REVIEW ARTICLE

Monoclonal Gammopathy of Undetermined Significance

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N Engl J Med 2025;393:1315-26.
DOI: 10.1056/NEJMra2412716

CME

Monoclonal gammopathy of undetermined significance (MGUS) is a common premalignant plasma-cell proliferative disorder that is present in approximately 5% of the general population over the age of 50 years.[1-4] This disorder is important not only because it is the precursor to plasma-cell cancers, including multiple myeloma, solitary plasmacytoma, and Waldenström's macroglobulinemia, but also because it is causally related to numerous serious nonmalignant disorders, collectively referred to as monoclonal gammopathy of clinical significance (MGCS).[5] MGUS is characterized by a limited yet monoclonal proliferation of plasma cells secreting abnormal levels of immunoglobulins (antibodies) that are identical to each other, with the same amino acid sequence, referred to as monoclonal (M) proteins.[6] These secreted M proteins are best appreciated as fully functioning human antibodies present in high concentrations that fortunately lack affinity to self-antigens (autoantibody characteristics) in most persons. As a result, MGUS remains asymptomatic in the absence of malignant transformation in most people. However, there is potential for serious harm if the M protein has or develops affinity for one or more organs in the body, resulting in MGCS.

History and Epidemiology

The presence of monoclonal proteins in the general population in the absence of symptoms was recognized in the 1950s by Jan Waldenström and referred to as essential hypergammaglobulinemia or benign monoclonal gammopathy.[7,8] In 1978, the term monoclonal gammopathy of undetermined significance was coined by Robert Kyle, who found that this disorder was not entirely benign and that there was a persistent risk of malignant transformation over time.[9] Initial population-based studies suggested that the prevalence of MGUS in the general population over the age of 50 years was approximately 3%, with a slightly higher prevalence among men than among women.[1,10,11] More recent studies using more sensitive detection methods show that the prevalence is higher, at approximately 5%.[2,3] The prevalence increases with age, with rates among persons older than 70 years of age that are double those among persons 50 to 70 years of age (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[1] The prevalence of MGUS among Black persons and among first-degree relatives of persons with multiple myeloma or a related disorder is 2 to 3 times as high as that in the general population.[11] Studies show that the age at onset may be approximately a decade earlier in Black people than in White people.[12] Obesity, sugar-sweetened beverages, radiation exposure, environmental exposure to pesticides and other carcinogens, chronic inflammation, and immunosuppression are other reported risk factors for MGUS.[13-19]

KEY POINTS

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

- Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma-cell disorder present in approximately 5% of the general population over the age of 50 years.
- MGUS is characterized by the presence of detectable monoclonal (M) proteins, which are identical copies of intact immunoglobulins, immunoglobulin light chains, or both that are secreted by the clonal plasma cells.
- MGUS is asymptomatic but can progress to cancer — specifically, multiple myeloma, Waldenström's macroglobulinemia, or solitary plasmacytoma — at a rate of 1% per year.
- A variety of systemic disorders, referred to collectively as monoclonal gammopathy of clinical significance (MGCS), can develop as a result of the secreted monoclonal immunoglobulin in persons with MGUS.
- The diagnosis of progression to cancer or MGCS usually requires histopathological confirmation to ensure that the clinical problem is attributable to the plasma-cell disorder.
- No therapy is needed for MGUS, and the schedule for clinical follow-up is dictated by underlying risk stratification.

DIAGNOSTIC CRITERIA AND CLASSIFICATION

The diagnostic criteria for MGUS and related disorders are listed in Table 1. Since bone marrow biopsy is an invasive procedure, it is not recommended for persons thought to have low-risk MGUS (Table S2) if all other criteria are met and there are no clinical concerns about cancer or MGCS.[21,22] The probability of 10% or higher bone marrow involvement in such persons is less than 5%.[23] An online calculator is helpful in estimating the need for a bone marrow biopsy in borderline circumstances (https://istopmm.com/riskmodel/). MGUS is subclassified into three clinical types on the basis of the predominant mode of malignant progression: IgM MGUS, non-IgM MGUS, and light-chain MGUS (Table 1).[4] Although in most persons, MGUS is diagnosed at a premalignant biologic stage, in the future, genomic studies may help identify the small subgroup of persons in whom malignant transformation has already occurred in order to enable accurate classification.[24,25]

PATHOGENESIS

The first pathogenetic event in MGUS is the development of primary cytogenetic abnormalities when memory B cells, plasma cells, or both respond to antigenic stimulation, such as infection or inflammation (Fig. 1A).[19,26,27] There are two main categories of primary cytogenetic abnormalities — trisomies and translocations within the immunoglobulin heavy locus (*IGH*) — resulting in two main biologic types of MGUS: hyperdiploid MGUS and MGUS with *IGH* translocations, respectively (Table S3).[28,29] In a small proportion of cases of MGUS, both trisomies and *IGH* translocations exist within the same clone. In IgM MGUS, primary *IGH* translocations are less common, but mutations in *MYD88* are seen in most cases and are important in the pathogenesis.

MGUS carries a risk of progression to cancer or MGCS (Fig. 1B).[5,30] Malignant progression is a clinically important event that is related to clone size and acquisition of one or more secondary cytogenetic abnormalities: APOBEC mutational signature, copy-number abnormalities, MYC structural variants, and mutations in driver genes such as *NRAS* and *KRAS* and genes in the mitogen-activated protein (MAP) kinase pathway (Fig. 1A).[25,31-33] Mutations in *CXCR4* may facilitate disease progression in IgM MGUS. Despite the presence of secondary cytogenetic abnormalities, the clone may stay dormant, which indicates that changes in the bone marrow microenvironment, defects in immune surveillance, or both may be needed for malignant transformation, at least in some cases.[19,34,35]

In most cases of MGCS, the pathogenesis is related to the antibody properties of the secreted M protein directly targeting one or more organs (Fig. 1B). In other cases, the pathogenesis is more complex. For instance, in immunoglobulin light-chain (AL) amyloidosis, the pathogenesis is related to deposition of misfolded immunoglobulin light chains in beta-pleated sheets in various organs.[36]

Table 1. Classification of Monoclonal Gammopathy of Undetermined Significance (MGUS), Diagnostic Criteria, and Major Disorders Associated with Disease Progression.*

Disorders	Diagnostic Criteria
MGUS (IgM MGUS, non-IgM MGUS, light-chain MGUS†)	Serum monoclonal protein level of <3 g/dl (or in the case of light-chain MGUS, an abnormal FLC ratio plus increased level of involved light chain) <10% Clonal plasma cells or lymphoplasmacytic cells in bone marrow‡ Absence of end-organ damage (e.g., CRAB criteria) that can be attributed to the plasma-cell proliferative disorder
Malignant progression of MGUS (multiple myeloma, solitary bone plasmacytoma, solitary extramedullary plasmacytoma, Waldenström's macroglobulinemia)	≥10% Clonal plasma or lymphoplasmacytic cells in bone marrow or presence of a biopsy-proven bony or extramedullary plasmacytoma For multiple myeloma: one or more myeloma-defining events§ For Waldenström's macroglobulinemia: anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly attributable to the underlying clonal proliferative disorder
Causally related nonmalignant disorders Multisystem disorders (AL amyloidosis, monoclonal immunoglobulin deposition disease, cryoglobulinemia) Major syndromes (POEMS syndrome¶, Schnitzler's syndrome, TEMPI syndrome, cold agglutinin disease) MGRS (PGNMID, C3 glomerulonephritis, monoclonal immunoglobulin crystalline membranous nephropathy)†† MGNS (monoclonal gammopathy–associated IgM neuropathy, monoclonal gammopathy–associated non-IgM neuropathy) MGTS Dermatologic diseases (necrobiotic xanthogranuloma, scleromyxedema)	Monoclonal protein, clonal plasma cells, or both in bone marrow required, with few exceptions‖ Likely causal relationship established on the basis of the presence of monoclonal protein (intact, light or heavy chain only, or fragments) or monoclonal plasma-cell or B-cell infiltrate** Specific diagnostic criteria for diagnosis of well-defined disorders and syndromes (e.g., AL amyloidosis, POEMS syndrome, cryoglobulinemia, and cold agglutinin disease)

* The information on diagnostic criteria is from Rajkumar et al.,[4] Dispenzieri,[5] and Bridoux et al.[20] AL denotes immunoglobulin light chain, MGNS monoclonal gammopathy of neurologic significance, MGTS monoclonal gammopathy of thrombotic significance, and TEMPI telangiectasias, elevated erythropoietin and erythrocytosis, monoclonal gammopathy, perinephric fluid, and intrapulmonary shunting.

† In light-chain MGUS, monoclonal protein may be absent in serum and urine, but the diagnosis is established on the basis of an abnormal kappa:lambda free light chain (FLC) ratio (<0.26 or >1.65) in conjunction with an increased level of the involved light chain and in the absence of immunoglobulin heavy-chain expression on immunofixation or mass spectrometry.

‡ Bone marrow aspiration can be deferred in persons with low-risk MGUS (IgG type, monoclonal [M] protein level of <15 g per deciliter, and normal FLC ratio) who have no clinical features suggestive of myeloma.

§ Myeloma-defining events (SLiM-CRAB criteria) include the CRAB criteria (hypercalcemia, renal insufficiency, anemia, and osteolytic bone lesions thought to be attributable to the clonal plasma-cell disorder) plus a clonal bone marrow plasma-cell percentage of 60% or higher, more than one focal lesion on magnetic resonance imaging that is 5 mm or more in diameter, and an involved:uninvolved serum FLC ratio of 100 or higher with involved FLC level of 100 mg per deciliter or higher and 24-hour urine monoclonal protein excretion exceeding 200 mg.

¶ Patients with POEMS (polyradiculoneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome may have evidence of cancer, with one or more osteosclerotic bone lesions.

‖ One exception is proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) with no evidence of monoclonal gammopathy in serum or urine or clonal involvement in bone marrow but with clear evidence that a monoclonal gammopathy is the cause of the renal injury on the basis of a histopathological examination of the glomerulus showing monoclonal immunoglobulin deposits.

** One exception is C3 glomerulonephritis in which complement activation by the monoclonal M protein occurs outside the kidney and the renal biopsy specimen shows only complement deposits, without any M protein.

†† Renal injury can be considered monoclonal gammopathy of renal significance (MGRS) only if there is evidence of a specific disorder attributable to the monoclonal protein, such as PGNMID, C3 glomerulonephritis, AL amyloidosis, or immunoglobulin deposition disease. A renal biopsy is required for diagnosis.

CLINICAL PRESENTATION

MGUS is asymptomatic in the absence of progression to cancer or an association with one of the MGCS disorders.[22] The diagnosis of MGUS is usually made incidentally when tests to detect M proteins are ordered as part of a broad workup in patients with fatigue, an elevated erythrocyte sedimentation rate, anemia, bone pain, osteoporosis, or infections.[6] MGUS is also diagnosed when multiple myeloma is considered in the differential diagnosis for patients presenting with osteolytic lesions, bone fractures, hypercalcemia, proteinuria, renal insufficiency, lymphadenopathy, or hepatosplenomegaly. Testing for M proteins should be performed only if there is clinical concern about a plasma-cell cancer or a suspicion that a monoclonal plasma-cell disorder or M protein

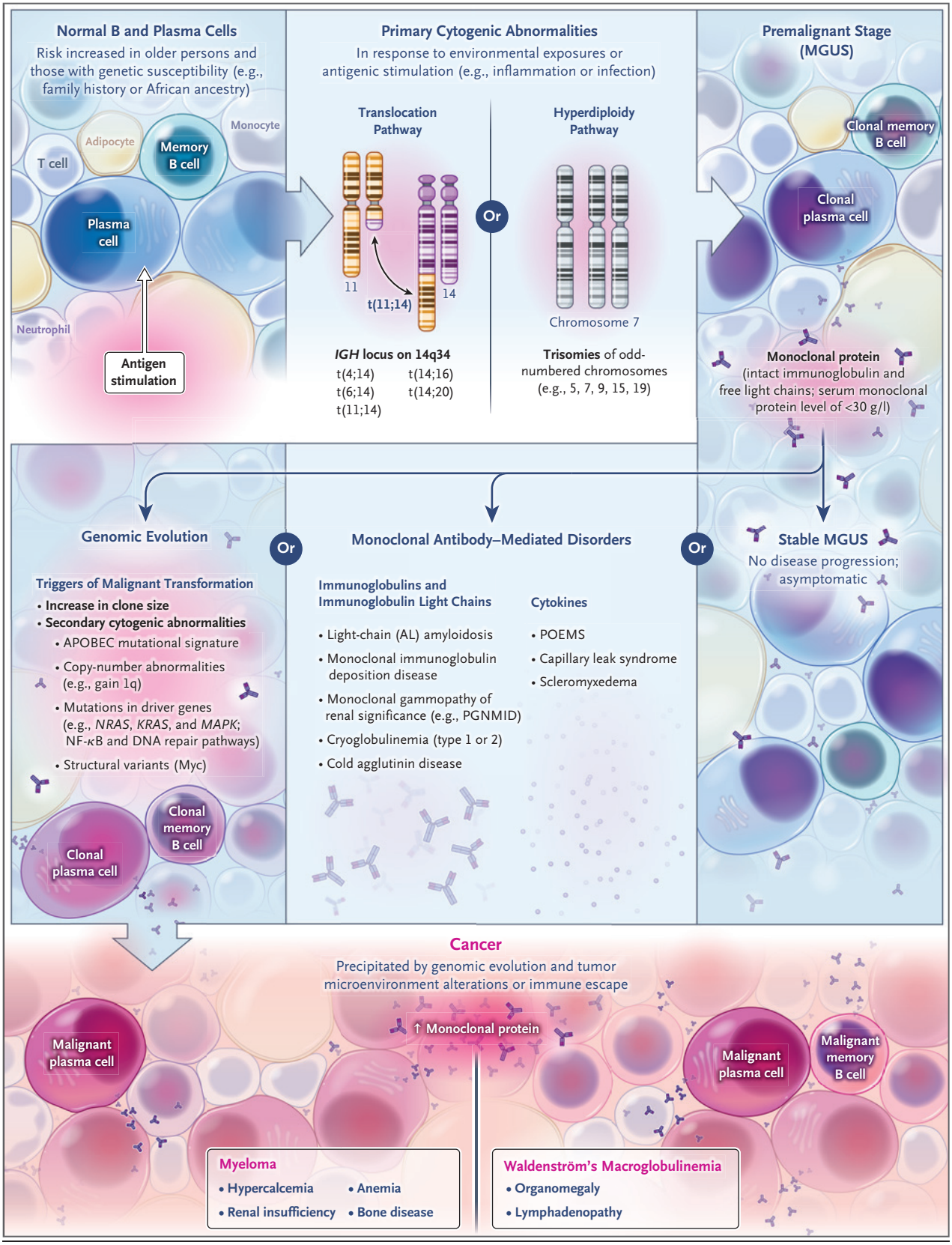


Figure 1 (facing page). Pathogenesis and Progression of Monoclonal Gammopathy of Undetermined Significance (MGUS).

The primary molecular genetic abnormalities that establish the premalignant clonal process, which occur in normal memory B cells and plasma cells responding to infection and inflammation, consist of either trisomies or one of the listed *IGH* translocations. The transition from precancer to cancer is related to acquisition of one or more secondary cytogenetic abnormalities, changes in the bone marrow microenvironment, and defects in immune surveillance. The premalignant clonal expansion clinically referred to as MGUS can progress to overt cancer or to nonmalignant disorders that are typically mediated by the monoclonal protein (immunoglobulin) secreted by these cells. NF-κB denotes nuclear factor κB, PGNMID proliferative glomerulonephritis with monoclonal immunoglobulin deposits, and POEMS polyradiculoneuropathy, organomegaly, endocrinopathy, M protein, and skin changes.

is the cause of a given clinical problem (i.e., suspected MGCS) or in specific circumstances, such as organ donation. Although MGUS is asymptomatic, some persons have suppression of uninvolved normal immunoglobulins and a slightly blunted response to vaccines.

LABORATORY TESTING

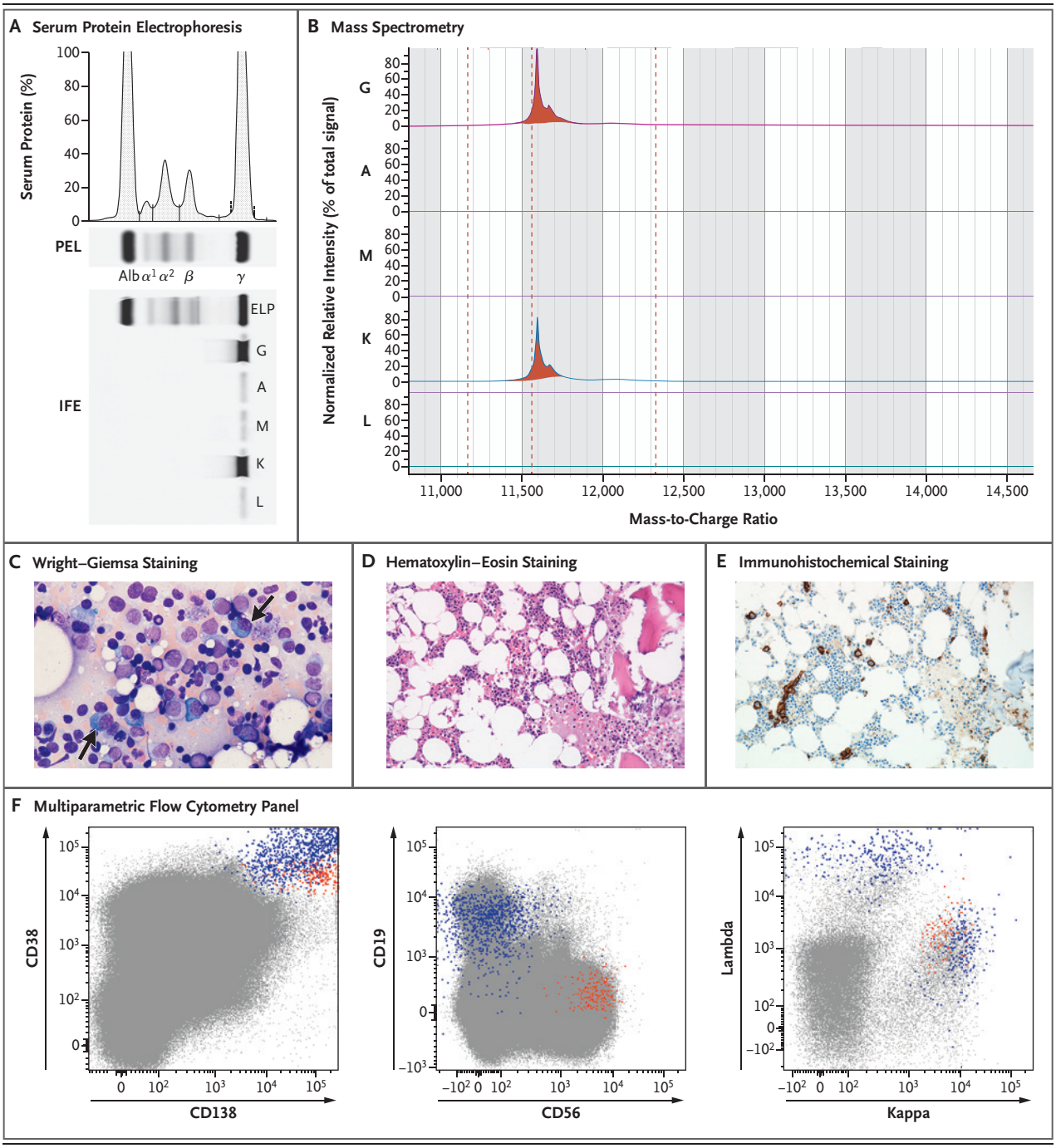
With serum protein electrophoresis, M proteins are detected as an abnormal narrow peak (like a church spire) on the densitometer tracing (Fig. 2A). For a diagnosis of MGUS, the serum M protein concentration must be less than 3 g per deciliter (Table 1).[4] The type of M protein can be ascertained with serum immunofixation on the basis of localization of the discrete heavy- and light-chain bands (Fig. 2A). Mass spectrometry is an alternative to immunofixation and is a more efficient, sensitive, and specific method for detecting M proteins (Fig. 2B).[37] If an M protein is detected, 24-hour urine electrophoresis is recommended to quantitate M proteins in the urine as a baseline and to detect albuminuria, which can occur with renal injury from MGCS. In approximately 20% of patients with MGUS, there is no expression of the normal immunoglobulin heavy chain, and the clonal cell secretes only free monoclonal light chains (light-chain MGUS). This subtype of MGUS is best identified with the serum free light-chain (FLC) assay, which measures free kappa and lambda light chains that are not bound to intact immunoglobulin (Table 1). The assay should therefore be performed, along with serum electrophoresis and immunofixation, for all patients in whom a clonal plasma-cell disorder is suspected. Clonality on the serum FLC assay is established by the presence of an abnormal ratio of the two light-chain concentrations.[38,39]

Bone marrow aspiration and biopsy, if performed, must show less than 10% clonal bone marrow plasma cells. Plasma cells can be easily identified on the basis of morphologic features (Fig. 2C and 2D) and positive immunohistochemical staining for CD138 (Fig. 2E). In IgM MGUS, the clonal cells may have lymphoid or mixed lymphoplasmacytic morphologic features. Clonality is established with flow cytometry (Fig. 2F) or immunohistochemistry. Baseline testing of bone marrow samples for cytogenetic abnormalities with the use of fluorescence in situ hybridization or sequencing is recommended, if available, to establish the biologic subtype of MGUS.

MGUS is differentiated from multiple myeloma and smoldering multiple myeloma on the basis of the M protein concentration, bone marrow plasma-cell percentage, and presence or absence of related cancer, especially myeloma-defining events such as hypercalcemia, renal insufficiency, anemia, or lytic bone lesions (i.e., the CRAB criteria) (Table 1).[4] The presence of end-organ damage does not automatically indicate that MGUS has progressed to cancer or MGCS, since there may be other causes for these findings. End-organ damage must be carefully investigated to determine whether the injury is attributable to a clonal plasma-cell disorder or another, unrelated problem. If indicated, whole-body, low-dose computed tomography (CT) or positron-emission tomography–CT or whole-body magnetic resonance imaging should be performed to rule out multiple myeloma and Waldenström's macroglobulinemia.[40]

CANCERS RESULTING FROM PROGRESSION OF MGUS

MGUS is the premalignant precursor of myeloma, Waldenström's macroglobulinemia, and solitary plasmacytoma (Table 1). In almost all patients with multiple myeloma, MGUS has been present for many years before the cancer is diagnosed.[41] The overall risk of progression of MGUS



to multiple myeloma or a related cancer is approximately 1% per year, on the basis of a population-based study involving 1384 persons.[42,43] In the subgroup of patients with light-chain MGUS, the risk of progression appears to be lower, at 0.3% per year.[10]

When non-IgM MGUS and light-chain MGUS progress to cancer, it is usually multiple myeloma or solitary plasmacytoma. In contrast, IgM MGUS usually progresses to Waldenström's macroglobulinemia (also referred to as lymphoplasmacytic lymphoma), which has a clinical phenotype of a low-grade lymphoproliferative disorder. IgM MGUS can progress to multiple myeloma with characteristic osteolytic lesions, but this is uncommon.[44]

Figure 2 (facing page). Diagnostic Testing for MGUS.
Serum protein electrophoresis and mass spectrometry can be used to detect monoclonal (M) protein; in serum protein electrophoresis, M protein is detected as an abnormal peak, and the type of protein can be determined by immunofixation. Panel A shows protein electrophoresis (PEL) with a monoclonal spike in the gamma region (top image) and serum immunofixation (IFE) with discrete bands in IgG and kappa (bottom image), indicating the presence of IgG kappa monoclonal protein. Alb denotes albumin; α^1, α^2, β, and γ denote globulins; ELP indicates the lane in which the total protein was electrophoresed; and G, A, M, K, and L denote antiserum against IgG, IgA, IgM, kappa light chain, and lambda light chain, respectively. Mass spectrometry can be used in place of immunofixation; Panel B shows normal spectrum, characterized by smooth curves and an absence of monoclonal protein spikes, as well as spikes in IgG and kappa, indicating the presence of IgG kappa monoclonal protein. Panel C shows Wright–Giemsa staining of a bone marrow aspirate with a slightly increased percentage of plasma cells (<10%) (arrows). Panel D shows hematoxylin and eosin staining of a bone marrow biopsy specimen with a few scattered plasma cells. Panel E shows CD138 immunohistochemical staining of a bone marrow biopsy specimen with a minimally increased percentage of plasma cells (brown staining). Panel F shows multiparametric flow cytometry with initial gating of plasma cells based on CD38 and CD138 expression (left image) and aberrant loss of CD19 and gain of CD56 expression in abnormal plasma cells (middle image), with confirmation that the abnormal plasma cells are kappa light-chain–restricted (right image). Normal (polyclonal) plasma cells are blue, and abnormal (monoclonal) plasma cells are red.

NONMALIGNANT DISORDERS CAUSALLY RELATED TO MGUS

More than 100 nonmalignant diseases have been reported to be associated with MGUS, but most such associations are coincidental rather than causal.[2,45] However, several well-defined nonmalignant diseases are known to be causally related to MGUS, and MGCS is the umbrella term for these disorders (Table 1).[5,22] "Nonmalignant" does not imply benign or indolent; in fact, some nonmalignant disorders, such as AL amyloidosis, may have an outcome similar to that of serious cancers.

An MGCS disorder may be diagnosed concurrently with the initial detection of an M protein as part of the workup for clinical problems such as nephrotic syndrome, peripheral neuropathy, or cardiomyopathy or during follow-up as a nonmalignant progression event in patients with known MGUS. Some investigators have used terms such as monoclonal gammopathy of renal significance (MGRS)[46] or monoclonal gammopathy of neurologic significance (MGNS)[47] to subclassify MGCS on the basis of the affected organ. The main goal of these broad terms is to inform clinicians that MGUS can cause serious disease independently of malignant progression. But for accurate diagnosis and appropriate management, it is important to discriminate among the several pathological diseases that each of these terms encompasses (Table 1). Furthermore, some of these disorders, such as AL amyloidosis, monoclonal immunoglobulin deposition disease, and cryoglobulinemia, affect multiple organs and do not fit well within an organ-based classification.

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

The kidney is particularly vulnerable in clonal plasma-cell disorders; the classic presentation is acute renal failure due to light-chain cast nephropathy in multiple myeloma. But even without malignant progression to multiple myeloma, many specific renal disorders can occur as a result of M proteins secreted by a premalignant MGUS clone.[20,46,48] MGUS can lead to proliferative glomerulonephritis through direct deposition of M protein in the mesangium and along capillary walls, resulting in an immune-mediated proliferative glomerulonephritis with immunoglobulin deposits (Fig. 3).[49,50] In other cases, M proteins activate the alternative pathway of complement in the circulation, leading to glomerular deposition of complement factors and resulting in C3 glomerulonephritis.[51] The diagnosis of these specific disorders requires careful investigations, as shown in Figure 3, with histopathological evidence that the renal lesions are directly related to a monoclonal gammopathy.[50,52] Renal injury can also occur in conjunction with other well-described, M protein–related systemic disorders such as AL amyloidosis and monoclonal immunoglobulin deposition disease (Table 1).

MONOCLONAL GAMMOPATHY OF NEUROLOGIC SIGNIFICANCE

The presence of an M protein in a patient with peripheral neuropathy is one of the most common reasons for an evaluation for MGUS in clinical practice. Both MGUS and neuropathy are

common in older adults, and most associations are therefore likely to be coincidental. In a subgroup of patients, however, MGUS is causally related to peripheral neuropathy. A large, population-based study from Iceland that involved 15,351 patients with MGUS and 58,619 matched controls showed a higher prevalence of peripheral neuropathy in the MGUS group than in the control group (6.5% vs. 2.8%).[53] Unlike the workup for proliferative glomerulonephritis with immunoglobulin deposits, which relies on histopathological features to establish a causal relationship, with peripheral neuropathy, the diagnosis is primarily based on the history and examination. The most well-described neurologic association with MGUS is IgM M protein–associated neuropathy, which has a classic clinical presentation of chronic distal, acquired, demyelinating, symmetric sensory neuropathy with M protein (DADS-M).[54] In approximately half of patients with this disorder, the IgM M protein binds to myelin-associated glycoprotein, but this is a nonspecific finding. In contrast, non-IgM M proteins rarely cause peripheral neuropathy, and the diagnosis of non-IgM neuropathy should generally not be considered unless the neuropathy is unexplained, progressive, and occurring in a younger patient, a subgroup in which the prevalence of MGUS is low. The clinical picture of non-IgM neuropathy is also different from that of IgM

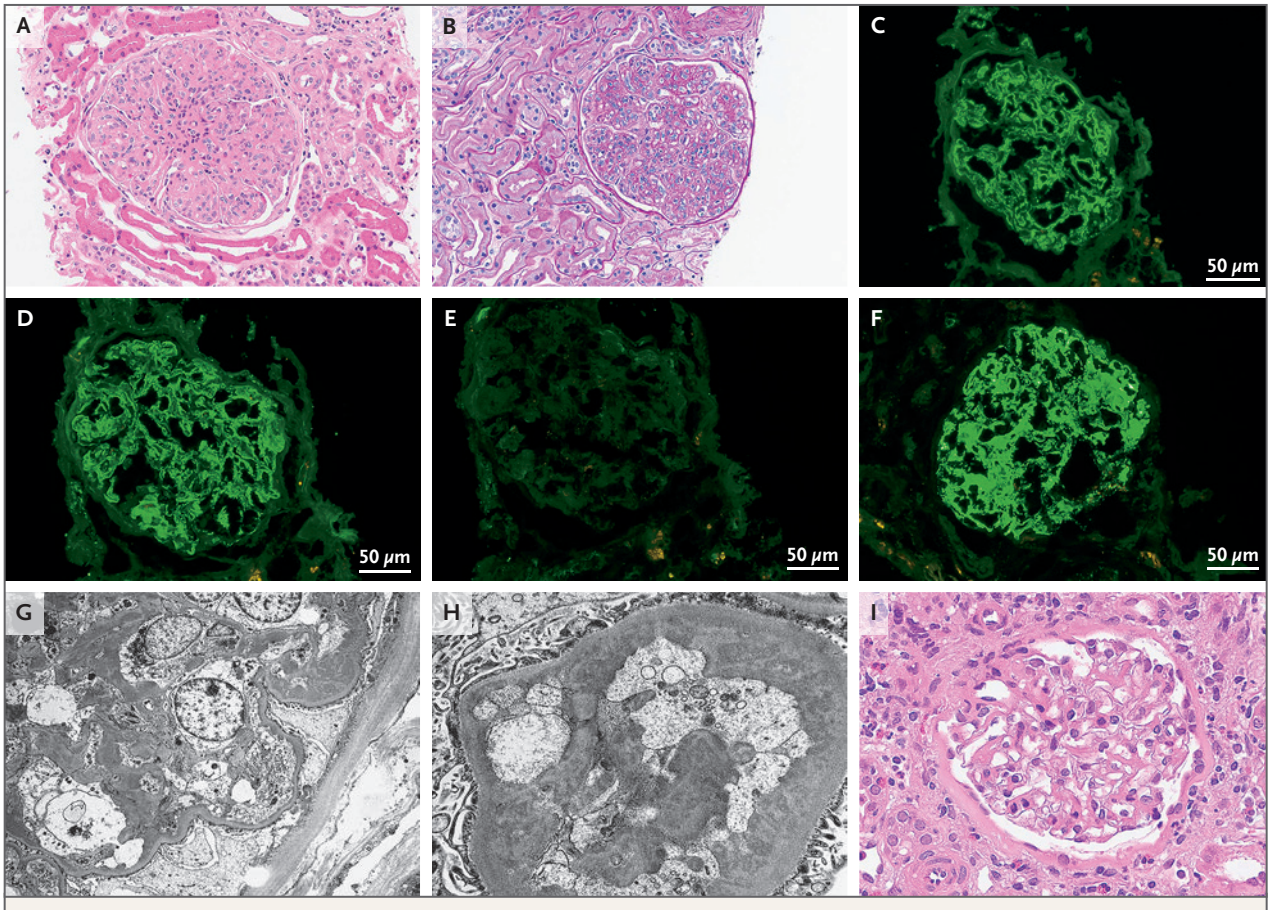


Figure 3. Kidney-Biopsy Specimen Showing Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits.

In Panels A and B, light microscopy shows a membranoproliferative pattern of injury (Panel A, hematoxylin and eosin staining; Panel B, periodic acid–Schiff staining), and in Panel C, immunofluorescence microscopy shows granular IgG along the glomerular capillary walls. In Panels D, E, and F, immunofluorescence microscopy shows bright staining for kappa light chains along the glomerular capillary walls (Panel D), negative staining for lambda light chains (Panel E), and bright staining for IgG3 (Panel F); findings for IgG1, IgG2, and IgG4 were negative (not shown). In Panels G and H, electron microscopy shows subendothelial deposits. Normal glomerulus is shown in Panel I (hematoxylin and eosin staining).

neuropathy, with features similar to those of chronic inflammatory demyelinating polyradiculoneuropathy, including distal and proximal involvement and motor involvement. Besides these types of peripheral neuropathy, nerve damage from M proteins may also occur in conjunction with two well-defined MGUS-related systemic disorders: AL amyloidosis and POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome.

OTHER NONMALIGNANT DISORDERS

A variety of dermatologic diseases have been associated with MGUS, including scleromyxedema and necrobiotic xanthogranuloma, as well as Schnitzler's syndrome (a rare disorder characterized by chronic urticaria and an IgM monoclonal gammopathy). A severe prothrombotic state induced by M proteins has recently been described; the state resolves after plasma-cell clone–directed therapy and has been considered the prototype disorder under the rubric of monoclonal gammopathy of thrombotic significance.[55,56]

MANAGEMENT OF MGCS

The treatment of any of the MGCS disorders requires precise diagnosis of the nature and extent of the injury. In general, once the diagnosis is established, plasma-cell or B-cell clone–directed therapy to reduce or eradicate the M protein should be considered. For well-established systemic disorders such as AL amyloidosis, POEMS syndrome, cryoglobulinemia, and monoclonal immunoglobulin deposition disease, there are clear algorithms for therapy, and a detailed discussion of these disorders is beyond the scope of this review.[36,57] Patients with MGRS due to proliferative glomerulonephritis with immunoglobulin deposits or C3 glomerulonephritis can benefit from treatments used for multiple myeloma, such as daratumumab or the bortezomib, cyclophosphamide, and dexamethasone regimen, in order to preserve renal function and prevent end-stage renal disease.[58] However, clone-directed therapy in patients with MGUS-associated peripheral neuropathy has had disappointing results and requires more study. For patients with IgM monoclonal gammopathy–associated neuropathy, a trial of intravenous immune globulin, rituximab, or both is reasonable.[59] For non-IgM monoclonal gammopathy–associated neuropathy with a presentation similar to that of chronic inflammatory demyelinating polyneuropathy, treatment usually comprises plasmapheresis, intravenous immune globulin, and glucocorticoids rather than clone-directed therapy.

CONDITIONS ASSOCIATED WITH MGUS

MGUS is associated with type 1 Gaucher's disease, and studies of this disease have provided important insights into the pathogenesis of monoclonal gammopathies.[27,60] In Gaucher's disease, M proteins target macrophage CD1d–presented glycosphingolipid antigens, which provides support for the mechanism shown in Figure 1, with chronic immune stimulation inducing somatic mutations that establish the clonal process.

The prevalence of MGUS with an unrelated clone is increased among patients with chronic lymphocytic leukemia, hairy-cell leukemia, or other lymphoid cancers.[61] MGUS has also been linked with an increased risk of fractures and venous thrombosis, as compared with the risk in a control population.[62-64] In contrast, new data suggest that patients with autoimmune diseases may not have an increased risk of MGUS.[65]

PROGNOSIS AND RISK STRATIFICATION FOR MGUS

Although the risk of malignant progression among patients with MGUS is considered to be 1% per year, the actual lifetime probability of progression is lower when adjusted for competing causes of death and is approximately 11% at 25 years.[43] The risk is persistent and does not diminish over time, even after 25 years of follow-up. The risk of progression to cancer can be refined on the basis of several known risk factors to help guide further diagnostic testing, counseling, and management. The risk increases proportionally with the serum M protein concentration and the degree of skewing in the serum FLC ratio. The risk is also higher with the IgM or IgA subtype of MGUS.[66] A risk stratification model that combines these three variables has been used to predict the risk of progression and to help with management decisions (Table S2).[67] For persons with all three risk factors (a serum M protein level of ≥1.5 g per deciliter, IgA or IgM MGUS, and an abnormal serum FLC ratio), the risk of progression at 20 years is 58%,

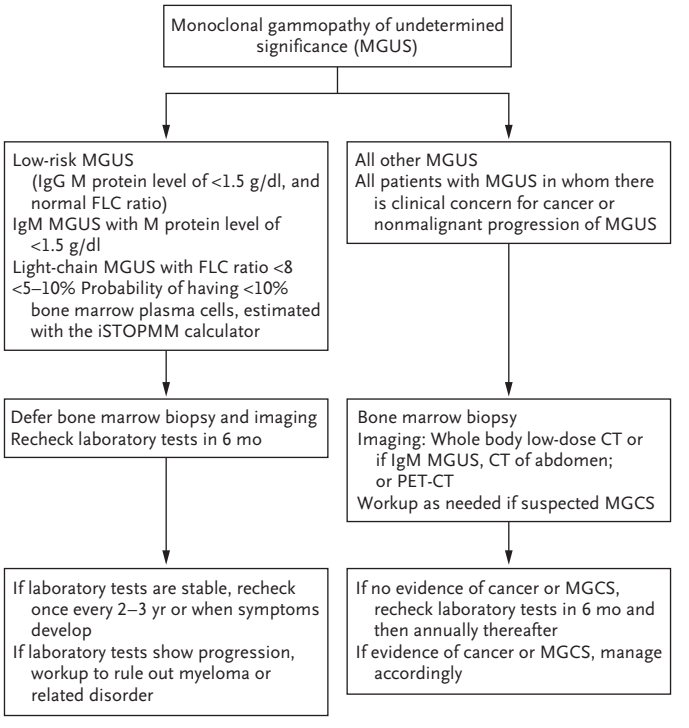


Figure 4. Management of MGUS.

The iSTOPMM (Iceland Screens, Treats, or Prevents Multiple Myeloma) calculator is available at https://istopmm.com/riskmodel/. In low-risk patients who are younger than 50 years of age, bone marrow biopsy and imaging may be considered a baseline evaluation, given the anticipated life expectancy. FLC denotes free light chain, and MGCS monoclonal gammopathy of clinical significance.

as compared with 5% for persons who have none of these risk factors. Other risk factors include suppression of normal (uninvolved) immunoglobulins (immunoparesis), the presence of high-risk cytogenetic abnormalities, and higher bone marrow plasma-cell involvement (5 to 9% clonal plasma cells vs. <5%). The PANGEA model predicts the risk of progression at baseline and also in a dynamic manner on the basis of the change in M protein levels over time.[68] Many ongoing studies are using genome sequencing, single-cell RNA sequencing, and immune and microenvironmental profiling to identify signatures that improve risk stratification and enable us to provide more precise prognostic information to each patient.[8,69]

In contrast to risk factors for malignant progression, risk factors for progression to MGCS have not been extensively studied. The effect of MGUS on overall survival in the absence of malignant progression has also been difficult to quantitate. A study in southeastern Minnesota showed that after the exclusion of all persons who had MGUS with progression to multiple myeloma or a related cancer, survival was lower among patients with MGUS than among age-matched controls.[43] Although the excess risk of death observed may have been related to conditions that led to testing for MGUS rather than a true adverse effect on survival, the increasing recognition of many clinically significant nonmalignant disorders associated with MGUS makes this finding an important consideration for further investigation.

MANAGEMENT OF MGUS

The approach to management of MGUS is shown in Figure 4. A baseline evaluation is performed to rule out malignant progression, including a complete blood count and serum calcium and creatinine levels. The CT bone survey and bone marrow biopsy can be omitted in persons with a clinical picture that is otherwise consistent with MGUS, since such persons are considered to be at low risk.[6,21]

No therapy is needed for MGUS. A complete blood count, serum calcium and creatinine measurements, and serum monoclonal protein and FLC studies should be repeated 6 months after the diagnosis has been established. Further follow-up is based on baseline risk status, as shown in Figure 4. The goal of follow-up is to improve outcomes by identifying progression of MGUS to cancer or MGCS before serious end-organ damage occurs.[70] Clinical trials involving selected high-risk persons with MGUS and patients with MGCS are ongoing.

Screening for MGUS in the general population is not recommended.[71] The Iceland Screens, Treats, or Prevents Multiple Myeloma (iSTOPMM) randomized trial is testing the effect of screening for MGUS on malignant and nonmalignant progression, but overall survival results are not expected for several years.[72] In the meantime, we recommend that screening be considered for the small group of persons at high risk — namely, those with two or more first-degree relatives who have MGUS, multiple myeloma, or Waldenström's macroglobulinemia and Black people with one or more affected first-degree relatives.[68,73]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 2006;354:1362-9.
2. Sigurbergsdóttir AY, Rögnvaldsson S, Thorsteinsdóttir S, et al. Disease associations with monoclonal gammopathy of undetermined significance can only be evaluated using screened cohorts: results from the population-based iStopMM study. Haematologica 2023;108:3392-8.
3. Murray D, Kumar SK, Kyle RA, et al. Detection and prevalence of monoclonal gammopathy of undetermined significance: a study utilizing mass spectrometry-based monoclonal immunoglobulin rapid accurate mass measurement. Blood Cancer J 2019;9:102.
4. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15(12):e538-e548.
5. Dispenzieri A. Monoclonal gammopathies of clinical significance. Hematology Am Soc Hematol Educ Program 2020; 2020:380-8.
6. Gonsalves WI, Rajkumar SV. Monoclonal gammopathy of undetermined significance. Ann Intern Med 2022;175(12): ITC177-ITC192.
7. Waldenstrom J. Studies on conditions associated with disturbed gamma globulin formation (gammopathies). Harvey Lect 1960;56:211-31.
8. Hevroni G, Vattigunta M, Kazandjian D, et al. From MGUS to multiple myeloma: unraveling the unknown of precursor states. Blood Rev 2024;68:101242.
9. Kyle RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. Am J Med 1978;64:814-26.
10. Dispenzieri A, Katzmann JA, Kyle RA, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet 2010;375:1721-8.
11. Landgren O, Graubard BI, Katzmann JA, et al. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutritional Examination Survey. Leukemia 2014;28: 1537-42.
12. Landgren O, Graubard BI, Kumar S, et al. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance in 12372 individuals 10-49 years old: a population-based study from the National Health and Nutrition Examination Survey. Blood Cancer J 2017;7(10):e618.
13. Landgren O, Rajkumar SV, Pfeiffer RM, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. Blood 2010;116: 1056-9.
14. Joseph JM, Hillengass J, Tang L, et al. Dietary risk factors for monoclonal gammopathy of undetermined significance in a racially diverse population. Blood Adv 2024;8:538-48.
15. Landgren O, Kyle RA, Hoppin JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood 2009;113:6386-91.
16. Landgren O, Zeig-Owens R, Giricz O, et al. Multiple myeloma and its precursor disease among firefighters exposed to the World Trade Center disaster. JAMA Oncol 2018;4:821-7.
17. Zeig-Owens R, Goldfarb DG, Luft BJ, et al. Myeloma precursor disease (MGUS) among rescue and recovery workers exposed to the World Trade Center disaster. Blood Cancer J 2022;12:120.
18. Mailankody S, Landgren O. HIV, EBV, and monoclonal gammopathy. Blood 2013; 122:2924-5.
19. Dhodapkar MV. Immune-pathogenesis of myeloma. Hematol Oncol Clin North Am 2024;38:281-91.
20. Bridoux F, Leung N, Hutchison CA, et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int 2015;87: 698-711.
21. Kyle RA, Durie BGM, Rajkumar SV, 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;24:1121-7.
22. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood 2018;131:163-73.
23. Mangiacavalli S, Cocito F, Pochintesta L, et al. Monoclonal gammopathy of undetermined significance: a new proposal of workup. Eur J Haematol 2013;91:356-60.
24. Chojnacka M, Diamond B, Landgren O, Maura F. Defining genomic events involved in the evolutionary trajectories of myeloma and its precursor conditions. Semin Oncol 2022;49:11-8.
25. Oben B, Froyen G, Maclachlan KH, et al. Whole-genome sequencing reveals progressive versus stable myeloma precursor conditions as two distinct entities. Nat Commun 2021;12:1861.
26. Kumar SK, Rajkumar SV. The multiple myelomas — current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol 2018;15:409-21.
27. Nair S, Sng J, Boddupalli CS, et al. Antigen-mediated regulation in monoclonal gammopathies and myeloma. JCI Insight 2018;3(8):e98259.
28. Maura F, Bergsagel PL. Molecular pathogenesis of multiple myeloma: clinical implications. Hematol Oncol Clin North Am 2024;38:267-79.
29. Samur MK, Aktas Samur A, Shah P, et al. Development of hyperdiploidy starts at an early age and takes a decade to complete. Blood 2025;145:520-5.
30. Fermand J-P, Bridoux F, Dispenzieri A, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood 2018;132: 1478-85.
31. Boyle EM, Deshpande S, Tytarenko R, et al. The molecular make up of smoldering myeloma highlights the evolutionary pathways leading to multiple myeloma. Nat Commun 2021;12:293.
32. Maura F, Landgren O, Morgan GJ. Designing evolutionary-based interception strategies to block the transition from precursor phases to multiple myeloma. Clin Cancer Res 2021;27:15-23.
33. Schavgoulidze A, Corre J, Samur MK, et al. RAS/RAF landscape in monoclonal plasma cell conditions. Blood 2024;144: 201-5.
34. Zavidij O, Haradhvala NJ, Mouhieddine TH, et al. Single-cell RNA sequencing reveals compromised immune microenvironment in precursor stages of multiple myeloma. Nat Cancer 2020;1: 493-506.
35. Cordas Dos Santos DM, Toenges R, Bertamini L, Alberge JB, Ghobrial IM. New horizons in our understanding of precursor multiple myeloma and early interception. Nat Rev Cancer 2024;24:867-86.
36. Gertz MA. Immunoglobulin light chain amyloidosis: 2024 update on diagnosis, prognosis, and treatment. Am J Hematol 2024;99:309-24.
37. Murray DL, Puig N, Kristinsson S, et al. Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report. Blood Cancer J 2021;11:24.
38. Katzmann JA, Clark RJ, Abraham RS, 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;48:1437-44.

39. Long TE, Indridason OS, Palsson R, et al. Defining new reference intervals for serum free light chains in individuals with chronic kidney disease: results of the iStopMM study. Blood Cancer J 2022;12:133.
40. Hillengass J, Usmani S, Rajkumar SV, et al. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. Lancet Oncol 2019;20(6):e302-e312.
41. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood 2009;113:5412-7.
42. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002;346:564-9.
43. Kyle RA, Larson DR, Therneau TM, et al. Long-term follow-up of monoclonal gammopathy of undetermined significance. N Engl J Med 2018;378:241-9.
44. Schuster SR, Rajkumar SV, Dispenzieri A, et al. IgM multiple myeloma: disease definition, prognosis, and differentiation from Waldenstrom's macroglobulinemia. Am J Hematol 2010;85:853-5.
45. Bida JP, Kyle RA, Therneau TM, et al. Disease associations with monoclonal gammopathy of undetermined significance: a population-based study of 17,398 patients. Mayo Clin Proc 2009;84:685-93.
46. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood 2012;120:4292-5.
47. Castillo JJ, Callander NS, Baljevic M, Sborov DW, Kumar S. The evaluation and management of monoclonal gammopathy of renal significance and monoclonal gammopathy of neurological significance. Am J Hematol 2021;96:846-53.
48. Mignano SE, Pascal V, Odioemene NE, et al. Monoclonal immunoglobulin crystalline membranous nephropathy. Am J Kidney Dis 2024;84:120-5.
49. Sethi S, Rajkumar SV. Monoclonal gammopathy-associated proliferative glomerulonephritis. Mayo Clin Proc 2013;88:1284-93.
50. Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis — a new look at an old entity. N Engl J Med 2012;366:1119-31.
51. Ravindran A, Fervenza FC, Smith RJH, Sethi S. C3 glomerulopathy associated with monoclonal Ig is a distinct subtype. Kidney Int 2018;94:178-86.
52. Leung N, Bridoux F, Batuman V, 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;15:45-59.
53. Rögnvaldsson S, Steingrímsson V, Turesson I, Björkholm M, Landgren O, Yngvi Kristinsson S. Peripheral neuropathy and monoclonal gammopathy of undetermined significance: a population-based study including 15,351 cases and 58,619 matched controls. Haematologica 2020;105:2679-81.
54. Chaudhry HM, Mauermann ML, Rajkumar SV. Monoclonal gammopathy-associated peripheral neuropathy: diagnosis and management. Mayo Clin Proc 2017;92:838-50.
55. Kanack AJ, Leung N, Padmanabhan A. Diagnostic complexity in monoclonal gammopathy of thrombotic significance. N Engl J Med 2024;391:1961-3.
56. Salmasi G, Murray DL, Padmanabhan A. More on monoclonal gammopathy of thrombotic significance. N Engl J Med 2024;391:1464.
57. Dispenzieri A. POEMS syndrome: update on diagnosis, risk-stratification, and management. Am J Hematol 2023;98:1934-50.
58. Zand L, Rajkumar SV, Leung N, Sethi S, El Ters M, Fervenza FC. Safety and efficacy of daratumumab in patients with proliferative GN with monoclonal immunoglobulin deposits. J Am Soc Nephrol 2021;32:1163-73.
59. Tomkins O, Leblond V, Lunn MP, Viala K, Weil DR, D'Sa S. Investigation and management of immunoglobulin M- and Waldenström-associated peripheral neuropathies. Hematol Oncol Clin North Am 2023;37:761-76.
60. Nair S, Branagan AR, Liu J, Boddupalli CS, Mistry PK, Dhodapkar MV. Clonal immunoglobulin against lysolipids in the origin of myeloma. N Engl J Med 2016;374:555-61.
61. Turesson I, Kovalchik SA, Pfeiffer RM, 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;123:338-45.
62. Melton LJ III, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopathy of undetermined significance. J Bone Miner Res 2004;19:25-30.
63. Thorsteinsdottir S, Lund SH, Lindqvist EK, et al. Bone disease in monoclonal gammopathy of undetermined significance: results from a screened population-based study. Blood Adv 2017;1:2790-8.
64. Rögnvaldsson S, Gasparini A, Thorsteinsdottir S, et al. Monoclonal gammopathy of undetermined significance and the risk of thrombotic events: results from iStopMM, a prospective population-based screening study. Br J Haematol 2025;206:899-906.
65. Sverrisdottir I, Thorsteinsdottir S, Rognvaldsson S, et al. Association between autoimmune diseases and monoclonal gammopathy of undetermined significance: an analysis from a population-based screening study. Ann Intern Med 2024;177:711-8.
66. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood 2005;106:812-7.
67. Eythorsson E, Rognvaldsson S, Thorsteinsdottir S, et al. Development of a multivariable model to predict the need for bone marrow sampling in persons with monoclonal gammopathy of undetermined significance: a cohort study nested in a clinical trial. Ann Intern Med 2024;177:449-57.
68. O'Donnell EK, Borden BA, Ghobrial IM. Early detection of precursor diseases of multiple myeloma. Hematol Oncol Clin North Am 2024;38:743-53.
69. Boiarsky R, Haradhvala NJ, Alberge J-B, et al. Single cell characterization of myeloma and its precursor conditions reveals transcriptional signatures of early tumorigenesis. Nat Commun 2022;13:7040.
70. Sigurdardottir EE, Turesson I, Lund SH, et al. The role of diagnosis and clinical follow-up of monoclonal gammopathy of undetermined significance on survival in multiple myeloma. JAMA Oncol 2015;1:168-74.
71. Rögnvaldsson S, Thorsteinsdóttir S, Kristinsson SY. Screening in multiple myeloma and its precursors: are we there yet? Clin Chem 2024;70:128-39.
72. Rögnvaldsson S, Love TJ, Thorsteinsdottir S, 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;11:94.
73. Rajkumar SV. The screening imperative for multiple myeloma. Nature 2020;587(7835):S63.