2. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia*. 2014;28(5):1122-1128.

3. Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia*. 2014;28(6):1346-1348.

4. Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. *J Clin Oncol*. 2007;25(15):1993-1999.

5. Turesson I, Velez R, Kristinsson SY, Landgren O. Patterns of improved survival in patients with multiple myeloma in the twenty-first century: a population-based study. *J Clin Oncol*. 2010;28(5):830-834.

6. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*. 2009;113(22):5412-5417.

7. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol*. 2003;121(5):749-757.

8. Kyle RA, Therneau TM, Rajkumar SV, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006;354(13):1362-1369.

9. 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(7):1537-1542.

10. 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(8):564-569.

11. Kyle RA, Durie BG, Rajkumar SV, et al; International Myeloma Working Group. 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(6):1121-1127.

12. 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(3):338-345.

13. 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(3):812-817.

14. Bird J, Behrens J, Westin J, et al; Haemato-oncology Task Force of the British Committee for Standards in Haematology, UK Myeloma Forum and Nordic Myeloma Study Group. UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). *Br J Haematol*. 2009;147(1):22-42.

15. Bladé J. Clinical practice. Monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2006;355(26):2765-2770.

16. Turesson I, Linet MS, Björkholm M, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. *Int J Cancer*. 2007;121(10):2260-2266.

17. Anonymous. *Patientregistret 1987-1996: Kvalitet och innehåll*. Stockholm, Sweden: EpC, National Board of Health and Welfare; 1998.

18. Axelsson U, Bachmann R, Hällén J. Frequency of pathological proteins (M-components) om 6,995 sera from an adult population. *Acta Med Scand*. 1966;179(2):235-247.

19. Kyle RA. Monoclonal gammopathy of undetermined significance. Natural history in 241 cases. *Am J Med*. 1978;64(5):814-826.

20. R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2008.

21. Therneau T. *A Package for Survival Analysis in S*. R package version 2.37-2.

22. Bianchi G, Kyle RA, Colby CL, et al. Impact of optimal follow-up of monoclonal gammopathy of undetermined significance on early diagnosis and prevention of myeloma-related complications. *Blood*. 2010;116(12):2019-2025.

23. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med*. 2013;369(5):438-447.

24. Landgren O. Monoclonal gammopathy of undetermined significance and smoldering myeloma: new insights into pathophysiology and epidemiology. *Hematology Am Soc Hematol Educ Program*. 2010;2010:295-302.

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

26. Kleber M, Ihorst G, Gross B, et al. Validation of the Freiburg Comorbidity Index in 466 multiple myeloma patients and combination with the international staging system are highly predictive for outcome. *Clin Lymphoma Myeloma Leuk*. 2013;13(5):541-551.

Invited Commentary

# Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma

Robert A. Kyle, MD; S. Vincent Rajkumar, MD

**In this issue of *JAMA Oncology*,** Sigurdardottir et al[1] raise an important point concerning the effect of diagnosis and follow-up of patients with monoclonal (M) gammopathy of undetermined significance (MGUS) on the survival of multiple myeloma (MM). In their study of 14 798 patients with MM diagnosed in Sweden from 1976 to 2005, 394 (2.7%) had a previously recognized MGUS. In an important finding, patients who developed MM and who had a previously recognized MGUS had a better overall survival (median survival, 2.8 years) than those patients with MM in whom MGUS had not previously been recognized (median survival, 2.1 years). The findings suggest a survival benefit for those patients with MM who had a previously recognized MGUS. The results of this study are similar to those of a recent report by Go et al[2] that also found that outcome of MM was better in patients with a prior diagnosis of MGUS compared with those diagnosed without a history of MGUS. However, the study suffers from the same drawbacks in that the results provide associations but cannot be used to determine causal relationships or to make public health decisions.

Related article page 168

MGUS is characterized by the presence of a serum M-protein concentration lower than 3 g/dL, the presence of fewer than 10% M-plasma cells in the bone marrow, and the absence of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder. The diagnosis and classification of MGUS, MM, and related disorders has been recently updated by the International Myeloma Working Group

(IMWG).[3] It has been shown that virtually all patients with MM have a preceding MGUS.[4] At least 15% of patients with symptomatic MM produce no M heavy chain (IgG, IgA, IgD, or IgE), and only M light chains (κ or λ chains) are produced. In these patients, the amount of light chains may progress to light-chain smoldering MM, which is characterized by the excretion of a urinary light-chain M-protein concentration of at least 0.5 g/24 h and/or more than 10% M-plasma cells in the bone marrow but without CRAB features.[5]

The central premise of the article by Sigurdardottir et al[1] is that the reason for better outcome in patients with MM with known MGUS is due to the probability that such patients were followed up closely and this led to a timely diagnosis of MM and fewer complications. It cannot be determined whether MM patients with a known MGUS in the Icelandic study[1] were followed more closely than those in whom a MGUS was not recognized, and hence it is difficult to attribute a causal relationship between follow-up and better prognosis. Other factors that may play a role include the possibility that MGUS is recognized clinically, is biologically different, and may be more long-standing than MGUS that is not recognized. Multiple myeloma is a clinical diagnosis, and the timing at which a patient is identified as having MM is subject to lead time bias in patients known to have MGUS. Second, the presence of comorbidities in those patients with MM with a known MGUS (which was the reason testing for MGUS was done in the first place) makes such patients more likely to seek medical care and thus be followed more closely before development of symptomatic MM. The occurrence of autoimmune disorders, infectious diseases, ischemic heart disease, congestive heart failure, cerebrovascular accidents, and renal disease were more common in the MM patients with prior recognition of MGUS because of closer follow-up, and this may have contributed to the longer survival of those with a previously recognized MGUS. This would have occurred regardless of the diagnosis of MGUS. Furthermore, the median survival of this MM cohort was less than 3 years compared with more than 5 years currently. Finally, we need to be careful about attributing changes in outcome as being secondary to better follow-up. Such data need to come from randomized clinical trials.

It is interesting to note that patients with a lower M-protein concentration were found to have shorter survival following the diagnosis of MM. However, as noted, it is not possible from the present study to determine any causal relationship between close follow-up or lack thereof of these patients and outcome of MM. For example, patients with small M spikes may have more light-chain excretion and higher prevalence of light-chain MM. Such patients are also at risk of AL amyloidosis in addition to MM. We feel that data from this article cannot be used to dismiss the risk-adapted approach to follow-up of MGUS recommended by the IMWG (and the Mayo Clinic). The IMWG recommendation for a risk-stratified approach to follow-up of MGUS is based on data indicating that the absolute risk of progression over a 20-year follow-up of a patient with low-risk MGUS is only 2% when competing causes of death are accounted for. This risk-stratification model used a cutoff of 1.5 g/dL for M-protein concentration; a lower threshold of 0.5 g/dL would result in an even lower absolute risk of progression. It is clear that public health attempts to reduce the probability of an event (eg, MM) and the prognosis of that event should always take into account the baseline risk. Furthermore, the IMWG risk stratification does not rely solely on M-protein concentration alone but also requires free light-chain ratio and M-protein type to be factored in.

This study indirectly suggests that knowledge of a prior MGUS may lead to better survival, but the mechanisms by which this occurs are not clear. We need prospective studies to address the value of follow-up in MGUS and the optimal approach to such follow-up. The risk-adapted approach is a compromise that ensures that scarce resources are focused on the patients most likely to benefit. We also need studies to address the question of the possible merits of screening for the presence of MGUS in a normal, older population. The cost, inconvenience, and anxiety produced by the awareness of potential progression of a recognized MGUS, as well as the low absolute risk of progression (0.5%-1% per year), probably override the possible potential benefit of screening for MGUS.

## ARTICLE INFORMATION

**Author Affiliations:** Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota.

**Corresponding Author:** Robert A. Kyle, MD, Division of Hematology, Department of Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (kyle.robert@mayo.edu).

**Published Online:** March 5, 2015. doi:10.1001/jamaoncol.2015.33.

**Conflict of Interest Disclosures:** None reported.

## REFERENCES

1. 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 [published online March 5, 2015]. *JAMA Oncol*. doi:10.1001/jamaoncol.2015.23.

2. Go RS, Gundrum JD, Neuner JM. Determining the clinical significance of monoclonal gammopathy of undetermined significance: a SEER-Medicare population analysis [published online September 25, 2014]. *Clinical Lymphoma Myeloma Leukemia*. doi:http://dx.doi.org/10.1016/j.clml.2014.09.004.

3. 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.

4. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood*. 2009;113(22):5412-5417.

5. Kyle RA, Larson DR, Therneau TM, et al. Clinical course of light-chain smouldering multiple myeloma (idiopathic Bence Jones proteinuria): a retrospective cohort study. *Lancet Haematol*. 2014;1(1):e28-e36.