

## Laboratory practice is central to earlier myeloma diagnosis

Drayson, Mark; Jennis, Tom; Laketic-Ijubojevic, Ira; Patel, Dina; Pratt, Guy; Renwick, Suzanne; Richter, Alex; Wheeler, Rachel; Sheldon, Joanna; Sadler, Ross; Stapleton, Mary; Willis, Fenella; Whiston, Mairi

DOI:  
[10.1111/bjh.19224](https://doi.org/10.1111/bjh.19224)

License:  
Creative Commons: Attribution-NonCommercial (CC BY-NC)

*Document Version*  
Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*  
Drayson, M, Jennis, T, Laketic-Ijubojevic, I, Patel, D, Pratt, G, Renwick, S, Richter, A, Wheeler, R, Sheldon, J, Sadler, R, Stapleton, M, Willis, F & Whiston, M 2024, 'Laboratory practice is central to earlier myeloma diagnosis: Utilizing a primary care diagnostic tool and laboratory guidelines integrated into haematology services', *British Journal of Haematology*. <https://doi.org/10.1111/bjh.19224>

[Link to publication on Research at Birmingham portal](#)

### General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

## GUIDELINE

# Laboratory practice is central to earlier myeloma diagnosis: Utilizing a primary care diagnostic tool and laboratory guidelines integrated into haematology services

Mark Drayson<sup>1</sup>  | Tom Jennis<sup>2</sup> | Ira Laketic-Ljubojevic<sup>2</sup> | Dina Patel<sup>3</sup> | Guy Pratt<sup>4</sup>  | Suzanne Renwick<sup>2</sup> | Alex Richter<sup>1</sup> | Rachel Wheeler<sup>5</sup> | Joanna Sheldon<sup>5</sup> | Ross Sadler<sup>6</sup> | Mary Stapleton<sup>7</sup> | Fenella Willis<sup>8</sup> | Mairi Whiston<sup>2</sup> | for Myeloma UK working group for laboratory best practice

<sup>1</sup>Clinical Immunology Service, University of Birmingham, Birmingham, UK

<sup>2</sup>Myeloma UK, Edinburgh, UK

<sup>3</sup>UK NEQAS Immunology, Immunochemistry & Allergy, Sheffield Teaching Hospitals, Sheffield, UK

<sup>4</sup>Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, UK

<sup>5</sup>Protein Reference Unit, South West London Pathology, St Georges Hospital, London, UK

<sup>6</sup>Oxford University Hospitals NHS Foundation Trust, Oxford, UK

<sup>7</sup>North Devon District Hospital, Barnstaple, UK

<sup>8</sup>St George's Hospital, London, UK

**Correspondence**

Mark Drayson, Institute of Immunity and Infection, University of Birmingham, B15 2TT, Birmingham, UK.  
 Email: [m.t.drayson@bham.ac.uk](mailto:m.t.drayson@bham.ac.uk)

**Funding information**

Myeloma UK

**Summary**

Treatment advances have greatly improved survival, but myeloma is among the worst of all cancers for delayed diagnosis, causing serious morbidities and early deaths. This delay is largely because the symptom profile of myeloma has very low specificity, and in primary care, myeloma is rare. However, initiating the journey to diagnosis simply requires considering myeloma and sending blood to test for monoclonal immunoglobulin. Laboratory tests reliably detect monoclonal immunoglobulin, which is present in 99% of myeloma cases, so why do health care systems have such a problem with delayed diagnosis? The Myeloma UK early diagnosis programme has brought together diverse expertise to investigate this problem, and this article was prepared by the programme's working group for laboratory best practice. It reviews evidence for test requesting, analysis and reporting, for which there is large variation in practice across the United Kingdom. It presents a 'GP Myeloma diagnostic tool' and how it can be integrated into laboratory practice alongside a laboratory best practice tool. It proposes improved requesting and integration with haematology services for reporting and interpretation. Here the laboratory has a central role in creating efficient and cost-effective pathways for appropriate and timely bone marrow examination for myeloma diagnosis.

**KEY WORDS**

earlier diagnosis, laboratory practice, myeloma

**BACKGROUND**

Myeloma is a cancer of bone marrow plasma cells that causes impaired immunity, pathological or fragility bone fractures, kidney damage and anaemia (Figure 1).<sup>1,2</sup> In the United Kingdom, it is the second most common blood cancer, with an incidence of 9 per 100,000 per year and a median age at diagnosis of 72.6 years. A diagnosis of myeloma is much less common in low-income countries where there is a lack of laboratory services to facilitate diagnosis.<sup>3,4</sup>

Intensive treatment with autologous stem cell transplantation (ASCT), proteasome inhibitors, immunomodulatory drugs, monoclonal and bispecific antibodies and CAR T-cell therapies have greatly improved survival. For younger patients eligible for ASCT, median survival is 10 years and for ineligible patients 4–5 years.<sup>5</sup> However, myeloma is among the worst of all cancers for delayed diagnosis, with consequent serious morbidities and early deaths. The median diagnostic interval in the United Kingdom was 163 days in one study, and there are similar delays associated with worse

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *British Journal of Haematology* published by British Society for Haematology and John Wiley & Sons Ltd.

## Myeloma Diagnostic Tool Guidance for Primary Care



Myeloma is a cancer of bone marrow plasma cells that secrete abnormal antibodies (paraprotein and free light chains (FLC)). This may result in multiple signs and symptoms, including anaemia, non-specific pain originating in the bones, fatigue, infections, and kidney damage. Although these signs and symptoms may seem unconnected, it is important to remember that myeloma usually presents with vague symptoms that are progressive. Early diagnosis is key to preventing end organ damage and improving survival.

When to suspect myeloma	
<p><b>Any of the following blood test abnormalities:</b></p> <ul style="list-style-type: none"> <li>● Raised <u>C</u>alcium</li> <li>● <u>R</u>enal impairment</li> <li>● <u>A</u>naemia</li> <li>● Raised ESR</li> </ul>	<p><b>Important factors to consider:</b></p> <p>Symptoms and findings persist without explanation or despite initial interventions.</p> <p>Red flags for myeloma investigation include <b>unexplained</b> symptoms and <b>more than one</b> symptom.</p> <p>The <b>CRAB</b> criteria for myeloma.</p>
<p><b>Symptom or finding:</b></p> <ul style="list-style-type: none"> <li>● <u>B</u>one pain – usually presents as unexplained pain, generalised or localised</li> <li>● <u>B</u>ack pain – persistent or severe/atypical</li> <li>● <u>G</u>enerally unwell – fatigue, weight loss, suspicion of underlying cancer</li> <li>● <u>R</u>ecurrent infections</li> <li>● <u>P</u>athological or fragility fractures, e.g. of the vertebra</li> <li>● <u>B</u>reathlessness – unexplained</li> </ul>	
What tests to request	
<ul style="list-style-type: none"> <li>● Serum protein electrophoresis for paraprotein</li> <li>● Serum free light chain (sFLC) assay <ul style="list-style-type: none"> <li>• If unavailable, urine Bence Jones protein (BJP)</li> </ul> </li> <li>● Serum immunoglobulins (IgG, IgA and IgM)</li> <li>● Full blood count</li> <li>● Corrected serum calcium</li> <li>● Serum creatinine</li> </ul>	

**FIGURE 1** Myeloma UK primary care myeloma diagnostic tool: when to test for myeloma.

outcome in other high-income countries.<sup>6–11</sup> Public Health England found 33% of 47 671 new myeloma patients (2006–2016) presented as an emergency and had high mortality in the first year after diagnosis, with a 12-month net survival of 61.7% versus 87.5% in those diagnosed following direct referral from primary care to haematology services.<sup>12</sup>

The Myeloma UK early diagnosis programme has brought together diverse expertise to investigate the problem of diagnostic delay for myeloma. This article was prepared by the programme's working group for laboratory best practice. It reviews the processes from test requesting to reporting and the evidence base for current practices. It presents the primary care myeloma diagnostic tool and how that might be integrated with laboratory requesting, reporting and test interpretation and the importance of integration with

haematology services. The tool provides simple thresholds for monoclonal immunoglobulin levels to distinguish, with high sensitivity and specificity, myeloma that requires treatment from the hundred times more common monoclonal gammopathy of undetermined significance (MGUS). This, along with the presence or absence of CRAB criteria (end-organ damage with hypercalcaemia, renal dysfunction, anaemia and bone involvement), facilitates an appropriate and timely bone marrow examination for myeloma diagnosis.<sup>1</sup>

### When to request tests for myeloma

The diagnostic delay for myeloma is largely because the symptom profile of myeloma is common, with very low

specificity, and that is compounded by the rarity of myeloma in primary care and non-haematology secondary care specialties.<sup>7,13–15</sup> In a study of 962 newly diagnosed patients (median age 67 years), the main presenting symptoms were: back pain (38%), other pain (31%), fatigue (16.1%), weight loss (9.3%), gastrointestinal symptoms (7.7%), respiratory symptoms (7.7%), infections (5.6%) and neurological symptoms (5.5%).<sup>16</sup> This broad spectrum of symptoms, which are all present in a wide range of other, much more common conditions, gives a low positive predictive value for any one presenting symptom.<sup>13,14</sup> Myeloma is therefore a cancer with high diagnostic difficulty and is deemed ‘harder to suspect’ than most other cancers.<sup>15</sup> Abnormal results from some commonly undertaken laboratory tests may also prompt consideration of a myeloma diagnosis: unexplained anaemia, elevated ESR, unexplained renal impairment, high serum protein level and hypercalcaemia.<sup>14,17</sup> Earlier diagnosis requires thinking of myeloma as a possible diagnosis and sending blood (with or without urine) to test for monoclonal immunoglobulin; the testing laboratory might offer this as a myeloma screen rather than the separate parts of serum immunoglobulins and electrophoresis and either serum FLC or urine electrophoresis. If there is no monoclonal immunoglobulin, then the diagnosis of myeloma has been excluded, with the exception of the 1% of myeloma cases that do not secrete detectable monoclonal immunoglobulin. For these non-secretors, bone marrow examination is prompted by clinical features, other laboratory results and radiology. When monoclonal immunoglobulin is identified then the differential diagnosis for its source, that is usually MGUS or myeloma, must be investigated to decide whether or not a bone marrow examination is required.

## Development of tests for monoclonal immunoglobulins

Myeloma cells secrete monoclonal immunoglobulin that is unique to the cancer clone, and in laboratory tests, this can usually be easily distinguished from polyclonal immunoglobulin secreted by normal plasma cells. In the laboratory, the monoclonal immunoglobulin may be whole antibody, that is two identical heavy chains (IgG subclasses 1–4, IgA subclasses 1–2, IgM, IgD or IgE) combined with two identical light chains (kappa or lambda) and/or monoclonal free light chains (FLC).

In 1847, Bence Jones described the first cancer biomarker, a protein present in the urine of a myeloma patient.<sup>18</sup> The development of serum protein electrophoresis in the 1950s enabled the identification of a band of proteins of homogeneous isoelectric point (whole monoclonal immunoglobulin/M-protein/paraprotein/gammopathy) in the serum of many patients with myeloma. In the 1960s, the Bence Jones protein was identified as monoclonal FLC. This urinary monoclonal FLC and the whole monoclonal immunoglobulin in serum were also then shown to be the products of the myeloma clone of plasma cells.<sup>19,20</sup>

Laboratory testing for monoclonal FLC relied on protein electrophoresis in urine until the early 2000s, when an assay was developed to quantify FLC in serum. The serum FLC test measures the levels of kappa and lambda FLC separately, providing a ratio of the kappa and lambda levels. The presence of monoclonal FLC at levels sufficient to perturb the normal ratio derived from polyclonal kappa and lambda FLC is a surrogate marker of monoclonal FLC. Studies have shown that the serum FLC test has greater sensitivity than urine electrophoresis for detecting and monitoring myeloma in patients who have light chain-only (LCO) myeloma and in non-secretory myeloma.<sup>21–23</sup> More recently, mass spectrometry and isoelectric focusing provide highly sensitive detection of monoclonal immunoglobulin that can be identified in most cases of non-secretory myeloma, although these tests are not widely available and are relatively expensive.<sup>24,25</sup>

## The clinical relevance of monoclonal immunoglobulin type and level in blood and urine

Central laboratory analysis of blood and urine from 5573 newly diagnosed myeloma patients enrolled in UK clinical trials showed the most common whole monoclonal immunoglobulin type was IgG (56%), followed by IgA (26%), but delayed diagnosis and poor outcome were most significant in the 576 LCO patients (10%), 70 IgD patients (1.2%) and in the 60 (1.1%) non-secretory (NS) cases defined by immunofixation negative in blood and urine.<sup>26</sup> Of the 60 non-secretors, 31 had abnormal serum FLC kappa lambda ratios, and in 23 of the 60 non-secretors, the FLC were >100 mg/L, allowing monitoring of response to treatment and for relapse. Of the 576 LCO patients, 113 (20%) had insufficient FLC levels in urine to monitor response to treatment, but all had serum FLC levels >100 mg/L, allowing monitoring of response to treatment and for relapse.<sup>26</sup>

Assessing monoclonal immunoglobulin type in 2592 patients enrolled in UK myeloma trials pre-2000, 361 (14%) LCO patients had worse median survival times (1.9 years) than 718 (28%) patients with IgA and 1513 (58%) patients with IgG monoclonal immunoglobulin (2.3 and 2.5 years respectively).<sup>27</sup> However, IgA and IgG patients with levels of FLC similar to those of LCO patients also had poor survival times because of renal impairment. FLC excretion was higher for lambda than for kappa types, but there was no difference in survival between the two FLC types when stratified for level of FLC excretion, indicating that care of renal function is vital to improving the survival of any patient with high levels of FLC. At diagnosis, LCO patients were younger, had worse performance status and had more lytic lesions, thought to reflect late and missed diagnoses.

Myeloma cast nephropathy causes up to 90% of severe acute kidney injury in myeloma patients and is caused by high levels (>500 mg/L) of nephrotoxic monoclonal FLC, and half of these patients have LCO myeloma.<sup>28,29</sup> Early

diagnosis and reduction of serum FLC levels are associated with renal recovery and improved survival.<sup>30,31</sup> Earlier diagnosis of these patients is achieved by short turnaround times for serum FLC test results and flagging to haematology new FLC level results >500 mg/L.<sup>32</sup>

Based on the time of adoption of novel myeloma therapies, IgD myeloma patients comprised 44/2789 (1.6%) and 70/5773 (1.2%) of the old (1980–2002) and recent (2002–2016) trials respectively.<sup>33</sup> Overall, IgD myeloma was associated with male predominance, low-level whole monoclonal immunoglobulin (<10 g/L), high levels of FLC and lambda light chain preference. Despite the old trial series being a younger group (median age: 59 vs. 63 years), there was a higher frequency of bone lesions, advanced stage at diagnosis, worse performance status, severe renal impairment and early deaths compared with the recent trials, suggesting earlier diagnosis in recent trials. In recent versus old trials, median survival for IgD myeloma patients was 48 versus 22 months.

IgM myeloma is rare. In the event of progression from IgM MGUS, it is usually to lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinaemia) or other lymphomas.<sup>34</sup> In old and recent UK trials (8562 patients), there were three cases of IgE myeloma.

### The differential diagnosis for source of monoclonal immunoglobulin

Monoclonal immunoglobulin detection usually involves measuring serum levels of whole immunoglobulins (IgG, IgA and IgM) and FLC, then using electrophoresis, immunofixation and the kappa lambda FLC ratio to assess for monoclonal immunoglobulin.<sup>1</sup> These simple tests are near 100% reliable for the detection of monoclonal immunoglobulin associated with myeloma, so why do our health care systems have such a problem with delayed diagnosis? While myeloma accounts for only 2% of cancers and the symptoms are non-specific, if the thresholds for testing for monoclonal immunoglobulin were low, and even approached that of screening, the problem of timely myeloma diagnosis would be greatly reduced. The main problem is that monoclonal immunoglobulins also occur in MGUS, which is defined by the presence of a monoclonal immunoglobulin and the absence of myeloma or lymphoma.<sup>35</sup> The prevalence of MGUS is dependent on age; when screening 75 422 Icelanders aged over 40 years, MGUS was found in 2%, 6% and 13% of age groups 40–59, 60–79 and 80–103 years respectively. Myeloma is always preceded by MGUS. IgG and IgA MGUS progress to myeloma with an annual risk of 1%; FLC MGUS progress to myeloma with an annual risk of 0.3%; and IgM MGUS progress to lymphoplasmacytic lymphoma with an annual risk of 2%.<sup>36–40</sup> For every new case of myeloma, there are 100 cases of MGUS in the population, and so MGUS is frequently revealed in investigations for myeloma, lymphoma and many other conditions.

### Clinical significance of MGUS and case for screening

Although MGUS can be readily and cheaply identified, current guidelines do not recommend screening due to (i) uncertainty about who will and will not progress to myeloma; (ii) a lack of treatments appropriate for early disease intervention; and (iii) health economic uncertainty of the impacts and burden of population screening. Currently, a diagnosis of MGUS is predominantly incidental to clinical investigation of other conditions. Estimates suggest that at 60 years of age, the proportion of prevalent cases that are clinically recognized is ~13%.<sup>41</sup> Thus, screening for MGUS could potentially create a much greater MGUS population to monitor, in which overall progression rates to myeloma will be low (~1% per annum).<sup>39</sup> An additional complexity is that IgG and IgA MGUS progress to myeloma, whereas IgM MGUS progresses to lymphomas, predominantly Waldenstrom's macroglobulinaemia (WM).

Significant numbers of MGUS patients experience a spectrum of chronic and potentially severe MGUS-associated morbidities that further reduce their life expectancy.<sup>42</sup> The term *Monoclonal Gammopathy of Clinical Significance (MGCS)* has recently been adopted to define this group of patients.<sup>43</sup> The more common of these morbidities are predominantly caused by the deposition of monoclonal immunoglobulin in tissues, as is seen in AL amyloidosis and a variety of renal pathologies grouped as Monoclonal Gammopathy of Renal Significance (MGRS).<sup>44</sup> In other types of MGCS, the mechanisms include the monoclonal immunoglobulin acting as autoantibodies, cytokines and complement activators. Aside from MGCS, MGUS patients have an increased risk of axial bone fractures, with the highest risk being noted in those with reduced lumbar bone mineral density.<sup>45</sup> There is an increased incidence of venous thromboembolic disease (VTE) and, to a lesser extent, arterial thrombosis.<sup>46</sup> Patients with MGUS have low levels of antibody against common pathogens and are at twice the risk of bacterial infection.<sup>47,48</sup>

In summary, many MGUS patients have significant morbidities for which effective interventions exist. Additionally, if they progress to myeloma, then their myeloma diagnosis is usually made at an earlier stage of the disease, and their survival is better compared to the majority of new myeloma patients in whom their MGUS had not been diagnosed.<sup>49,50</sup> Previous guidelines have not recommended screening for MGUS, but as stratification of the risk of progression and low-toxicity anti-MGUS therapies become available, that is likely to change.<sup>51,52</sup> The ongoing iStopMM study (Iceland screens, treats or prevents multiple myeloma) has consented 80 759 (54.3%) of the 148 708 adults in Iceland over the age of 40. A total of 75 422 participants (93.4%) have provided a serum sample for screening for monoclonal immunoglobulin. Of those, 3725 (4.9%) had MGUS. Early results show that patients in the intensive follow-up arm of the study had significantly higher detection rates of myeloma and WM.<sup>53,54</sup> The PROMISE (Predicting Progression of Developing

Myeloma in a High-Risk Screened Population) study in the United States screens for MGUS and smouldering myeloma among African Americans and first-degree relatives of patients with myeloma, who are at least 40 years of age, and prospectively follows them to determine clinical, immune and genomic predictors of progression to MM.<sup>55</sup>

### Distinguishing myeloma from MGUS by simple thresholds for whole monoclonal immunoglobulin level and the kappa lambda serum FLC ratio

In central laboratory analysis of 3177 newly diagnosed UK myeloma patients, 24 patients (0.8%) were non-secretors defined by immunofixation negative for monoclonal immunoglobulin in blood and urine and serum FLC kappa lambda ratio within the normal reference range for FreeLite™ (0.26–1.65).<sup>56</sup> The 3153 myeloma patients with secretory disease were tested for the percentage of myeloma patients who would be undetected at diagnosis according to various serum FLC kappa lambda ratio ranges and whole monoclonal immunoglobulin level thresholds. Combining a kappa lambda ratio range of (0.26–1.65) with whole monoclonal immunoglobulin level thresholds of <5 g/L, <10 g/L and <15 g/L, the percentage of patients missed were 0.4%, 0.7% and 0.9% respectively. The kappa lambda ratio range of (0.26–1.65) is based on the diagnostic range for FreeLite™ found in 282 sera from healthy donors aged 20–90 years.<sup>57</sup> However, the kappa lambda ratio is often outside of this diagnostic range in several conditions, including chronic infection (osteomyelitis, endocarditis, HIV, EBV), inflammation, IgG4-related disease, autoimmune diseases (RA, SLE, Sjogren), neoplasm (lung, liver, gastric, rare T-cell lymphomas), liver disease (cirrhosis, chronic hepatitis) and renal failure.<sup>58</sup> Combining a kappa lambda ratio range of (0.1–7) with whole monoclonal immunoglobulin level thresholds of <5, <10 and <15 g/L, the percentage of patients missed were 0.5%, 1.2% and 2.0% respectively.<sup>56</sup> For 711 MGUS patients combining a kappa lambda FLC ratio range of (0.1–7) with whole monoclonal immunoglobulin level thresholds of <5, <10 and <15 g/L, the percentage of MGUS patients excluded were 89.5%, 93.4% and 95.5%. The use of the serum FLC ratio range of 0.1–7.0 in combination with a whole monoclonal immunoglobulin level thresholds of 10 g/L included 97.9% of myeloma cases and excluded 93.4% of MGUS cases. The 2.1% of myeloma patients missed ( $n=66$ ) included 0.8% ( $n=24$ ) of non-secretors.<sup>56</sup>

### Monoclonal immunoglobulin/gammopathy detection in routine laboratory practice

Guidelines for the role of laboratory testing in the diagnosis of myeloma are largely written from the perspective of a request from a clinician who has a strong suspicion of myeloma, knows what tests to request and how to interpret the results.<sup>1,17,59–61</sup> This is usually not the reality in clinical

practice, where primary and secondary care clinicians may have limited knowledge of the tests required and the interpretation of the results. Close integration of laboratory testing and haematology services can provide guidance in both these areas. Further, many immunoglobulin requests are made for reasons other than assessment for monoclonal immunoglobulin.

Testing for serum immunoglobulin levels and for monoclonal immunoglobulin is most relevant to the investigation of myeloma and B lymphoid neoplasia, including chronic lymphocytic leukaemia and B-cell non-Hodgkin lymphomas. Specialists including in haematology, nephrology, dermatology and neurology may request immunoglobulins and monoclonal immunoglobulin because of the rare conditions associated with MGUS.<sup>43,44</sup> Testing is equally relevant to the investigation of suspected antibody deficiency that may be primary or, much more likely, secondary, with B lymphoid neoplasia and MGUS among the commonest causes. However, in routine hospital clinical chemistry and immunology laboratories, less than half of requests indicate that any of the above may be the reason for requesting serum IgG, IgA and IgM. Serum immunoglobulin levels are of use in the investigation of many conditions and appear in guidelines for the investigation of liver disease and renal disease, and are commonly undertaken in autoimmune disease (including rheumatoid arthritis and systemic lupus erythematosus) and infections.<sup>62–65</sup>

In a 2017 UK survey with 118 responding hospital laboratories, 35% of all requests (for serum immunoglobulins and electrophoresis) made no mention of a B-cell neoplasia or associated symptoms in the clinical details (unpublished UKNEQAS study). This survey revealed marked variation in the delivery of these tests across the participating laboratories. There appeared to be a focus on automated high-throughput of large numbers of samples rather than guiding appropriate requesting of such testing. Deskilling of the interpretation of the electrophoresis patterns was also noted, with some laboratories reporting staff who were not professionally registered reading the serum and urine electrophoresis and the immunofixations. The turnaround times reported in the survey were variable, with a surprising number of labs reporting turnaround times in weeks rather than days. Communication of clinically significant results was also patchy, with a surprising number of laboratories making no attempt to inform the GP, requestor or Clinical Haematology of significant abnormal results.

### Myeloma diagnostic tool; guidance for primary care

Myeloma screening must be accessible for both primary and secondary care teams.

This requires education and an integrated approach with haematology services. The Myeloma UK early diagnosis programme has published a primary care myeloma diagnostic tool that describes when to suspect myeloma and what tests to request.<sup>66</sup> This tool is available at <https://academy.myelo>

[ma.org.uk/resources/gp-myeloma-diagnostic-tool/](https://ma.org.uk/resources/gp-myeloma-diagnostic-tool/) and is freely available for integration into laboratory requesting and reporting systems.

## Monoclonal Gammopathy Lab Tool

The Myeloma UK laboratory working group has produced a Monoclonal Gammopathy Lab Tool (Figure 2) available at <https://academy.myeloma.org.uk/resources/laboratory-practice/>.

The primary recommendation of the lab tool is that the testing laboratory should collaborate with Clinical

Haematology to create effective, shared patient flow pathways for new monoclonal gammopathy patients. The tool helps order recommendations for the improvement of myeloma screening in a diagnostic laboratory. These recommendations have been broken down into the three main phases of testing: preanalytical, analytical and postanalytical.

## Preanalytical phase: Ordering of tests

A myeloma screen must include serum electrophoresis and total immunoglobulin measurements as the core test. Two thirds of immunoglobulin requests do not state or

### Monoclonal Gammopathy Lab Tool



This tool will help order recommendations for the improvement of myeloma screening in a diagnostic laboratory. These recommendations have been broken down into the three main phases of testing; pre-analytical, analytical, and post-analytical.

Primary recommendation		●	Essential
The testing laboratory should collaborate with Clinical Haematology to create effective, shared patient flow pathways for new monoclonal gammopathy patients.		●●●	Optimal
<b>1. Pre-analytical phase: ordering of tests</b>			
●	1.1 Myeloma screening is accessible for both primary and secondary care teams		
	1.2 A myeloma screen includes serum electrophoresis and total immunoglobulin measurements as the core test		
	1.3 A second assay is included in a myeloma screen – this should be either urine electrophoresis or serum free light chains		
	1.4 Serum free light chains are a part of the testing repertoire of the laboratory (either in-house or as a referred test)		
●●	1.5 Myeloma screening is available on electronic patient requesting platforms – both primary and secondary care		
	1.6 Calcium levels, serum creatinine and a full blood count are also requested at the time of the myeloma screen		
●●●	1.7 Ordering is available on electronic patient requesting as a batch test, to allow comprehensive testing to be performed		
	1.8 Appropriate repeat test intervals are installed into the testing laboratory LIMS system to reduce burden of unnecessary testing for total immunoglobulins, urine electrophoresis and serum free light chains		
<b>2. Analytical phase: analytical testing of samples</b>			
●	2.1 The laboratory must have UKAS accreditation (ISO15189) for all assays involved in the myeloma screen		
	2.2 The laboratory successfully participates in ISO17043 accredited EQA programmes for their myeloma screen analytes		
	2.3 All abnormal serum electrophoresis results in new patients are followed up with either immunosubtraction or immunofixation		
	2.4 All abnormal urine electrophoresis results are followed up with urine immunofixation		
	2.5 All newly identified free light chain monoclonal proteins via serum immunofixation have IgD/IgE immunofixation performed		
	2.6 All new abnormal serum free light chain ratio results are evaluated and if monoclonality suspected, confirmed by immunofixation		
	2.7 The laboratory has a robust protocol for reporting significant new monoclonal gammopathy patients		
	2.8 The laboratory has a reflex protocol to add on serum free light chains on initial serum electrophoresis/immunoglobulin results of concern		
●●	2.9 The turnaround time for serum electrophoresis/total immunoglobulins is 3 days or less		
	2.10 The laboratory has a consistent protocol for reporting the size of the paraprotein		
●●●	2.11 The laboratory has a safety-net protocol for ensuring that a full myeloma screen is performed on all suitable samples		
<b>3. Post-analytical phase: interpretation and reporting of results</b>			
●	3.1 The laboratory issues interpretive guidance to clinical users for serum electrophoresis/total immunoglobulin, serum free light chain and urine electrophoresis results		
●●	3.2 The laboratory and Clinical Haematology collaborate to risk stratify all new monoclonal proteins, to determine the most appropriate management pathway for the patient		
	3.3 The laboratory contributes to the monitoring process of low-risk MGUS patients, providing interpretation of monitoring bloods		

FIGURE 2 Monoclonal Gammopathy Lab Tool.

are not related to myeloma screening, but the patient may nevertheless have myeloma. Abnormalities in these tests should prompt consideration of testing for FLC monoclonal immunoglobulin.

Testing for FLC monoclonal immunoglobulin should always be part of a myeloma screen, either by serum FLC testing or urine protein electrophoresis for BJP. The UK BSH Guideline, NICE guideline, European and International Myeloma Working Group Guidelines all recommend the use of serum rather than urine FLC testing<sup>1,17,59,67</sup> because the use of serum FLC testing will improve the detection of non-secretory and oligosecretory LCO myeloma as well as cases of MGRS and AL amyloidosis.<sup>44,68–70</sup> However, in some cases, serum FLC testing gives normal results despite the presence of BJP in the urine, so it may be necessary to use all three tests to fully investigate myeloma in cases with strong clinical indications.<sup>71</sup> Urine protein electrophoresis methods may be favoured due to health and economic reasons, but they should have suitable sensitivity.<sup>72</sup>

Myeloma is preceded by MGUS for many years, and so if no serum whole or FLC monoclonal immunoglobulin is found, then there is little point in testing for these again for 12 months in the absence of strong clinical indicators. If monoclonal immunoglobulins are found at levels below the threshold for urgent referral to haematology, then the tests should be repeated in a few months. There is a consensus that all patients with newly diagnosed MGUS should have appropriate blood tests (full blood count, creatinine, serum calcium and whole and FLC monoclonal immunoglobulin levels) performed 6 months after diagnosis, with annual follow-up thereafter, although the interval can be longer for patients with low-risk MGUS.<sup>73</sup> The rationale for this approach is based on the observation that the risk of MGUS transformation is highest during the first year after diagnosis.<sup>74</sup>

## Analytical phase

It is important that the laboratory be alert to suspicious findings when reporting immunoglobulin, electrophoresis and serum FLC results and have robust protocols for further investigation, for example by immunofixation. [Figure 3](#) provides some guidance on this, but lab interpretation is vital.

All abnormal serum electrophoresis results in new patients should be followed up with immunotyping (immunofixation or immunosubtraction) ([Figure 2](#) [2.3]). At myeloma diagnosis, the whole monoclonal immunoglobulin is <10 g/L in 5% of IgG myeloma cases and 11% of IgA myeloma cases, although most of these low-level whole monoclonal immunoglobulins are associated with high levels of FLC monoclonal immunoglobulin.<sup>56</sup> This is particularly important for IgA monoclonal immunoglobulin, where the monoclonal band/s can be obscured by other proteins in the beta 2 region of the electrophoretic

strip. An elevated total IgA level is common in laboratory practice, but particularly if associated with low IgG and/or IgM levels, should prompt immunofixation and serum FLC testing.

All newly identified light chain monoclonal proteins via serum immunofixation should have IgD/IgE immunofixation performed ([Figure 2](#) [2.5]). Conventional immunofixation has six lanes: total protein, immunoglobulins G, A and M heavy chains, and kappa and lambda light chains. If there is a light chain band in the absence of a heavy chain band, that may be FLC or an IgD or IgE monoclonal immunoglobulin.

All new abnormal serum FLC ratio results should be evaluated, and if monoclonality is suspected, confirmed by immunofixation ([Figure 2](#) [2.6]; See also earlier section *Distinguishing myeloma from MGUS by simple thresholds for monoclonal immunoglobulin level and the kappa lambda serum FLC ratio*). Levels of serum FLC are elevated by increased immunoglobulin secretion and reduced glomerular filtration; it is an abnormal ratio that is the focus for the detection of FLC monoclonal immunoglobulin. A ratio outside of the kit manufacturers normal range (FreeLite™ 0.26–1.65) can be caused by many conditions apart from FLC M-Ig, while the kappa lambda ratios outside of the 0.1–7 range are almost always attributable to FLC monoclonal immunoglobulin.<sup>56,58</sup> Results in between these two ranges that might be associated with low levels of FLC monoclonal immunoglobulin, as in light-chain amyloid and MGRS, should prompt immunofixation of urine. All samples with a new whole monoclonal immunoglobulin should have serum FLCs tested because the kappa lambda FLC ratio is important to risk stratification for progression of MGUS to myeloma or lymphoma.<sup>36,37</sup>

## Postanalytical phase interpretation and reporting of results

This is an area that particularly needs to be discussed and agreed upon with the local haematology services. Clinical comments sent out with laboratory results and flagging systems for significantly abnormal results are essential to ensure the appropriate and timely referral of patients with high-risk MGUS and multiple myeloma. A balance needs to be struck between causing delayed diagnosis of myeloma and referring patients with MGUS to haematology outpatients as an urgent suspicion of cancer.

The laboratory should issue interpretive guidance to clinical users for serum electrophoresis/total immunoglobulin levels, serum FLC and urine electrophoresis. Adding interpretation to raw monoclonal immunoglobulin results is often difficult because of a lack of clinical details, especially when the whole monoclonal immunoglobulin levels are <10 g/L and the serum kappa lambda FLC ratio is close to the laboratory reference range. This is because in clinical practice, most new whole monoclonal immunoglobulin and abnormal serum FLC ratios derive from MGUS plasma cell clones or are small abnormalities in the FLC ratio caused by conditions unrelated



## Myeloma Diagnostic Tool: Guidance for Primary Care



Response to results	
<ul style="list-style-type: none"> <li>Any paraprotein/abnormal sFLC ratio <b>with</b> significant symptoms indicative of an urgent problem (e.g. spinal cord compression, acute kidney injury)</li> </ul>	Recommend <b>immediate referral</b> to Clinical Haematology
<ul style="list-style-type: none"> <li>Moderate concentration of paraprotein (IgG &gt; 15 g/L, IgA or IgM &gt; 10 g/L)</li> <li>Identification of an IgD or IgE paraprotein (regardless of concentration)</li> <li>Significant abnormal sFLC ratio (&lt;0.1 or &gt;7)               <ul style="list-style-type: none"> <li>Identification of BJP</li> </ul> </li> </ul>	Recommend <b>urgent referral</b> to Clinical Haematology (2-week rule)
<ul style="list-style-type: none"> <li>Minor concentration of paraprotein (IgG &lt; 15 g/L, IgA or IgM &lt; 10 g/L) <b>without</b> relevant symptoms</li> <li>Minor abnormal sFLC ratio (&gt;0.1 and &lt;7, but outside normal range)</li> </ul> <p>This pattern is common in elderly patients</p>	<p>Recommend <b>recheck</b> serum and urine in 2–3 months to confirm pattern and assess any progression.</p> <p>Patients whose paraprotein concentration increases (25% and &gt; 5 g/L) or develop symptoms will need an <b>urgent referral</b>.</p> <p><b>Discuss</b> with your Clinical Haematology Department if results not clear or concerns.</p>
<ul style="list-style-type: none"> <li>No serum paraprotein</li> <li>Normal sFLC ratio (0.26–1.65)*               <ul style="list-style-type: none"> <li>No BJP</li> </ul> </li> <li>Normal immunoglobulin levels</li> </ul> <p>*some laboratories may have a slightly different reference range</p>	Myeloma very <b>unlikely</b> but symptoms may still need to be investigated with other clinical specialties

NICE guideline [NG12] Suspected cancer: recognition and referral <https://www.nice.org.uk/guidance/ng12>  
 NICE guideline [NG35] Myeloma: diagnosis and management <https://www.nice.org.uk/guidance/ng35>

For any queries or additional resources for healthcare professionals on myeloma and related conditions, please visit [academy.myeloma.org.uk](https://academy.myeloma.org.uk) or email us at [earlydiagnosis@myeloma.org.uk](mailto:earlydiagnosis@myeloma.org.uk)

Published November 2020 • Updated March 2022

**FIGURE 3** Myeloma UK primary care myeloma diagnostic tool: response to results.

to neoplastic plasma cells, including kidney disease, inflammation and infection. Furthermore, myeloma arises in an age range in which these conditions are common.

Within the laboratory, applying a whole monoclonal immunoglobulin threshold of 10 g/L with a serum FLC ratio range (<0.1 or >7) can exclude over 93% of MGUS cases and provide 98% sensitivity for the detection of myeloma (see [Figure 3](#)).<sup>56</sup> Whole monoclonal immunoglobulin levels >30 g/L and kappa lambda FLC ratio >100 both fulfil the diagnostic criteria for myeloma.<sup>1,35</sup> FLC levels >500 mg/L with a serum FLC ratio range <0.1 or >7 are caused by myeloma and have a high risk of cast nephropathy.<sup>28,29,58</sup> Early diagnosis and reduction of serum FLC levels (sFLC) are associated

with renal recovery and improved survival.<sup>30,31</sup> Earlier diagnosis of these patients is achieved by short turnaround times for serum FLC tests and telephoning to haematology with new FLC levels >500 mg/L.<sup>32</sup> As discussed above in the re-ordering of tests, the laboratory should contribute to the monitoring process of low-risk MGUS patients by providing interpretation of monitoring blood results.<sup>73</sup>

## CONCLUSION

Myeloma patients continue to experience delayed diagnosis, leading to worse outcomes. Earlier diagnosis of these

patients can be achieved by collaboration between the laboratory and haematologists, with prompt laboratory analysis by well-trained staff, preagreed interpretive comments that guide next actions and pro-active communication of significant results by the laboratory to requesting clinicians. In addition, a strategy agreed together with primary care for monitoring low-risk MGUS patients will also facilitate effective detection of myeloma, and the laboratory has a key role to play in this.

## ACKNOWLEDGEMENTS

Our thanks for input to the manuscript from Sarah Linstead and Joanne Morris.

## FUNDING INFORMATION

Myeloma UK.

## ORCID

Mark Drayson  <https://orcid.org/0000-0002-1528-7564>

Guy Pratt  <https://orcid.org/0000-0002-6937-2852>

## REFERENCES

- Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol.* 2014;15(12):538–48.
- van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. *Lancet.* 2021;397(10272):410–27.
- Cowan AJ, Allen C, Barac A, Basaleem H, Bensenor I, Curado MP, et al. Global burden of multiple myeloma: a systematic analysis for the Global Burden of Disease Study 2016. *JAMA Oncol.* 2018;4:1221–7.
- Acquah ME, Hsing AW, McGuire V, Wang S, Birmann B, Dei-Adomakoh Y. Presentation and survival of multiple myeloma patients in Ghana: a review of 169 cases. *Ghana Med J.* 2019;53(1):52–8.
- Kumar SK, Dimopoulos MA, Kastritis E, Terpos E, Nahi H, Goldschmidt H, et al. Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia.* 2017;31:2443–8.
- Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. *Lancet Oncol.* 2012;13(4):353–65.
- Howell DA, Smith AG, Jack A, Patmore R, Macleod U, Mironska E, et al. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematol.* 2013;13:9.
- Friese CR, Abel GA, Magazu LS, Neville BA, Richardson LC, Earle CC. Diagnostic delay and complications for older adults with multiple myeloma. *Leuk Lymphoma.* 2009;50(3):392–400.
- Goldschmidt N, Zamir L, Poperno A, Kahan NR, Paltiel O. Presenting signs of multiple myeloma and the effect of diagnostic delay on the prognosis. *J Am Board Fam Med.* 2016;29(6):702–9.
- Lacey K, Bishop JF, Cross HL, Chondros P, Lyratzopoulos G, Emery JD. Presentations to general practice before a cancer diagnosis in Victoria: a cross-sectional survey. *Med J Aust.* 2016;205(2):66–71.
- Kariyawasan CC, Hughes DA, Jayatillake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. *QJM.* 2007;100(10):635–40.
- National Cancer Intelligence Network. Routes to Diagnosis 2006–2016 Workbook. 2016 [Cited 2021 Nov 13]. Available from: [http://www.ncin.org.uk/publications/routes\\_to\\_diagnosis](http://www.ncin.org.uk/publications/routes_to_diagnosis)
- Forbes LJ, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation: a survey of cancer patients. *Br J Cancer.* 2014;111(3):581–8.
- Shephard EA, Neal RD, Rose P, Walter FM, Litt EJ, Hamilton WT. Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case-control study using electronic records. *Br J Gen Pract.* 2015;65(631):e106–13.
- Koo MM, Hamilton W, Walter FM, Rubin GP, Lyratzopoulos G. Symptom signatures and diagnostic timeliness in cancer patients: a review of current evidence. *Neoplasia.* 2018;20(2):165–74.
- Atkin C, Iqbal G, Planche T, Pratt G, Yong K, Wood J, et al. Diagnostic pathways in multiple myeloma and their relationship to end organ damage: an analysis from the Tackling Early Morbidity and Mortality in Myeloma (TEAMM) trial. *Br J Haematol.* 2021;192(6):997–1005.
- Sive J, Cuthill K, Hunter H, Kazmi M, Pratt G, Smith D, et al. Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline. *Br J Haematol.* 2021;193(2):245–68.
- Bence JH. Papers on chemical pathology, lecture III. *Lancet.* 1847;2:88–92.
- Gally JA, Edelman GM. Physicochemical properties of Bence-Jones proteins in the form of I-chain dimers. *Biochim Biophys Acta.* 1965;94:175–82.
- Grey HM, Mannik M, Kunkel HG. Individual antigenic specificity of myeloma proteins. Characteristics and localization to subunits. *J Exp Med.* 1965;121:561–75.
- Bradwell AR, Carr-Smith HD, Mead GP, Tang LX, Showell PJ, Drayson MT, et al. Highly sensitive, automated immunoassay for immunoglobulin free light chains in serum and urine. *Clin Chem.* 2001;47(4):673–80.
- Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. *Lancet.* 2003;361(9356):489–91.
- Drayson M, Tang LX, Drew R, Mead GP, Carr-Smith H, Bradwell AR. Serum free light-chain measurements for identifying and monitoring patients with nonsecretory multiple myeloma. *Blood.* 2001;97(9):2900–2.
- Giles HV, Cook MA, Drayson MT, Cook G, Wright NJ, North SJ, et al. Redefining non-measurable multiple myeloma using mass spectrometry. *Blood.* 2022;139(6):946–50.
- Chapman JR, Thoren KL. Tracking of low disease burden in multiple myeloma: using mass spectrometry assays in peripheral blood. *Best Pract Res Clin Haematol.* 2020;33(1):101142.
- Heaney JLJ, Campbell JP, Griffin AE, Birtwistle J, Shemar M, Child JA, et al. Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests. *Br J Haematol.* 2017;178(2):220–30.
- Drayson M, Begum G, Basu S, Makkuni S, Dunn J, Barth N, et al. Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. *Blood.* 2006;108(6):2013–9.
- Royal V, Leung N, Troyanov S, Nasr SH, Écotière L, LeBlanc R, et al. Clinicopathologic predictors of renal outcomes in light chain cast nephropathy: a multicenter retrospective study. *Blood.* 2020;135(21):1833–46.
- Hutchison CA, Batuman V, Behrens J, Bridoux F, Sirac C, Dispenzieri A, et al. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. *Nat Rev Nephrol.* 2011;8(1):43–51.
- Hutchison CA, Cockwell P, Stringer S, Bradwell A, Cook M, Gertz MA, et al. Early reduction of serum-free light chains associates with renal recovery in myeloma kidney. *J Am Soc Nephrol.* 2011;22:1129–36.
- Hutchison CA, Bladé J, Cockwell P, Cook M, Drayson M, Femand J, et al. Novel approaches for reducing free light chains in patients with myeloma kidney. *Nat Rev Nephrol.* 2012;8(4):234–43.
- Rana R, Pratt G, Cook M, Drayson MT, Ramasamy K, Sadler R, et al. Improving the diagnostic pathway in patients presenting with acute

- kidney injury secondary to de novo multiple myeloma: a short report. *BMJ Open Qual.* 2021;10(3):e001085.
33. Agbuduwe C, Iqbal G, Cairns D, Menzies T, Dunn J, Gregory W, et al. Clinical characteristics and outcomes of IgD myeloma: experience across UK national trials. *Blood Adv.* 2022;6(17):5113–23.
  34. Feyler S, O'Connor SJ, Rawstron AC, Subash C, Ross FM, Pratt G, et al. IgM myeloma: a rare entity characterized by a CD20-CD56-CD117- immunophenotype and the t(11;14). *Br J Haematol.* 2008;140(5):547–51.
  35. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia.* 2010;24(6):1121–7.
  36. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ III, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood.* 2005;106(3):812–7.
  37. Turesson I, Kovalchik SA, Pfeiffer RM, Kristinsson SY, Goldin LR, Drayson MT, et al. Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. *Blood.* 2014;123(3):338–45.
  38. Perez-Persona E, Mateo G, Garcia-Sanz R, Mateos MV, de Las Heras N, de Coca AG, et al. Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells. *Br J Haematol.* 2010;148(1):110–4.
  39. Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Kumar S, Cerhan JR, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2018;378(3):241–9.
  40. Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ III, Colby CL, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet.* 2010;375(9727):1721–8.
  41. Therneau TM, Kyle RA, Melton LJ III, Larson DR, Benson JT, Colby CL, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. *Mayo Clin Proc.* 2012;87(11):1071–9.
  42. Kristinsson SY, Bjorkholm M, Andersson TML, Eloranta S, Dickman PW, Goldin LR, et al. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. *Haematologica.* 2009;94(12):1714–20.
  43. Feraud JP, Bridoux F, Dispenzieri A, Jaccard A, Kyle RA, Leung N, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. *Blood.* 2018;132(14):1478–85.
  44. Leung N, Bridoux F, Batuman V, Chaidos A, Cockwell P, D'Agati VD, et al. The evaluation of monoclonal gammopathy of renal significance: a consensus report of the International Kidney and Monoclonal Gammopathy Research Group. *Nat Rev Nephrol.* 2019;15(1):45–59.
  45. Melton LJ 3rd, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopathy of undetermined significance. *J Bone Miner Res.* 2004;19(1):25–30.
  46. Kristinsson SY, Pfeiffer RM, Bjorkholm M, Goldin LR, Schulman S, Blimark C, et al. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood.* 2010;115(24):4991–8.
  47. Karlsson J, Andreasson B, Kondori N, Erman E, Riesbeck K, Hogevik H, et al. Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance. *Clin Vaccine Immunol.* 2011;18(6):969–77.
  48. Gregersen H, Madsen KM, Sorensen HT, Schönheyder HC, Ibsen JS, Dahlerup JF. The risk of bacteremia in patients with monoclonal gammopathy of undetermined significance. *Eur J Haematol.* 1998;61(2):140–4.
  49. Sigurdardottir EE, Turesson I, Lund SH, Lindqvist EK, Mailankody S, Korde N, et al. The role of diagnosis and clinical follow-up of monoclonal gammopathy of undetermined significance on survival in multiple myeloma. *JAMA Oncol.* 2015;1(2):168–74.
  50. Go RS, Gundrum JD, Neuner JM. Determining the clinical significance of monoclonal gammopathy of undetermined significance: a SEER-Medicare population analysis. *Clin Lymphoma Myeloma Leuk.* 2015;15(3):177–86.
  51. Atkin C, Richter A, Sapey E. What is the significance of monoclonal gammopathy of undetermined significance? *Clin Med (Lond).* 2018;18(5):391–6.
  52. Tomasson MH, Ali M, De Oliveira V, Xiao Q, Jethava Y, Zhan F, et al. Prevention is the best treatment: the case for understanding the transition from monoclonal gammopathy of undetermined significance to myeloma. *Int J Mol Sci.* 2018;19(11):3621.
  53. Rognvaldsson S, Love TJ, Thorsteinsdottir S, Reed ER, Óskarsson JB, Pétursdóttir Í, et al. Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. *Blood Cancer J.* 2021;11(5):94.
  54. Kristinsson SY, Rognvaldsson S, Thorsteinsdottir S, Reed ER, Oskarsson JTT, Petursdottir I, et al. Screening for monoclonal gammopathy of undetermined significance: a population-based randomized clinical trial. First results from the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) Study (Abstract). *Blood.* 2021;138:156. <https://doi.org/10.1182/blood-2021-152333>
  55. Ghobrial I. Predicting Progression of Developing Myeloma in a High-Risk Screened Population (PROMISE). Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03689595https://www.clinicaltrials.gov/ct2/show/NCT03689595>
  56. Heaney JL, Richter A, Bowcock S, Pratt G, Child JA, Jackson G, et al. Excluding myeloma diagnosis using revised thresholds for serum free light chain ratios and M-protein levels. *Haematologica.* 2020;105(4):e169–71.
  57. Katzmann JA, Clark RJ, Abraham RS, Bryant S, Lymp JF, Bradwell AR, et al. Serum reference intervals and diagnostic ranges for free kappa and free lambda immunoglobulin light chains: relative sensitivity for detection of monoclonal light chains. *Clin Chem.* 2002;48(9):1437–44.
  58. Hutchison CA, Plant T, Drayson M, Cockwell P, Kountouri M, Basnayake K, et al. Serum free light chain measurement aids the diagnosis of myeloma in patients with severe renal failure. *BMC Nephrol.* 2008;9:11. <https://doi.org/10.1186/1471-2369-9-11>
  59. Myeloma: diagnosis and management NICE guideline [NG35]. 2016.
  60. Willrich MAV, Murray DL, Kyle RA. Laboratory testing for monoclonal gammopathies: focus on monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *Clin Biochem.* 2018;51:38–47.
  61. Dispenzieri A, Kyle R, Merlini G, Miguel JS, Ludwig H, Hajek R, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia.* 2008;23(2):215–24.
  62. Newsome PN, Cramb R, Davison SM, Dillon JF, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. *Gut.* 2018;67(1):6–19.
  63. Fernández-Ruiz M, López-Medrano F, Varela-Peña P, Lora-Pablos D, García-Reyne A, González E, et al. Monitoring of immunoglobulin levels identifies kidney transplant recipients at high risk of infection. *Am J Transplant.* 2012;12(10):2763–73.
  64. Hull RP, Goldsmith DJ. Nephrotic syndrome in adults. *BMJ.* 2008;336(7654):1185–9.
  65. Yuzawa Y, Yamamoto R, Takahashi K, Katafuchi R, Tomita M, Fujigaki Y, et al. Evidence-based clinical practice guidelines for IgA nephropathy 2014. *Clin Exp Nephrol.* 2016;20(4):511–35.
  66. <https://academy.myeloma.org.uk/resources/gp-myeloma-diagnostic-tool/>
  67. Caers J, Garderet L, Kortüm KM, O'Dwyer ME, van de Donk NWCJ, Binder M, et al. European Myeloma Network recommendations on

- tools for the diagnosis and monitoring of multiple myeloma: what to use and when. *Haematologica*. 2018;103(11):1772–84.
68. Dejoie T, Corre J, Caillon H, Hulin C, Perrot A, Caillot D, et al. Serum free light chains, not urine specimens, should be used to evaluate response in light-chain multiple myeloma. *Blood*. 2016;128:2941–8.
69. Feraud JP, Bridoux F, Kyle RA, Kastiris E, Weiss BM, Cook MA, et al. How I treat monoclonal gammopathy of renal significance (MGRS). *Blood*. 2013;122(22):3583–90.
70. Gillmore JD, Wechalekar A, Bird J, Cavenagh J, Hawkins S, Kazmi M, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haematol*. 2015;168(2):207–18.
71. Beetham R, Wassell J, Wallage MJ, Whiteway AJ, James JA. Can serum free light chains replace urine electrophoresis in the detection of monoclonal gammopathies? *Ann Clin Biochem*. 2007;44(Pt6):516–22.
72. Beetham R. Detection of Bence Jones protein in practice. *Ann Clin Biochem*. 2000;37:563–70.
73. Stern S, Chaudhuri S, Drayson M, Henshaw S, Karunanithi K, Willis F, et al. Investigation and management of the monoclonal gammopathy of undetermined significance (MGUS). A British Society for Haematology Good Practice Paper.
74. Go RS, Heien HC, Sangaralingham LR, Habermann EB, Shah ND. Estimating the risk of progression of monoclonal gammopathy of undetermined significance into lymphoplasmacytic malignancies in the United States: determining demographic differences using a national dataset [abstract]. *Blood*. 2016;128(22):843.

**How to cite this article:** Drayson M, Jennis T, Laketic-Ljubojevic I, Patel D, Pratt G, Renwick S, et al. Laboratory practice is central to earlier myeloma diagnosis: Utilizing a primary care diagnostic tool and laboratory guidelines integrated into haematology services. *Br J Haematol*. 2024;00:1–11. <https://doi.org/10.1111/bjh.19224>