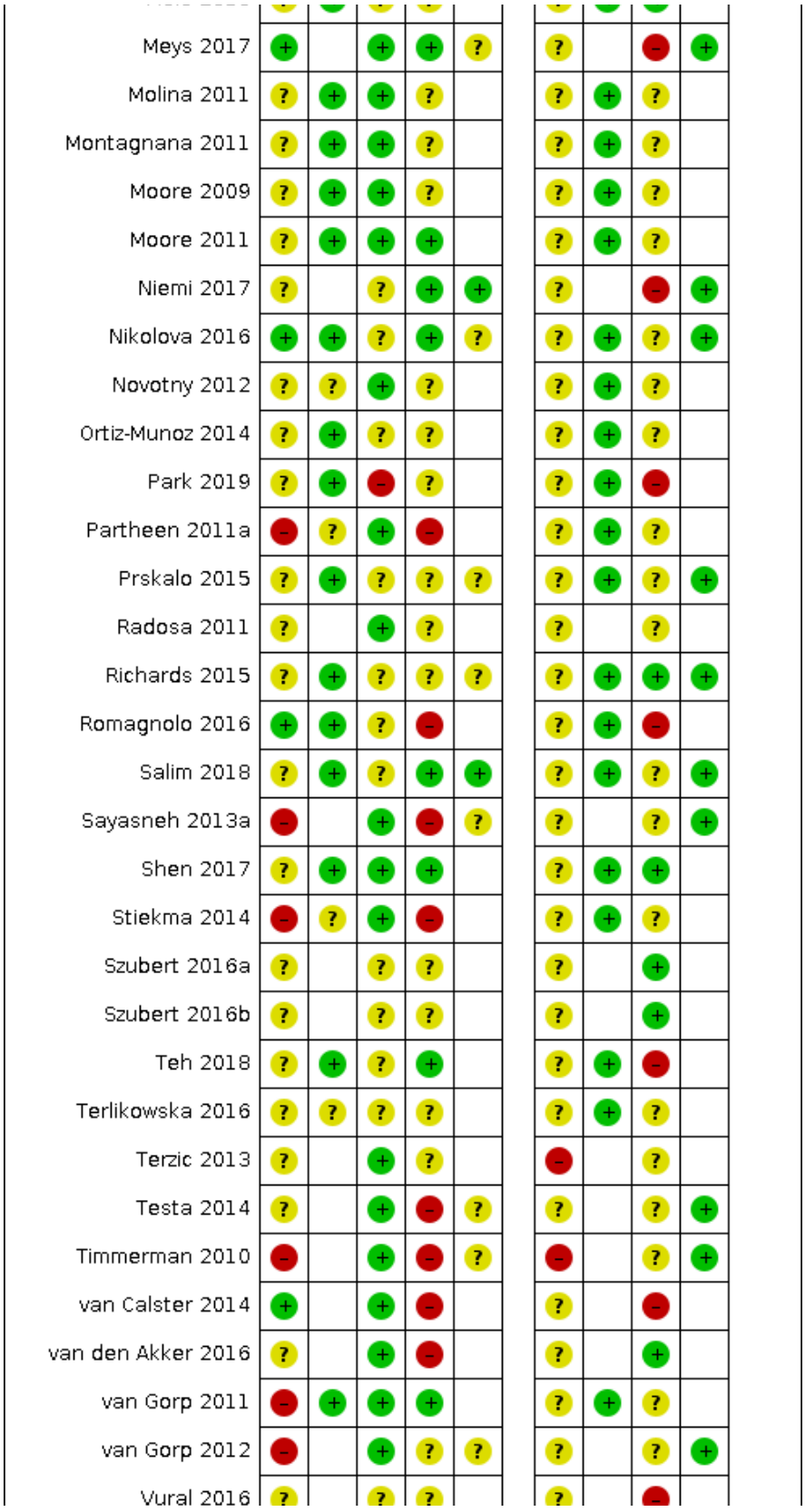
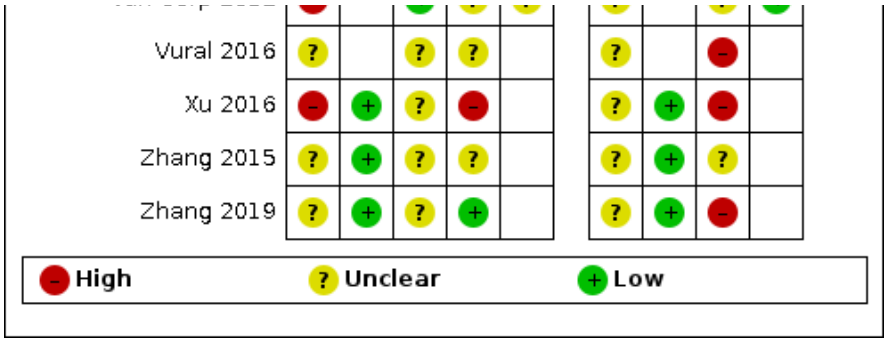


Figure 14. (Continued)



LR2 Figure 15

Figure 15. Risk of bias and applicability concerns summary: Logistic Regression 2 model. Review authors' judgements about each domain for each included study.

Figure 15. (Continued)

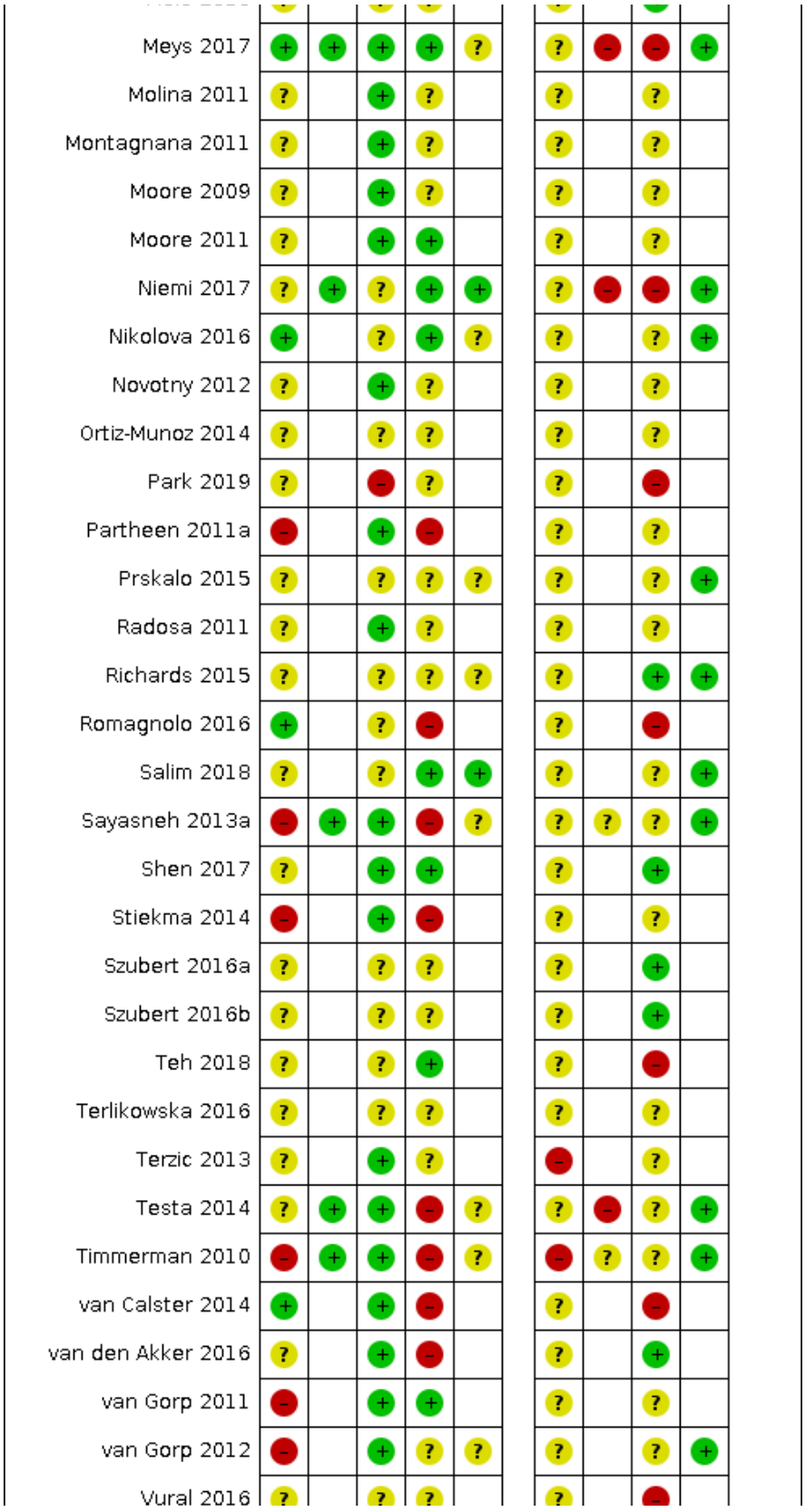
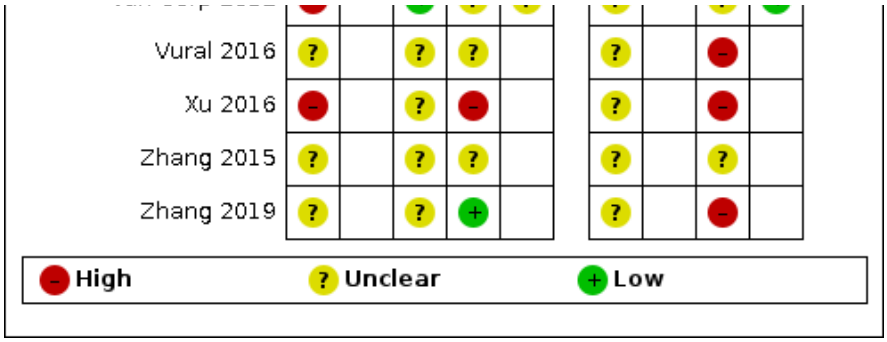


Figure 15. (Continued)



ADNEX Figure 16

Figure 16. Risk of bias and applicability concerns summary: Assessment of Different NEoplasias in the adneXa model. Review authors' judgements about each domain for each included study.

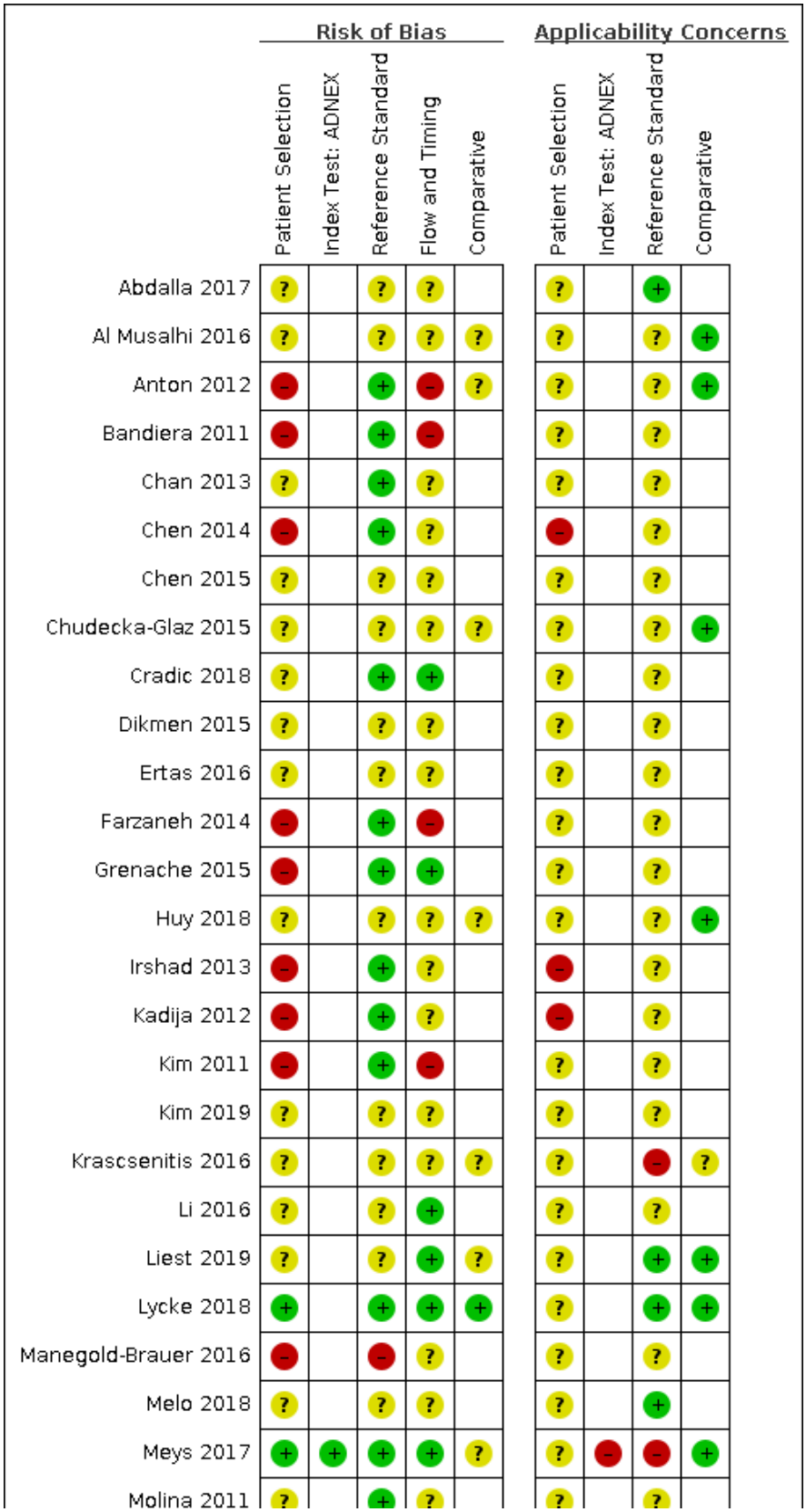


Figure 16. (Continued)

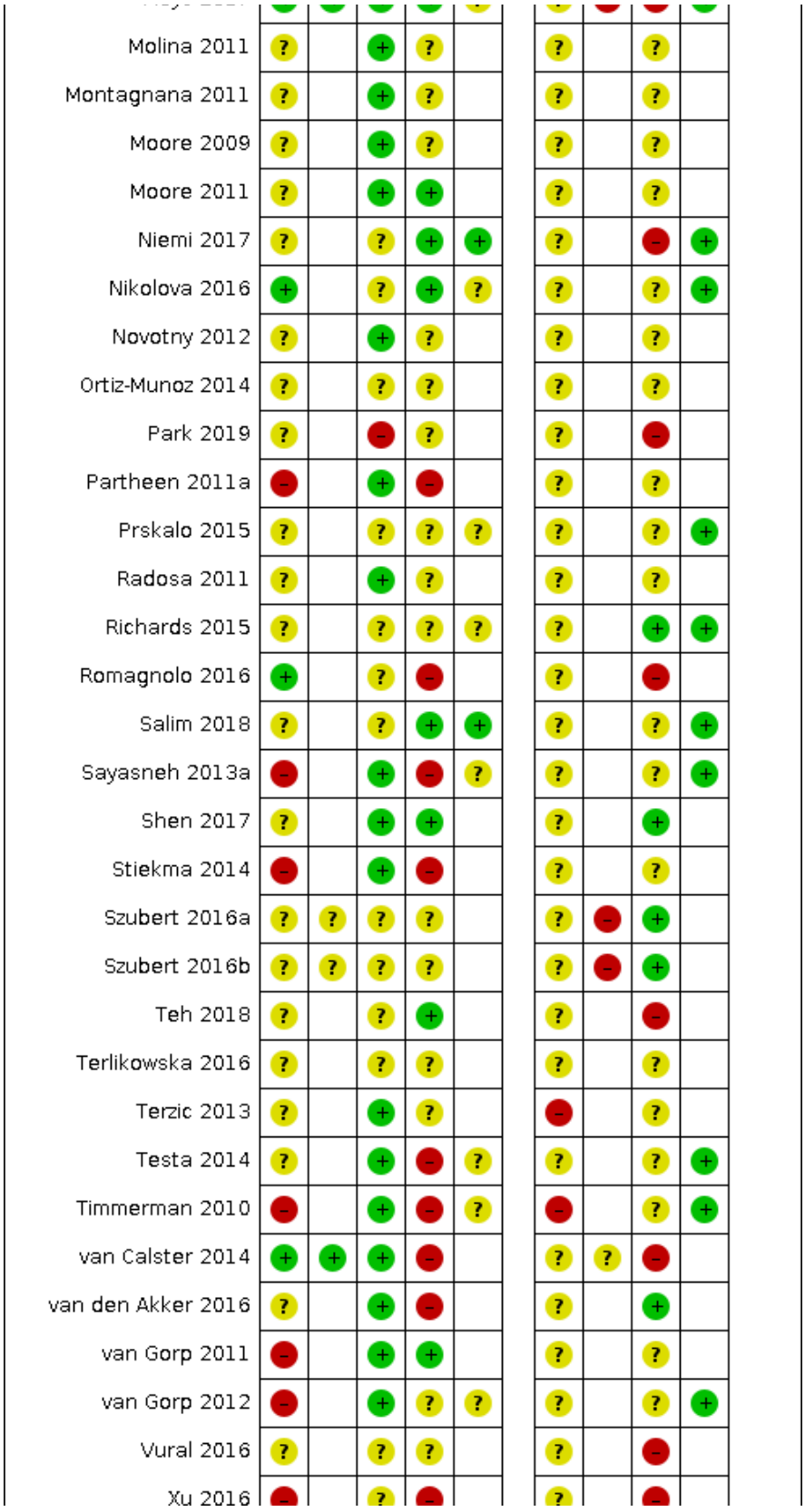
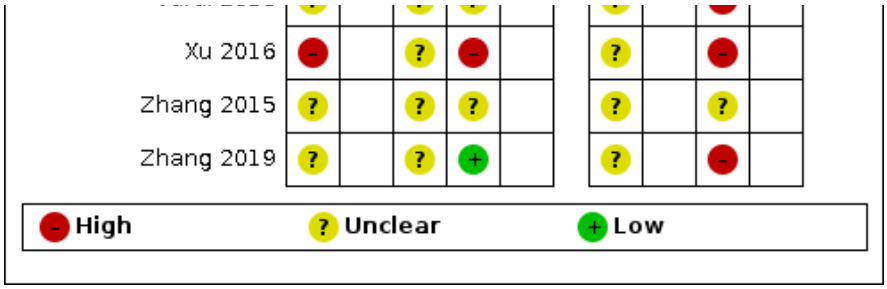


Figure 16. (Continued)



Appendix 6. List of systematic reviews and guidelines included for reference checking

List of systematic reviews and guidelines (25 studies)

1. Multianalyte testing for the evaluation of adnexal masses (Structured abstract). Health Technology Assessment Database [Internet]. 2012 [cited HTA Y/U]; (1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32013000454/frame.html.

2. Alcazar JL, Jurado M. Three-dimensional ultrasound for assessing women with gynecological cancer: a systematic review. Gynecologic Oncology. 2011;120(3):340-6.

3. Brun JL, Fritel X, Aubard Y, Borghese B, Bourdel N, Chabbert-Buffet N, et al. Management of presumed benign ovarian tumors: updated French guidelines. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;183:52-8.

4. Dodge JE, Covens AL, Lacchetti C, Elit LM, Le T, Devries-Aboud M, et al. Management of a suspicious adnexal mass: a clinical practice guideline. Current Oncology. 2012;19(4):e244-57.

5. Duffy MJ, Bonfrer JM, Kulpa J, Rustin GJS, Soletormos G, Torre GC, et al. CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. International Journal of Gynecological Cancer. 2005;15(5):679-91.

6. Ebell MH, Culp MB, Radke TJ. A Systematic Review of Symptoms for the Diagnosis of Ovarian Cancer. American Journal of Preventive Medicine.50(3):384-94.

7. Ferraro S, Braga F, Lanzoni M, Boracchi P, Biganzoli EM, Panteghini M. Serum human epididymis protein 4 vs carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review. Journal of Clinical Pathology. 2013;66(4):273-81.

8. Fischerova D. [Recommended guidelines of diagnosis for women with an ovarian cyst or tumour]. Ceska Gynekologie. 2014;79(6):477-86.

9. Geomini P, Kruitwagen R, Bremer GL, Cnossen J, Mol BW. The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstetrics and gynecology. 2009;113(2 Pt 1):384-94.

10. Harris RD, Javitt MC, Glanc P, Brown DL, Dubinsky T, Harisinghani MG, et al. ACR Appropriateness Criteria clinically suspected adnexal mass. Ultrasound Quarterly. 2013;29(1):79-86.

11. Hayes, Inc. Ca 125 for ovarian cancer screening in average-risk women (Structured abstract). Health Technology Assessment Database [Internet]. 2005 [cited PENDING (UPDATE 91-08)- FT NOT FOUND (2). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32006000089/frame.html.

12. Kaijser J, Sayasneh A, van Hoorde K, Ghaem-Maghami S, Bourne T, Timmerman D, et al. Presurgical diagnosis of adnexal tumours using mathematical models and scoring systems: a systematic review and meta-analysis. Human Reproduction Update. 2014;20(3):449-62.

13. Karlsen NS, Karlsen MA, Hogdall CK, Hogdall EVS. HE4 tissue expression and serum HE4 levels in healthy individuals and patients with benign or malignant tumors: a systematic review. Cancer Epidemiology, Biomarkers & Prevention. 2014;23(11):2285-95.

(Continued)
14. Kinkel K, Hricak H, Lu Y, Tsuda K, Filly RA. US characterization of ovarian masses: a meta-analysis (Structured abstract). Radiology [Internet]. 2000 [cited DARE Y/U]; (3):[803-11 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12000002350/frame.html.

15. Kinkel K, Lu Y, Mehdizade A, Pelte M-F, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization - meta-analysis and Bayesian analysis. Radiology. 2005;236(1):85-94.

16. Le T, Giede C, Salem S, Lefebvre G, Rosen B, Bentley J, et al. Initial evaluation and referral guidelines for management of pelvic/ovarian masses. Journal of Obstetrics & Gynaecology Canada: JOGC. 2009;31(7):668-80.

17. Li F, Tie R, Chang K, Wang F, Deng S, Lu W, et al. Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: a meta-analysis. BMC Cancer. 2012;12:258.

18. Lin J, Qin J, Sangvatanakul V. Human epididymis protein 4 for differential diagnosis between benign gynecologic disease and ovarian cancer: a systematic review and meta-analysis. European Journal of Obstetrics, Gynecology, & Reproductive Biology. 2013;167(1):81-5.

19. Mol BW, Boll D, De Kanter M, Heintz AP, Sijmons EA, Oei SG, et al. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. Gynecologic Oncology. 2001;80(2):162-7.

20. Nunes N, Ambler G, Foo X, Naftalin J, Widschwendter M, Jurkovic D. Use of IOTA simple rules for diagnosis of ovarian cancer: meta-analysis. Ultrasound in Obstetrics & Gynecology. 2014;44(5):503-14.

21. Reed N, Millan D, Verheijen R, Castiglione M, Group EGW. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2010;21 Suppl 5:v31-6.

22. Wang J, Gao J, Yao H, Wu Z, Wang M, Qi J. Diagnostic accuracy of serum HE4, CA125 and ROMA in patients with ovarian cancer: a meta-analysis (Provisional abstract). Tumor Biology [Internet]. 2014 [cited DARE N]; (6):[6127-38 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cldare/articles/DARE-12014021188/frame.html.

23. Yang Z, Wei C, Luo Z, Li L. Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis.[Erratum appears in Onco Targets Ther. 2014;7:135]. OncoTargets and therapy. 2013;6:957-66.

24. Zhe S, Jun Z, Huamei M, Qiuli C, Minlian D, Yanhong L, et al. Four cases of ovarian adrenal rest tumors in Chinese girls with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Hormone Research in Paediatrics Conference: 53rd Annual Meeting of the European Society for Paediatric Endocrinology, ESPE. 2014;82(pp 331).

25. Zhen S, Bian LH, Chang LL, Gao X. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: A meta-analysis. Molecular and Clinical Oncology. 2014;2(4):559-66.

HISTORY

Protocol first published: Issue 12, 2015

CONTRIBUTIONS OF AUTHORS

- Guarantor of the review: SS, JD, CD.
- Conceiving the idea: SS, CD, JD.
- Designing and co-ordinating the review: NR, CD, SS, JD.
- Designing search strategies: SB, NR, CD, SS, RN.
- Screening, data extraction, quality assessment: NR, RC, CD, PSh, PSa.
- Obtaining and screening data on unpublished studies: NR, RC, PSh, PSa.
- Data management of the review: NR, PSh, PSa, CD.
- Analysis and interpretation of data: SM, KS, NR, SS, CD, JD.
- Writing the review: CD, NR, SS, PSh.
- Providing general advice on the review: CD, SS, JD.
- Securing funding for the review: SS, CD, JD.

DECLARATIONS OF INTEREST

This review and participation of all authors in it has been funded as part of a programme of research (ROCkeTS – Refining Ovarian Cancer Test Accuracy Scores).

CD: received funding from the NIHR HTA to support this review in a methodological capacity.

NR: my participation in this review is funded by the NIHR grant listed.

PSh: none known.

JD: this work is a funded project, funded by the NIHR HTA Commissioning Board.

SB: none known.

SM: co-applicant on one funded government funded grant (mpMRI imaging) and one recently submitted grant (circulating DNA) for the diagnosis of ovarian cancer.

PSa: none known

RC: none known.

SB: none known.

KS: my participation in this review is funded by the NIHR grant listed.

SS: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other

External sources

- National Institute for Health Research (HTA programme: 13/13/01), UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Search strategy

We did not restrict our searches to English Language publications but we were unable to consider non-English publications due to time and resource limitations. The volume of non-English publications not considered by this review is explicit in the results of the search strategy. For pragmatic reasons, we conducted searches for the period 2015 to 2019 in a restricted number of bibliographic databases. We did not search the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) websites for the period 2015 to 2019 as part of the search update for this test combination review; these literature resources were originally checked in 2015 as part of a generic protocol covering four reviews, specifically for a review of biomarkers for the diagnosis of ovarian cancer (OC).

Type of studies

Case-control studies where healthy controls could not be disaggregated from women with benign ovarian pathology were excluded. Studies concerned only with the development of multivariable models were excluded. Where papers reported data on both the development and validations of a multivariable model, we extracted only the validation data.

Index test

We did not include all thresholds reported in each study. For each index test version within an individual study we extracted up to four thresholds. We prioritised extraction of results in the following order: 1. from prespecified thresholds, 2. thresholds commonly used in clinical guidelines, 3. thresholds commonly used in the published literature and 4. thresholds reported as main outcomes in studies included in this review.

Target condition

We excluded studies reporting exclusively on metastatic disease to the ovary or recurrent OC. We disaggregated data to exclude cancers metastatic to the ovary and recurrent OCs in studies where possible; studies where the these data were unavailable or the information was available but could not be disaggregated was downgraded as unclear or high, respectively, for reference standard applicability

Data extraction

A single review author (NR or PSh or PSa) extracted study characteristic data and a second review author (RC) independently checked 30% of studies. Any differences were resolved by discussion.

A single review author (NR or PSh or PSa) extracted methodological quality data, and a second review author (RC) independently checked 30% of studies. Any differences were resolved by discussion.

Quality assessment

A separate domain for multivariable models was not considered necessary, particularly as we did not include studies only reporting development of multivariate models. Instead, we added two questions to the participant domain of QUADAS-2 drawing on the PROBAST (prediction model risk of bias assessment) tool for diagnostic and prediction models (Wolf 2019): 1. Prespecification of thresholds and 2. comparable assessment of all model/test components.

Statistical analysis

We compared test accuracy in pre- and postmenopausal women by adding a covariate in the bivariate model and calculating differences and 95% confidence intervals using non-linear estimating methods, taking advantage of advances in analysis methods compared to simple testing of differences using likelihood ratio tests. We presented the impact of using tests and test comparisons using absolute numbers of average women in a hypothetical population at a range of clinically relevant prevalence, representative of primary care and a range of specialist settings instead of restricting to a single prevalence representative of a primary care setting. This approach was adopted to illustrate the clinical utility of index tests in multiple settings, reflecting their potential use in clinical practice.

Heterogeneity and sensitivity analyses

We were unable to carry out the following planned heterogeneity analyses due to insufficient studies with differences in the relevant study characteristics or with these study characteristics reported: generalist (primary care/community/family practice) versus specialist setting (cancer unit/cancer centre/gynaecological oncology); histological subtype, reference standard QUADAS-2 domain risk of bias (high/unclear versus low); case-control study versus other study designs; 12 months' follow-up versus less than 12 months' follow-up for study participants not receiving surgery initially following a negative index test result.

We did not carry out sensitivity analyses leaving out highly influential studies as this was not considered necessary; including only studies with low concern about applicability in the patient selection domain of QUADAS-2 as there were insufficient studies; or classification of borderline tumours as malignant or benign as this proved too simple an approach given the heterogeneity in approach to management and reporting of borderline tumours in included studies. Instead, where data allowed, we compared estimates of the test accuracy of each index test for studies using an inappropriate grouping (studies excluding borderline ovarian tumours and studies where the management of borderline ovarian tumours was unclear) with studies using an appropriate grouping (studies combining borderline ovarian tumours with malignant ovarian tumours) using the hierarchical summary receiver operating characteristic (HSROC) model.

INDEX TERMS

Medical Subject Headings (MeSH)

Biomarkers; Carcinoma, Ovarian Epithelial; Cross-Sectional Studies; Menopause; *Ovarian Neoplasms [diagnostic imaging]; Sensitivity and Specificity

MeSH check words

Female; Humans