# Monoclonal Gammopathy of Undetermined Significance: Follow-up Patterns in the United States and Concordance With Clinical Practice Guidelines

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# Abstract

**Objective:** To determine follow-up practice patterns of US patients with monoclonal gammopathy of undetermined significance (MGUS) and their concordance with 4 clinical practice guidelines.

**Patients and Methods**: In a retrospective analysis of adult patients using the OptumLabs Data Warehouse database, we identified those who had an incident diagnosis of MGUS from January 1, 2006, through December 31, 2013, no history or subsequent diagnosis of lymphoplasmacytic malignancy, and at least 2 years of follow-up.

**Results:** A total of 11,676 patients with MGUS were included in the study. During the first 2 years after MGUS diagnosis, the distribution of patients by mean interval between visits was as follows: less than 6 months, 12.7%; every 6 to 12 months, 25.2%; every 13 to 24 months, 17.7%; and longer than 24 months, 44.4%. A higher proportion of patients were followed up at intervals of less than 13 months over time, from 32.7% to 41.1% (P<.001). Patients 60 years or older were more likely to be followed up at intervals of less than 13 months; those from the Northeast or younger than 50 years were more likely to be followed up at intervals longer than 24 months compared with their counterparts (P<.001). More than half of the patients 80 years or older were followed up at intervals of less than 6 months (12.3%), 6 to 12 months (27.8%), or 13 to 24 months (18.2%). Only approximately half of the patients (41.1%-58.8%) with MGUS diagnosed in 2013 were concordant with any of the 4 clinical guidelines.

**Conclusion:** The MGUS follow-up practice patterns varied geographically and demographically and were frequently discordant with guideline recommendations. A large proportion of patients with limited life expectancy had frequent follow-up visits.

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onoclonal gammopathy of undetermined significance (MGUS) is a common condition. We previously estimated that approximately 540,000 people living in the United States have a clinical diagnosis of MGUS.<sup>1</sup> Although MGUS is generally considered a benign condition with a low rate of transformation to lymphoplasmacytic malignancies (LPMs), the risk continues indefinitely.<sup>2</sup> Therefore, patients are followed up regularly to anticipate such an event at an early stage with the hope of preventing serious cancer-related complications, improving overall survival, and perhaps improving quality of

life. Two retrospective population studies suggest that patients with MGUS benefit clinically from follow-up.<sup>3,4</sup> However, no prospective data support the value of such a practice.<sup>5</sup> Even with a conservative estimate using the Medicare reimbursement rate, the health care cost of MGUS follow-up in the United States alone is likely to be more than \$100 million annually.<sup>1</sup>

The optimal follow-up of patients with MGUS, including the frequency of visits and the type of ancillary tests to order, is unknown. Nevertheless, 4 international clinical practice guidelines, all based on expert



From the Division of Hematology (R.S.G.) and Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery (R.S.G., H.C.H., LR.S., E.B.H., N.D.S.), Mayo Clinic, Rochester, MN. consensus, are available: 2009 guidelines from the UK Myeloma Forum and Nordic Myeloma Study Group (UK-Nordic),<sup>6</sup> 2010 guidelines from the International Myeloma Working Group (IMWG), 2010 guidelines from a panel giving international expert consensus (IEC),<sup>8</sup> and 2014 guidelines from the European Myeloma Network (EMN).9 Although the recommendations vary, most endorse approximately one annual follow-up visit with myeloma-related ancillary tests. These follow-up visits are generally recommended indefinitely or until life expectancy becomes limited (Table 1). How patients with MGUS are followed up in the United States and whether clinical practice guidelines are being followed remain unknown.

The goal of this study was to determine the follow-up practice patterns of patients with MGUS in the United States and their concordance with clinical practice guidelines. We investigated the frequency of visits, types of laboratory or imaging tests performed, and variances in such practice patterns among demographic subgroups and geographic locations.

# PATIENTS AND METHODS

We conducted a retrospective claims data analysis using the OptumLabs Data Warehouse (Optum Inc). OptumLabs was founded in 2013 by Mayo Clinic and Optum, a commercial data, infrastructure services, and care organization that is part of UnitedHealth Group. OptumLabs has a database of deidentified information on more than 150 million privately insured and Medicare Advantage enrollees throughout the United States and is compliant with the Health Insurance Portability and Accountability Act. It includes individuals of all ages and races from all 50 states. The plan provides fully insured coverage for inpatient, outpatient, and pharmacy services.<sup>10</sup> This study was exempt from institutional review board approval because of the preexisting and deidentified nature of the data set.

We identified adult enrollees (aged  $\geq 18$  years) who had an incident MGUS diagnosis ( $\geq 1$  inpatient or outpatient claim with an *International Classification of Diseases, Ninth Revision* code of 273.1; N=69,473) from January 1, 2006, through December 31, 2013. To

allow for adequate follow-up, we excluded patients who had enrollment periods of less than 2 years after an incident MGUS diagnosis (n=52,550). We also excluded patients with a history (any time before or within the incident MGUS diagnosis; n=4888) or a subsequent diagnosis ( $\geq 3$  months; n=359) of any LPM ( $\geq 1$  inpatient or >1 outpatient claim linked to International Classification of Diseases, Ninth Revision codes 203.0-203.2, 238.6, 273.3, and 277.3-277.39) to ensure that follow-up was for MGUS and not for LPM. Patients with LPM were excluded because MGUS-specific tests are similar to those used in follow-up of patients with LPM so that early stages of LPM could be misdiagnosed as MGUS in claims data.

We defined a follow-up visit as the occurrence of either of the following 2 scenarios: (1) a subsequent face-to-face encounter after the incident date linked to an MGUS diagnosis claim regardless of whether an ancillary test was performed and (2) ancillary tests performed and linked to an MGUS diagnosis claim without a face-to-face encounter. In the first scenario, all tests performed within 7 days of a face-to-face visit were considered part of the same visit. In the second scenario, all tests with an MGUS diagnosis claim performed in the same month were grouped together as 1 ancillary test-only visit. For face-to-face visits, we used Current Procedural Terminology codes to identify any outpatient visits (codes 99201-99205, 99211-99215, and 99241-99245) linked to an MGUS diagnosis after the incident MGUS date. For the MGUS-related ancillary tests performed, we used Current Procedural Terminology codes to identify the following: bone marrow aspirate (38221) or biopsy (38220), calcium (80048, 80050, 80053, 80069, 82310, and 82330), complete blood cell count (80050, 85025, and 85027), creatinine (80048, 80050, 80053, 80069, and 82565), serum protein electrophoresis (SPEP) (84155 and 84165), urine protein electrophoresis (84156 and 84166), immunofixation (86334 and 86335), serum free light chains (FLCs) (83883), and skeletal survey (76062, 77074, and 77075). For a test to be considered part of MGUS follow-up, it had to be linked to an MGUS diagnosis.

Because current practice guidelines have various follow-up interval recommendations, we evaluated guideline concordance in

TABLE 1. Comparison of 4 Follow-up Guidelines for Patients With Monoclonal Gammopathy of Undetermined Significance								
Patient risk category and recommended tests	UK Myeloma Forum and Nordic Myeloma Study Group (2009) <sup>6</sup>	International expert consensus (2010) <sup>8</sup>	International Myeloma Working Group (2010) <sup>7</sup>	European Myeloma Network (2014) <sup>9</sup>				
Patient risk								
Low	First year, every 3-4 mo; then every 6-12 mo if condition is stable	First 2 y, every 4-6 mo; then every 6-24 mo	At 6 mo; then every 2-3 y if condition is stable	At 6 mo; then every 1-2 y if condition is stable <i>or</i> No follow-up				
High	At least every 3-4 mo	First 2 y, every 4-6 mo; then every 6-24 mo	At 6 mo; then every 1 y if condition is stable	At 6 mo; then every 1 y thereafter				
Any risk, but life expec- tancy <5 y	Can consider discontinuing follow-up	Not mentioned	Not mentioned	No follow-up				
Recommended tests	Quantification of monoclonal protein Serum urea nitrogen Complete blood cell count Calcium Creatinine Electrolytes Immunoglobulin levels	Quantification of monoclonal protein	Quantification of monoclonal protein Complete blood cell count	Quantification of monoclonal protein Complete blood cell count Calcium Creatinine				

patients who received a diagnosis in 2013 (the most recent year in which  $\geq 2$  years of followup data were available) according to 2 followup models (Table 1): the UK-Nordic/IEC model (aggressive follow-up model, with recommended intervals of every 3-6 months for high-risk patients and every 6-12 months for low-risk patients and an overall average interval of every 3-12 months) and the IMWG/ EMN model (conservative follow-up model, with recommended intervals of every 6-12 months for high-risk patients and every 12-

TABLE 2. Demographic Characteristics of Patients According to Area of Residence in the United States <sup>a</sup>							
Characteristic	Midwest	Northeast	South	West	All regions		
Patients (No. [%])	3194 (27.4)	2085 (17.9)	5156 (44.2)	1241 (10.6)	,676 ( 00.0)		
Age (y) Mean ± SD Median (IQR) Range	66.2±13.2 67 (57-77) 19 to ≥87	61.7±14.8 61 (52-73) 18 to ≥87	60.9±13.5 61 (52-71) 18 to ≥87	61.5±13.5 61 (53-72) 18 to ≥87	$62.5 \pm 13.8$ 62 (54-73) 18 to $\geq 87$		
Sex (No. [%]) Male Female	1433 (44.9) 1761 (55.1)	932 (44.7) 1153 (55.3)	2116 (41.0) 3040 (59.0)	559 (45.0) 682 (55.0)	5040 (43.2) 6636 (56.8)		
Race/ethnicity (No. [%]) <sup>b</sup> Asian Black Hispanic White Unknown	29 (0.9) 367 (11.5) 40 (1.3) 2136 (66.9) 622 (19.5)	51 (2.4) 135 (6.5) 189 (9.1) 1051 (50.4) 659 (31.6)	74 (1.4) 961 (18.6) 325 (6.3) 2687 (52.1) 1109 (21.5)	68 (5.5) 17 (1.4) 93 (7.5) 717 (57.8) 346 (27.9)	222 (1.9) 1480 (12.7) 647 (5.5) 6591 (56.4) 2736 (23.4)		
Age (No. [%]) <50 y 50-59 y 60-69 y 70-79 y ≥80 y	338 (10.6) 675 (21.1) 758 (23.7) 779 (24.4) 644 (20.2)	399 (19.1) 519 (24.9) 478 (22.9) 390 (18.7) 299 (14.3)	997 (19.3) 1371 (26.6) 1359 (26.4) 924 (17.9) 505 (9.8)	220 (17.7) 328 (26.4) 335 (27.0) 212 (17.1) 146 (11.8)	1954 (16.7) 2893 (24.8) 2930 (25.1) 2305 (19.7) 1594 (13.7)		

 $^{a}$ IQR = interquartile range.

<sup>b</sup>Race and ethnicity were assessed to examine demographic disparity in follow-up. Categories were provided by OptumLabs, and data were based on responses from patients on their insurance policy applications.







tests ordered during monoclonal gammopathy of undetermined significance (MGOS) follow-up. A, Frequency of specific tests ordered. B, Frequency of the more common test combinations is shown above the bars, which show the combinations of tests performed during follow-up. The MGUS-specific tests include free light chain (FLC) studies, immunofixation (IFX), skeletal survey, serum protein electrophoresis (SPEP), or urine protein electrophoresis (UPEP). CBC = complete blood cell.

24 months or more for low-risk patients and an overall average interval of every 6 to >24 months).<sup>7,9</sup> The follow-up of a patient is considered to be concordant with the particular guideline if the average of the follow-up intervals falls within the average interval recommended by the particular guideline of interest. Because most guidelines recommend more aggressive follow-up for higher-risk patients and we do not know the risk status of the present patients, we performed best-case scenario sensitivity analyses by assuming that 24.3% of the patients in the cohort were at high or high-intermediate risk (an estimated 37%-58% absolute risk of progression at 20 years) and, conversely, that 75.7% were at low or low-intermediate risk (an estimated 5%-21% absolute risk of progression at 20 years) according to the Mayo Clinic risk stratification model.<sup>11</sup> In each sensitivity analysis, we assumed the highest possible guideline concordant rate according to MGUS risk stratification (Table 1).

We examined the follow-up patterns of patients with MGUS within 2 years of their incident MGUS diagnosis dates. We used the  $\chi^2$  test to measure differences among categorical variables and an extension of the Wilcoxon trend test to analyze follow-up patterns over time. We performed additional sensitivity anal-

yses by including only follow-ups with an MGUS diagnosis in the primary billing position. Analyses were performed using SAS software, version 9.4 (SAS Institute Inc) and the Stata 14 statistical package (StataCorp LP).

#### RESULTS

A total of 11,676 patients with MGUS met the study criteria (Table 2). The median patient age was 62 years (range, 18 to  $\geq$ 87 years), and most patients were women (56.8%, n=6636). During the first 2 years after MGUS diagnosis, the distribution of patients by mean interval between visits was as follows: less than 6 months, 12.7%; every 6 to 12 months, 25.2%; every 13 to 24 months, 17.7%; and longer than 24 months or no follow-up at all, 44.4%. This distribution changed significantly over time, with a higher proportion of patients being followed up at intervals of less than 13 months, from 32.7% in 2006 to 41.1% in 2013 (P<.001) (Figure 1, A). The follow-up patterns according to sociodemographic subgroup and geographic location are shown in Figure 1, B. Compared with their counterparts, patients 60 years or older were more likely to be followed up at intervals of less than 13 months, and those from the Northeast or those younger than 50 years were more likely to be followed up at intervals longer than 24 months

(P<.001) (Figure 1, B). More than half of the patients 80 years or older were followed up at intervals of less than 6 months (12.3%), 6 to 12 months (27.8%), or 13 to 24 months (18.2%).

The tests ordered during follow-up are shown in Figure 2, A. The most common tests were complete blood cell count, calcium, and creatinine, which were ordered at more than half of the follow-up visits (56.6%-67.9%). Various MGUS-specific tests (bone marrow biopsy, FLCs, immunofixation, SPEP, urine protein electrophoresis, or skeletal survey) were ordered in 88.3% of the visits. In 11.8% of the follow-ups, a face-to-face visit was not associated with any ancillary test, whereas in 31.5%, the follow-up consisted of ancillary tests only without a face-to-face visit. The more common test combinations during follow-up visits are shown in Figure 2, B. The test combination of complete blood cell count, calcium, creatinine, and SPEP with or without FLCs or immunofixation was ordered in 26.0% of the visits.

Less than half of the patients (41.1%) diagnosed in 2013 were concordant with the aggressive guidelines (UK-Nordic/IEC). Similarly, just slightly more than half of the patients (58.8%) were concordant with the conservative (IMWG/EMN) guidelines. In the best-case scenario analyses, in which we extrapolated the proportions of high- and low-risk patients to calculate the best possible concordance rates according to MGUS risk, the concordance rate increased to 83.1% for the conservative model but did not change for the aggressive model (Figure 3).

An MGUS was the diagnosis in the primary billing position for most visits, whether a faceto-face visit (77.3%) or an ancillary test-only visit (77.1%). To increase the specificity of the visits and tests, we performed sensitivity analyses by including only follow-up visits wherein an MGUS diagnosis was in the primary billing position. The results are shown in Supplemental Figures 1 and 2 (available online at http:// www.mcpiqojournal.org). Relative to the main analysis, the proportion of patients in the sensitivity analysis who were followed up at intervals of less than 6 months decreased and the proportion followed up at intervals longer than 24 months increased. However, we found a similar trend of more aggressive follow-up over time and similar guideline concordance rates.

### DISCUSSION

To our knowledge, this is the first study investigating MGUS follow-up patterns in the United States after the publication of several international consensus practice guidelines.<sup>6-9</sup> The major findings were that (1) practice patterns varied according to demographic and geographic factors, (2) follow-up for approximately half the patients lacked concordance with any of the clinical practice guidelines, and (3) patients 80 years or older potentially had excessive follow-up.

Data on MGUS follow-up patterns in the United States are scarce. One report, published in 1993, was derived from the Established Populations for Epidemiologic Studies of the Elderly, a stratified random household sampling of people older than 65 years who lived in 5 adjacent counties in the Piedmont region of North Carolina.<sup>12</sup> The study participants were interviewed in person or by phone annually to obtain information about chronic medical conditions, disabilities, and institutionalization. Compared with participants who did not have a diagnosis of MGUS, the 106 patients with MGUS had a similar total number of outpatient visits over a 12-month period. The authors concluded that followup of patients with MGUS was inadequate perhaps because of lack of physician awareness of the existing guideline.<sup>13</sup> The only other report, a study published in 2010, included 116 patients with MGUS from southeastern Minnesota. Only 69% of the patients were considered to have had optimal follow-up, arbitrarily defined as follow-up every 6 to 36 months. High-risk patients were more likely to be optimally followed up than low-risk patients (81% vs 64%).<sup>14</sup> In contrast to these reports, the present study included a population of patients that was much larger and racially and geographically diverse.

In the present study, we found statistically significant variability in the average intervals of MGUS follow-up. Approximately 2 in 5 patients were followed up at least once every 12 months. However, a similar ratio of patients was either followed up at intervals longer than 24 months or did not have any follow-up at all. Except for the EMN guideline,<sup>9</sup> all the other guidelines recommend at least one follow-up visit during the first 6 months after MGUS diagnosis in order not to miss a diagnosis of evolving LPM.<sup>6-8</sup> Patients who were younger than 50 years or were treated in the Northeast were followed up less frequently compared with their counterparts. Currently, no data support a differential risk of MGUS progression to LPM according to age or other demographic features.<sup>2,15</sup> Therefore, a more conservative follow-up approach in the younger population is not evidence based. In approximately 1 in 4 patients with smoldering multiple myeloma, the condition does not progress to active disease,<sup>16</sup> so one potentially positive effect of a conservative follow-up approach is a lower rate of diagnosis of smoldering LPMs, which minimizes overdiagnoses of these types of cancers.<sup>14</sup>

Only approximately half of the patients had follow-up patterns that were concordant with any of the existing clinical practice guidelines. This finding did not change substantially even with sensitivity analyses that excluded visits wherein MGUS was not the diagnosis in the primary billing position (Supplemental Figures 1 and 2). The reasons for the discordance could not be gleaned from the study but might be related to physician or patient factors. It is possible that many US hematologistoncologists were unaware of the guidelines because the guidelines were formed by consensus groups from either European or international groups. It is also possible that many patients with MGUS received follow-up care from non-hematologist-oncologists who were not aware of the guidelines. Nonetheless, actual guideline awareness cannot be determined without performing a survey of physicians. Also unknown is the proportion of patients with MGUS in the United States who are followed up by non-hematologist-oncologists. Finally, because approximately half the patients with clinically diagnosed MGUS are younger than 62 years,<sup>1</sup> they may be less inclined to return for follow-up visits if they are otherwise in good health. This may partly explain the finding of less frequent follow-up visits in those younger than 50 years.

Follow-up of MGUS is analogous to screening a select group of patients who are at higher risk for LPM. Nearly half the patients 80 years or older in the present study were followed up at intervals of at least once every 12 months. Compared with follow-up for cancers in which routine screening is recommended by the US Preventive Services Task Force, this frequency of MGUS follow-up can be



**FIGURE 3.** Concordance of monoclonal gammopathy of undetermined significance follow-up with current guidelines. EMN = European Myeloma Network; IEC = international expert consensus; IMWG = International Myeloma Working Group; UK-Nordic = UK Myeloma Forum and Nordic Myeloma Study Group.

considered excessive because of the relatively short life expectancy of patients in this age group, the low risk of LPM transformation, and the overall rarity and incurability of LPMs. The US Preventive Services Task Force recommends against routine screening above certain age limits for patients with breast cancer (75 years), cervical cancer (65 years), colorectal cancer (75 years), and lung cancer (80 years), although these cancers are much more common than LPMs and mostly curable when detected at early stages.<sup>17</sup>

The present study has limitations. Because this was a claims-based study, undercoding, overcoding, and miscoding were possible. Nonetheless, the large study population with patients cared for in a wide multitude of practices across the country makes systematic coding errors unlikely. Because a clinic visit can be for multiple medical problems and laboratory tests ordered were not necessarily specific for MGUS, the frequency of MGUS follow-up could have been overestimated. However, we considered only visits and tests that were linked to an MGUS diagnostic claim, and in nearly 80% of the visits and tests, MGUS was the diagnosis in the primary billing position. Moreover, when we performed sensitivity analyses that

included only patients who had MGUS diagnosis in the primary billing position, we obtained similar findings. Therefore, such an overestimation would have been minimal. We could not determine follow-up patterns based on MGUS risk stratification because laboratory test results were not available. Three of the 4 guidelines recommend more frequent followup for higher-risk patients. Not knowing the risk composition of this study population would have adversely affected the guideline concordance rate. To overcome this, we estimated the proportion of higher- and lowerrisk patients according to the Olmsted County, Minnesota, population data and performed best-case scenario sensitivity analyses and found similar results.<sup>11</sup> Because we did not include patients with MGUS in whom LPM subsequently developed, we likely excluded a proportion of higher-risk patients with MGUS. Therefore, this cohort might be enriched with lower-risk patients. However, LPM subsequently developed in only 3% of those with an incident MGUS diagnosis, so this would have affected the results minimally. Finally, we analyzed the follow-up patterns during only the first 2 years after MGUS incident diagnosis. Follow-up patterns beyond this period may be different.

#### CONCLUSION

The MGUS follow-up practice patterns in the United States varied geographically and demographically. Because current MGUS follow-up guidelines are empirically derived, their recommendations are not uniform and are sometimes conflicting.<sup>6-9</sup> Only approximately half the patients had follow-up practices that were concordant with any of the 4 practice guidelines. A large proportion of patients with limited life expectancy continued to undergo close follow-up. Discontinuation of such follow-up is reasonable according to the current practice of terminating cancer screening for solid tumors in this population. Further studies are necessary to evaluate the optimal pattern of MGUS follow-up according to actual clinical outcomes.

#### ACKNOWLEDGMENTS

The Kern Center provided analytical support. Otherwise, the funding sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

### SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: EMN = European Myeloma Network; FLC = free light chain; IEC = international expert consensus; IMWG = International Myeloma Working Group; LPM = lymphoplasmacytic malignancy; MGUS = monoclonal gammopathy of undetermined significance; SPEP = serum protein electrophoresis; UK-Nordic = UK Myeloma Forum and Nordic Myeloma Study Group

Grant Support: This study was supported by the Mayo Clinic Division of Hematology, the Mayo Clinic Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, and the Binks Foundation (R.S.G.).

Potential Competing Interests: The authors report no competing interests.

Data previously presented: Portions of this article were published in abstract form: Go RS, Heien HC, Sangaralingham LR, Habermann EB, Shah ND. Monoclonal gammopathy of undetermined significance (MGUS) follow-up practice patterns in the US: frequency of visits, types of tests and concordance with clinical practice guidelines. *Blood.* 2016;128:5906.

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