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## Management of Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering Multiple Myeloma (SMM)

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### Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is defined as a serum M protein level of less than 3 g/dL, less than 10% clonal plasma cells in the bone marrow, and the absence of end-organ damage. The prevalence of MGUS is 3.2% in the white population but is approximately twice that high in the black population. MGUS may progress to multiple myeloma, AL amyloidosis, Waldenström macroglobulinemia, or lymphoma. The risk of progression is approximately 1% per year, but the risk continues even after more than 25 years of observation. Risk factors for progression include the size of the serum M protein, the type of serum M protein, the number of plasma cells in the bone marrow, and the serum free light chain ratio. Smoldering (asymptomatic) multiple myeloma (SMM) is characterized by the presence of an M protein level of 3 g/dL or higher and/or 10% or more monoclonal plasma cells in the bone marrow but no evidence of end-organ damage. The overall risk of progression to a malignant condition is 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% to 2% per year for the following 10 years. Patients with both MGUS and SMM must be followed up for their lifetime.

### Monoclonal Gammopathy of Undetermined Significance

#### Definition

The term “monoclonal gammopathy of undetermined significance” (MGUS) was introduced over three decades ago. [1] MGUS is defined as a serum M (monoclonal) protein < 3 g/dL, < 10% clonal plasma cells in the bone marrow, and most importantly, the absence of end-organ damage that can be attributed to the plasma cell proliferative disorder. End-organ damage is characterized by CRAB features (hypercalcemia, renal insufficiency, anemia, bone lesions) related to the plasma cell proliferative disorder.[2]

#### Recognition of a monoclonal gammopathy

If myeloma or a related disorder is suspected, a patient can be screened effectively for an M protein using serum protein electrophoresis, serum immunofixation, and the free light chain (FLC) assay.[3] Agarose gel electrophoresis is the preferred method for detection of an M protein. If a localized band or spike or suspicion of either is found, immunofixation is needed to confirm the presence of an M protein and to determine its heavy chain and light chain type.

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All patients who present with back pain, anemia, renal insufficiency, hypercalcemia, age-inappropriate osteopenia, or osteolytic lesions must be screened for the presence of an M protein. Utilizing only serum protein electrophoresis, serum immunofixation, and the FLC assay, 426 of 428 patients with MGUS, smoldering multiple myeloma (SMM), multiple myeloma (MM), AL amyloidosis, or solitary plasmacytoma were identified.[3]

Electrophoresis and immunofixation of an aliquot from a 24-hour urine specimen were unnecessary for screening, but these must be done if a serum M protein is found.[3] In a recent study, 94% of 1,877 patients with a monoclonal plasma cell proliferative disorder were identified with only two tests—serum protein electrophoresis and the FLC assay. These two tests identified 100% of patients with MM or Waldenström macroglobulinemia (WM), 99.5% of those with SMM, 96% of patients with AL amyloidosis, and 89% of patients with MGUS.[4] The clinician should screen for an M protein if there is only a low clinical suspicion of MM, WM, AL amyloidosis, or a related disorder. Berenson et al[5] recommend screening for MGUS in all patients with age-inappropriate osteoporosis or osteopenia.

### Prevalence of MGUS

Approximately 1.5% of persons older than 50 years and 3% of the population more than 70 years of age in Sweden, the United States, and western France have an M protein without evidence of MM or a related disorder.[6–8] In Olmsted County, Minnesota, a population-based study reported serum samples from 21,463 (77%) of the 28,038 enumerated residents who were 50 years of age or older. MGUS was found in 694 (3.2%) of this population (Table 1). The prevalence was 5.3% in persons 70 years of age or older and 8.9% in men older than 85 years. Age-adjusted rates were higher in men than in women (4.0% vs 2.7%) (Figure 1).[9] The size of the M protein was < 1.5 g/dL in 80% of those with MGUS and ≥ 2 g/dL in only 4.5%. Reduced concentration of uninvolved immunoglobulins was present in 28% of the 447 patients tested.

The Olmsted County study involved a predominantly white population. However, the prevalence of MGUS is approximately twice as high in African-Americans as in whites. In one study in North Carolina, 8.6% of 916 African-American patients had an M protein compared with 3.6% of white patients.[10] The prevalence of MGUS in African-Americans was 3.0-fold higher than in whites in a report of 4 million African-American and white male veterans admitted to Veterans Affairs hospitals.[11] The age-adjusted prevalence of MGUS was 5.8% in 917 black men aged 50 to 74 years from Ghana. Interestingly, the prevalence did not increase with advancing age.[12] In contrast, the prevalence of MGUS is lower in Japanese patients. In a study of 52,802 persons in Nagasaki City, Japan, 2.4% of patients 50 years of age or older and 4.4% of those ≥ 80 years of age had MGUS.[13]

### Prevalence of light-chain MGUS

Light-chain MGUS is defined as the presence of an abnormal free light chain ratio with no heavy chain expression plus an increased concentration of the involved light chain. In our southeastern Minnesota cohort in whom 18,353 persons were tested, 146 had light chain MGUS; the prevalence of light-chain MGUS was 0.8%.[14]

### Etiology and risk factors

The cause of MGUS is not known. There is a genetic element in some patients. In a study of 911 relatives of 97 MGUS probands and 232 MM probands, the prevalence of MGUS in first-degree relatives was 6.9% in those 50 to 59 years of age, 14.6% in those 70 to 79 years of age, and 21% in persons ≥ 80 years of age. The risk of MGUS in relatives of patients with MM was increased two-fold, while the risk in relatives of patients with MGUS was increased 3.3-fold. This suggests a shared environmental and/or genetic effect.[15]

Radiation exposure may also be a factor. MGUS developed in 1,082 of 52,525 Nagasaki atomic bomb survivors. The prevalence of MGUS was 2.7% in persons within 1.5 km of the explosion (a 1.4-fold increase compared with those beyond 3.0 km). Persons younger than 20 years of age at the time of the bombing had increased prevalence of MGUS, but no difference was seen in older patients.[16]

The risk of MM in agricultural workers has been higher in a number of case control studies. [17] This increased risk has been attributed to insecticides, herbicides, and fungicides, as well as other environmental agents. In a report of 555 men from a well-characterized prospective cohort of persons applying restricted-use pesticides, 6.8% of those > 50 years of age had MGUS compared with 3.7% in 9,469 men from Olmsted County, Minnesota. The age-adjusted prevalence of MGUS was 1.9-fold greater among the male pesticide workers. [18]

In a report of 1,000 black women and 996 white women of similar age, 3.9% of the black women had MGUS, while 2.1% of the white women had MGUS. Multivariate analysis revealed that obesity (odds ratio [OR] = 1.8), black race (OR = 1.8) and increasing age (OR = 2.5) were independently associated with an excess risk of MGUS. [19]

### Clinical course and prognosis

MGUS is a common finding in medical practice. It is asymptomatic and is found unexpectedly during laboratory testing of an apparently normal person, or it may be found during the evaluation of an unrelated disorder. It is important to determine whether the M protein will remain stable or progress to MM or a related plasma cell proliferative disorder.

### Progression of MGUS

**In a referral population—**In a referral population of 241 patients seen at the Mayo Clinic, the actuarial risk of progression was 17% at 10 years, 34% at 20 years, and 39% at 25 years; a rate of approximately 1.5% per year (Figure 2).[20] More than two-thirds of the 64 patients whose condition progressed developed MM. The interval from recognition of MGUS to the diagnosis of MM ranged from 1 to 32 years (median, 10.6 years). The diagnosis of MM was made 20 years after recognition of MGUS in 10 patients. WM developed in 7 patients, AL amyloidosis in 8, and a malignant lymphoproliferative disorder in 5 patients (Table 2). Death occurred without progression to symptomatic MM or a related disorder in 138 patients (57%) (Table 3).

**In a southeastern Minnesota population-based study—**In order to eliminate the bias that occurs with referral populations, we conducted a population-based study of 1,384 patients with MGUS from the 11 counties of southeastern Minnesota who were evaluated from 1960 to 1994.[21] The median age at diagnosis of MGUS was 72 years (in contrast to 64 years for the cohort of 241 referred patients). These patients were observed for a total of 11,009 person-years (median, 15.4 years; range, 0 to 35 years). MM, AL amyloidosis, lymphoma with IgM serum protein, WM, plasmacytoma, or chronic lymphocytic leukemia (CLL) developed in 115 patients (8%) during follow-up (Table 4). At 10 years, 10% had progressed; at 20 years, 21% had progressed; and at 25 years, 26% had progressed – approximately 1% per year (Figure 3). Patients were at risk for progression even after 25 years of follow-up. The 115 patients with progression to a plasma cell disorder was 7.3 times the number expected on the basis of the incidence rates in the general population. It must be emphasized that patients are at risk for progression of MGUS even after more than 25 years of observation.

**In other series**—Similar findings have been reported in a Swedish study of 64 patients with MGUS.[22] In another group, 13 of 128 patients with MGUS developed a malignant disease during a median follow-up of 66 months.[23] In another study, 6.8% of 335 patients with MGUS progressed during a median follow-up of 70 months.[24] In a group of 1,324 patients with MGUS in North Jutland, Denmark, malignancy caused death in 97 patients, compared with 4.9 deaths expected.[25] In the Danish Cancer Registry, 64 new cases of malignancy were found among 1,229 patients with MGUS (5 expected; relative risk [RR], 12.9).[26] In a series of 504 Icelandic patients with MGUS, a related malignancy developed in 51 (10%) after a median follow-up of 6 years.[27]

### Other manifestations

Kristinsson et al[28] reported hazard ratios for venous thrombosis of 3.4, 2.1, and 2.1 one, five, and ten years after MGUS diagnosis in a group of 5,326 MGUS patients and 20,161 matched controls from Sweden. Cohen et al[29] reported a venous thromboembolic rate of 2.2 per 100 person-years in 166 patients with MGUS. This was not significantly differently than the 1.4 per 100 person-years in 465 control patients. The authors suggested that the increased venous thromboembolic rate reported with MGUS may have been due mainly to underlying conditions that led to testing for a monoclonal protein rather than to MGUS itself.

In a population-based study from Sweden, 5,326 MGUS patients were compared to 20,161 matched controls. The risk of fracture was increased in the MGUS patients (hazard ratio [HR], 1.74), and at 10-year follow-up, the risk of vertebral/pelvic fractures had increased (hazard ratio, 2.37).[30]

### Mode of detection of progression

From our southeastern Minnesota cohort, we identified 116 patients with MGUS with satisfactory follow-up who subsequently progressed to MM. Serial follow-up with laboratory testing led to the diagnosis of MM in 16%, while the diagnosis was made only after a serious MM-related complication in 45%. Workup of less serious symptoms led to the diagnosis in 25%, while evaluation of an unrelated medical condition resulted in the diagnosis of MM in 11%. This study suggests that routine follow-up of MGUS does not detect MM in the majority of patients.[31]

### Risk factors for progression

It is not possible to predict which patients with MGUS will remain stable and which will experience progression at a subsequent time.[32] However, a number of parameters are helpful in predicting the likelihood of progression of MGUS to MM.

**Size of the M protein**—The size of the M protein at the time of recognition of MGUS is the most important predictor of progression.[21] Twenty years after recognition of MGUS, the risk of progression to MM or a related disorder was 14% for patients with an initial M protein value of 0.5 g/dL, 25% for those in whom the value was 1.5 g/dL, 41% for those in whom the value was 2.0 g/dL, and 49% in those with an M spike of 2.5 g/dL. The risk of progression in a patient with an M protein of 1.5 g/dL was almost double that of a patient with an M protein of 0.5 g/dL. The risk of progression with an M protein of 2.5 g/dL was 4.6 times that of a patient with an M protein of 0.5 g/dL. Also, a progressive increase in the size of the M protein during the first year of follow-up is an important risk factor for progression. [33]

**Type of serum M protein**—In our series of 1,384 patients, those who had an IgM or an IgA monoclonal protein had an increased risk of progression compared with patients who had an IgG protein.[21]

**Bone marrow plasma cells**—The presence of more than 5% bone marrow plasma cells was an independent risk factor for progression in one series.[ 34] Baldini et al[24] recognized a malignant transformation rate of 6.8% during follow-up when the bone marrow plasma cell was less than 10%; however, the rate was 37% for those with bone marrow plasmacytosis of 10% to 30%.

**Serum FLC ratio**—In a study of 1,148 of the 1,384 MGUS patients from southeastern Minnesota, we found an abnormal FLC ratio in 33%. Progression occurred in 7.6% of these patients at 15 years of follow-up. The risk of progression in patients with an abnormal FLC ratio was higher than in patients with a normal ratio (HR, 3.5) and was independent of the concentration and type of serum M protein.[35]

### Role of flow cytometry and cytogenetics

Perez-Persona et al[36] reported that a marked preponderance of abnormal plasma cells in the bone marrow as assessed by flow cytometry was associated with a significantly higher risk of progression to MM in a cohort of 407 patients with MGUS and 93 with SMM. The most important risk factors were the presence of 95% aberrant plasma cells together with DNA aneuploidy.[ 36] Although fluorescence in situ hybridization (FISH) reveals almost the same number and type of abnormalities as in MM, there is little evidence that this has a role in assessing the risk of the progression of MGUS to MM. No convincing evidence exists at present, but the gene expression profile may be of benefit in predicting the risk of progression.

In a study of 1,400 patients with MGUS over the past 3 decades, Varettoni et al[37] found a significant reduction in the size of the M protein and number of bone marrow plasma cells in those diagnosed more recently. They concluded that more recently diagnosed MGUS had more favorable presenting features and probably a better outcome.[37] Rossi et al[38] also reported that patients with an M protein  $\leq 1.5$  g/dL, absence of light chain proteinuria, and normal serum levels of uninvolved immunoglobulins had a more favorable prognosis.

### Risk stratification model for MGUS

A risk stratification model for predicting the risk of progression of MGUS using simple laboratory markers has been developed. Those with risk factors consisting of an elevated serum M protein value ( $> 1.5$  g/dL), IgA or IgM MGUS, and an abnormal serum FLC ratio had an absolute risk of progression at 20 years of 58% (high risk), compared with a risk of only 5% when none of these risk factors were present (low risk) (Table 5).[35] Plasma cell disorders developed in 10% of our southeastern Minnesota MGUS patients after 20 years of follow-up, whereas 72% had died of other causes.

### Differential diagnosis

Clinical and laboratory findings are helpful in differentiating a patient with MGUS from one with MM. A bone marrow aspirate and biopsy as well as a radiographic bone survey are indicated in all patients with an M protein value  $\geq 1.5$  g/dL and in all patients who have an abnormality in their complete blood cell count (CBC), creatinine level, or calcium level. The reduction of uninvolved immunoglobulins in serum or the presence of an M protein in the urine (Bence Jones proteinuria) is of little help in distinguishing between patients with MGUS and those with MM because these abnormalities may be present in both MGUS and MM. Those with a serum M protein  $\geq 3$  g/dL or bone marrow plasma cells  $\geq 10\%$  without

CRAB features are considered to have SMM.[39] The presence of osteolytic lesions or pathologic fractures strongly suggests MM, but metastatic carcinoma may also produce lytic lesions and be associated with an unrelated monoclonal protein and plasmacytosis. Abnormalities were found in magnetic resonance imaging (MRI) in 86% of 44 patients with MM, but none were present in those patients with MGUS. Although an elevated plasma cell labeling index usually indicates symptomatic MM, one-third of patients with symptomatic MM have a normal labeling index. Symptomatic MM is often associated with circulating monoclonal plasma cells in the peripheral blood.[40] FISH is not helpful in distinguishing between MGUS and MM because abnormalities detected with FISH may be found in both conditions. Conventional cytogenetic studies rarely reveal an abnormal karyotype in MGUS because of the low proliferative rate and the small number of plasma cells.

The differentiation of symptomatic MM from MGUS or SMM depends mainly on the presence or absence of end-organ damage due to the underlying plasma cell proliferative disorder. MGUS and SMM are distinguished from each other by the size of the serum M protein and the number of bone marrow plasma cells.

### Management of MGUS

At follow-up, after MGUS has first been recognized, a complete history and physical examination should be performed with emphasis on symptoms and findings that might suggest AL amyloidosis or MM. The physician should obtain a CBC and serum calcium and creatinine measurements, and should perform a qualitative test for the presence of urine protein. If proteinuria is found, a 24-hour collection of urine is needed, followed by electrophoresis and immunofixation of a concentrated aliquot. After 3 to 6 months, serum protein electrophoresis should be repeated to exclude MM and WM, since the M protein is usually recognized by chance and may represent an early MM or WM. It is important to detect MM before complications such as renal failure or pathologic fractures occur.

**Low-risk MGUS**—These patients have a serum M spike < 1.5 g/dL, IgG isotype, and a normal FLC ratio. Their absolute risk of progression at 20 years is 5%, compared to 58% for the high-risk group. Patients with low-risk MGUS do not require a bone marrow examination or skeletal radiography if the clinical evaluation, CBC, and serum creatinine and calcium values suggest only MGUS. On the other hand, a bone marrow examination is required if the patient has any CRAB features, such as unexplained anemia, renal insufficiency, hypercalcemia, or bone lesions. A patient with low-risk MGUS should be followed with serum protein electrophoresis 6 months after the diagnosis of MGUS to exclude the possibility of early MM or WM, and if stable, can be followed until symptoms suggestive of a plasma cell malignancy arise.

**Intermediate- and high-risk MGUS**—Patients with intermediate-risk MGUS have one or two abnormal risk factors, while all three risk factors are abnormal in those with high-risk MGUS—ie, the serum M protein is > 1.5 g/dL, the protein type is IgA or IgM, and the FLC ratio is abnormal. Intermediate-risk and high-risk patients should have a bone marrow aspirate and biopsy with both conventional cytogenetics and FISH. If available, a plasma cell labeling index and a search for circulating plasma cells in the peripheral blood using flow cytometry are useful.[41] Intermediate- or high-risk MGUS patients with the IgM isotype should have a CT scan of the abdomen since asymptomatic retroperitoneal lymph nodes may be present. If there is evidence of MM or WM, lactate dehydrogenase,  $\beta_2$ -microglobulin, and C-reactive protein levels should be measured. If the results of these tests are satisfactory, patients should be followed with serum protein electrophoresis and CBC in 6 months and then annually for life. In addition, patients must be instructed to contact their

physician if there is any change in their clinical condition. Treatment is not indicated unless it is part of a clinical trial.[42]

## Smoldering (Asymptomatic) Multiple Myeloma (SMM)

### Definition

Smoldering (asymptomatic) multiple myeloma is characterized by the presence of an M protein level of  $\geq 3$  g/dL and/or  $\geq 10\%$  monoclonal plasma cells in the bone marrow but no evidence of end-organ damage.[2] SMM must be distinguished from MGUS because of the higher risk of progression to MM or a related disorder associated with the former. The risk of progression for SMM is 10% per year vs 1% per year for MGUS.

### Clinical course and prognosis

In a cohort of 276 patients fulfilling the criteria for SMM, 163 (59%) developed symptomatic MM or AL amyloidosis during follow-up. The cumulative probability of progression to active MM or AL amyloidosis was 51% at 5 years, 66% at 10 years, and 73% at 15 years (Figure 3). The median time to progression was 4.8 years.[43] The overall risk of progression was 10% per year for the first 5 years, approximately 3% per year for the next 5 years, and 1% to 2% per year for the last 10 years. The risk of progression to symptomatic MM was 522 times the risk of developing MM in a normal population. The risk of AL amyloidosis was increased by a factor of 50-fold. Symptomatic MM accounted for 97% of those who progressed. The risk of progression in patients with SMM is much greater than the fixed 1% per year risk of progression in patients with MGUS. During 2,131 cumulative person-years of follow-up (median, 6.1 years; range, 0 to 29 years), 85% of the patients died.

The cumulative probability of progression at 15 years was 87% for the patients with  $\geq 10\%$  plasma cells in the bone marrow and  $\geq 3$  g/dL of M protein, 70% for the patients with  $\geq 10\%$  plasma cells and  $< 3$  g/dL of M protein, and 39% for those with  $< 10\%$  plasma cells and  $\geq 3$  g/dL of M protein. The median times to progression were 2 years, 8 years, and 19 years, respectively, for the three groups. The type of serum heavy chain (IgA) had a significant effect on the multivariate model containing the number of bone marrow plasma cells and size of the serum M protein.

### Risk factors for progression

The size of the serum M protein and the number of plasma cells in the bone marrow are the most important factors for progression. The FLC ratio ( $< 0.125$  and  $\geq 8$ ) is an independent additional risk factor for progression.[44] Gender, hemoglobin level, type of serum heavy chain, serum albumin level, presence and type of urinary light chain, and reductions in levels of uninvolved immunoglobulins are not significant risk factors for progression.[43] The presence of occult bone lesions on MRI increases the risk of progression in patients with SMM.[45] In another report, the median time to progression in 72 patients with SMM was 1.5 years in the presence of an abnormal MRI vs 5 years for those with a normal MRI.[46]

### Risk stratification model

A risk model incorporating the three risk factors (abnormal FLC ratio, bone marrow plasma cells  $\geq 10\%$ , and serum M protein  $\geq 3$  g/dL) predicted for survival. Patients with one, two, or three risk factors had 5-year progression rates of 25%, 51%, and 76%, respectively.[ 44] The presence of more than 95% aberrant plasma cells detected by flow cytometry together with immunoparesis can identify three prognostic groups in SMM, with progression rates at 5 years of 72%, 46%, and 4% if a patient has two, one, or none of the above risk factors.[36]

## Management

A CBC, measurement of calcium and creatinine levels, serum protein electrophoresis, and a 24-hour urine collection for electrophoresis and immunofixation should be performed at diagnosis. A bone marrow biopsy and skeletal survey are essential. An MRI of the spine and pelvis is recommended because the presence of occult lesions predicts a more rapid progression. The blood tests should be repeated 2 to 3 months after the initial recognition of SMM to exclude the possibility of symptomatic MM. If the results are stable, testing should be repeated every 4 to 6 months for 1 year, and if still stable, the interval between evaluations can be lengthened to every 6 to 12 months. A skeletal survey and bone marrow examination should be performed if there is evidence of progression in the above-mentioned studies.

Observation is the standard of care. There are no data to show that early treatment at the smoldering myeloma stage can prolong survival. However, clinical trials are ongoing to determine whether early therapy with newer agents can prolong the time to progression—and most importantly, prolong survival. In the United States, the Eastern Cooperative Oncology Group has recently activated a trial testing the role of lenalidomide (Revlimid) in SMM; this agent has shown promise in this setting in recent studies.[47]

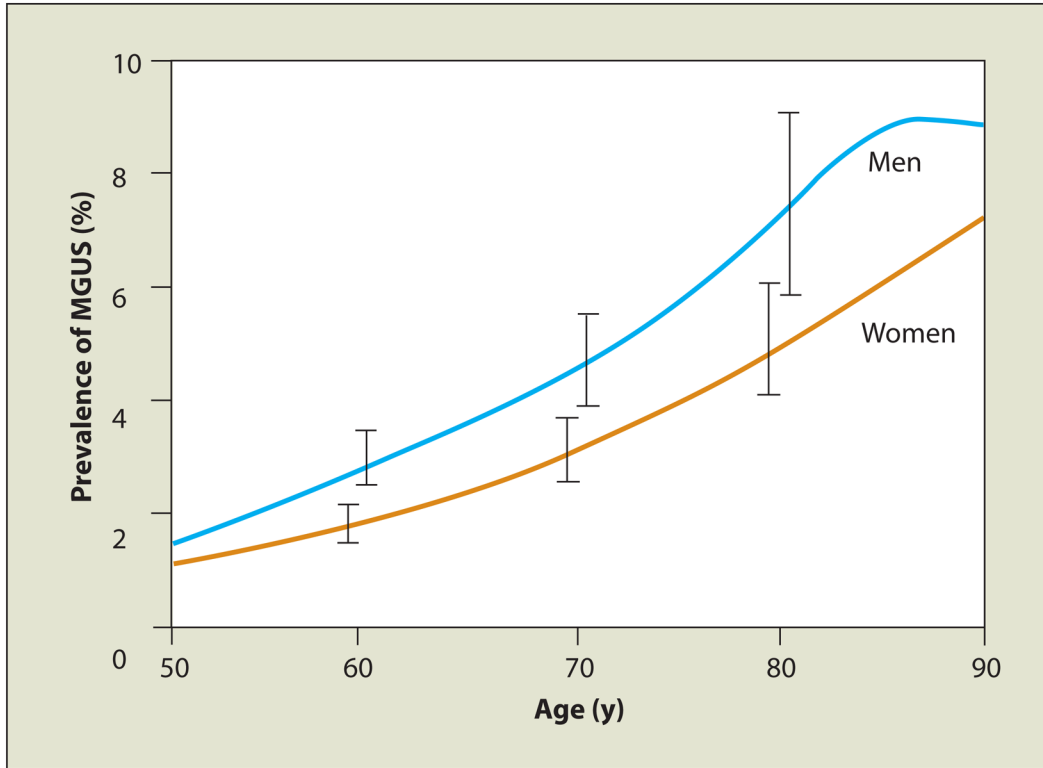
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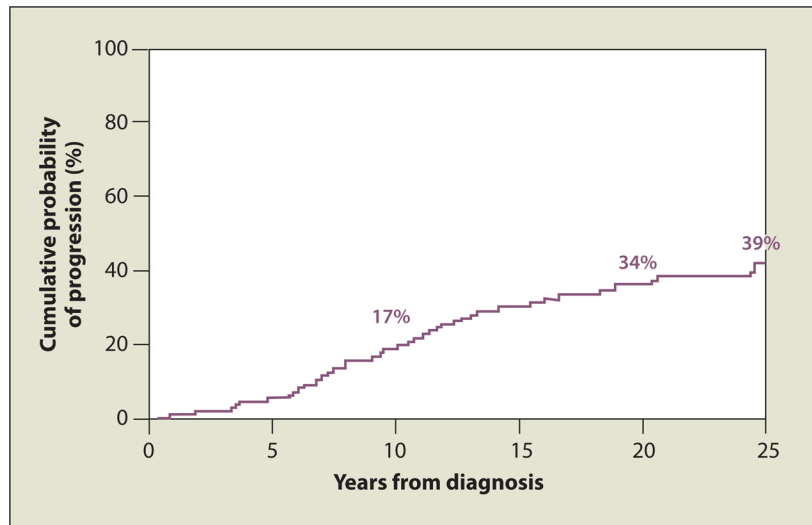
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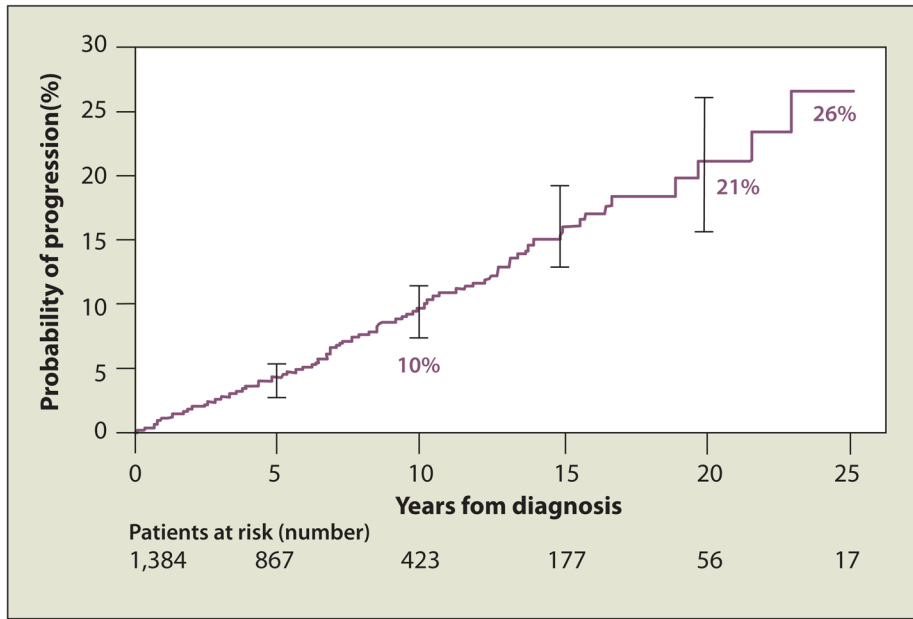
**Figure 1. Prevalence of MGUS According to Age**

The bars represent 95% confidence intervals. Ages greater than 90 years have been collapsed to 90 years. MGUS = monoclonal gammopathy of undetermined significance. From Kyle RA et al. N Engl J Med. 2006.[9] Copyright © 2006 by the Massachusetts Medical Society. All rights reserved.



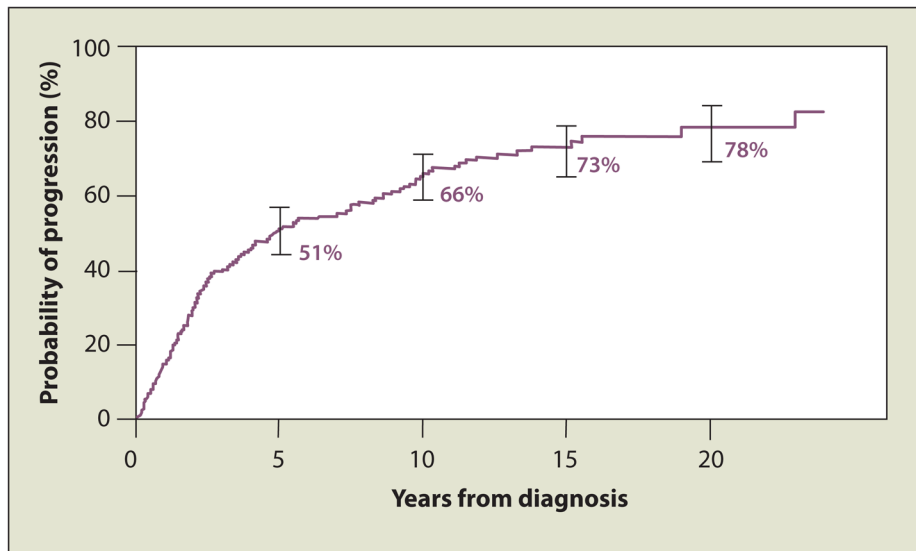
**Figure 2. Rate of Development of Multiple Myeloma or Related Disorders in 241 Patients With Monoclonal Gammopathy of Undetermined Significance**

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**Figure 3. Probability of Progression among 1384 Residents of Southeastern Minnesota in Whom Monoclonal G amopathy of Undetermined Significance (MGUS) was Diagnosed from 1960 through 1994**

The curve shows the probability of progression of MGUS to multiple myeloma, IgM lymphoma, primary amyloidosis, macroglobulinemia, chronic lymphocytic leukemia, or plasmacytoma (115 patients). The bars show 95% confidence levels. Modified from Kyle RA et al. *N Engl J Med.* 2002.[43] Copyright © 2002 by the Massachusetts Medical Society. All rights reserved. Used with permission.



**Figure 4. Probability of Progression to Active Multiple Myeloma or Primary Amyloidosis in Patients with Smoldering Multiple Myeloma**

Bars denote 95% confidence levels. From Kyle RA et al. *N Engl J Med.* 2007.[43]  
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**Table 1**

Prevalence of MGUS According to Age Group and Sex Among Residents of Olmsted County, Minnesota

| Age                                  | Men                         | Women                         | Total                           |
|--------------------------------------|-----------------------------|-------------------------------|---------------------------------|
| Number/Total Number (%) <sup>a</sup> |                             |                               |                                 |
| 50–59 y                              | 82/4038 (2.0)               | 59/4335 (1.4)                 | 141/8373 (1.7)                  |
| 60–69 y                              | 105/1858 (3.7)              | 73/3155 (2.3)                 | 178/6019 (3.0)                  |
| 70–79 y                              | 104/2864 (5.6)              | 101/2650 (3.8)                | 205/4508 (4.6)                  |
| 80 y                                 | 59/709 (8.3)                | 111/1854 (6.0)                | 170/2563 (6.6)                  |
| Total                                | 350/9469 (3.7) <sup>b</sup> | 344/11,994 (2.9) <sup>b</sup> | 694/21,463 (3.2) <sup>b,c</sup> |

<sup>a</sup>The percentage was calculated as the number of patients with MGUS divided by the number who were tested.

<sup>b</sup>Prevalence was age-adjusted to the 2000 US total population as follows: men, 4.0% (95% confidence interval, 3.5 to 4.4); women, 2.7% (95% confidence interval, 2.4 to 3.0); and total, 3.2% (95% confidence interval, 3.0 to 3.5).

<sup>c</sup>Prevalence was age- and sex-adjusted to the 2000 US total population.

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**Table 2**

## Development of Multiple Myeloma or a Related Disorder in 64 Patients With MGUS

|                             | Number (%) of patients | Interval to Disease (y) |       |
|-----------------------------|------------------------|-------------------------|-------|
|                             |                        | Median                  | Range |
| Multiple myeloma            | 44 (69)                | 10.6                    | 1–32  |
| Macroglobulinemia           | 7 (11)                 | 10.3                    | 4–16  |
| Amyloidosis                 | 8 (12)                 | 9.0                     | 6–19  |
| Lymphoproliferative disease | 5 (8)                  | 8.0                     | 4–19  |
| Total                       | 64 (100)               | 10.4                    | 1–32  |

<sup>a</sup>The percentage was calculated as the number of patients with MGUS divided by the number who were tested.

<sup>b</sup>Prevalence was age-adjusted to the 2000 US total population as follows: men, 4.0% (95% confidence interval, 3.5 to 4.4); women, 2.7% (95% confidence interval, 2.4 to 3.0); and total, 3.2% (95% confidence interval, 3.0 to 3.5).

<sup>c</sup>Prevalence was age- and sex-adjusted to the 2000 US total population.

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**Table 3**

## Course of 244 Patients With MGUS

| Patient Group | Description   | Number (%) of patients at follow-up <sup>a</sup> |
|---------------|---|--|
| 1             | Living patients with no substantial increase of M protein level                 | 14 (6)   |
| 2             | M Protein level 3.0 g/dL but no multiple myeloma or related disorder            | 25 (10)  |
| 3             | Died of unrelated causes  | 138 (57)   |
| 4             | Developed multiple myeloma, macroglobulinemia, amyloidosis, or related disorder | 64 (27)  |

<sup>a</sup>Person-years of follow-up = 3579 (median, 13.7 years per patient; range, 0–39 years).

MGUS = monoclonal gammopathy of undetermined significance. From Kyle RA et al. Mayo Clinic Proc. 2004.[20] Used with permission.

**Table 4**

Risk of Progression Among 1384 Residents of Southeastern Minnesota in Whom Monoclonal Gammopathy of Undetermined Significance was Diagnosed From 1960 Through 1994

| Type of Progression          | Number of Patients | Number of Patients <sup>a</sup> | Relative Risk (95% CI) |
|------------------------------|--------------------|---------------------------------|------------------------|
| Multiple myeloma             | 75                 | 3.0                             | 25.0 (20 – 32)         |
| Lymphoma                     | 19 <sup>b</sup>    | 7.8                             | 2.4 (2 – 4)            |
| Primary amyloidosis          | 10                 | 1.2                             | 8.4 (4 – 16)           |
| Macroglobulinemia            | 7                  | 0.2                             | 46.0 (19 – 95)         |
| Chronic lymphocytic leukemia | 3 <sup>c</sup>     | 3.5                             | 0.9 (0.2 – 3)          |
| Plasmacytoma                 | 1                  | 0.1                             | 8.5 (0.2 – 47)         |
| Total                        | 115                | 15.8                            | 7.3 (6 – 9)            |

<sup>a</sup>Expected numbers of cases were derived from the age- and sex-matched white population of the Surveillance, Epidemiology, and End Results program in Iowa, except for primary amyloidosis, data for which are from Kyle et al. *Blood*. 1992.[48]

<sup>b</sup>All 19 patients had serum IgM monoclonal protein. If the 30 patients with IgM, IgA, or IgG monoclonal protein and lymphoma were included, the relative risk would be 3.9 (95% CI, 2.6 – 5.5).

<sup>c</sup>All 3 patients had serum IgM monoclonal protein. If all 6 patients with IgM, IgA, or IgG monoclonal protein and chronic lymphocytic leukemia were included, the relative risk would be 17 (95% CI, 0.6 – 3.7).

CI = confidence interval.

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**Table 5**

Risk-Stratification Models to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders

|  | Number (%) of patients | Risk of Progression at 20 Years (%) |               |                |
|--|------------------------|-------------------------------------|---------------|----------------|
|  |                        | Relative                            | Absolute Risk | Competing Risk |
| Serum M protein < 1.5 g/dL,<br>IgG subtype, and normal FLC ratio                                 | 449                    | 1                                   | 5             | 2              |
| One risk factor abnormal   | 420                    | 5.4                                 | 21            | 10             |
| Two risk factors abnormal  | 226                    | 10.1                                | 37            | 18             |
| Three risk factors abnormal (serum M protein ≥ 1.5 g/dl, IgM or IgA subtype, abnormal FLC ratio) | 53                     | 20.8                                | 58            | 27             |

FLC = free light chain. This research was originally published in Blood (Rajkumar SV et al. Blood. 2005.[35]) and subsequently modified. Copyright © 2005 by the American Society of Hematology.