



Australian Government

Repatriation Medical Authority

REPATRIATION MEDICAL AUTHORITY

STATEMENT OF REASONS

**RE: DECISION NOT TO MAKE STATEMENTS OF PRINCIPLES FOR
MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)**

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PART I INTRODUCTION

1. The Repatriation Medical Authority (the Authority) does not propose to make Statements of Principles under subsection 196B (2) or (3) of the *Veterans' Entitlements Act 1986* (the Act) in respect of monoclonal gammopathy of undetermined significance (MGUS). The Authority published a notice of an investigation into "monoclonal gammopathy of undetermined significance (MGUS)" in the *Commonwealth of Australia Gazette* on 8 January 2019.
2. Having carried out the investigation as notified, the Authority declares that it does not propose to make a Statement of Principles concerning MGUS for the purposes of subsection 196B(2) or (3) of the Act. The Authority is of the view that MGUS is an asymptomatic, abnormal laboratory finding which does not require medical treatment. Hence it is not a disease or injury as defined in section 5D of the Act and is not a condition for which a Statement of Principles could be determined.

PART II BACKGROUND TO THE INVESTIGATION

3. At its meeting of 12 December 2018, the Authority noted a summary paper of the United States National Academies of Sciences, Engineering, and Medicine's Eleventh Biennial Update on Vietnam Veteran Exposure to Herbicides and Health Outcomes which comprehensively evaluates scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various components of those herbicides, including 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) (Agent Orange Update). Sufficient evidence of an association between exposure to at least one of the chemicals of interest (COIs) and MGUS was a new inclusion among the findings. The Authority considered a discussion paper prepared by the Principal Medical Officer concerning the issues raised in the Agent Orange Update.
4. Following deliberation, the Authority agreed to notify an investigation under subsection 196G(1) of the Act to ascertain if Statements of Principles concerning monoclonal gammopathy of undetermined significance could be determined. An investigation notice was placed in the *Commonwealth of Australia Gazette* on 8 January 2019.

PART III SUBMISSIONS RECEIVED BY THE AUTHORITY PURSUANT TO SECTION 196F

5. Subsequently, a request for investigation relating to MGUS was received on 13 March 2019 from a veteran eligible to make a request under the Act. The veteran contends that his high exposure to solvents (in particular trichloroethylene) has caused his MGUS.
6. The veteran advises that he is presently being treated by a specialist for this condition. He was advised of the Authority's investigation notified on 8 January 2019 and was invited to provide further information regarding his contention.

7. The veteran provided a further submission on 20 March 2019. Three files were attached as follows:
 - a. Durie BGM (2004). Epidemiology of Multiple Myeloma and Related Disease. IN: Current Clinical Oncology: Biology and Management of Multiple Myeloma. Chapter 2, pp 13-15. (Ed. JR Berenson), Humana Press Inc, Totowa, NJ.
 - b. A blog published by Dr. Brian GM Durie on 9 October 2015, titled "More evidence links toxic chemical exposure to MGUS and myeloma" at <https://brianduriemd.myeloma.org/content/more-evidence-links-toxic-chemical-exposure-mgus-and-myeloma>. This blog includes links to articles concerning chemical exposure and myeloma, and to the following articles specifically concerning Agent Orange exposure and MGUS:
 - i. Landgren O, Michalek JE, Shim Y, et al (2015). Agent Orange exposure and monoclonal gammopathy of undetermined significance: An operation ranch hand veteran cohort study. JAMA Oncol, 1(8): 1061-1068. ID 090967
 - ii. Munshi NC (2015). Association of Agent Orange with plasma cell disorder: Further evidence. JAMA Oncol, 1(8): 1035-6. ID 090966
 - c. File containing excerpts from the article "The Relationship between Multiple Myeloma and Occupational Exposure to Six Chlorinated Solvents" including link to the article <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3094509/#!po=35.0000>:
 - i. Gold LS, Stewart PA, Milliken K, et al (2011). The relationship between multiple myeloma and occupational exposure to six chlorinated solvents. Occup Environ Med, 68(6): 391–9. ID 064272

PART IV EVIDENCE/INFORMATION AVAILABLE TO THE REPATRIATION MEDICAL AUTHORITY

8. The following information was available to the Authority.
 - a) A literature search was conducted using the Pubmed search engine, limited to English language, using the Medical Subject Heading (MeSH) search terms: ("Monoclonal Gammopathy of Undetermined Significance/chemically induced"[Mesh] OR "Monoclonal Gammopathy of Undetermined Significance/etiology"[Mesh]). The search identified 600 articles. The above search was supplemented by specific searches for "monoclonal gammopathy of undetermined significance" and various factors of interest, internet searches, manual searches of reference lists, review of citations and consideration of relevant sections of textbooks.
 - b) A discussion paper prepared by a research officer of the Secretariat for the December 2018 Repatriation Medical Authority meeting.
 - c) A briefing paper dated June 2019 prepared for presentation to the Authority by a research officer of the Secretariat.

- d) The submission from the applicant.

PART V DISEASE AND INJURY

9. Section 5D of the Act defines disease and injury relevantly as follows:

disease means:

- (a) any physical or mental ailment, disorder, defect or morbid condition (whether of sudden onset or gradual development); or
- (b) the recurrence of such an ailment, disorder, defect or morbid condition;

but does not include:

- (c) the aggravation of such an ailment, disorder, defect or morbid condition; or
- (d) a temporary departure from:
 - (i) the normal physiological state; or
 - (ii) the accepted ranges of physiological or biochemical measures;

that results from normal physiological stress (for example, the effect of exercise on blood pressure) or the temporary effect of extraneous agents (for example, alcohol on blood cholesterol levels);

[and]

injury means any physical or mental injury (including the recurrence of a physical or mental injury) but does not include:

- (a) a disease; or
- (b) the aggravation of a physical or mental injury.

10. The proper meaning of what constitutes a disease or injury for the purposes of determining a Statement of Principles under the Act is to be determined by the Authority.¹ In considering these terms, the Authority has regard to ordinary dictionary definitions, medical dictionaries, and its expert knowledge. In determining whether a condition is a disease or injury as defined, the Authority is entitled to have regard to the connotations of the words 'disease or injury' as used and understood in their ordinary meaning.²
11. Being familiar with the ordinary English meanings of the terms that are used in section 5D, the Authority considered whether MGUS was "a particular kind of injury, disease or death" within the ordinary meaning of those terms. It also relied upon its expert medical knowledge and had regard to internationally agreed concepts in considering whether MGUS may represent a disease state.

¹ Ryan D, SC (2013) Memorandum. Available at <http://www.rma.gov.au/foi/what.htm>.

² *Comcare v Mooi* (1996) 42 ALD 495.

PART VI REASONS FOR THE DECISION

12. MGUS is a benign, asymptomatic disorder in which clonal plasma or lymphoplasmacytic cells produce a monoclonal immunoglobulin, known as an M protein or paraprotein.³
13. MGUS is classified into two major biological subtypes, immunoglobulin M (IgM) MGUS and non-IgM MGUS, related to the subtype of immunoglobulin produced.
14. Immunoglobulin M (IgM) MGUS typically arises from clonal lymphoplasmacytic cells, and is defined by a serum IgM paraprotein concentration of less than 30 g/L, bone marrow lymphoplasmacytic infiltration of less than 10%, and no evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end organ damage that can be attributed to the underlying lymphoproliferative disorder.⁴
15. Non-IgM MGUS typically arises from mature plasma cells, and is defined by a serum IgG, IgA or rarely IgD M protein at a concentration of less than 30 g/L, bone marrow clonal plasma cells of less than 10%, and absence of end organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (known by the acronym CRAB) and amyloidosis that can be attributed to the underlying plasma cell proliferative disorder.⁵
16. Non-IgM MGUS also includes light-chain MGUS which is defined by an abnormal free light chain ratio and an increased level of the involved free light chain with complete absence of heavy chain expression. The urinary light chain excretion must be less than 0.5 grams per 24 hours. Again, bone marrow clonal plasma cells must be less than 10%, and there is no end organ damage or amyloidosis attributable to the plasma cell disorder.
17. MGUS is a common condition in the older population. MGUS of any isotype is present in over 3% of the population aged over 50 years and increases with age to 8.9% in people older than 85 years.⁶ The mean age at diagnosis of MGUS is 70 years, and less than 2 percent of patients are diagnosed before the age of 40.⁷
18. There are no clinical symptoms or signs in MGUS, and there is no impairment or disability.

³ Go RS, Rajkumar SV (2018). How I manage monoclonal gammopathy of undetermined significance. *Blood*, 131(2): 163-73. ID 090404

⁴ Cook JR, Swerdlow SH, Sohani AR, et al (2017). IgM monoclonal gammopathy of undetermined significance. *Who Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th Edition, Chapter 13: 236. IARC Press, Lyon. ID 091414

⁵ McKenna RW, Kyle RA, Kuehl WM, et al (2017). Plasma cell neoplasms. *Who Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th Edition, Chapter 13: 457-68. IARC Press, Lyon. ID 091415

⁶ Manier S, Salem KZ, Liu D, et al (2016). Future directions in the evaluation and treatment of precursor plasma cell disorders. *Asco Educational Book*, 2016: e400-6. ID 090606

⁷ Rajkumar SV (2018). Diagnosis of monoclonal gammopathy of undetermined significance. Retrieved 21 January 2019, from <https://www.uptodate.com/contents/diagnosis-of-monoclonal-gammopathy-of-undetermined-significance>. ID 090400

19. MGUS is commonly diagnosed when a monoclonal protein is detected as an incidental finding on protein electrophoresis performed as part of an evaluation for one of a wide variety of clinical symptoms and disorders.⁸
20. MGUS may have been present for decades prior to the laboratory finding. A population-based prevalence study (Therneau et al 2012) estimated that approximately one-quarter of men and women diagnosed with MGUS at age 70 had had a monoclonal protein for more than 20 years.⁹
21. MGUS requires no treatment, and no therapy is known to prevent its transformation or progression to myeloma or other haematological malignancy.¹⁰ Recommendations for follow-up include reassessment of all patients with MGUS after 6 months with a range of laboratory tests to determine clinical stability and detect rapidly evolving lymphoproliferative malignancy.¹¹ After initial follow-up, patients with low-risk MGUS need additional follow-up of MGUS only if symptoms concerning for lymphoproliferative malignancies develop. All other patients with MGUS should have an annual follow-up. The purpose of follow-up in MGUS is to detect early progression of MGUS into lymphoproliferative malignancy, with the expectation that major complications will be minimized and survival prolonged because of the initiation of timely treatment.
22. Current practice guidelines do not recommend routine screening for MGUS in the general population because of the lack of proven benefit and absence of curative or preventive therapy.¹²
23. With regard to prognosis, MGUS is stable in most cases.¹³ However in a small proportion of people, there is progression to a plasma cell neoplasm, Waldenstrom macroglobulinaemia, other B-cell neoplasms or primary amyloidosis, dependent on the subtype of MGUS. The risk of progression of MGUS is lifelong, around 1% per year, and lower for light-chain MGUS (0.3% per year), although particular characteristics, including the size and type of the M protein, have been identified that affect the risk.
24. MGUS is a risk factor or risk marker for several other diseases. MGUS has been reported to be associated with over 130 non-malignant diseases, and while some associations are likely to be coincidental, some associations have been verified and

⁸ Rajkumar SV (2018). Diagnosis of monoclonal gammopathy of undetermined significance. Retrieved 21 January 2019, from <https://www.uptodate.com/contents/diagnosis-of-monoclonal-gammopathy-of-undetermined-significance>.

⁹ Therneau TM, Kyle RA, Melton J, et al (2012). Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. *Mayo Clin Proc*, 87(11): 1071-9. ID 090998

¹⁰ Anguille S, Bryant C (2013). Monoclonal gammopathy of undetermined significance. *CMAJ*, 185(15): 1345.

¹¹ Go RS, Rajkumar SV (2018). How I manage monoclonal gammopathy of undetermined significance. *Blood*, 131(2): 163-73.

¹² Go RS, Rajkumar SV (2018). How I manage monoclonal gammopathy of undetermined significance. *Blood*, 131(2): 163-73.

¹³ McKenna RW, Kyle RA, Kuel WM, et al (2017). Plasma cell neoplasms. *Who Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th Edition, Chapter 13: 457-68. IARC Press, Lyon. ID 091415

are now considered to be causally related to MGUS.¹⁴ These include monoclonal gammopathy–associated peripheral neuropathy, monoclonal immunoglobulin deposition disease, and monoclonal gammopathy–associated proliferative glomerulonephritis. These conditions are considered separate diseases. Currently, the RMA Statements of Principles concerning deep vein thrombosis, pulmonary thromboembolism and immune thrombocytopaenia include MGUS as a specific risk factor. The broader entity monoclonal gammopathy is included as a risk factor in the SOPs concerning chilblains and peripheral neuropathy.

25. The Authority has concluded that MGUS is an incidental, abnormal laboratory finding which is asymptomatic and produces no clinical signs, impairment or disability. The Authority notes that there is no treatment for MGUS and there is a low rate of transformation into a malignant disease. As such, although MGUS may be a risk factor for other diseases, it does not itself satisfy the requirements of a disease as defined in section 5D of the Act.

PART VII DECISION

26. The Authority is of the view that although MGUS is an abnormal finding, it is not an "ailment, disorder, defect or morbid condition" within the terms of section 5D of the Act and not a disease.
27. The Authority declares that it does not propose to make a Statement of Principles concerning MGUS, for the purposes of subsection 196B(2) or (3) of the Act, for the reason that the Authority concluded that MGUS is not a "disease" as defined in section 5D of the Act.



Professor Nicholas Saunders AO
Chairperson
Repatriation Medical Authority

21 June 2019

¹⁴ Go RS, Rajkumar SV (2018). How I manage monoclonal gammopathy of undetermined significance. Blood, 131(2): 163-73.

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