

What is the significance of monoclonal gammopathy of undetermined significance?

Authors: Catherine Atkin,^{A,*} Alex Richter^{B,*} and Elizabeth Sapey^{C,*}

ABSTRACT

Monoclonal gammopathy of undetermined significance (MGUS) is characterised by the presence of a monoclonal paraprotein in the blood, without the characteristic end organ damage seen in multiple myeloma. MGUS is more common in older age groups and has a risk of progression to myeloma of 1% per year. Population screening is not currently recommended, but retrospective studies have suggested improvements in myeloma outcomes in those under MGUS follow-up; in addition, MGUS has associated complications, including fracture, osteoporosis, renal disease and infection, which can be treated. Given this increasing evidence of disease related directly to MGUS, strategies for early identification might be needed. In this review, we discuss the complications of MGUS and whether MGUS fulfils the criteria needed to implement a screening programme. We also highlight areas where more evidence is needed, including identification of a higher risk population to make screening more practical and economically viable.

KEYWORDS: Myeloma, screening, complications, paraprotein

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a plasma cell disorder, often recognised as a precursor stage in the development of multiple myeloma.¹ The monoclonal (M) paraprotein that characterises MGUS is produced by a clonal population of plasma cells, which produce an abnormal immunoglobulin (IgG, IgA, IgM, IgE, IgD or light-chain only), detectable by serum or urine protein electrophoresis, where the abnormal paraprotein appears as a 'band' or 'spike'.

MGUS has three key diagnostic features: (a) the presence of a monoclonal paraprotein within the serum, at a level <30 g/L; (b) a proliferation of clonal plasma cells within the bone marrow, but forming <10% of the bone marrow; and (c) absence of features of the typical end-organ damage associated with

multiple myeloma.² On detection of a monoclonal paraprotein, the presence of underlying haematological malignancy should be excluded.³ Presence of a higher level of paraprotein, a higher percentage of plasma cells within the bone marrow, or end-organ damage related to the plasma cell disease is representative of smouldering multiple myeloma or symptomatic multiple myeloma, rather than of MGUS (Fig 1).

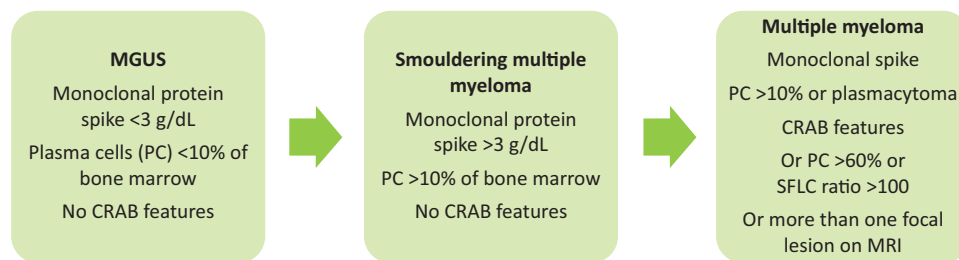
The prevalence of MGUS increases with age. The median age at diagnosis is 70 years,⁴ affecting 3.2% of those over 50, increasing to 8.9% of over 85-year olds.⁵ MGUS is most often diagnosed as an incidental finding during investigations for other conditions in patients with other comorbidities.⁶ Rates of MGUS vary depending on ethnicity, with studies conducted in the USA showing a rate three times higher in black Americans compared with Caucasians.⁷

Several mechanisms have been suggested to account for the development of MGUS, including cytogenetic and bone marrow microenvironment changes. Chromosomal translocations are common, often involving regions responsible for the heavy-chain component of immunoglobulin. The most common translocation is t(11;14)(q13;q32), a translocation between the Ig heavy-chain locus on chromosome 14 and the gene encoding Cyclin D1 on chromosome 11, which has been demonstrated in 25% of patients with MGUS.⁸ Dysregulation of Cyclin D proteins,⁹ involved in cell cycle progression,¹⁰ has also been noted in patients with MGUS as well as patients with multiple myeloma,¹¹ however, the process is varied and results from an accumulation of many events.¹²

Population-based screening for MGUS has not been recommended, as advised by the European Myeloma Network⁶ and by a joint recommendation from the UK Myeloma Forum and Nordic Myeloma Study Group.¹³ Both recommendations were produced through consultation with an expert panel, with Myeloma UK contributing to the UK Myeloma Forum recommendations. These guidelines suggest that, because there are no nontoxic, economically viable treatments available to prevent progression to multiple myeloma, knowledge of a potential premalignant condition without treatment to prevent progression might place an unnecessary burden on patients.¹³ However, MGUS itself carries a risk of complications other than progression to myeloma (Table 1). Furthermore, several premalignant or potentially life-threatening conditions have been included in voluntary screening programmes, with evidence of improved patient outcomes,³³ for example, the aortic aneurysm screening programme.³⁴ Also, several Royal Colleges provide guidance to assist doctors to empower patients to understand risk during screening processes.^{35,36} Is there now enough evidence to support screening in a general population?

Authors: ^Aclinical research fellow, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK; ^Bsenior lecturer and consultant in clinical immunology, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK; ^Creader and consultant in respiratory medicine, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK; *Authors contributed equally.

Fig 1. Definition of multiple myeloma and precursor plasma cell disorders, including monoclonal gammopathy of undetermined significance (adapted from International Myeloma Working Group definition).² CRAB = hypercalcaemia, renal impairment, anaemia, bone disease; MGUS = monoclonal gammopathy of undetermined significance; MRI = magnetic resonance imaging; SFLC = serum free light chain



Monitoring MGUS improves diagnostic delay in myeloma

MGUS occurs before multiple myeloma¹ and current guidance recommends that patients who are diagnosed with MGUS undergo specialist follow-up and annual monitoring, because the risk of progression to myeloma is 1% per year and does not decrease with time;⁵ however, currently, we do not actively screen for MGUS. Although the timing of transformation to myeloma is unpredictable, patients can be risk stratified to increase monitoring of those with the highest risk of progression to malignant disease, including those with: a high serum monoclonal protein level (>15 g/L); a progressive increase in monoclonal protein over the first year after diagnosis; and an IgA or IgM non-IgG subtype of monoclonal protein.^{37,38}

There is considerable early morbidity and mortality in myeloma. This early mortality is often related to infection, with complications, such as renal failure and fracture, frequently present at, or soon after, diagnosis.³⁹ Compared with other cancers in the UK, myeloma has one of the longest diagnostic intervals,⁴⁰ and this long pathway to diagnosis is associated with increased complications and later-stage disease at diagnosis.⁴¹

Detecting MGUS should allow the earlier diagnosis of myeloma, but the utility of early diagnosis was questioned previously,

because outcome studies of other asymptomatic haematological malignancies, such as follicular lymphoma,⁴² had been negative. However, there are new therapies for myeloma and a treatment pipeline is being tested in clinical trials. Lenalidomide has been shown to improve time to progression in patients with high-risk smouldering multiple myeloma,⁴³ and early results assessing daratumumab, a human IgG1 monoclonal antibody (mAb) that binds with high affinity to CD38,⁴⁴ also suggest improved outcomes in these patients.⁴⁵

Even before these new therapies, studies have suggested better outcomes in patients with myeloma previously under follow-up for MGUS compared with those without a previous diagnosis,⁴⁶ including a population study that described a myeloma survival benefit in having a prior diagnosis of MGUS.⁴⁷ These results were also analysed as a nested case-control study to allow for improvements in myeloma treatments over time and still showed improved survival with prior knowledge of MGUS.⁴⁷

A registry study suggested that MGUS follow-up is associated with fewer complications at diagnosis of active malignancy, including several myeloma-associated comorbidities.⁴⁸ MGUS itself has several recognised complications, and diagnosing this disease might similarly improve outcomes from MGUS-related complications.

Table 1. Known complications of MGUS, with relative risk compared with population, proposed underlying mechanism and available treatment options^a

Complication	Risk compared with population	Suggested pathological mechanism	Potential treatment
Fracture ¹⁴	1.7	Increased osteoclast activity and bone resorption ¹⁵⁻¹⁸	Bone protection with bisphosphonates
Osteoporosis ^{19,20}	1.2 (or higher)		
Infection ^{21,22}	2.2	Hypogammaglobulinaemia ²¹ Reduction in specific antibody ²³	Early treatment of infective symptoms; vaccinations
Renal disease ^{24,25}		Monoclonal Ig deposition disease, ²⁴⁻²⁶ proliferative glomerulonephritis, ²⁷ light-chain proximal tubulopathy ²⁸	Dependent on mechanism: chemotherapy
Neuropathy ^{19,29}	5.9 (CIDP) 3.2 (autonomic)	Antibodies against myelin-associated glycoprotein (MAG) in myelin sheath of peripheral nerves ³⁰	IV immunoglobulin; chemotherapy; rituximab (in clinical trials)
Thrombosis ³¹	2.1	Inflammation related: raised inflammatory mediators, including IL-6 ³²	Consideration of thromboprophylaxis in high-risk situations

^aThe known complications of MGUS, with relative risk compared with the general population given where available from current studies (as referenced) and treatment options.

MGUS-related complications

Bone disease

Although the presence of bone disease, particularly lytic bone lesions, is used as a marker of end-organ damage representative of myeloma, patients with MGUS are also at increased risk of osteoporosis and skeletal fracture.

The rate of vertebral fractures in MGUS is higher than in controls,³⁹ with a 1.7 times higher risk of fracture over 5 years in MGUS.¹⁴ There was no significant difference in the risk of fracture depending on the Ig class of MGUS or on the concentration of paraprotein. This suggests that all patients with MGUS, including those classified as having 'low-risk' MGUS, have an increased risk of fracture.

This increased risk of skeletal fracture appears to be related to alterations in bone metabolism, decreased bone mineral density and osteoporosis.⁴⁹ Indeed, one study described only 20% of patients with MGUS having normal bone mineral density, whereas 53.8% were osteopaenic and 26.2% had osteoporosis, and those with lower bone mineral density were more likely to have had vertebral fractures.⁵⁰

Compared with matched controls, patients with MGUS have more porous cortical bone,⁵¹ and lower trabecular thickness, which can affect bone strength.⁵² Studies have also suggested that MGUS is associated with abnormal bone turnover, with increased bone resorption,^{15,17} and higher levels of macrophage protein 1-alpha (MIP-1 α), which increases osteoclast function.⁵²

Some small studies have demonstrated that bisphosphonates can be used to treat osteoporosis in patients with MGUS, reducing the risk of skeletal fracture. A study suggested that patients with MGUS and osteoporosis treated with alendronate demonstrated a mean improvement in bone mineral density at the lumbar spine,⁵³ a finding that has been replicated.²⁰ Therefore, a diagnosis of MGUS and appropriate screening for osteoporosis could enable effective treatment. However, current guidelines do not recommend specific screening for osteoporosis in patients with MGUS, and further trials to determine the health benefit and economics of screening are needed.

Infection

Patients with MGUS are at increased risk of infection, with an incidence ratio of bacteraemia of 2.2 compared with expected rates based on age- and sex-matched registry data.²¹ This increased risk of infection could have several underlying mechanisms. Evidence of hypogammaglobulinaemia is found in a quarter of patients with MGUS.²¹ Levels of specific antibody have also been shown to be lower in patients with MGUS compared with controls, including antibody to *Staphylococcus*, *Moraxella*, varicella zoster virus, and *Candida*.²³

Recognition of this increased infection risk allows management by early antibiotic use, vaccination, and referral for specialist input in recurrent infections. Trials of vaccination in patients with myeloma have been small, but suggest that 40–50% of patients display protective antibody levels following vaccination.⁵⁴ Response rates are higher in patients with MGUS²² and early vaccination before transformation to myeloma could confer a degree of long-term protection in this already 'at-risk' group. Once again, guidelines do not currently recommend a specific vaccination programme for patients with MGUS, and trials would be needed to assess the benefit of vaccination in reducing infection rates.

Renal disease

Similar to myeloma, MGUS is a cause of renal impairment and, although the presence of renal disease is used as a diagnostic criterion for multiple myeloma, renal impairment has also been shown to occur in patients who do not meet the other criteria necessary for a diagnosis of myeloma as per the International Myeloma Working Group (IMWG) criteria.^{26,27} The renal complications associated with MGUS are so well recognised that it is referred to as 'monoclonal gammopathy of renal significance' to indicate the causal relationship between the monoclonal gammopathy and renal damage.⁵⁵

Mechanisms include monoclonal immunoglobulin deposition disease,^{25,26} proliferative glomerulonephritis resulting from deposition of monoclonal IgG,²⁷ and light-chain proximal tubulopathy.²⁸ Reducing monoclonal protein production by treatment with chemotherapy can improve outcomes. Untreated, light-chain deposition disease leads to end-stage renal disease in 63% of patients within 5 years, and the subsequent requirement for dialysis or transplantation, with its associated morbidity and mortality. Patients with monoclonal protein-related renal disease have a high risk of disease recurrence post transplantation if the underlying monoclonal protein is not treated.²⁸ A small study assessing outcomes in those with light-chain deposition disease showed that 60% of those who were treated with chemotherapy when their creatinine was <354 $\mu\text{mol/L}$ either maintained or improved their renal function.²⁵ However, further research is needed into the impact of treating MGUS-related renal disease with chemotherapy, because there is some concern that early treatment might lead to the selection of treatment-resistant clones and, therefore, treatment-resistant disease.⁵⁶ Careful assessment is needed in those with MGUS who develop renal impairment, to determine whether this is related to the MGUS itself or to other, more common causes in this population with multiple comorbidities.

Neuropathy

MGUS can also cause neuropathy with an increased risk of chronic inflammatory demyelinating polyradiculoneuropathy and autonomic neuropathy.¹⁹ MGUS producing an IgM monoclonal protein is more commonly associated with neuropathy than is IgG- or IgA-producing disease⁵⁷ because IgM can interact as an antibody against myelin-associated glycoprotein in the myelin sheath of peripheral nerves.³⁰ Several treatment options have been suggested for IgM paraprotein-associated neuropathy, including intravenous immunoglobulin (IVIg), chemotherapy and rituximab,²⁹ with reported improvements in disability after 4 weeks in a small, short-term trial of IVIg treatment.⁵⁸ A small randomised controlled trial of cyclophosphamide and prednisolone versus placebo did not show any improvement in functional outcomes, but suggested benefits in terms of sensation and muscle strength,⁵⁹ and two small randomised controlled studies of rituximab showed some improvement in symptoms.^{60,61} However, assessment by further larger trials is needed.

Thrombosis

As with other recognised complications of myeloma, the risk of venous thrombosis is increased in patients with MGUS;³² however, routine anti-thrombotic prophylactic treatment is not currently recommended.⁶

Should we routinely screen for MGUS?

Currently, there is evidence that MGUS monitoring could lead to improvements in myeloma outcomes, although this evidence is limited. Also, there is evidence that the complications associated with MGUS are preventable and/or manageable and screening for MGUS might be justified on this basis alone.

Screening programmes within the NHS in the UK are evaluated by the National Screening Committee,⁶² and are implemented after consultation and assessment against specific criteria based around five broad areas: the medical condition in question; the method of testing; the interventions available; proposed screening programme itself; and how the programme would be implemented.

The medical condition

Screening programmes identify conditions that are an 'important health problem', particularly those that are common or serious.⁶³ Although rates of MGUS are low, it is associated with severe complications and can progress to malignancy. There is also increasing knowledge of the natural history of the disease, although more research is needed to allow identification of those patients with MGUS that will progress to myeloma.

The method of testing

The method of testing for MGUS fulfils most of the required elements for a screening test; a safe, simple, validated screening blood test, which is performed in a way acceptable to the target population.⁶³

The intervention available

Screening criteria requires evidence that intervention at a presymptomatic stage improves outcomes. There is increasing evidence of the risk of complications and need for intervention in MGUS, and MGUS remains a condition that is largely identified in asymptomatic patients. There is concern that diagnosing a premalignant condition might cause unnecessary anxiety, as seen in patients with ductal carcinoma *in situ* (DCIS).⁶⁴ However, in a system focused on patient-centred care and shared decision making, further public and patient involvement could determine whether screening would be acceptable.

Proposed screening programme

There is currently no robust evidence available showing direct benefits from screening for MGUS. National screening recommendations ask for 'high quality randomised controlled trials' showing impacts on morbidity or mortality; however, there have been no published randomised trials in MGUS screening or follow-up. These studies would be challenging and costly, requiring a large study population followed up over a prolonged period. The economic and health service impact of MGUS screening also needs to be considered.⁶³ The cost of any potential screening programme could be reduced by narrowing the population in which screening is implemented and, indeed, this is a common practice during screening. For example, aortic aneurysm screening is currently offered to all men in England at the age of 65.⁶⁵ For MGUS, targeted screening would be supported through identification of a high-risk population where the rate of MGUS is higher, for instance in those with comorbidities that are known to be associated with MGUS.

Implementation of the screening programme

An MGUS screening programme would require a clear pathway for local follow-up and investigation of identified patients. This is particularly important because the tests being performed have the potential to identify patients with smouldering myeloma, as well as active multiple myeloma, which can be asymptomatic at diagnosis, and might be diagnosed incidentally.⁶⁶ Other B cell-related haematological malignancies, such as lymphoplasmacytic lymphoma, might also be identified.

Such a pathway would require healthcare infrastructure on a national basis, as well as collaboration between many different teams, including primary and secondary care.⁶⁷ To justify the needed investment, the pathways would require a robust evidence base that balances the cost of a programme against any potential healthcare savings. Research would also have to inform how often screening should be repeated.

Does MGUS meet the criteria for screening?

The accumulating evidence around MGUS, its impact on health and the ability to reduce or mitigate health impacts supports the proposal that MGUS fulfils many of the criteria needed to implement a screening programme. However, there are some criteria where further evidence is needed, including larger trials of the management of MGUS-related complications and the economic impact of the disease and its diagnosis. Although long-term follow-up studies of patients with MGUS might provide some of this evidence, this is likely to take many years.

Conclusion

Monoclonal gammopathy of undetermined significance carries a risk of progression to myeloma and is associated with several complications, including renal impairment, infection and fracture, which can have not only significant morbidity but also potential treatments. Current guidelines do not recommend routine testing without clinical suspicion of MGUS and the detection rates are low, with significant diagnostic delay. As a condition, MGUS now fulfils many criteria needed to recommend population screening, but more evidence is needed regarding the wider health burden related to MGUS. Perhaps it is time to rethink our current policies to reflect our new understanding of this condition; however, until screening is adopted, diagnosis will continue to rely on clinicians having a high index of suspicion in patients who present with the complications of MGUS or myeloma. ■

Author contributions

This review was written equally by CA, AR and ES; all authors have approved the final, submitted version.

Conflicts of interest

CA has no conflicts of interest to declare. AR has no conflicts of interest but declares funding from Fight For Sight and the Medical Research Council outside the current article. ES has no conflicts of interest but declares funding from NIHR, Wellcome Trust, British Lung Foundation, Alpha 1 Foundation and Medical Research Council outside the current article.

References

- 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.
- International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. <http://imwg.myeloma.org/internationalmyeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiplemyeloma/> [Accessed 30 July 2018].
- Bird J, Owen R, D'Sa S *et al*. Guidelines for the diagnosis and management of multiple myeloma 2014. London: British Society for Haematology, 2015.
- Kristinsson SY, Bjorkholm M, Andersson TM *et al*. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance: a population-based study. *Haematologica* 2009;94:1714–20.
- Kyle RA, Durie BG, 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.
- van de Donk NW, Palumbo A, Johnsen HE *et al*. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. *Haematologica* 2014;99:984–96.
- Landgren O, Gridley G, Turesson I *et al*. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood* 2006;107:904–6.
- Kaufmann H, Ackermann J, Baldia C *et al*. Both IGH translocations and chromosome 13q deletions are early events in monoclonal gammopathy of undetermined significance and do not evolve during transition to multiple myeloma. *Leukemia* 2004;18:1879.
- Hoyer JD, Hanson CA, Fonseca R *et al*. The (11;14)(q13;q32) translocation in multiple myeloma. A morphologic and immunohistochemical study. *Am J Clin Pathol* 2000; 113: 831–7.
- Yang K, Hitomi M, Stacey DW. Variations in cyclin D1 levels through the cell cycle determine the proliferative fate of a cell. *Cell Div* 2006;1:32.
- Bergsagel PL, Kuehl WM, Zhan F *et al*. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood* 2005;106:296–303.
- Walker BA, Wardell CP, Melchor L *et al*. Intracлонаl heterogeneity is a critical early event in the development of myeloma and precedes the development of clinical symptoms. *Leukemia* 2014;28:384–90.
- Bird J, Behrens J, Westin J *et al*. 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;147:22–42.
- Kristinsson SY, Tang M, Pfeiffer RM *et al*. Monoclonal gammopathy of undetermined significance and risk of skeletal fractures: a population-based study. *Blood* 2010;116:2651–5.
- Vejlgaard T, Abildgaard N, Jans H, Nielsen JL, Heickendorff L. Abnormal bone turnover in monoclonal gammopathy of undetermined significance: analyses of type I collagen telopeptide, osteocalcin, bone-specific alkaline phosphatase and propeptides of type I and type III procollagens. *Eur J Haematol* 1997;58:104–8.
- Pecherstorfer M, Seibel MJ, Woitge HW *et al*. Bone resorption in multiple myeloma and in monoclonal gammopathy of undetermined significance: quantification by urinary pyridinium cross-links of collagen. *Blood* 1997;90:3743–50.
- Politou M, Terpos E, Anagnostopoulos A *et al*. Role of receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin and macrophage protein 1-alpha (MIP-1a) in monoclonal gammopathy of undetermined significance (MGUS). *Br J Haematol* 2004;126:686–9.
- Kurihara N, Bertolini D, Suda T, Akiyama Y, Roodman GD. IL-6 stimulates osteoclast-like multinucleated cell formation in long term human marrow cultures by inducing IL-1 release. *J Immunol* 1990;144:4226–30.
- Bida JP, Kyle RA, Therneau T *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.
- Berenson JR, Yellin O, Boccia RV *et al*. Zoledronic acid markedly improves bone mineral density for patients with monoclonal gammopathy of undetermined significance and bone loss. *Clin Cancer Res* 2008;14:6289–95.
- Gregersen H, Madsen K, Sorensen H. The risk of bacteremia in patients with monoclonal gammopathy of undetermined significance. *Eur J Haematol* 1998;61:140–4.
- Karlsson J, Hogevik H, Andersson K *et al*. Pneumococcal vaccine responses in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance. *Trials Vaccinol* 2013;2(Suppl C):31–8.
- Karlsson J, Andreasson B, Kondori N *et al*. Comparative study of immune status to infectious agents in elderly patients with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy of undetermined significance. *Clin Vaccine Immunol* 2011;18:969–77.
- Pozzi C, D'Amico M, Fogazzi GB, Curioni S, Ferrario F, Pasquali S *et al*. Light chain deposition disease with renal involvement: clinical characteristics and prognostic factors. *Am J Kidney Dis* 42:1154–63.
- Heilman RL, Velosa JA, Holley KE, Offord KP, Kyle RA. Long-term follow-up and response to chemotherapy in patients with lightchain deposition disease. *Am J Kidney Dis* 1992;20:34–41.
- Lin J, Markowitz GS, Valeri AM *et al*. Renal monoclonal immunoglobulin deposition disease: the disease spectrum. *J Am Soc Nephrol* 2001;12:1482–92.
- Nasr SH, Satoskar A, Markowitz GS *et al*. Proliferative glomerulonephritis with monoclonal IgG deposits. *J Am Soc Nephrol* 2009;20:2055–64.
- Kapur U, Barton K, Fresco R, Leehey DJ, Picken MM. Expanding the pathologic spectrum of immunoglobulin light chain proximal tubulopathy. *Arch Pathol Lab Med* 2007;131:1368–72.
- Lunn M, Nobile-Orazio E. Immunotherapy for IgM anti-myelinassociated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database Syst Rev* 2016;10:CD002827.
- Campagnolo M, Ferrari S, Dalla Torre C *et al*. Polyneuropathy with anti-sulfatide and anti-MAG antibodies: clinical, neurophysiological, pathological features and response to treatment. *J Neuroimmunol* 2015;281:1–4.
- Kristinsson SY, Pfeiffer RM, Bjorkholm M *et al*. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. *Blood* 2010;115:4991–8.
- Srkalovic G, Cameron MG, Rybicki L *et al*. Monoclonal gammopathy of undetermined significance and multiple myeloma are associated with an increased incidence of venothromboembolic disease. *Cancer* 2004;101:558–66.
- Loud JT, Murphy J. Cancer screening and early detection in the 21st century. *Sem Oncol Nurs* 2017;33:121–8.
- Scott RAP. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 360:1531–9.
- Royal College of Obstetricians and Gynaecologists. *Understanding how risk is discussed in healthcare*. London: RCOG, 2015.
- NHS. *Thinking of having a private screening test?* London: NHS, 2014.
- 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.

- 38 Cesana C, Klersy C, Barbarano L *et al*. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *J Clin Oncol* 2002;20:1625–34.
- 39 Augustson B, Begum G, Dunn J *et al*. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United Kingdom Medical Research Council trials between 1980 and 2002—Medical Research Council Adult Leukaemia Working Party. *J Clin Oncol* 2005;23:9219–26.
- 40 Lyraztopoulos G, Saunders CL, Abel GA *et al*. The relative length of the patient and the primary care interval in patients with 28 common and rarer cancers. *Br J Cancer* 2015;112(Suppl 1): S35–40.
- 41 Kariyawasan CC, Hughes DA, Jayatilake MM, Mehta AB. Multiple myeloma: causes and consequences of delay in diagnosis. *QJM* 2007;100:635–40.
- 42 Ardeschna KM, Qian W, Smith P *et al*. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol* 15:424–35.
- 43 Mateos M-V, Hernandez M-T, Giraldo P *et al*. Lenalidomide plus dexamethasone versus observation in patients with high-risk smoldering multiple myeloma (QuiRedex): long-term followup of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17:1127–36.
- 44 Usmani SZ, Weiss BM, Plesner T *et al*. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. *Blood* 2016;128:37.
- 45 Hofmeister C, Chari A, Cohen YC *et al*. Daratumumab monotherapy for patients with intermediate or high-risk smoldering multiple myeloma (SMM): CENTAURUS, a randomized, open-label, multicenter phase 2 study. *Blood* 2017;130(Suppl):510.
- 46 Kyle RA, Gertz MA, Witzig TE *et al*. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;78:21–33.
- 47 Sigurdardottir E, Turesson I, Lund S *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.
- 48 Go RS, Gundrum JD, Neuner JM. Determining the clinical significance of monoclonal gammopathy of undetermined significance: a SEER-Medicare population analysis. *Clin Lymphoma Myeloma Leuk* 2015;15:177–86.
- 49 Dizdar O, Erman M, Cankurtaran M *et al*. Lower bone mineral density in geriatric patients with monoclonal gammopathy of undetermined significance. *Ann Hematol* 2008;87:57–60.
- 50 Pepe J, Petrucci MT, Nofroni I *et al*. Lumbar bone mineral density as the major factor determining increased prevalence of vertebral fractures in monoclonal gammopathy of undetermined significance. *Br J Haematol* 2006;134:485–90.
- 51 Farr JN, Zhang W, Kumar SK *et al*. Altered cortical microarchitecture in patients with monoclonal gammopathy of undetermined significance. *Blood* 2014;123:647–9.
- 52 Ng AC, Khosla S, Charatcharoenwithaya N *et al*. Bone microstructural changes revealed by high-resolution peripheral quantitative computed tomography imaging and elevated DKK1 and MIP-1alpha levels in patients with MGUS. *Blood* 2011;118:6529–34.
- 53 Pepe J, Petrucci MT, Mascia ML *et al*. The effects of alendronate treatment in osteoporotic patients affected by monoclonal gammopathy of undetermined significance. *Calcif Tissue Int* 2008;82:418–26.
- 54 Hargreaves RM, Lea JR, Griffiths H *et al*. Immunological factors and risk of infection in plateau phase myeloma. *J Clin Pathol* 1995;48:260.
- 55 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.
- 56 Barlogie B, van Rhee F, Shaughnessy JD *et al*. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. *Blood* 2008;112:3122–5.
- 57 Ramchandren S, Lewis RA. An update on monoclonal gammopathy and neuropathy. *Curr Neurol Neurosci Rep* 2012;12:102–10.
- 58 Comi G, Roveri L, Swan A *et al*. A randomised controlled trial of intravenous immunoglobulin in IgM paraprotein associated demyelinating neuropathy. *J Neurol* 2002;249:1370–7.
- 59 Niermeijer JM, Eurelings M, van der Linden MW *et al*. Intermittent cyclophosphamide with prednisone versus placebo for polyneuropathy with IgM monoclonal gammopathy. *Neurology* 2007;69:50–9.
- 60 Leger JM, Viala K, Nicolas G *et al*. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology* 2013;80:2217–25.
- 61 Dalakas MC, Rakocevic G, Salajegheh M *et al*. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol* 2009;65:286–93.
- 62 House of Commons Science and Technology Committee. *National Health Screening. Third Report of Session 2014–2015*. London: The Stationery Office Ltd, 2014.
- 63 Public Health England. *UK NSC: evidence review process*. London: Public Health England, 2017.
- 64 Kennedy F, Harcourt D, Rumsey N, White P. The psychosocial impact of ductal carcinoma in situ (DCIS): a longitudinal prospective study. *Breast* 2010;19:382–7.
- 65 Abominal aortic aneurysm screening. www.nhs.uk/conditions/abdominal-aortic-aneurysm-screening/ [Accessed 30 July 2018].
- 66 Howell DA, Warburton F, Ramirez AJ *et al*. Risk factors and time to symptomatic presentation in leukaemia, lymphoma and myeloma. *Br J Cancer* 2015;113:1114–20.
- 67 McShane CM, Murphy B, Lim KH, Anderson LA. Monoclonal gammopathy of undetermined significance as viewed by haematology healthcare professionals. *Eur J Haematol* 2018;100:20–6.

Address for correspondence: Dr Elizabeth Sapey, Institute of Inflammation and Ageing, Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham B15 2GW, UK. Email: e.sapey@bham.ac.uk