Monoclonal gammopathy and primary care

Even though most patients diagnosed with monoclonal gammopathy of undetermined significance will never develop malignant disease, follow-up is needed to identify those patients at risk of progression.

A finding of monoclonal gammopathy (M-spike) becomes increasingly common with patient age. The presence of monoclonal protein (M-protein) is found in approximately 3% to 4% of those over age 50, 5% over age 65, and almost 10% of those 85 or older.\(^1\) When considered as a group, patients with monoclonal gammopathy of undetermined significance (MGUS) have an approximately 1% cumulative chance per year of ultimately developing a malignant plasmaproliferative disorder such as multiple myeloma (MM), Waldenstrom macroglobulinemia (WM), or systemic AL amyloidosis.

What is monoclonal gammopathy, and when can it be encountered in general clinical practice?

Monoclonal gammopathy is the increased production of immunoglobulin secreted by an abnormally expanded clone of B-cells in an amount that can be identified by serum protein electrophoresis (SPE) or immunofixation of the serum and or urine.\(^1^2\) The monoclonal protein found can consist of light chains attached to heavy chains (whole immunoglobulin) or free light chains (FLC) alone. The discovery of a monoclonal protein can occur in a wide variety of clinical situations.\(^1^4\)

Dr Brigden is medical director of the Jack Ady Cancer Centre in Lethbridge, Alberta. He is also a clinical associate professor at the University of Calgary and associate adjunct professor at the University of Lethbridge. Dr Venner is a hematologist at the Cross Cancer Institute and a clinical assistant professor at the University of Alberta. He was the recipient of the first Conjoint Plasma Cell Dyscrasia Fellowship with the leukemia/BMT program of British Columbia and the London School of Medicine, St Bartholomew’s Hospital. He also served as locum consultant at the National Amyloidosis Centre, University College London, before assuming his current position.
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Initially, monoclonal gammopathy may be discovered:

- Entirely by chance.
- As part of an investigation for a clinical condition such as nephrotic syndrome, peripheral neuropathy, or congestive heart failure.
- During the investigation of skeletal symptoms or findings such as back pain, compression fractures, osteoporosis without known risk factor, or lytic bone lesions.
- With laboratory follow-up of hypergammaglobulinemia or hypogammaglobulinemia.
- With laboratory follow-up of an elevated erythrocyte sedimentation rate.
- With laboratory follow-up of abnormal values for individual serum immunoglobulins (IgG, IgA, IgM).
- As part of an investigation for a collagen vascular disease or inflammatory arthritis such as rheumatoid arthritis, polymyalgia rheumatica, scleroderma, or systemic lupus.
- As part of an investigation for suspected immunodeficiency or unexplained chronic infections.
- As part of the staging process for common hematological malignancies such as chronic lymphocytic leukemia, Hodgkin disease, or non-Hodgkin lymphoma.
- As part of an investigation for suspected myeloma, Waldenstrom macroglobulinemia, or systemic AL amyloidosis.

A monoclonal protein is often discovered incidentally on routine blood testing in an outpatient setting when completing the workup for patients with hypergammaglobulinemia or hypogammaglobulinemia, an elevated sedimentation rate, or an asymptomatic rise in serum protein levels. Patients who present with back pain, anemia, renal insufficiency, significant proteinuria, hypercalcemia, age-inappropriate osteopenia, osteolytic bone lesions, or unexplained peripheral neuropathy are often screened for the presence of an M-protein.\(^2\)\(^4\)

Many malignant and benign medical conditions commonly encountered in clinical practice may be associated with monoclonal gammopathy (see box\(^1\)\(^2\)\(^4\)). On very rare occasions, an M-protein may be detected and then not be found in subsequent follow-up investigations. This is most likely to occur when only a very small amount of M-protein is detected and detection is by immunofixation alone.\(^5\)

**Differential diagnosis for monoclonal gammopathy**

**Malignant**

**Plasma cell disease**
- Monoclonal gammopathy of undetermined significance
- Multiple myeloma
- Smouldering multiple myeloma
- AL amyloidosis
- Other rarer malignant plasma cell disorders

**B-cell (usually IgM) disease**
- Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia
- Chronic lymphocytic leukemia
- Small lymphocytic lymphoma
- Marginal zone lymphoma
- Other indolent lymphomas (rare)

**Benign**

**Autoimmune/inflammatory disease**
- Rheumatoid arthritis, ankylosing spondylitis
- Systemic lupus erythematos, scleroderma, Sjogren syndrome
- Vasculitis, polymyalgia rheumatica
- Paraprotein-associated neuropathies

**Infectious disease**
- Viral infections (EBV, CMV, HIV, HBV, HCV)
- Severe acute infections
- Subacute or chronic infections (osteomyelitis, endocarditis, abscess)

**Posttransplant effect**
- Response to stem cell or solid organ transplantation

When monoclonal protein is found, what investigations should be undertaken?

Past studies have found there was no follow-up in over 50% of cases where a monoclonal protein was discovered incidentally.\(^6\) Today we recognize that serum protein electrophoresis should be used to investigate in all cases of hypogammaglobulinemia or hypergammaglobulinemia, or when there are abnormally low serum levels of total immunoglobulins, including individual Ig classes.\(^1\)\(^3\) Serum protein electrophoresis is usually performed...
on an agarose gel. If a monoclonal protein is identified, it appears as a sharply defined spike (Figure 1). If the cause of the hypergammaglobulinemia is actually polyclonal in nature, as in the case of a chronic infectious or inflammatory state such as cirrhotic liver disease, a broad-based curve rather than a sharp spike will be seen.

The identification of an M-spike is always followed by immunofixation, which is performed with specific antisera against the various classes of immunoglobulin to confirm the presence of a monoclonal protein and identify specific associated heavy and light chain types, such as kappa or lambda (Figure 2). In cases with low serum immunoglobulin levels or generalized hypogammaglobulinemia, but no detectable serum monoclonal protein on SPE, immunofixation should also be performed, along with serum FLC analysis. Urine protein electrophoresis (UPE) and immunofixation of an aliquot from a 24-hour urine specimen may not be necessary on initial screening, but these tests must be performed when a serum or urine monoclonal protein is found in order to complete the baseline workup.

The relatively recent introduction of sensitive methods to measure low levels of free light chains in serum has established that both normal and malignant plasma cells secrete free light chains as well as whole immunoglobulin. An abnormal kappa-lambda serum FLC ratio can be used as a surrogate marker for the secretion of monoclonal free light chains. An abnormal kappa-lambda ratio is defined as less than 0.26 or greater than 1.65. This ratio is often abnormal even when the renal reabsorption threshold for light chains has not been exceeded, meaning that very small amounts of free light chains do not appear in the urine. This makes serum FLC testing ideal for detecting and monitoring the rarer cases of myeloma with very little immunoglobulin secretion (oligosecretory MM) as well as for identifying AL amyloidosis, where the amount of monoclonal protein is also often minute. Thus, during the initial investigation of a monoclonal gammopathy, in addition to blood...
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Counts, routine chemistries, SPE, and immunofixation, a serum FLC assay should also be performed since virtually 100% of cases of MM, WM, AL amyloidosis, and MGUS can initially be identified with these three non-invasive tests.1,2,7

What distinguishes MGUS from frankly malignant plasmaproliferative disease?
MGUS by definition is a monoclonal gammopathy characterized by a serum monoclonal protein of less than 30 g/L, plasma cells of less than 10% in the bone marrow, and, most importantly, by the absence of end-organ damage that can be attributed to the malignant plasma cell proliferation seen in multiple myeloma or the hyperviscosity, lymphadenopathy, and hepatosplenomegaly seen in Waldenstrom macroglobulinemia.2-4 In MM, end-organ damage is defined by the so-called CRAB features: hypercalcemia, renal insufficiency, anemia, bone lesions. Various defining features of MGUS, smoldering MM, MM, and WM are compared in Table 1.2,8

As noted earlier, the incidence of MGUS increases with age; MGUS is also more common in males than in females, and almost three times more prevalent in African Americans than Americans of European descent.2-4 While the precise cause of MGUS remains unknown, as in the case of MM, there is higher incidence in agricultural workers and those with a history of significant exposure to insecticides, herbicides, and fungicides.2-4 Prior radiation is also a risk factor, and there is familial tendency, with a 3.5-fold increased risk in relatives of a propositus.1-3 Interestingly, although conventional cytogenetics rarely detect an abnormality in MGUS, with FISH analysis, the same cytogenetic abnormalities typical of MM are found to be present in a high proportion of MGUS patients. This suggests a complex evolutionary etiology, including the accumulation of successive genetic “hits,” possibly combined with a progressive alteration and deregulation of the bone marrow microenvironment.2,3,8

How should MGUS be managed?
Studies have shown that MGUS patients have increased osteoclastogenesis as well as an abnormally high rate of bone reabsorption.9,10 Not surprisingly, patients with MGUS also experience a much higher degree of bone loss and fracture than age- and sex-matched controls.2-4,9 Specifically, there is an increased likelihood of developing vertebral and hip fractures.9,10 For this reason, the Nordic Myeloma Study Group and the UK Myeloma Forum have both recommended that anyone with age-inappropriate bone loss or vertebral

<table>
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<tr>
<th>Table 1. Defining features of the common beta cell clonal disorders, including monoclonal gammopathy of undetermined significance (MGUS).</th>
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<tbody>
<tr>
<td><strong>Asymptomatic</strong></td>
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<tr>
<td>MGUS</td>
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<tr>
<td><strong>M-spike</strong></td>
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<tr>
<td><strong>Bone marrow clonal cell population</strong></td>
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<tr>
<td><strong>CRAB criteria</strong></td>
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<tr>
<td><strong>Related organ or tissue impairment</strong></td>
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<tr>
<td>*Calcium: &gt; 0.25 mmol/L above the upper limit of normal or &gt; 2.75 mmol/L</td>
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<tr>
<td>Renal insufficiency: creatine &gt;173 mmol/L</td>
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<tr>
<td>Anemia: Hb 20 g/L below the lower limit of normal or Hb &lt; 100 g/L</td>
</tr>
<tr>
<td>Bone lesions: lytic lesions or osteoporosis with compression fractures1,2,3</td>
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</tbody>
</table>

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compression fractures, but without definitive known risk factors, should undergo monoclonal protein screening.\(^1,3\) Similarly, MGUS patients with T scores less than -1.0 should maintain a minimum oral intake of 1000 IU of vitamin D daily as well as a calcium intake between 1000 and 1500 mg/per day.\(^2,3\) Those identified with frank osteoporosis should be treated with bisphosphonates or other appropriate therapy.\(^9,10\)

There is an increased risk of peripheral neuropathy with MGUS. Accordingly, the various expert consensus groups have suggested that patients presenting with idiopathic peripheral neuropathy should be screened for MGUS. With screening, approximately 10% of patients presenting with idiopathic peripheral neuropathy will be found to have monoclonal gammopathy.\(^7,4\) Population-based cohort studies have suggested that MGUS patients may not have a higher risk of developing peripheral neuropathy, and most associated cases are unlikely to be caused by the actual MGUS.\(^11\) However, patients with an IgM-related neuropathy are often found to have serum-antimyelin-associated glycoprotein antibodies on testing, and may respond to appropriate therapies such as plasmapheresis and the administration of cytotoxic agents or the monoclonal antibody rituximab.\(^11\)

Other investigations have shown that MGUS patients are also more likely to experience thromboembolic events such as deep vein thrombosis.\(^12\) One study identified a relative risk of 3.3 for DVT with MGUS, with the greatest risk existing during the first year after diagnosis.\(^2,3,12\) Despite this observation, there is no evidence to date that any unique prophylactic measures should be taken.

What clinical features of MGUS indicate a risk of progression? In a series of longitudinal studies conducted over 50 years, Kyle and other researchers confirmed that virtually all cases of MM are preceded by MGUS, with a median duration of more than 10 years.\(^3,4,8\) Interestingly, patients were found to be at risk for progression even after 30 to 40 years of follow-up.\(^2,3\) However, it was simultaneously recognized that despite an average overall risk for progression of 1% per year, not all patients with MGUS ultimately developed symptomatic malignant MM, WM, or AL amyloidosis.\(^1,3\) This realization has stimulated efforts to discover which factors might help to stratify the risk for progression in individual cases. A Spanish group recently found that a preponderance of phenotypically abnormal plasma cells on bone marrow flow cytometry were associated with significant risk for progression.\(^4,8\) However, such an approach requires both invasive bone marrow sampling and an adequate sample.

Kyle and other researchers ultimately found a way to stratify MGUS patients into four groups at low, low-intermediate, intermediate, and high yearly risk for progression.\(^3,8\) To do this, they identified three easily quantifiable risk factors:

- An M-protein level greater than 15 g/L.
- The presence of IgA or IgM (i.e., non-IgG) protein.
- An abnormal FLC ratio.

Kyle also confirmed that the presence of more than 5% plasma cells in a bone marrow aspiration biopsy sample was an independent risk factor for progression, although the invasive nature of such a procedure eliminated this factor from the list of “easily quantifiable” risk factors.\(^3,4\) Interestingly, neither the presence or type of urine light chain nor the presence of an associated reduction in the noninvolved immunoglobulin classes (each abnormality exists in approximately 30% of newly diagnosed MGUS) has been found to be predictive for later progression.\(^2,4\)

Low-risk patients, those with none of the three risk factors, are known to have an absolute risk of progression to a plasma proliferative disorder at 20 years of only 5%. Approximately 70% of patients with new, incidentally discovered MGUS will fall into this category. The low-intermediate-risk patients, those with one risk factor, have a 21% risk of progression. The intermediate-risk patients, those with two risk factors, have a 37% risk of progression, while risk increases to 58% for patients in the high-risk group, who have three risk factors.\(^3,4\)

In established MGUS, what follow-up testing should be undertaken? For those patients with MGUS that does progress, the median time to progression is around 5 years, and overall progression risk is highest in the first 5 years.\(^3,8,13\) No uniformly predictable pattern for progression has been identified, with only 50% of patients ultimately developing MM. Five different patterns of progression from baseline monoclonal protein levels (Figure 3) have been identified by Kyle:

- Sudden, rapid increase.
- Gradual, steady increase.
- Initial stability followed by gradual increase.
- Initial stability followed by sudden increase.
- Ongoing relative stability over a number of years followed by the development of lytic lesions, anemia, or renal insufficiency/progressive M-protein proteinuria.

The existence of this last group
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makes it essential that MGUS follow-up include not only laboratory testing but also periodic history taking and physical examination. In fact, a study of MGUS patients experiencing optimal follow-up found that scheduled visits detected changes leading to the diagnosis of MM or WM in only 16% of cases, while myeloma-related complications (bone pain/fractures, anemia/fatigue, hypercalcemia, renal failure) were responsible for diagnosis in 45% of cases, and findings from diagnostic workup for less serious symptoms accounted for another 25%.14

Patients with low-risk MGUS do not require initial bone marrow examination, skeletal survey, or other imaging studies unless there are accompanying CRAB features, such as bone pain, anemia, or abnormal renal function. If there are no CRAB features and screening test results for AL amyloidosis and WM are negative, then patients may be followed with SPE (serum FLC optional) at 6 months initially, and then annually if they remain stable (Figure 4). Alternatively, a longer follow-up period of 2 to 3 years or even a symptom-based recall may suffice. Repeat annual visit testing should include history taking and physical examination, routine chemistries, and SPE, with serum FLC optional, unless the initial clonal protein discovered is light chain alone. It is important to note that the test of choice for those patients with light chain alone MGUS is serum FLC. In these instances, the SPE and UPE results can be misleading.

Patients with intermediate-risk and high-risk MGUS should have a bone marrow aspiration biopsy with conventional cytogenetics and FISH analysis, as well as a skeletal survey. Early specialist referral may also be considered for this group. If impending vertebral fracture or spinal cord compression is suspected, magnetic resonance imaging of the spine should also be performed. In this situation, the patient should be considered to have MM rather than MGUS. MRI may also prove helpful in confirming suspected progression from MGUS to MM because an abnormal signal on T1- or T2-weighted images strongly suggests pathological bone marrow infiltration. Patients with intermediate- or high-risk MGUS with an IgM monoclonal protein should have an initial abdominal CT scan, since unsuspected asymptomatic retroperitoneal lymphadenopathy may be present. If the results of these tests are normal, patients with IgM MGUS may be followed with SPE and routine blood work in 6 months, and then annually for life.

At the time of follow-up, radiological re-evaluation should be performed only if there have been symptoms and signs suggestive of bone disease development or progression. Patients with MGUS and known osteoporosis or osteopenia should have a follow-up bone density study every 2 years, and be assessed for response to any anti-resorptive therapy.

Patients followed regularly should be referred for subspecialty evaluation when symptoms compatible with the diagnosis of MM, lymphoma, WM, or AL amyloidosis develop. Referral might also be considered with development of unexplained new onset anemia, cytopenias, hypercalcemia, albuminuria, CHF, neuropathy, or an
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increase in the concentration of the monoclonal protein by more than 30% (minimum absolute increase of 5 g/L). All patients should be asked to make contact immediately with any significant change, such as the occurrence of bone pain and symptoms of fatigue.²⁻⁴,⁸

It is important to realize that interlaboratory variation in serial monoclonal protein SPE, UPE, and FLC determinations can be as high as 25%. For individual values, the biological coefficient of variation is around 8% for SPE and approaches 30% for UPE and FLC. This means that for any change between two serial observations to be truly significant, a 30% difference would be required for SPE values, and more than 70% in the case of UPE and FLC values.¹⁶

When should the possibility of AL amyloidosis be considered and further testing undertaken?

In AL amyloidosis, the abnormal monoclonal light chain (frequently lambda) causes systemic proteotoxicity by misfolding and aggregating in fibrils, thus interacting with and depositing in various tissues.⁴⁻⁸,¹⁷ The clinical presentation in amyloidosis usually depends on the organ system involved predominantly (Table 2). Hence, the differential diagnosis is based on early recognition of organ damage. For instance, early renal biopsy should be strongly considered for any patient with low-level proteinuria and renal failure or, alternatively, heavy proteinuria/nephrotic syndrome. Hepatomegaly, abnormal liver function, or liver failure related to amyloid deposition may initially present with nonspecific symptoms such as asthenia and unintentional weight loss, or simply an unanticipated elevation in alkaline phosphatase. Gastrointestinal tract involvement may manifest with gut motility

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**Figure 4. Management of patient with monoclonal protein found on serum protein electrophoresis, positive immunofixation, or abnormal serum free light chain ratio.**

*CRAB features include hypercalcemia, renal failure, anemia, bone lesions
†Repeat visits at more frequent intervals if M-protein value is progressively increasing
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problems, malabsorption, diarrhea, or recurrent gastrointestinal bleeding.\textsuperscript{4,17} Peripheral neuropathy is frequently seen and is typically sensory in nature. Carpal tunnel syndrome is highly associated with amyloidosis, although the syndrome is secondary to soft tissue fibril deposits around the carpal tunnel rather than to direct nerve damage. Autonomic neuropathy may manifest with postural hypotension or symptoms of abnormal gut motility.\textsuperscript{17}

A high index of suspicion is especially important in the case of cardiac amyloidosis, since by the time clinical symptoms are evident, irreversible cardiac damage has frequently occurred.\textsuperscript{4,17} With cardiac amyloidosis, both conduction system and pump function may be affected, producing arrhythmias, heart failure, or both. Heart failure is typically diastolic in nature with systolic dysfunction not appearing until late in the disease course. Troponin T and the N-terminal fragment of proatriuretic peptide (NT-proBNP) are sensitive markers of cardiac dysfunction in AL amyloidosis, with increases often noted several months before the onset of symptoms or detectable echocardiographic features.\textsuperscript{4} Unfortunately, elevations are not specific and may be noted in a variety of other cardiac diseases. Since almost all patients with cardiac amyloidosis also have an abnormal FLC ratio, a higher index of suspicion for occult involvement has been suggested for all MGUS patients manifesting this abnormality.\textsuperscript{7}

A definitive diagnosis requires the identification by pathology of amyloid deposition in affected organs.\textsuperscript{17} Often an easier-to-obtain surrogate tissue can be biopsied (bone marrow or fat aspirate), but if the biopsy results are negative, then tissue from an affected organ is required. Congo red staining should be routinely performed on any bone marrow biopsy done as part of a workup for a newly discovered M-protein. Importantly, AL amyloidosis is frequently associated with a low-level monoclonal gammopathy, making it imperative that symptoms and signs typically associated with amyloid are actively pursued with M-proteins of any level.\textsuperscript{17} In addition, the monoclonal protein most often present is free lambda light chain alone. Thus, if AL amyloid is suspected, an FLC assay should always be ordered in addition to the UPE and SPE.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Clinical presentation</th>
<th>Red flags</th>
<th>Approximate incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Malnutrition</td>
<td>Unexplained fatigue, dyspnea, or edema \ Weight loss</td>
<td>75%</td>
</tr>
<tr>
<td>Heart</td>
<td>Nonischemic heart failure \ Arrhythmias \ Restrictive cardiac wall thickening \ Low electrocardiographic voltage \ Late gadolinium enhancement at MRI</td>
<td>NT-proBNP &gt; 332 ng/l (100% sensitivity) \ BNP &gt; 73 ng/L (90% sensitivity)</td>
<td>70%</td>
</tr>
<tr>
<td>Kidney</td>
<td>Nephrotic syndrome \ Renal failure</td>
<td>Proteinuria &gt; 0.5 g/d (predominantly albumin)</td>
<td>70%</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatomegaly without scan defects</td>
<td>Elevation of ALP or yGT in the absence of other causes</td>
<td>20%</td>
</tr>
<tr>
<td>PNS/ANS</td>
<td>Nondiabetic symmetric ascending peripheral neuropathy (small fibre, axonal) \ Postural hypertension \ Bladder and bowel dysfunction</td>
<td>Neuropathic pain and loss of sensitivity to temperature \ Erectile dysfunction \ Onset of hypotension or resolution of hypertension</td>
<td>15%</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>Purpura (periorbital) \ Macroglossia \ Claudication of the jaw \ Muscular pseudohypertrophy \ Articular or soft tissue deposits</td>
<td>Carpal tunnel syndrome</td>
<td>10%</td>
</tr>
</tbody>
</table>

ALP = alkaline phosphatase, BNP = b-type natriuretic peptide, NT-proBNP = N-Terminal pro b-type natriuretic peptide, PNS/ANS = peripheral nervous system/autonomic nervous system, yGT = y-glutamyl transpeptidase.\textsuperscript{4,17}
Summary
Since more than 70% of patients with MGUS discovered incidentally are in the low-risk category for progression, and because MGUS itself occurs predominantly in older individuals, more than 90% of patients diagnosed with MGUS today will probably never develop multiple myeloma or another malignant plasmacytoid disorder.2,4 Patients can be followed using three established and easily quantifiable risk factors: an M-spike greater than 15 g/L, the presence of non-IgG type protein, and an abnormal FLC ratio.4,18 It is likely that most patients in the low-risk category do not require annual follow-up and could be seen at less frequent intervals.18

In the next few years, greater precision in identifying high-risk patients can allow for chemoprevention or complication prevention trials, especially if more sensitive predictive biomarkers for progression can be discovered.2,18 Whatever developments are ahead, our aging population makes it likely that primary care providers will increasingly encounter and need to manage patients with MGUS. Using the guidelines and recommendations now available, primary care providers can play a significant role in managing such patients, especially those found to be at low risk for progression.

Competing interests
None declared.

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References