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Diagnosis and Management of Monoclonal Gammopathy of Undetermined Significance
A Review

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IMPORTANCE Nearly 5% of adults have the precursor malignant condition monoclonal gammopathy of unknown significance (MGUS). Management centers on differentiating MGUS from more serious conditions to determine additional diagnostic testing, monitoring, and potential therapy.

OBSERVATIONS MGUS is defined by the absence of end-organ damage or symptoms, a small amount of monoclonal immunoglobulin (M protein), and low volume of plasma cells. MGUS must be distinguished from overt malignant diseases like multiple myeloma (MM), immunoglobulin light-chain (AL) amyloidosis, and monoclonal gammopathy of clinical significance (MGCS), all of which cause organ damage or symptoms. Although testing for M proteins is often prompted by clinical findings (eg, osteoporosis or autoimmune disease), recent evidence from screened populations suggests that previous MGUS disease associations were likely overestimated and that testing for M proteins should be reserved for when malignant disease or MGCS is suspected. Risk of progression to malignant disease ranges from 0.5% to 1%, meaning most patients have indolent disease. Guideline-concordant management of MGUS is determined by predicted risk of progression to malignant disease, which depends on subtype of immunoglobulin, M protein concentration, and free light chain ratio. Patients with low-risk MGUS can safely defer bone marrow biopsy and advanced imaging, and should undergo periodic laboratory monitoring. Intermediate- and high-risk MGUS should trigger bone marrow biopsy and bone imaging to detect overt MM and shorter monitoring intervals. Advanced molecular testing may improve on current risk stratification to target monitoring and treatment to those with highest risk of malignant progression and avoid overtreatment of those with low-risk disease. Management will also be informed by results of several clinical trials to clarify the risks and benefits of screening, optimal monitoring strategy, predictors of progression, and potential preventive or curative therapies.

CONCLUSIONS AND RELEVANCE Evidence-based management of MGUS currently rests on separating clinically indolent from high-risk precursor disease. Research using novel detection methods, incorporating molecular testing into risk stratification, and evaluating screening, monitoring, and therapeutic or lifestyle interventions has the potential to improve outcomes.

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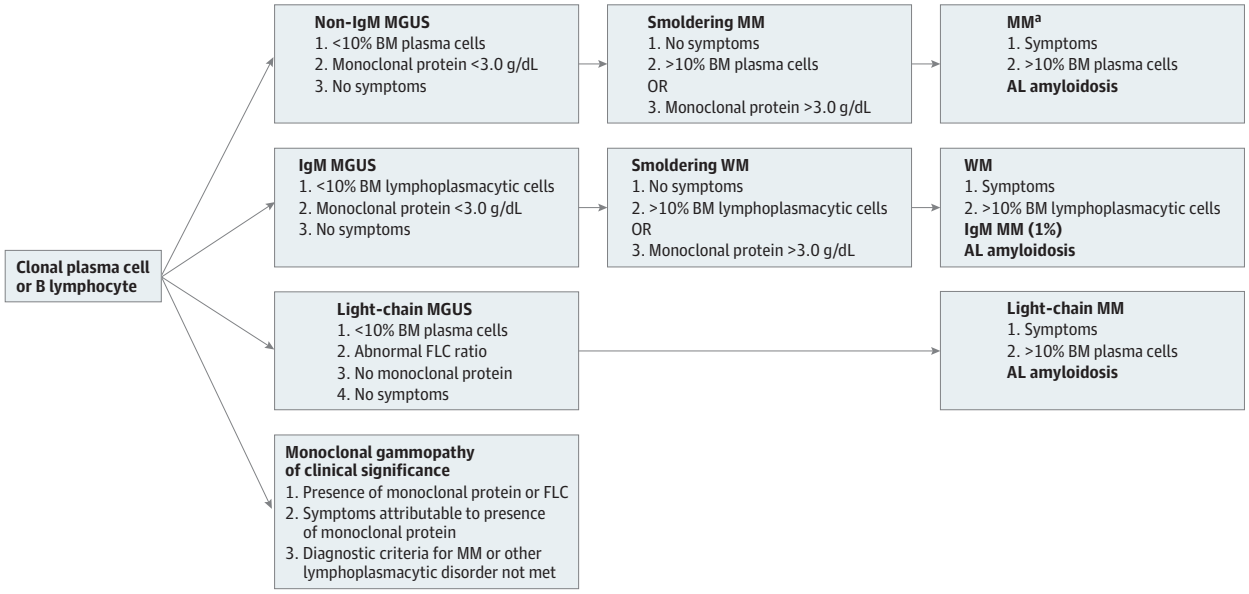
Monoclonal gammopathy of undetermined significance (MGUS) affects more than 4% of adults older than 50 years and is a common laboratory finding encountered by internists.[1,2] Monoclonal gammopathy refers to the presence of a monoclonal immunoglobulin (M protein) or free light chain (FLC) in plasma, urine, or both that is produced by clonal plasma cells or B lymphocytes. Monoclonal gammopathy can indicate multiple myeloma (MM), immunoglobulin light-chain (AL) amyloidosis, or other lymphoid malignant disease. Rarely, monoclonal gammopathy can cause symptoms in the absence of malignant disease, which is called *monoclonal gammopathy of clinical significance* (MGCS). The precursor malignant condition MGUS is confirmed when end-organ damage or clinical symptoms are absent and only a small amount of M protein and low volume of bone marrow plasma cells are present.[3]

Distinguishing between these scenarios is the principal task for clinicians. MGUS is often detected incidentally, and the rate of conversion to MM or other lymphoproliferative disorders is 0.5% to 1% per year.[1] Caring for patients with MGUS therefore requires recognizing that most will never progress, while also remaining vigilant for signs and symptoms that suggest high risk of hematologic malignant disease or rare cases of MGCS. Moreover, how to predict which patients will progress from MGUS to more serious disease and whether screening or early detection or treatment is of benefit are the subjects of ongoing research.

Figure 1. Terminology and Diagnostic Criteria for Monoclonal Gammopathies



Diagnostic criteria from Rajkumar et al.[3] AL indicates amyloid light chain; BM, bone marrow; FLC, free light chain; IgM, immuglobulin M; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; WM, Waldenström macroglobulinemia.

[a]Or presence of myeloma-defining event (bone marrow plasma cells are greater than or equal to 60%, a serum FLC ratio greater than or equal to 100, or more than 1 focal lesion on magnetic resonance imaging).

In this review, we summarize the latest evidence on the diagnosis and management of MGUS to guide clinical decision-making.

Observations

A PubMed search was performed for English-language studies published between July 1, 2014, to September 1, 2024, using the search term *monoclonal gammopathy of undetermined significance* to identify clinical trials, systematic reviews, and meta-analyses in English. We manually screened references of guidelines and systematic and narrative reviews to identify additional relevant articles. We also searched for active or recently completed clinical trials at ClinicalTrials.gov. Articles were prioritized for inclusion based on relevance to generalist clinicians, recency, and rigor of study design, favoring randomized clinical trials when available or meta-analyses of observational studies when not. We included 116 articles, including 13 clinical trials, 4 meta-analyses, 5 systematic reviews, 15 expert clinical guidance, 16 narrative reviews, 52 cohort studies, and 12 cross-sectional studies.

Pathobiology

The M proteins in MGUS are produced by malignant transformation of plasma cells or B lymphocytes. M proteins can be intact combinations of heavy-chain immunoglobulins—IgG, IgA, or IgM (or rarely IgD and IgE)—bound to κ or λ light chains. They can also be exclusively κ or λ FLC unbound to heavy chains. By definition, MGUS is an asymptomatic condition with no evidence of end-organ damage due to plasma cell proliferation or M protein deposition, known as the CRAB criteria for hypercalcemia, kidney insufficiency, anemia, and bone lesions.[3] Laboratory diagnostic criteria include a serum M protein concentration of less than 3 g/dL or an abnormal ratio of κ to λ FLC with increased levels of the involved light chain, and fewer than 10% plasma or lymphoplasmacytic cells in the bone marrow (**Figure 1**).[3] MGUS is typically divided into non-IgM MGUS, which progresses to MM or AL amyloidosis at a rate of 1% annually; IgM MGUS, which progresses to the lymphoplasmacytic lymphoma Waldenstrom macroglobulinemia (or rarely IgM MM) at a rate of 1.5% annually[4]; and light-chain MGUS, which progresses to AL amyloidosis or light-chain MM. Other lymphomas, such as chronic lymphocytic leukemia, can also produce M proteins.

The classic understanding of monoclonal gammopathy progression is that it is a 3-step process from the precursor MGUS to an intermediate smoldering stage to overt malignant disease. Smoldering multiple myeloma (SMM) is diagnosed when the M protein is greater than or equal to 3 g/dL, bone marrow contains between 10% and 59% plasma or lymphoplasmacytic cells, and there is no evidence of end-organ damage or biomarker or imaging evidence of a myeloma-defining event (bone marrow plasma cells are greater than or equal to 60%, a serum FLC ratio greater than or equal to 100, or more than 1 focal lesion on magnetic resonance imaging [MRI]).[3] Risk for progression from SMM to MM or related disorders is considerably higher at 10% per year for the first 5 years after diagnosis.[5] MM is diagnosed when there are greater than or equal to 10% plasma cells in the bone marrow (or biopsy-proven bony or extramedullary plasma cell tumor [plasmacytoma]) and end-organ damage. MM is also diagnosed when myeloma-defining events are present.[3] Figure 1 gives additional detail on diagnostic criteria for other monoclonal gammopathies.

Monoclonal gammopathies that do not meet criteria for active MM can also cause rare but serious systemic disorders. In light-

Table 1. Monoclonal Gammopathies of Clinical Significance by Organ System

Organ system	Example	Suggestive symptoms
Neurologic	• IgM-associated peripheral neuropathy • POEMS • CANOMAD	• Progressive, unexplained small-fiber peripheral neuropathy • Carpal tunnel syndrome • Spinal stenosis • Orthostatic hypotension
Kidney	• Immunoglobulin-related amyloidosis • Monoclonal immunotactoid glomerulonephritis • Type 1 cryoglobulinemic glomerulonephritis • Light-chain proximal tubulopathy • Monoclonal immunoglobulin deposition disease • Proliferative glomerulonephritis with monoclonal immunoglobulin deposits • C3 glomerulopathy with monoclonal gammopathy • Thrombotic microangiopathy with monoclonal gammopathy	• Elevated creatinine levels • Nephrotic syndrome
Dermatologic	• Cryoglobulinemia • Schnitzler syndrome • Acquired C1 esterase inhibitor • Necrobiotic xanthogranuloma	• Urticarial rash • Vasculitis • Recurrent angioedema
Endocrine	• Insulin autoimmune syndrome	• Unexplained hypoglycemia
Hematologic	• Cold agglutinin disease • Acquired von Willebrand disease • TEMPI • Monoclonal gammopathy of thrombotic significance	• Bleeding or bruising • Hemolytic anemia • Acquired telangiectasias, erythrocytosis, perinephric fluid collections, hypoxemia • Thrombosis
Rheumatologic	• Scleromyxedema	Progressive skin mucinosis
Ophthalmologic	• Crystalline keratopathy • Corneal copper deposition	• Eye pain, photophobia, vision loss
Other	• Capillary leak syndrome • Crystal-storing histiocytosis	• Spontaneous attacks of shock and peripheral edema • Multiorgan failure

Abbreviations: CANOMAD, chronic ataxic neuropathy, ophthalmoplegia, IgM-MGUS, cold agglutinin, dialosyl antibodies; Ig, immunoglobuin; POEMS, polyneuropathy, organomegaly, endocrinopathy, λ-MGUS, skin changes; TEMPI, telangiectasias, erythrocytosis, elevated erythropoietin level, MGUS, perinephric fluid collections, intrapulmonary shunting.

chain AL, monoclonal FLCs misfold and deposit in tissues leading to organ-specific symptoms, including nephrotic-range proteinuria (primarily albuminuria), peripheral neuropathy, and cardiomyopathy.[6] There is growing recognition of other rare instances in which a monoclonal gammopathy meets laboratory criteria for MGUS but causes clinically significant symptoms or end-organ damage (ie, MGCS).[7] The most affected organs in MGCS are nerves, the kidneys, and the skin, and specific MGCS and their clinical characteristics and symptoms are outlined in **Table 1**. Diagnosis often requires biopsy of the affected organ (eg, skin or glomerulus) for histopathologic confirmation of monoclonal immunoglobulin deposition, and subspecialty consultation is recommended.

Table 2. Testing in Monoclonal Gammopathy

Test	Method	Purpose
Serum protein electrophoresis	Agarose gel-based assay that separates proteins based on size, shape, and charge	Detects and quantifies monoclonal protein
Immunofixation	Gel-based assay that uses targeted anti-sera (eg, anti-IgG, anti-immunoglobulin M, anti-κ light chain)	Identifies subtype of monoclonal protein and confirms monoclonality
Serum free light chains	Nephelometric assay that quantifies unbound (free) κ and λ light chains	Detects light chain–only MGUS, immunoglobulin light chain amyloidosis or MM

Abbreviations: MGUS, monoclonal gammopathy of unknown significance; MM, multiple myeloma.

Epidemiology and Risk Factors

MGUS is present in about 4% of adults based on cohort studies conducted in Scandinavia, Europe, the US, and Japan.[8-14] The prevalence of MGUS increases with age, affecting 3% of those older than 50 years, 5% older than 70 years, and 9% older than 85 years.[11] MGUS is twice as common in men than in women. Studies conducted among Black Americans and Black persons living in Ghana demonstrated a 2- to 3-fold increased risk of MGUS diagnosis, but rate of progression to MM is similar to that described in White Americans.[15-17]

Although most cases of MGUS are sporadic, family clusters of MM suggest the possibility of a genetic predisposition.[18] Relatives of patients with MGUS have a 4-fold risk of developing MGUS and 3-fold risk of developing MM, supporting a shared genetic and/or environmental risk factor.[19] Genome-wide association studies have also shown an association between common single-nucleotide variants and increased incidence of MGUS and MM.[20]

Testing and Diagnosis

Evaluation for monoclonal gammopathy involves a trio of complementary tests: the serum protein electrophoresis (SPEP), immunofixation (IFE), and serum FLC (**Table 2**). Combined, these tests identify more than 97% of patients with a monoclonal gammopathy.[21] Using agarose gel to separate proteins, SPEP detects and quantifies the amount of M protein but cannot distinguish the subtype (eg, IgG, IgM).[22] IFE is a gel-based assay that confirms an M protein is monoclonal (rather than polyclonal as in inflammation or infection), identifies the subtype using targeted antibodies, and is more sensitive than SPEP for small M proteins.[23] Novel mass spectrometry–based testing that is more sensitive than existing methods may supplant current methods.[24] In a screening study of more than 7500 individuals who were predominantly high risk for monoclonal gammopathy, mass spectrometry identified monoclonal gammopathy in 36% of individuals, with 26% of gammopathies identified by mass spectrometry alone.[24] Notably, the clinical significance of these newly identified gammopathies is unknown, although they do correlate with all-cause mortality. Therapeutic recombinant monoclonal antibodies (such as infliximab and rituximab) can show up as small M proteins on SPEP, but another benefit of mass spectrometry is that it can distinguish these exogenous therapeutic antibodies from endogenous monoclonal gammopathies.[25]

Table 3. Risk Stratification of Monoclonal Gammopathy of Unknown Significance[a]

Risk category	Definition	Cumulative absolute risk of progression at 20 y, %	Cumulative absolute risk of progression at 20 y adjusting for competing risk of death, %
Low risk	M protein ≤1.5 g/dL; immunoglobulin G subtype; normal FLC ratio	5	2
Intermediate risk	Any 1 of the above factors	21	10
	Any 2 of the above factors	37	18
High risk	All 3 of the above factors	58	27

Abbreviation: FLC, free light chain.

[a] Adapted from Kyle et al.[5]

Some clonal plasma cells produce only κ or λ FLC that are not bound to heavy immunoglobulin. Serum FLC is used to detect normal and clonal FLC, and a ratio of κ to λ FLC is reported. Because measurement of FLC alone cannot distinguish between monoclonal vs polyclonal FLC, it can be difficult to tease out a monoclonal process from small FLC elevations that commonly occur with aging or in conditions like renal dysfunction or inflammation. Recently, the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study prospectively screening more than 40 000 individuals led to new proposed reference ranges for serum FLC, proposing an FLC ratio reference range of 0.44 to 2.16 in individuals younger than 70 years with preserved renal function and an FLC ratio of 0.46 to 2.59 for those 70 years or older. Using this new reference range, the rate of false-positive light-chain MGUS diagnoses among individuals with preserved renal function decreases by 80%.[26] In addition, new FLC reference ranges have been proposed based on renal function with an FLC range of 0.46 to 2.62 for an estimated glomular filtration rate (eGFR) of 45 to 59 mL/min/1.73 m^2; 0.48 to 3.38 mL/min/1.73 m^2 for eGFR 30 to 44 mL/min/1.73 m^2, and 0.54 to 3.30 mL/min/1.73 m^2 for eGFR lower than 30 mL/min/1.73 m^2.[27] Urine studies (urinalysis and 24-hour urine collection for urine protein electrophoresis and urine IFE) should be performed if a there is an abnormal serum M protein or FLC ratio. Finally, a complete blood count, serum calcium, and creatinine levels are used to screen for end-organ dysfunction and determine the need for additional diagnostic testing.

Signs or Symptoms That Warrant Testing

Although MGUS is asymptomatic, evaluation for M proteins is often triggered by symptoms. For example, a patient presenting with peripheral neuropathy may undergo testing that reveals an M protein, but the peripheral neuropathy is later found to be unrelated. Until recently, MGUS was associated with and presumed to cause more than 100 clinical conditions, including thrombosis, autoimmune disease, low bone density, and increased mortality.[28-31] Evaluation for MGUS is even recommended by clinical guidelines for some of these conditions.[32] In a minority of cases of MGCS, a biopsy of the affected tissue provides evidence of a causal relationship.[7] Most previously reported disease associations were derived from retrospective cohorts of patients diagnosed with MGUS during workup for other signs or symptoms, many of whom had multiple comorbidities. The iStopMM study screened 75 422 participants for MGUS and compared with those who were diagnosed clinically after presenting with signs or symptoms that triggered testing.[33] Those who were diagnosed clinically (ie, after presenting with signs or symptoms) had more comorbidities—including kidney disease, endocrine disorders, neurologic disease, liver disease, and autoimmune conditions—than those diagnosed by screening alone (3.23 vs 2.36; mean difference, 0.68; 95% CI, 0.46-0.90). These results suggest that at least some of the previously reported disease associations were overestimated due to selection bias.

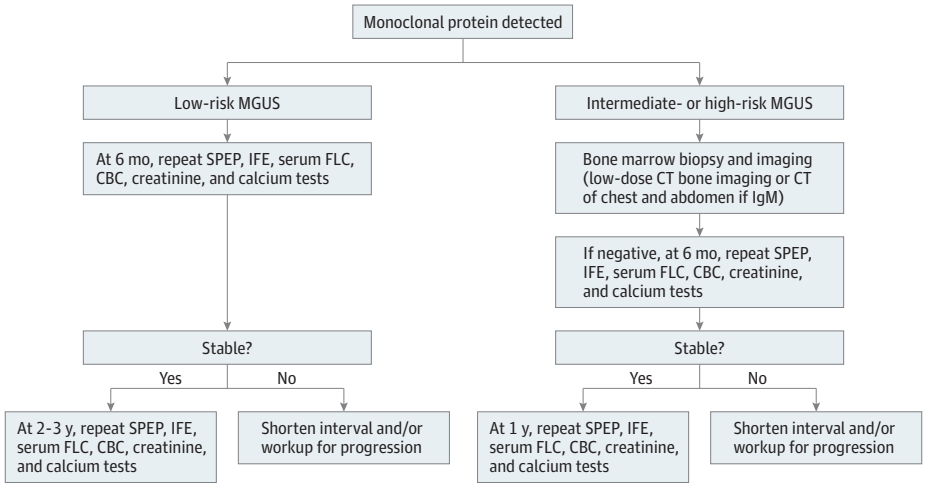
Thus, MGUS testing should not be reflexively ordered in patients with comorbid conditions but rather targeted to those whose symptoms suggest malignant disease or MGCS. MM, Waldenström macroglobulinemia (WM), and lymphoma typically present with end-organ manifestations that, if otherwise unexplained, should prompt evaluation for M proteins. Unexplained anemia can occur due to bone marrow suppression or replacement by malignant cells.[34] Altered balance between osteoclast activity and osteoblast activity can lead to bone pain, osteolytic bone lesions, or fractures.[35] These in turn can lead to hypercalcemia. Kidney dysfunction (elevated creatinine or proteinuria) can also occur due to light-chain cast nephropathy.[3] Other constitutional symptoms that can indicate plasma cell or lymphoproliferative malignant disease include recurrent infections due to suppressed normal Ig production, unintentional weight loss, fatigue, or night sweats. The second category that warrants testing is M protein disorders that are not overtly malignant but cause symptoms. Findings that, if otherwise unexplained, should prompt consideration of AL amyloidosis include progressive peripheral neuropathy, congestive heart failure with preserved ejection fraction, nephrotic syndrome, malabsorption, elevated alkaline phosphatase, voice changes, macroglossia, and excessive bruising or bleeding. M protein testing to evaluate for MGCS should be performed in cases where symptoms are present (Table 1); confirmatory biopsy showing immunoglobulin deposition is often required.

Risk Stratification

For patients who are confirmed to have MGUS, the most commonly used guidance recommends basing clinical decisions on risk of progression to MM.[5] Subtype of immunoglobulin, M protein concentration, and FLC ratio were combined into the Mayo Clinic model.[36] The model separates MGUS into low- (0 of 3 criteria), intermediate- (1-2 of 3 criteria) and high-risk (all 3 criteria) groups (**Table 3**). The risk of progression over 20 years in the derivation cohort was 5% for low-risk MGUS, 21% to 37% for intermediate-risk MGUS, and 58% for high-risk MGUS. Importantly, nearly three-quarters of the high-risk group had not progressed after 20 years accounting for the competing risk of death. A caveat when interpreting these risk estimates is that because patients in the cohort did not universally undergo bone marrow biopsy or advanced imaging, both the MGUS and SMM cohort may have included patients with undetected MM, resulting in an overestimate of risk.[1]

These risk estimates inform recommendations for additional testing. Current guidance recommends bone marrow biopsy to evaluate for SMM or MM in all but patients with low-risk MGUS.[5]

Figure 2. Strategy for Management of MGUS Based on Risk of Malignant Progression



CBC, complete blood cell count; CT, computed tomography; FLC, free light chains; IFE, immunofixation; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; SPEP, serum protein electrophoresis.

Many experts recommend bone imaging with either low-dose whole-body computed tomography (CT) or MRI in patients with intermediate- or high-risk MGUS or bony symptoms to rule out MM.[37-39] If imaging is clinically indicated in IgM MGUS (eg, due to presence of constitutional symptoms), then CT of the chest and abdomen is preferred over bone imaging to search for adenopathy and organomegaly suggestive of WM or other lymphoproliferative disorders.[4,5]

Several new models have been developed with the goal of improving predictive accuracy of progression risk and informing the decision to pursue a bone marrow biopsy to exclude SMM or MM. The PANGEA (Personalized Progression Prediction in Patients With MGUS or SMM) model incorporates age, dynamic measures like hemoglobin decline or change in kidney function, and optional bone marrow biopsy results.[40] A model developed using iStopMM data on screened patients with MGUS uses biomarkers to generate personalized risk predictions to identify patients with presumed MGUS in whom bone marrow biopsy may be deferred due to low risk of SMM or MM.[41] These models require external validation before being adopted into guidelines and clinical practice.

In addition, application of more advanced technologies—including genomics, immune profiling of the microenvironment, and single-cell RNA sequencing—to monoclonal gammopathies may lead to disease definitions and risk stratification that are more biologically precise.[42] Additional molecular data may disrupt the classic 3-step pathophysiology model and reclassify some MGUS as similar to MM, with rapid evolution to symptoms and end-organ damage, and some SMM as similar to MGUS, with an indolent course. None of these tools is available clinically. Studies are underway incorporating emerging technologies to refine risk stratification and potentially identify a high-risk group that may benefit from earlier intervention and a low-risk group that is at risk of overdiagnosis and overtreatment.[43]

Screening

There is no current evidence base to support screening for MGUS in the general population, and it is not recommended in clinical guidelines.[5,44,45] The potential benefits of screening remain unknown given the low risk of progression and lack of proven treatments. There is also potential for harm, such as emotional distress of a precursor malignant diagnosis and burdens of follow-up testing. Two ongoing studies will provide insight on whom to screen, predictors of progression after screening, and merits of different postscreening strategies. In the iStopMM population-based screening study, those diagnosed with MGUS were randomized to undergo no further follow-up, undergo follow-up according to current guidelines, or more intensive follow-up.[46] The PROMISE study is screening those at high risk of MGUS (eg, with a first-degree family member with MM) and examining factors that contribute to disease progression.[24]

Management and Prevention

The current standard of care for MGUS is monitoring for progression to MM.[5,44,45] This recommendation is based on studies showing reduced morbidity and mortality in patients with MGUS who were monitored before progression to MM.[47] How often to monitor patients with MGUS is not known but will be informed by ongoing screening studies. A proposed strategy for MGUS management informed by risk of progression is presented in **Figure 2**.

For low-risk MGUS, guidelines recommend against performing a bone marrow biopsy or any additional imaging. Repeated monitoring is suggested in 6 months. Those with an increase in M protein over time are at highest risk of progression vs those with stable M protein; risk of progression is highest in the first year following diagnosis and declines thereafter.[48] Thus, the screening interval can be lengthened to every 2 to 3 years or with new symptoms for those with stable laboratory findings. Patients with intermediate- or high-risk MGUS and those with progressive increase in M protein should undergo evaluation by a hematologist that includes bone marrow biopsy and either bone or CT imaging. Of note, this guidance does not apply to patients with limited life expectancy (eg, less than 3 to 5 years), who will not derive benefit during their remaining lifespan.

There are no approved treatments to eliminate or prevent progression of MGUS. It remains a matter of debate whether exposing patients with low risk of progression to the risks and inconveniences of treatment has net clinical benefit. Nevertheless, several clinical trials of pharmacologic and behavioral interventions are underway (eg, NCT03820817, NCT05640843).

Limitations

Limitations of this Review include that it was not a systematic review, such that some pertinent evidence may not be included. In addition, we did not conduct formal assessment of the quality of included studies.

Conclusions

MGUS is common, often discovered incidentally and indolent but can cause significant morbidity and mortality when it progresses to overt malignant disease or is associated with rare M protein–associated disorders. Currently, treatment is predicated on identifying high-risk cases that require invasive testing, more intensive monitoring, and treatment. Equally important in management is identifying patients with low-risk disease who are unlikely to be affected by MGUS and may be monitored. Novel technologies may provide more granular details about how to distinguish high- from low-risk disease based on molecular data. Results of highly anticipated ongoing studies will advance our understanding of optimal risk stratification, screening methods, monitoring strategies, and potential interventions and have the potential to greatly improve outcomes.

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