



# Monoclonal gammopathy of undetermined significance: Using risk stratification to guide follow-up

Varying combinations of 3 measurable factors determine a patient's risk of progressing toward multiple myeloma and influence monitoring decisions. This review—and accompanying algorithm—can guide your approach.

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## PRACTICE RECOMMENDATIONS

► For monoclonal gammopathy of undetermined significance (MGUS) patients at low risk, repeat serum protein electrophoresis (SPE) in 6 months. If no significant elevation of M-protein is found, repeat SPE every 2 to 3 years. **(A)**

► For patients with smoldering multiple myeloma, order SPE every 2 to 3 months in the first year following diagnosis; repeat every 4 to 6 months in the following year and every 6 to 12 months thereafter. **(B)**

### Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

**CASE ►** A 54-year-old man's lab results following a routine annual examination reveal a level of IgM M-protein just under 1.5 g/dL. All other lab values, including free light chain (FLC) ratio and bone marrow exam, are normal. No clinical evidence of a related disorder is found. What is the risk that this patient's condition could progress toward multiple myeloma, and how would you follow up?

**T**he patient with a monoclonal gammopathy has an abnormal proliferation of monoclonal plasma cells that secrete an immunoglobulin, M-protein. This proliferation occurs most often in the bone marrow but can also be found in extra-medullary body tissue. The condition can begin insidiously, remain stable, or progress to frank malignancy causing bone and end-organ destruction. The major challenge is to separate stable, asymptomatic patients who require no treatment from patients with progressive, symptomatic myeloma who require immediate treatment.

An increased, measurable level of serum monoclonal immunoglobulins or FLCs is called monoclonal gammopathy of undetermined significance (MGUS) when there is <3 g/dL monoclonal protein in the serum, <10% monoclonal plasma cells in the bone marrow, and an absence of beta-cell proliferative disorders, lytic bone lesions, anemia, hypercalcemia, or renal insufficiency (TABLE 1).<sup>1,2</sup> Serum and marrow measurements exceeding these values indicate progression of disease to a premalignancy stage. Continued proliferation of plasma cells in the bone marrow results in anemia and bone destruc-

**TABLE 1**

**MGUS criteria established by IMWG<sup>1</sup> and WHO<sup>2</sup>**

M-protein in serum <3 g/dL
Bone marrow clonal plasma cells <10%, and low level of plasma cell infiltration in a trephine biopsy
No evidence of B-cell proliferative disorder (MM, WM, AL)
No M-protein or only small amounts of monoclonal light chain in urine
Absence of lytic bone lesions, anemia, hypercalcemia, or renal insufficiency related to the M-protein

AL, amyloid light-chain; IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; WM, Waldenström macroglobulinemia; WHO, World Health Organization.

**>**  
Risk for MGUS progression increases markedly with a serum M-protein concentration  $\geq 1.5$  g/dL, a non-IgG isotype, or an abnormal serum FLC ratio (<0.26 or >1.65).

tion, while the increase in M-protein leads to end-organ destruction. This final malignant state is multiple myeloma (MM).

**Detailed classification of MGUS: A roadmap for monitoring patients**

Extensive epidemiologic and clinical studies have refined the classification of MGUS<sup>3-5</sup> and related disorders (TABLES 2-4),<sup>3</sup> providing physicians with guidance on how to monitor patients. There are 3 kinds of monoclonal gammopathies, each reflecting a particular type of immunoglobulin involvement—non-IgM, IgM, or light chain. Additionally, within each type of gammopathy, patient-specific characteristics determine 3 categories of clinical significance: premalignancy with low risk of progression (1%-2% per year<sup>3</sup>); premalignancy with high risk of progression (10% per year<sup>3</sup>); and malignancy.

Non-IgM MGUS with a high risk of progression is designated smoldering multiple myeloma (SMM) (TABLE 2).<sup>3</sup> IgM MGUS with a high risk of progression is defined as smoldering Waldenström macroglobulinemia (SWM), with a predisposition to progress to Waldenström macroglobulinemia (WM) and, rarely, to IgM MM (TABLE 3).<sup>3</sup>

More recently, it has been reported that approximately 20% of the cases of MM belong to a new entity called light-chain MM that features an absence of heavy chain (IgG, IgA, IgM, IgD, or IgE) secretion in serum.<sup>6</sup> The premalignant precursor is light-chain MGUS (LC-MGUS). The criteria for LC-MGUS and idiopathic Bence Jones proteinuria are found in TABLE 4.<sup>3</sup> Idiopathic Bence Jones protein-

uria is equivalent to SMM and SWM due to its higher risk of progression (10%/year)<sup>3</sup> to light-chain MM.

**Prevalence of MGUS**

In general, the prevalence of all types of MGUS increases with age and is affected by race, sex, family history, immunosuppression, and pesticide exposure. The Caucasian American population >50 years exhibits a prevalence of MGUS of approximately 3.2%;<sup>7</sup> the African American population exhibits a significantly higher prevalence of 5.9% to 8.4%.<sup>7</sup> Native Asians have a lower rate of MM, and, as expected, a lower MGUS prevalence than is seen in the Western population (Thailand  $\approx$ 2.3%,<sup>8</sup> Korea  $\approx$ 3.3%,<sup>9</sup> Japan  $\approx$ 2.1%,<sup>10</sup> China  $\approx$ 0.8%<sup>11</sup>). The overall prevalence of the 3 types of MGUS is 4.2% in Caucasians.<sup>6</sup>

**Distinguishing stable from progressing disease**

The Mayo Clinic's risk stratification model<sup>12</sup> further specifies risk of disease progression based on 3 indicators: serum M-protein concentration, Ig isotype of M-protein, and serum FLC ratio.

**■ MGUS.** A marked increase in risk for disease progression is associated with a serum M-protein concentration  $\geq 1.5$  g/dL, a non-IgG isotype, or an abnormal serum FLC ratio (<0.26 or >1.65, reflecting an increase in either the kappa or lambda light chain).<sup>12</sup> An MGUS patient exhibiting all 3 of these features has a 58% absolute risk of developing MM after 20 years of follow-up. A patient

TABLE 2

Non-IgM MGUS: Defining criteria and related disorders<sup>3</sup>

Type of monoclonal gammopathy	Premalignancy with low risk of progression (1%-2% per year)	Premalignancy with high risk of progression (10% per year)	Malignancy
IgG IgA IgD IgE	<p>Non-IgM MGUS</p> <p>All 3 criteria must be met:</p> <ul style="list-style-type: none"> <li>• Serum monoclonal protein &lt;3 g/dL</li> <li>• Clonal BM plasma cells &lt;10%</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</li> </ul>	<p>SMM</p> <p>Both criteria must be met:</p> <ul style="list-style-type: none"> <li>• Serum monoclonal protein (IgG or IgA) ≥3 g/dL or clonal BM plasma cells ≥10%</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to a PCPD</li> </ul>	<p>MM</p> <p>All 3 criteria must be met except as noted:</p> <ul style="list-style-type: none"> <li>• Clonal BM plasma cells ≥10%</li> <li>• Presence of serum or urinary monoclonal protein (except in patients with true nonsecretory MM)</li> <li>• Evidence of end-organ damage that can be attributed to the underlying PCPD, specifically: <ul style="list-style-type: none"> <li>• Hypercalcemia: serum calcium ≥11.5 mg/dL or</li> <li>• Renal insufficiency: serum creatinine &gt;2 mg/dL or estimated creatinine clearance &lt;40 mL/min</li> <li>• Anemia: normochromic, normocytic with hemoglobin &gt;2 g/dL below lower limit of normal or hemoglobin &lt;10 g/dL</li> <li>• Bone lesions: lytic lesions or severe osteopenia attributed to a PCPD or pathologic fractures</li> </ul> </li> </ul>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FISH, fluorescent in situ hybridization; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCPD, plasma cell proliferative disorder; SMM, smoldering multiple myeloma.

Source: Rajkumar SV et al. *Mayo Clin Proc.* 2010.<sup>3</sup> Reprinted with permission from Elsevier.

with 2 of the 3 abnormalities has a 37% risk of progressing to MM, and one who has just one abnormality has a 21% risk. In contrast, an MGUS patient who has an M-protein level <1.5 g/dL, an IgG isotype, and normal FLC range has only a 5% risk of progression to MM in the same 20 years.<sup>12</sup>

The Spanish Group risk stratification model<sup>13</sup> is based on 2 risk factors: a high proportion of abnormal plasma cells (aPC) within the bone marrow plasma cell (BMPC) compartment (ie, ≥95% CD56+/CD19-); and an evolving subtype of the disease (defined as an increase in the level of serum M-protein by at least 10% during the first 6 months of follow-up, or a progressive and constant increase of the M-protein until overt MM develops). The 7-year cumulative probability of

progression of MGUS to MM: 2% for patients with neither risk factor, 16% with one risk factor, and 72% with both risk factors.<sup>13</sup>

■ **SMM.** Classification of this progressive state is defined by a serum level of monoclonal protein (IgG, IgA, IgD, or IgE) ≥3 g/dL or a concentration of clonal bone marrow plasma cells ≥10%; and by an absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to a plasma cell proliferative disorder (TABLE 2).<sup>3</sup> Both laboratory and clinical criteria must be met.

According to the Mayo Clinic risk stratification model, likelihood of progression reflects combinations of 3 factors: bone marrow plasmacytosis ≥10%, a serum M-protein level ≥3 g/dL, and a serum FLC ratio ≤0.125

TABLE 3

**IgM MGUS:\* Defining criteria and related disorders<sup>3</sup>**

Type of monoclonal gammopathy	Premalignancy with low risk of progression (1%-2% per year)	Premalignancy with high risk of progression (10% per year)	Malignancy	
IgM	<p>IgM MGUS</p> <p>All 3 criteria must be met:</p> <ul style="list-style-type: none"> <li>• Serum monoclonal protein &lt;3 g/dL</li> <li>• Clonal BM lymphoplasmacytic cells &lt;10%</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</li> </ul>	<p>SWM</p> <p>Both criteria must be met:</p> <ul style="list-style-type: none"> <li>• Serum IgM monoclonal protein ≥3 g/dL or BM lymphoplasmacytic infiltration ≥10%</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</li> </ul>	<p>WM</p> <p>All criteria must be met:</p> <ul style="list-style-type: none"> <li>• IgM monoclonal gammopathy (regardless of size of M-protein)</li> <li>• ≥10% BM lymphoplasmacytic infiltration (usual intertrabecular) by small lymphocytes with plasmacytoid or plasma cell differentiation and typical immunophenotype (eg, surface IgM+, CD5±, CD10-, CD19+, CD20+, CD23-) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma</li> <li>• Anemia, symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly attributable to the underlying lymphoproliferative disorder</li> </ul>	<p>IgM myeloma</p> <p>All criteria must be met:</p> <ul style="list-style-type: none"> <li>• Symptomatic monoclonal PCPD characterized by a serum IgM monoclonal protein regardless of size</li> <li>• Presence of ≥10% plasma cells on BM biopsy</li> <li>• Presence of lytic bone lesions related to the underlying plasma cell disorder or translocation t(11;14) on FISH</li> </ul>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FISH, fluorescent in situ hybridization; MGUS, monoclonal gammopathy of undetermined significance; PCPD, plasma cell proliferative disorder; SWM, smoldering Waldenström macroglobulinemia; WM, Waldenström macroglobulinemia.

\*Conventionally IgM MGUS is considered a subtype of MGUS. Unless otherwise specified, when the term MGUS is used in general, it includes IgM MGUS.

Source: Rajkumar SV et al. *Mayo Clin Proc.* 2010.<sup>3</sup> Reprinted with permission from Elsevier.

or ≥8.<sup>14</sup> Using this stratification scheme, the risk over 10 years of progressing from SMM to MM is 84% for those with all 3 risk factors, 65% with 2 factors, and 52% with one factor.<sup>14</sup> As SMM is defined, there is no upper limit of bone marrow involvement. However, Rajkumar et al<sup>15</sup> found that progression time was significantly shorter ( $P<.001$ ) among patients with ≥60% bone marrow involvement, compared with those having <60% involvement.

The Spanish Group risk stratification model<sup>13</sup> uses the same model applied to MGUS: a proportion of abnormal plasma cells in the BMPC compartment ≥95% CD56+/-CD19-; and an evolving subtype of disease.

The 3-year cumulative probability of progression of SMM to MM is 46% for those with both risk factors, 12% for those with one factor, and <1% for those with no risk factors.<sup>13</sup>

■ **LC-MGUS.** The classification of LC-MGUS (TABLE 4)<sup>3</sup> is primarily from a Mayo Clinic study<sup>6</sup> and research on risk stratification is underway at 2 other institutions. False-positive results are possible in patients with renal<sup>16</sup> and inflammatory<sup>17</sup> disorders.

**Applying risk stratification to patient management**

The current approach to a patient with clear-

TABLE 4

Light-chain MGUS: Defining criteria and related disorders<sup>3</sup>

Type of monoclonal gammopathy	Premalignancy with low risk of progression (1%-2% per year)	Premalignancy with high risk of progression (10% per year)	Malignancy
Light chain	<p>Light-chain MGUS</p> <p>All criteria must be met:</p> <ul style="list-style-type: none"> <li>• Abnormal FLC ratio (&lt;0.26 or &gt;1.65)</li> <li>• Increased level of the appropriate involved light chain (increased <math>\kappa</math> FLC in patients with ratio &gt;1.65 and increased <math>\lambda</math> FLC in patients with ratio &lt;0.26)</li> <li>• No immunoglobulin heavy chain expression on immunofixation</li> <li>• Clonal BM plasma cells &lt;10%</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</li> </ul>	<p>Idiopathic Bence Jones proteinuria</p> <p>All criteria must be met:</p> <ul style="list-style-type: none"> <li>• Urinary monoclonal protein on urine protein electrophoresis <math>\geq 500</math> mg/24 hr and/or clonal BM plasma cells <math>\geq 10\%</math></li> <li>• No immunoglobulin heavy chain expression on immunofixation</li> <li>• Absence of end-organ damage such as CRAB that can be attributed to the PCPD</li> </ul>	<p>Light-chain MM*</p> <p>Same as MM except no evidence of immunoglobulin heavy chain expression on immunofixation</p>

BM, bone marrow; CRAB, hypercalcemia, renal insufficiency, anemia, and bone lesions; FLC, free light chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PCPD, plasma cell proliferative disorder.

\*Conventionally, light chain MM is considered a subtype of MM. Unless otherwise specified, when the term MM is used in general, it includes light chain MM.

Source: Rajkumar SV et al. *Mayo Clin Proc.* 2010.<sup>3</sup> Reprinted with permission from Elsevier.

ly defined MGUS is a prudent “watch and wait” strategy that specifies monitoring details based on risk category (**ALGORITHM**).<sup>1,18</sup>

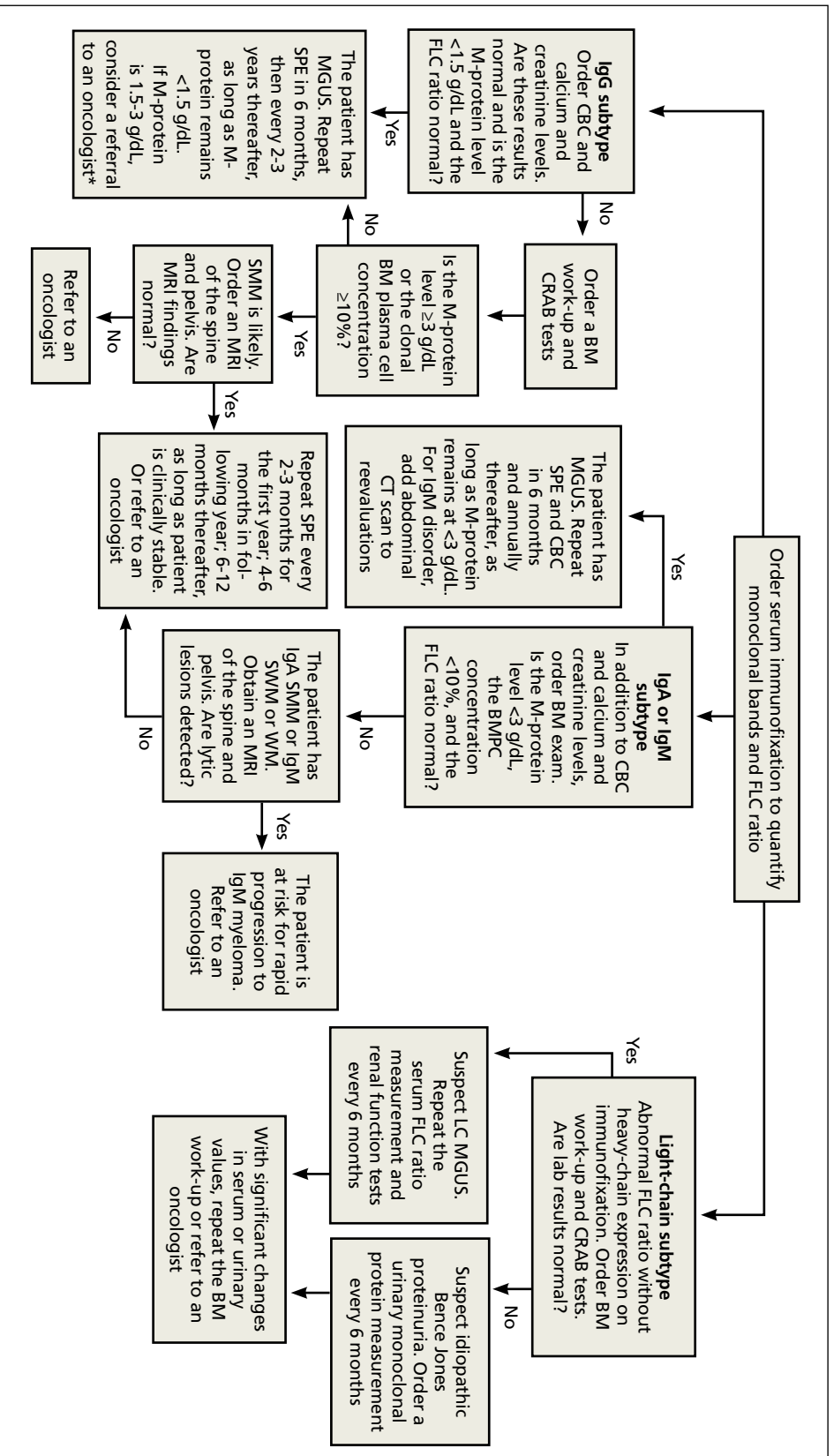
■ **MGUS.** In the low-risk MGUS group (IgG subtype, M-protein <1.5 g/dL, and normal FLC ratio)<sup>3</sup> there is no need for bone marrow examination or skeletal radiography. Repeat the serum protein electrophoresis (SPE) in 6 months, and if there is no significant elevation of M-protein, repeat the SPE every 2 to 3 years.<sup>1,19,20</sup> However, if other findings are suggestive of plasma cell malignancy (anemia, renal insufficiency, hypercalcemia, or bone lesions), bone marrow examination and computed tomographic (CT) scan are advised. Further evaluation of an incidental detection of MGUS is also important since it is occasionally associated with bone diseases,<sup>21</sup> arterial and venous thrombosis,<sup>22</sup> and an increased risk ( $P<.05$ ) of developing bacterial (pneumonia, osteomyelitis, septicemia, pyelonephritis, cellulitis, endocarditis, and meningitis) and viral (influenza and herpes zoster) infections.<sup>23</sup>

Patients in the intermediate- and high-risk MGUS groups with serum monoclonal protein  $\geq 1.5$  g/dL, IgA or IgM subtype or an abnormal FLC ratio should undergo tests for CRAB and have bone marrow aspirate and biopsy with cytogenetics, flow cytometry, and fluorescence in situ hybridization (FISH). Patients with IgM MGUS should also undergo a CT scan of the abdomen to rule out the presence of asymptomatic retroperitoneal lymph nodes.<sup>1,19</sup> If the BM examination and CT scan yield negative results, repeat SPE and complete blood count (CBC) after 6 months and annually thereafter for life. IgD or IgE MGUS is rare, and patients exhibit a progression similar to the 20-year risk seen with MGUS generally.

■ **SMM.** Given the increased risk of progression from SMM to MM compared with MGUS (all risk groups), the 2010 International Myeloma Working Group (IMWG) has suggested monitoring SMM patients more frequently—ie, SPE every 2 to 3 months in

ALGORITHM

Work-up strategies for patients with a monoclonal band in the serum or urine<sup>1,18</sup>



BM, bone marrow; BMPC, bone marrow plasma cells; CBC, complete blood count; CRAB, hypercalcemia, renal insufficiency, anemia, bone lesions; CT, computed tomography; FLC, free light chain; LC, light chain; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MRI, magnetic resonance imaging; SMM, smoldering multiple myeloma; SPE, serum protein electrophoresis; SWM, smoldering Waldenström myeloma; WM, Waldenström macroglobulinemia.

\*Because the 20-year risk of developing MM progressively increases as M-protein rises above 1.5 g/dL,<sup>18</sup> consultation with an oncologist may be warranted if M-protein remains ≥1.5 g/dL or if there are suggestive clinical signs or abnormal test results: elevated creatinine, anemia, or hypercalcemia.

the first year following diagnosis.<sup>1</sup> Repeat SPE in the second year every 4 to 6 months, and, if results are clinically stable, every 6 to 12 months thereafter. In addition to a baseline bone marrow examination (including cytogenetics, flow cytometry, and FISH studies), consider ordering magnetic resonance imaging of the spine and pelvis to detect occult lesions, as their presence predicts a more rapid progression to MM.<sup>24</sup> During the course of the follow-up, evaluate any unexplained anemia or renal function impairment for its origin. A report of MGUS progression over more than a decade to SMM and then to MM illustrates prudent monitoring of a patient.<sup>25</sup>

■ **LC-MGUS.** Once LC-MGUS is detected, first rule out AL-amyloidosis, light-chain deposition disease, or cast nephropathy. If no malignant state is present, repeat the FLC serum assay every 6 months with renal function tests. Idiopathic Bence Jones proteinuria and LC-MGUS have some overlap and both entities put patients at risk for developing MM or amyloidosis. It is not uncommon for MGUS to be accompanied by Bence Jones proteinuria.

In addition to a thorough history and physical examination, recommended follow-up for both of these entities includes CBC, creatinine, serum FLC, and 24-hour urine protein electrophoresis.<sup>6</sup> With idiopathic Bence Jones proteinuria, a monoclonal protein evident on urine protein electrophoresis at >500 mg/24 hr must be followed up with tests for other signs of malignancy (CRAB) and BM examination to exclude the possibility of MM.<sup>6</sup>

## Treatment of MGUS to prevent progression

Multiple myeloma is still an incurable disease. Since MGUS is a precursor of MM, attempts have been made to either slow its progression or eradicate it. Several independent intervention studies<sup>26</sup> for the precursor diseases MGUS and SMM have been conducted or are ongoing. Thus far, no conclusive preventive treatment has been found and the 2010 IMWG guidelines do not recommend preventive therapy for MGUS and SMM patients by means of any drug, unless it is a part of a clinical trial.<sup>1</sup>

**CASE ►**The patient profiled at the start of this article has one abnormal risk factor (IgM isotype) and has a low risk of progression to MM. Management should follow the steps outlined in the **ALGORITHM**<sup>1,18</sup> for low-risk IgM MGUS: repeat SPE, CBC, and CT scan in 6 months and annually thereafter. If any abnormality is observed, rule out the possibilities of IgM SWM, IgM WM, or rapid progression to MM, and consider referral to an oncologist. **JFP**

### CORRESPONDENCE

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►  
Likelihood of SMM progression varies with the combination of 3 factors: bone marrow plasmacytosis  $\geq 10\%$ , a serum M-protein level  $\geq 3$  g/dL, and a serum FLC ratio  $\leq 0.125$  or  $\geq 8$ .

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