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GUIDELINE

Investigation and management of the monoclonal gammopathy of undetermined significance

A British Society for Haematology Good Practice Paper

Simon Stern[1] | **Satarupa Chaudhuri**[2] | **Mark Drayson**[3] | **Sarah Henshaw**[4] | **Kamaraj Karunanithi**[5] | **Fenella Willis**[6] | **on behalf of the Haemato-Oncology Task Force of the British Society for Haematology and the UK Myeloma Forum**

[1]Epsom and St Helier University Hospitals NHS Trust, Sutton, UK
[2]Pennine Acute Hospitals NHS Trust, Bury, UK
[3]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[4]Nottingham University Hospitals NHS Trust, Nottingham, UK
[5]University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK
[6]St George's University Hospitals NHS Foundation Trust, London, UK

Correspondence
BSH Administrator, British Society for Haematology, 100 White Lion Street, London, N1 9PF, UK.
Email: bshguidelines@b-s-h.org.uk

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Summary
This Good Practice Paper provides recommendations for the diagnosis, risk stratification and management of the monoclonal gammopathy of undetermined significance (MGUS). It describes the recently recognised entity of the monoclonal gammopathy of clinical significance (MGCS), and recommends how it should be managed. The potential for targeted population screening for MGUS is also discussed.

KEYWORDS
MGCS, MGUS, monoclonal gammopathy of clinical significance, monoclonal gammopathy of undetermined significance, screening for MGUS

METHODOLOGY

This Good Practice Paper was compiled according to the BSH process at BSH Guidelines Development Process (PDF). (b-s-h.org.uk). The British Society for Haematology (BSH) produces Good Practice Papers to recommend good practice in areas where there is a limited evidence base, but for which a degree of consensus or uniformity is likely to be beneficial to patient care.

Literature review

A literature search was performed using the EMBASE and MEDLINE databases using the following search terms: monoclonal gammopathy of undetermined significance; monoclonal protein; M-protein; monoclonal component; paraprotein; monoclonal gammopathy; abnormal MGUS; MGRS; MGCS. The search was limited to randomised controlled trials, cohort and case–control studies and systematic reviews with publications in English.

Review of the manuscript

Review of the manuscript was performed by the British Society for Haematology (BSH) Haemato-Oncology Task Force, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH. It has also been reviewed and contributed to by the Myeloma UK MGUS Working Group.

INTRODUCTION

Monoclonal gammopathies are clonal plasma cell expansions that are markedly greater than the expansions seen in normal polyclonal antibody responses. Monoclonal gammopathy of undetermined significance (MGUS) is characterised by the presence of a monoclonal protein (paraprotein) quantified as <30 g/L, <10% clonal plasma cells in the bone marrow (BM) and the absence of features of the typical end-organ damage associated with multiple myeloma (MM) or related lymphoplasmacytic malignancies[1] (LPMs) such as lymphoplasmacytic lymphoma. The prevalence of MGUS increases with age. The median age of those with MGUS is 70 years, affecting 3.2% of those over 50, increasing to 8.9% of those over 85-year olds.[2]

The clinical importance of MGUS relies on its risk of progression to MM and LPMs,[3] and its association with several non-malignant co-morbidities, recently characterised as the monoclonal gammopathy of clinical significance (MGCS).[4] In this Good Practice Paper we will focus on the diagnosis of MGUS and best laboratory practice, the risk stratification and subsequent management of patients newly diagnosed with MGUS and the possible future role for targeted screening for the condition.

DIAGNOSIS AND BEST LABORATORY PRACTICE

The monoclonal immunoglobulin involved in MGUS may be complete immunoglobulin (Ig) molecules (paraprotein or M-protein) and/or free light chains (FLCs) in the serum and urine (light-chain MGUS). The secreted monoclonal immunoglobulins are visible by unique electrophoretic mobility against the background of polyclonal immunoglobulin.

MGUS is often diagnosed incidentally when serum protein electrophoresis and immunofixation (IFE) are requested to investigate a high-serum protein level or other clinical disorders. In addition, the prevalence of MGUS is higher in patients admitted acutely to hospital compared with previous population estimates.[5] It is to be expected that such patients will be investigated for MGUS, particularly if they present with renal impairment, pain and/or osteoporosis or recurrent infection.

Laboratory investigation of monoclonal gammopathy of undetermined significance

Several individual steps need to be followed to fully investigate the presence of MGUS and, if present, to determine its clinical significance:

- Serum IgG, IgA and IgM levels and serum protein electrophoresis (SPE) should *both* be carried out.[6]
- On detection of a paraprotein, IFE should be performed to confirm the type of monoclonal protein. IFE is tenfold more sensitive than SPE for the detection of monoclonal proteins. Specialised laboratories can measure lower levels of monoclonal immunoglobulin than IFE using mass spectrometry,[7] a technique that can be relevant to the tracking of low-level disease.
- The monoclonal protein should be quantified by densitometry of the monoclonal peak. Quantification of monoclonal IgA by electrophoresis can be complicated by migration into the beta region. International Myeloma Working Group (IMWG) guidance recommends that for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred.[8]
- Monoclonal FLC can be demonstrated in the urine by IFE and quantitated as urinary Bence Jones protein (BJP). However, this is less sensitive than measuring serum kappa and lambda FLC levels and calculating the FLC ratio as FLC are reabsorbed by the renal tubules after filtration.[9–11] Consequently, these latter tests should be performed whenever a new paraprotein is discovered or when monoclonal gammopathy is suspected in the absence of a detectable paraprotein.
- Carry out further blood tests if they have not yet been requested. These should include a full blood count (FBC), serum creatinine, estimated glomerular filtration rate (eGFR) and corrected serum calcium.

Laboratory diagnostic order sets for myeloma diagnosis and MGUS monitoring are especially helpful in General Practice to ensure adequate monitoring of intact M-protein and FLCs.

Management of abnormal results

The major problem facing the laboratories reporting newly diagnosed monoclonal proteins is that they usually have few clinical details accompanying the samples. The primary care physician faces the challenge of unfamiliarity with the laboratory tests and the fact that MM is a relatively uncommon cancer. Compounding this is that these tests also reveal the 100 times more common condition of MGUS. In clinical practice, most M-proteins derive from MGUS plasma cell clones, whereas abnormal serum FLC ratios either derive from MGUS plasma cell clones or are small abnormalities in the FLC ratio caused by conditions unrelated to neoplastic plasma cells, including kidney disease, inflammation and infection. Myeloma arises in an age range in which these conditions are common.

Clinical comments sent out with laboratory results and flagging systems for significantly abnormal results are essential to ensure the appropriate and timely referral of patients with high-risk MGUS and MM. Within the laboratory, applying an M-protein threshold of 10 g/L and a serum FLC ratio range (<0.1 or >7) gives high specificity and sensitivity for MM diagnosis. If both thresholds are exceeded that provides 98% sensitivity for the detection of myeloma and excludes 95% of MGUS cases.[12] Patients are, therefore, highly unlikely to have MM if the M-protein is <10 g/L and

the FLC ratio is 0.1–7. To aid primary care clinicians in the interpretation of laboratory results, diagnostic tools such as the Myeloma UK GP Myeloma Diagnostic Tool lays out a strategy for applying these thresholds in clinical practice and provides guidelines for referral (Figure 1).

Recommendations

- **Upon detection of a new M-protein, IFE should be performed to confirm the type of monoclonal protein and a serum FLC assay should also be carried out to measure FLC levels and calculate the FLC ratio.**
- **Laboratory diagnostic sets are essential to ensure all the correct tests are performed in patients with suspected MGUS or myeloma.**
- **Laboratory flagging systems are essential to alert primary or secondary care physicians to a significantly abnormal result and the appropriate referral pathway.**

RISK STRATIFICATION OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Progression of MGUS to MM or LPMs occurs at a rate of approximately 1% per year.[13] It is worth stressing that IgM MGUS is much more likely to progress to lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia than to MM.

Even after >25 years of follow-up, the risk of progression does not decrease. As many MGUS patients have advanced age and comorbidities, they will often die from unrelated diseases. Recognition of risk factors for progression is of clear benefit. Not only does this allow the identification of patients at the highest risk, who will benefit most from further investigations, such as BM examination, and subsequent close monitoring, but it also provides reassurance to patients at low risk who do not need to be subjected to further tests.

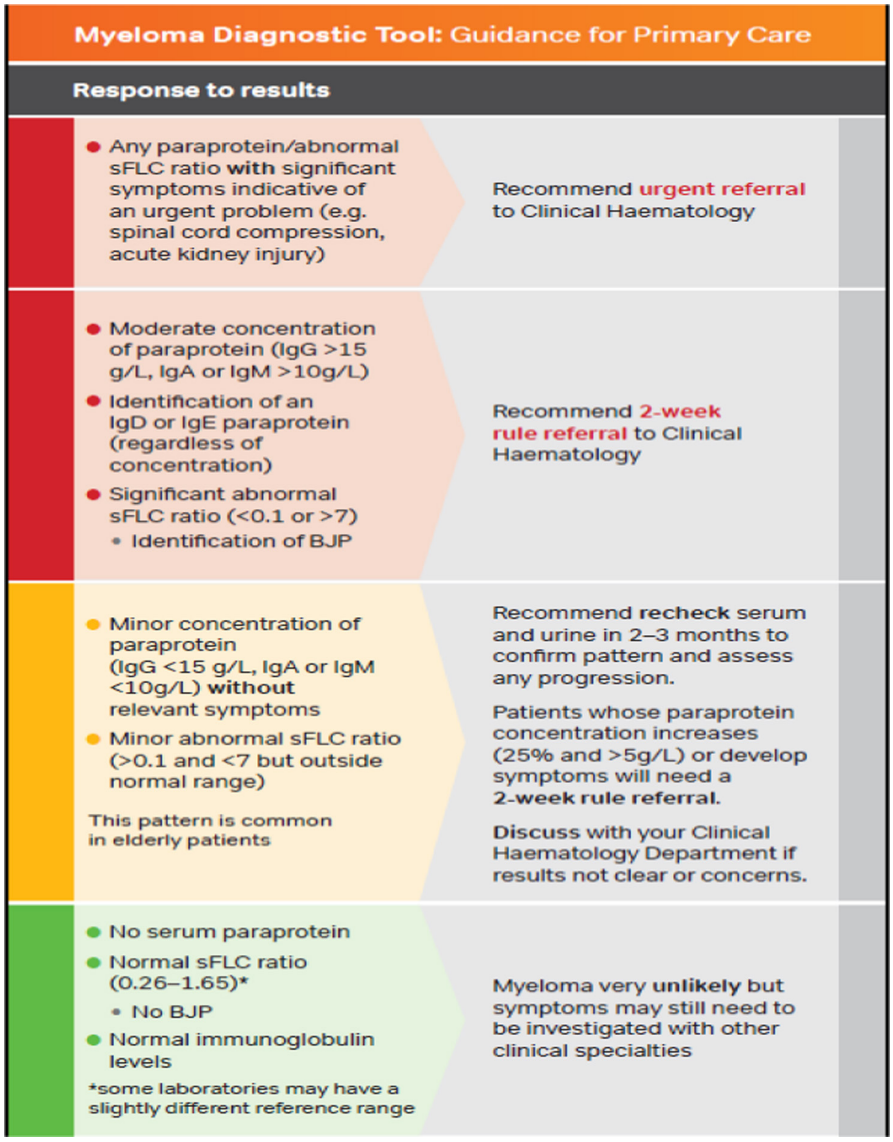

FIGURE 1 Taken from the Myeloma UK Myeloma Diagnostic Tool, Guidance for Primary Care (reproduced with permission).

Predictors of transformation of monoclonal gammopathy of undetermined significance

Presenting features are helpful in stratifying the risk for progression of MGUS to symptomatic disease. This will help to individualise future monitoring. Important variables include the size of the BM plasma cell clone[14] and M-protein levels.[13,15] In addition, there are several known clinical risk factors (e.g. family history, male sex and advanced age) and probably some unknown factors that cause some patients to progress at a faster rate.[16]

Other biological characteristics have predictive value, such as heavy-chain isotype (IgA/IgM > IgG),[13,15,17,18] abnormal serum FLC ratio,[15] presence of Bence Jones proteinuria,[14,17] detection of circulating plasma cells[19] or clonal B cells,[20] the proportion of abnormal plasma cells on flow cytometry,[14] clonal heterogeneity[21] and abnormal metaphase cytogenetics.[21] Several imaging techniques may be useful in predicting progression of MGUS such as magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT).[22] Finally, a rapid progressive increase of the M-protein (evolving MGUS) predicts progression to malignant disease.[23]

The risk of progression for light-chain MGUS is lower compared with the risk of progression in conventional MGUS. In a population-based cohort study, only 3 of 133 light-chain MGUS patients experienced progression to MM (all three developed light-chain MM) during 1100 patient-years of follow-up (progression rate: 0.27% per year).[24] However, to avoid complexity, light-chain MGUS is generally managed in the same way as MGUS involing a whole paraprotein. The same applies to patients with more than one paraprotein, in whom data is sparse.

Risk stratification for monoclonal gammopathy of undetermined significance

Risk stratification models designed to predict MGUS progression have been published, and the most widely cited models are summarised in Table 1. In the Mayo Clinic risk stratification model, the risk of progression is increased with a serum monoclonal protein measuring >15 g/L, a non-IgG isotype (IgA or IgM) and an abnormal serum-free light-chain ratio (<0.26 or >1.65). At the time of presentation, MGUS patients can be stratified based on the number of risk factors present[15] (see Table 2). Using this model, low-risk patients had a 2% absolute risk of disease progression at 20 years. High-risk patients were identified as those with a large (>15 g/L) IgA or IgM monoclonal protein and an abnormal FLC ratio. These patients had a 27% absolute risk of progression at 20 years. It should be remembered that falling GFRs have a differential effect on the clearance of kappa (monomers) and lambda (dimers) FLC causing the polyclonal kappa: lambda FLC ratio to increase, although this increase varies between methods for measuring FLC. For example, with the FREELITE™ method, the normal FLC ratio is 0.54–3.30 for an eGFR <30 mL/min.[25]

As an alternative, the Spanish PETHEMA Study Group identified (i) DNA aneuploidy (hyperdiploidy or hypodiploidy) and (ii) a ratio of abnormal/normal plasma cells (measured by flow cytometry) within the BM plasma cell compartment ≥95% as independent variables predictive of progression in patients with MGUS. Patients with 0 risk factors had a 4% risk of progression at 5 years, those with one risk factor had a 46% risk of progression at 5 years and patients with two risk factors had a 72% risk of progression at 5 years.[14] A practical consideration for this model is that a BM examination is required. The same group published a follow-up study in 2010, exploring the prognostic value of (i) evolving MGUS (defined as ≥10% increase in M-protein by the third year of follow-up) and (ii) ≥95% abnormal BM plasma cells. Patients with zero risk factors had a 2% cumulative probability of progression (CPP) at 7 years, those with one risk factor had a 16% CPP at 7 years and patients with two risk factors had a 72% CPP at 7 years.[26]

Finally, a Swedish study found that a combination of four clinical parameters: the 3 Mayo Clinic criteria plus the presence of immune paresis could predict the risk of progression, ranging from a CPP of 4% at 10 years for those with zero risk factors to 40% at 10 years for those with all four risk factors.[27]

To date, there have been no head-to-head comparisons between the above risk stratification models. It is, therefore, not possible to state the degree of concordance between them.

TABLE 1 Risk stratification models predicting MGUS progression to multiple myeloma or related disorders.

2005 Mayo Clinic study[15]	2014 Swedish study[27]	2010 Spanish study[26]	2007 Spanish study[14]
Risk factors	**Risk factors**	**Risk factors**	**Risk factors**
Serum M-protein >15 g/L	Serum M-protein >15 g/L	Aberrant phenotype in >95% of BM PCs	Aberrant phenotype in >95% of BM PCs
Non-IgG sub-type	Non-IgG sub-type	Evolving MGUS[b]	DNA aneuploidy
Abnormal FLC ratio	Abnormal FLC ratio		
	Immune paresis[a]		

Abbreviations: BM PCs, bone marrow plasma cells; FLC, free light chain; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

[a]Reduction below the normal limit in the levels of >1 uninvolved immunoglobulins.

[b]>10% increase in M-protein by the third year as confirmed by two consecutive measurements separated by >1 month.

TABLE 2 Mayo Clinic MGUS Risk Stratification Model.

Risk of progression	No. of abnormal risk factors	No of patients	Absolute risk of progression at 20 years
Low	0	449	2%
Low-intermediate	1	420	10%
High-intermediate	2	226	18%
High risk	3	53	27%

Note: The three risk factors are defined as an abnormal κ/λ FLC ratio (<0.26 or >1.65), a high serum monoclonal protein concentration (>15 g/L), and a non–IgG subtype (IgA or IgM).

Abbreviations: FLC, free light chain; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

Recommendations

- **Patients with newly diagnosed MGUS should be risk stratified at diagnosis using a validated published model, to optimise their initial management and further follow-up. Models that do not involve a BM examination are preferable.**
- **Risk stratification can take place either in secondary care or in primary care, directed by local guidelines produced in secondary care.**

CLINICAL COURSE AND MANAGEMENT OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Further investigation and management

All patients with newly diagnosed MGUS should have their clinical history taken and examination performed before proceeding with more detailed investigations. Particular emphasis should be on symptoms and signs suggestive of MGCS (see below) and additional investigations added as indicated. All patients should have[28]:

- FBC, serum creatinine, eGFR, corrected calcium, albumin
- Urine dipstick for proteinuria, followed by urine protein: creatinine ratio/albumin: creatinine ratio if positive
- SPE with measurement of M-protein level and residual immunoglobulins
- Serum FLC assay
- Urinary protein electrophoresis to identify the presence of BJP

The decision on whether or not to perform expensive imaging and invasive BM investigations can be difficult, but there is published evidence to provide guidance. For example, a large study found that the probability of finding >10% of BM plasma cells in patients with IgG MGUS with an M-protein <15 g/L was very low (4.7%). The probability of finding bone lesions in those patients was just 2.5%.[29] It has also been shown that in patients with low-risk MGUS according to the Mayo Clinic risk stratification model, the lifetime risk of progression to MM or LPM was just 2%.[15] Thus, imaging and BM examination can be deferred in low risk and probably also low-intermediate risk MGUS patients. As these groups comprise >50% of all MGUS patients, health care costs can be minimised without adversely affecting clinical outcomes. Based on this risk-stratified approach, more intensive investigations can be limited as follows:

High-intermediate and high-risk patients on the Mayo Clinic risk stratification model or those otherwise suspected of having an MM or an LPM should undergo the following investigations:

- Serum lactate dehydrogenase and beta-2 microglobulin levels
- Imaging investigations: low dose whole body CT, whole-body MRI or PET-CT scan if MM suspected[30] or CT scan of neck to pelvis if there is a clinical suspicion of an LPM or another sub-type of non-Hodgkin lymphoma with an associated paraprotein.
- BM aspirate with immunophenotyping and fluorescence in-situ hybridisation cytogenetics and BM trephine biopsy
- Urine protein: creatinine ratio/albumin:creatinine ratio and serum N-terminal pro-B type natriuretic peptide (NTproBNP) for early identification of AL amyloidosis.

Follow-up of patients with monoclonal gammopathy of undetermined significance

The follow-up of MGUS patients is potentially labour-intensive and expensive. Therefore, based on the models discussed above, risk-stratified follow-up should be initiated, with an emphasis on not following up those patients who are unlikely to progress within their lifetimes.

The goal of follow-up in MGUS is to detect early progression into MM or LPM, with the expectation that major complications will be minimised and survival prolonged owing to the initiation of timely treatment. There is, however, no evidence from prospective randomised studies to support this approach. Two population-based studies, a Swedish study and the SEER database analysis, have shown better overall survival among MM patients who had a diagnosis of MGUS or follow-up prior to the discovery of MM,[31,32] but this does not confirm a causal relationship between follow-up and better outcomes, as these results may be the result of lead-time bias.

Despite these caveats, given the seriousness of certain MM and LPM complications and the relative ease with which testing for M-proteins can be performed, several clinical practice guidelines have recommended routine follow-up of selected MGUS patients.[2,33,34] It is notable that one of these guidelines does not recommend following up

TABLE 3 Monoclonal Gammopathy of Clinical Significance (MGCS): mechanisms and organ involvement.

Disease	Organ(s) involved	Mechanism	Gammopathy isotype
Scleromyxoedema	Skin	Unknown	IgG
Acquired cutis laxa	Skin	Unknown	IgG
IgM-associated peripheral neuropathy	Nerves	Autoantibody activity	IgM (anti-MAG)
Cold agglutinin disease	Red blood cells	Autoantibody	IgM
Sporadic late-onset nemaline myopathy	Skeletal and cardiac muscle	Unknown	IgM
Type 2 mixed cryoglobulinaemia	Multiple	Immune complex	IgM
POEMS syndrome	Multiple	Cytokine-mediated (VEGF)	Lambda Light chains, IgA
Systemic capillary leak syndrome	Multiple	Unknown	IgG/IgA
Schnitzler syndrome	Skin and bone	Unknown	IgM

patients with a life expectancy of less than 5 years,[34] although that issue is not addressed in the other guidelines. There is, however, a consensus that all patients with newly diagnosed MGUS should have appropriate blood tests (FBC, creatinine, serum calcium, paraprotein and serum FLC levels) performed 6 months after diagnosis, with annual follow-up thereafter, although the interval can be longer for patients with low-risk MGUS. The rationale for this approach is based on the observation that the risk of MGUS transformation is highest during the first year after diagnosis.[35] The recommendation for ongoing follow-up is reinforced by the fact that an individual patient's risk stratification can evolve with time, e.g. intermediate to high risk, with consequences for the approach to investigation and management.[36]

For those patients with MGUS requiring long-term follow-up, there are a variety of possible clinical models, in either the primary or secondary care settings. All the models need to be adequately resourced and overseen by well-trained and motivated staff to be successful. The monitoring of high-intermediate and high-risk patients is well-suited to virtual clinics in secondary care, a form of service delivery that has become more prevalent in the field of plasma cell disorders since the onset of the COVID-19 pandemic.[37]

During the follow-up of patients with MGUS, a rising M-protein or serum FLC level should raise concerns about the possibility of progression, but it is only picked up in about 50% of MGUS patients who do progress.[38] An evolving pattern, with a rise in M-protein over 3 successive annual measurements, was shown to be associated with clinically significant progression in approximately 50% of patients over 10 years.[23] These findings suggest that the often-recommended follow-up of most, if not all, MGUS patients is a sub-optimal approach, and a more targeted approach may be justified.

In addition to rises in M-protein level, progression should be considered if any of the following unexplained signs, symptoms or laboratory abnormalities arise: progressive back or generalised unexplained pain, anaemia and/or rise in the erythrocyte sedimentation rate (ESR),[39] breathlessness not caused by anaemia, diarrhoea, fracture, hepatomegaly, hypercalcemia, hyperviscosity (in the setting of IgM M-protein), intestinal pseudo-obstruction, lytic lesion, macroglossia, nephrotic syndrome, neuropathy (autonomic, sensory or motor), purpura and renal insufficiency. Any concern for progression should prompt additional testing such as appropriate imaging studies or BM or other tissue biopsy.[40] Bearing in mind that the evolution from MGUS to MM may be abrupt, patients should also be advised to obtain medical evaluation promptly if clinical symptoms occur.

Monoclonal gammopathy of clinical significance

Although by definition MGUS is an asymptomatic condition, it has become increasingly apparent in recent years that the underlying B-cell clone is associated with potentially severe organ damage due to direct toxicity of the monoclonal immunoglobulin or other mechanisms. Consequently, the term monoclonal gammopathy of clinical significance (MGCS) has become widely used to describe this clinical scenario.[4] The kidney is a major target for monoclonal immunoglobulin-related organ damage, hence the well-described clinical concept of the monoclonal gammopathy of renal significance (MGRS).[41] The investigation and management of MGRS will be described in a separate British Society for Haematology Good Practice Paper.

Other target organs, such as the skin, peripheral nerves and cardiac muscle, can be involved in MGCS (see Table 3), and the principle of management to prevent further tissue damage requires the use of systemic chemotherapy to control the underlying B-cell clone.[4] The decision to instigate such treatment should be made by a multi-disciplinary team (MDT) with suitable sub-specialty representation.

Clinical associations with monoclonal gammopathy of undetermined significance

In addition to diseases that can be classified as falling under the MGCS umbrella, there are other conditions associated with MGUS that health care professionals following up MGUS patients should be aware of. Care must be taken to distinguish those complications that are truly secondary to the monoclonal gammopathy from those due to an unrelated process. Indeed, as most of the studies in this area have been

performed in patients with incidentally diagnosed MGUS who were being treated for other diseases, there is the likelihood that they will have been affected by selection bias.

Fracture

It has been suggested that patients with MGUS have an increased risk of axial bone fractures, with the highest risk being noted in those with reduced lumbar bone mineral density.[42] The risk of fracture does not differ by immunoglobulin isotype or M-protein concentration at diagnosis, and fracture does not per se predict disease progression. The pathophysiologic basis for this finding is unclear, although both an imbalance between bone resorption and bone formation and altered bone microstructure have been postulated.[43] It does not seem to be due to increased rates of osteoporosis.[44] However, it is still advisable to ensure that vitamin D and calcium levels are optimised in patients with MGUS. The International Myeloma Working Group has suggested giving bisphosphonate therapy to MGUS patients with proven osteoporosis,[45] but it is not yet known if this intervention reduces the incidence of fragility fractures.[46]

Thromboembolic disease

In patients with MGUS, an increased incidence of venous thromboembolic disease (VTE) and to a lesser extent arterial thrombosis has been reported in a few studies.[47,48] A hypercoagulable state secondary to an ongoing clonal plasma cell activity has been suggested as the aetiology, although the risk of VTE does not appear to be related to the M-protein concentration at diagnosis, and primary VTE thromboprophylaxis is not recommended.

Infection

Patients with MGUS appear to be 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.[49] This increased infection risk supports early antibiotic use, vaccination and referral for specialist input in recurrent infections. The response to vaccinations tends to be higher in MGUS than in MM,[50] so the vaccination of patients before transformation to myeloma might confer a degree of long-term protection in this high-risk group of patients.

Information and support for patients diagnosed with monoclonal gammopathy of undetermined significance

Patients and their families need appropriate information and support regarding the clinical and psychological ramifications of a diagnosis of MGUS. Individuals living with MGUS have an increased risk of progression to malignant disorders and require monitoring throughout their lifetimes. This can have a negative impact on their mental health. Watch and wait in cancer, sometimes referred to by patients as 'watch and worry', can be hard to manage psychologically.[51] Mishel developed an 'Uncertainty in Illness Model' in which patients go through four stages in illness, namely ambiguity, complexity, information and unpredictability. This was later reconceptualised for chronic illness by various authors.[52–54] This reconceptualisation demonstrated that if there is uncertainty at diagnosis this is a negative factor. Furthermore, when the possible negative outcome is progression to a malignant condition, skilled psychological support is required to ameliorate anxiety relating to this uncertainty. Taking this into consideration, any MGUS monitoring service, particularly the secondary care monitoring of high-risk MGUS, should provide clear information and psychological support at each review where practicable.

Each clinical review should provide a full explanation of the results of investigations and an explanation of what this means for their disease. Patients should be educated and given information on the potential symptoms they should be aware of, for example, new pain or recurrent infections.

Recommendations

- **Newly diagnosed patients with MGUS should undergo blood and urine tests to enable risk stratification using the Mayo criteria.**
- **Newly diagnosed patients with low or low-intermediate-risk MGUS do not require BM examination or imaging investigations.**
- **High-intermediate or high-risk patients MGUS patients should undergo further blood and urine tests, a BM examination and a whole body imaging investigation at diagnosis.**
- **Newly diagnosed MGUS patients should have appropriate blood tests (FBC, creatinine, serum calcium, paraprotein and serum FLC levels) performed 6 months after diagnosis, with annual follow-up thereafter, although the interval can be longer for patients with low-risk MGUS and further investigations reduced if life expectancy is short.**
- **Patients with high-intermediate and high-risk MGUS should be followed up in secondary care, with formal risk assessment taking place every 3 years.**
- **During the follow-up of MGUS patients, a progressively rising M-protein or serum FLC level should raise concerns about the possibility of progression, as should the development of anaemia, a rise in ESR, renal impairment or hypercalcaemia.**
- **Any decision to treat MGCS with systemic chemotherapy should be made by a MDT with suitable sub-specialty representation.**
- **Patients with MGUS require clear information and psychological support at the time of their diagnosis and during their follow-up.**

SCREENING FOR MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

There are no current guidelines that recommend screening for MGUS. This may be in part due to the erroneous concept that MGUS is a benign pre-malignant condition. However, as stated earlier it is becoming increasingly clear that MGUS is associated with increased risks of multi-modal morbidities,[34] MGCS[4] and an excess of death that is independent of malignant progression.[55] These observations have led to recent proposals to consider establishing screening for MGUS.[56,57]

Evidence is growing that patients diagnosed with MM following a prior knowledge of MGUS have superior outcomes.[31] However, in the absence of guidelines recommending screening, just 3%–10% of patients reach their diagnosis of MM having had a prior MGUS diagnosis.[31] This increases the risk of MM being diagnosed late or via an emergency presentation, events that are associated with poorer outcomes in terms of morbidity and mortality.[58,59] It is, therefore, at least plausible to suggest that screening for MGUS could result in better outcomes for patients eventually diagnosed with myeloma. A further potential argument for screening could be made on the grounds that some of the complications of MGUS, for example, osteoporosis and renal disease, are preventable and/or manageable.

The purpose of screening is to identify asymptomatic individuals at higher risk of developing a particular disease so that they may benefit from early intervention that can lead to improved survival or quality of life. The lack of a clinically proven low toxicity intervention has resulted in screening not being recommended in previous MGUS guidelines.[56]

In view of the lack of evidence on which to base screening programmes for MGUS, there is certainly a clear need for large population studies to determine the appropriateness of screening for MGUS as a means of improving the long-term prognosis of the condition. The ongoing iStopMM study (Iceland Screens Treats or Prevents Multiple Myeloma) aims to screen for MGUS in approximately 120 000 adults in Iceland over the age of 40, and will assess the benefits and harms of such screening.[60] The overall and disease-specific mortality will be compared between participants randomised to different follow-up protocols. The hypothesis is that an early detection of myeloma, resulting from the follow-up of MGUS, will improve overall survival and decrease complications associated with the diagnosis and treatment of myeloma. Early results suggest that patients in the intensive follow-up arm of the study had significantly higher detection rates of lymphoproliferative disorders, specifically smouldering Waldenstörm macrogloulinaemia, smouldering myeloma and MM, demonstrating that enhanced detection of these malignancies through screening is possible.[61] Results from longer-term follow-up are required to determine whether this enhanced detection translates to better patient outcomes and to evaluate the degree of psychological burden caused to patients from screening.

The PROMISE (Predicting Progression of Developing Myeloma in a High-Risk Screened Population) study in the United States screens for MGUS and smouldering myeloma among African Americans and first-degree relatives of patients with MM, who are at least 40 years of age. This prospective study follows them to determine clinical, immune and genomic predictors of progression to MM.[62] Results may suggest that there is value in a targeted approach to screening.

These studies will provide invaluable information, but they do not focus on morbidities other than myeloma and it may take up to 15 years until they are fully informative. An alternative to this prospective approach would be to use national biobanks. These bioresources could be used to highlight biomarkers in patients identified as having MGUS, associated with risks of multi-morbidities and cancer progression. Laboratory techniques that have the potential to be useful include mass spectrometry-based metabolomics[63] and mutational analysis of circulating cell-free DNA.[64] In addition to the laboratory studies, the retrospective clinical information obtained from the biobank patients' records would facilitate a cost-effectiveness analysis of various targeted MGUS screening strategies.

Recommendations

- **Although current evidence does not support screening for MGUS, more trials of screening and monitoring are warranted, with the use of a targeted approach for higher-risk patients to improve cost-effectiveness.**
- **Continual re-appraisal of the balance between risk and benefit of screening for MGUS is required as early intervention for the condition continues to evolve.**

AUTHOR CONTRIBUTIONS

Simon Stern proposed the Good Practice Paper and Chaired the Writing Group. All the authors contributed to the writing and revising of the Good Practice Paper.

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ORCID

Simon Stern https://orcid.org/0000-0003-1831-9549

TWITTER

Simon Stern @DrSStern
Haemato-Oncology Task Force of the British Society for Haematology and the UK Myeloma Forum @BritSocHaem

REFERENCES

1. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–48. https://doi.org/10.1016/s1470-2045(14)70442-5
2. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, 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(6):1121–7. https://doi.org/10.1038/leu.2010.60
3. Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Kumar S, Cerhan JR, et al. Long-term follow-up of monoclonal Gammopathy of undetermined significance. N Engl J Med. 2018;378(3):241–9. https://doi.org/10.1056/NEJMoa1709974
4. Fermand JP, Bridoux F, Dispenzieri A, Jaccard A, Kyle RA, Leung N, et al. Monoclonal gammopathy of clinical significance: a novel concept with therapeutic implications. Blood. 2018;132(14):1478–85. https://doi.org/10.1182/blood-2018-04-839480
5. Atkin C, Reddy-Kolanu V, Drayson MT, Sapey E, Richter AG. The prevalence and significance of monoclonal gammopathy of undetermined significance in acute medical admissions. Br J Haematol. 2020;189(6):1127–35. https://doi.org/10.1111/bjh.16487
6. Willrich MAV, Murray DL, Kyle RA. Laboratory testing for monoclonal gammopathies: focus on monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Clin Biochem. 2018;51:38–47. https://doi.org/10.1016/j.clinbiochem.2017.05.001
7. Chapman JR, Thoren KL. Tracking of low disease burden in multiple myeloma: using mass spectrometry assays in peripheral blood. Best Pract Res Clin Haematol. 2020;33(1):101142. https://doi.org/10.1016/j.beha.2020.101142
8. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International myeloma working group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328–e46. https://doi.org/10.1016/S1470-2045(16)30206-6
9. Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. Lancet. 2003;361(9356):489–91. https://doi.org/10.1016/S0140-6736(03)12457-9
10. Dejoie T, Corre J, Caillon H, Hulin C, Perrot A, Caillot D, et al. Serum free light chains, not urine specimens, should be used to evaluate response in light-chain multiple myeloma. Blood. 2016;128(25):2941–8. https://doi.org/10.1182/blood-2016-07-726778
11. Heaney JLJ, Campbell JP, Griffin AE, Birtwistle J, Shemar M, Child JA, et al. Diagnosis and monitoring for light chain only and oligosecretory myeloma using serum free light chain tests. Br J Haematol. 2017;178(2):220–30. https://doi.org/10.1111/bjh.14753
12. Heaney JLJ, Richter A, Bowcock S, Pratt G, Child JA, Jackson G, et al. Excluding myeloma diagnosis using revised thresholds for serum free light chain ratios and M-protein levels. Haematologica. 2020;105(4):e169–e71. https://doi.org/10.3324/haematol.2019.224360
13. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A Long-term study of prognosis in monoclonal Gammopathy of undetermined significance. N Engl J Med. 2002;346(8):564–9. https://doi.org/10.1056/NEJMoa01133202
14. Pérez-Persona E, Vidriales M-B, Mateo G, García-Sanz R, Mateos MV, de Coca AG, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood. 2007;110(7):2586–92. https://doi.org/10.1182/blood-2007-05-088443
15. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ III, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood. 2005;106(3):812–7. https://doi.org/10.1182/blood-2005-03-1038
16. Ho M, Patel A, Goh CY, Moscvin M, Zhang L, Bianchi G. Changing paradigms in diagnosis and treatment of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Leukemia. 2020;34(12):3111–25. https://doi.org/10.1038/s41375-020-01051-x
17. Cesana C, Klersy C, Barbarano L, Nosari AM, Crugnola M, Pungolino E, et al. Prognostic factors for malignant transformation in monoclonal Gammopathy of undetermined significance and smoldering multiple myeloma. J Clin Oncol. 2002;20(6):1625–34. https://doi.org/10.1200/jco.2002.20.6.1625
18. Katzmann JA, Clark R, Kyle RA, Larson DR, Therneau TM, Melton LJ III, et al. Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. Leukemia. 2013;27(1):208–12. https://doi.org/10.1038/leu.2012.189
19. Kumar S, Rajkumar SV, Kyle RA, Lacy MQ, Dispenzieri A, Fonseca R, et al. Prognostic value of circulating plasma cells in monoclonal Gammopathy of undetermined significance. J Clin Oncol. 2005;23(24):5668–74. https://doi.org/10.1200/jco.2005.03.159
20. Isaksson E, Björkholm M, Holm G, Johansson B, Nilsson B, Mellstedt HÅ, et al. Blood clonal B-cell excess in patients with monoclonal gammopathy of undetermined significance (MGUS): association with malignant transformation. Br J Haematol. 1996;92(1):71–6. https://doi.org/10.1046/j.1365-2141.1996.294826.x
21. Papanikolaou X, Waheed S, Dhodapkar MV, Usmani SZ, Heuck C, van Rhee F, et al. DNA flow cytometry and metaphase cytogenetics can predict progression of asymptomatic monoclonal Gammopathies (AMG) to symptomatic multiple myeloma

(MM). Blood. 2012;120(21):2915–5. https://doi.org/10.1182/blood.V120.21.2915.2915

22. Heuck C, Sexton R, Dhodapkar M, Zhang Q, Usmani S, Nair B, et al. SWOG S0120 observational trial for MGUS and asymptomatic multiple myeloma (AMM): imaging predictors of progression for patients treated At UAMS. Blood. 2011;118(21):3955–5. https://doi.org/10.1182/blood.V118.21.3955.3955
23. Rosiñol L, Cibeira MT, Montoto S, Rozman M, Esteve J, Filella X, et al. Monoclonal Gammopathy of undetermined significance: predictors of malignant transformation and recognition of an evolving type characterized by a progressive increase in M protein size. Mayo Clin Proc. 2007;82(4):428–34. https://doi.org/10.4065/82.4.428
24. Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ III, Colby CL, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. Lancet. 2010;375(9727):1721–8. https://doi.org/10.1016/S0140-6736(10)60482-5
25. Long TE, Indridason OS, Palsson R, Rognvaldsson S, Love TJ, Thorsteinsdottir S, et al. Defining new reference intervals for serum free light chains in individuals with chronic kidney disease: results of the iStopMM study. Blood Cancer J. 2022;12(9):133. https://doi.org/10.1038/s41408-022-00732-3
26. Pérez-Persona E, Mateo G, García-Sanz R, Mateos MV, de Las Heras N, de Coca AG, et al. Risk of progression in smouldering myeloma and monoclonal gammopathies of unknown significance: comparative analysis of the evolution of monoclonal component and multiparameter flow cytometry of bone marrow plasma cells. Br J Haematol. 2010;148(1):110–4. https://doi.org/10.1111/j.1365-2141.2009.07929.x
27. Turesson I, Kovalchik SA, Pfeiffer RM, Kristinsson SY, Goldin LR, Drayson MT, 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):338–45. https://doi.org/10.1182/blood-2013-05-505487
28. Mouhieddine TH, Weeks LD, Ghobrial IM. Monoclonal gammopathy of undetermined significance. Blood. 2019;133(23):2484–94. https://doi.org/10.1182/blood.2019846782
29. Mangiacavalli S, Cocito F, Pochintesta L, Pascutto C, Ferretti V, Varettoni M, et al. Monoclonal gammopathy of undetermined significance: a new proposal of workup. Eur J Haematol. 2013;91(4):356–60. https://doi.org/10.1111/ejh.12172
30. Chantry A, Kazmi M, Barrington S, Goh V, Mulholland N, Streetly M, et al. Guidelines for the use of imaging in the management of patients with myeloma. Br J Haematol. 2017;178(3):380–93. https://doi.org/10.1111/bjh.14827
31. Sigurdardottir EE, Turesson I, Lund SH, Lindqvist EK, Mailankody S, Korde N, 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(2):168–74. https://doi.org/10.1001/jamaoncol.2015.23
32. 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(3):177–86 e4. https://doi.org/10.1016/j.clml.2014.09.004
33. Berenson JR, Anderson KC, Audell RA, Boccia RV, Coleman M, Dimopoulos MA, et al. Monoclonal gammopathy of undetermined significance: a consensus statement. Br J Haematol. 2010;150(1):28–38. https://doi.org/10.1111/j.1365-2141.2010.08207.x
34. van de Donk NW, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, 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(6):984–96. https://doi.org/10.3324/haematol.2013.100552
35. Go RSHH, Sangaralingham LR, Habermann EB, Shah ND. Estimating the risk of progression of monoclonal gammopathy of undetermined significance into lymphoplasmacytic malignancies in the United States: determining demographic differences using a national dataset [abstract]. Blood. 2016;128(22):843.
36. Landgren O, Hofmann JN, McShane CM, Santo L, Hultcrantz M, Korde N, et al. Association of immune marker changes with progression of monoclonal gammopathy of undetermined significance to multiple myeloma. JAMA Oncol. 2019;5(9):1293–301. https://doi.org/10.1001/jamaoncol.2019.1568
37. Terpos E, Engelhardt M, Cook G, Gay F, Mateos MV, Ntanasis-Stathopoulos I, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European myeloma network (EMN). Leukemia. 2020;34(8):2000–11. https://doi.org/10.1038/s41375-020-0876-z
38. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009;113(22):5412–7. https://doi.org/10.1182/blood-2008-12-194241
39. Koshiaris C, Van den Bruel A, Oke JL, Nicholson BD, Shephard E, Braddick M, et al. Early detection of multiple myeloma in primary care using blood tests: a case-control study in primary care. Br J Gen Pract. 2018;68(674):e586–e93. https://doi.org/10.3399/bjgp18X698357
40. Go RS, Rajkumar SV. How I manage monoclonal gammopathy of undetermined significance. Blood. 2018;131(2):163–73. https://doi.org/10.1182/blood-2017-09-807560
41. Leung N, Bridoux F, Hutchison CA, Nasr SH, Cockwell P, Fermand JP, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood. 2012;120(22):4292–5. https://doi.org/10.1182/blood-2012-07-445304
42. Melton LJ 3rd, Rajkumar SV, Khosla S, Achenbach SJ, Oberg AL, Kyle RA. Fracture risk in monoclonal gammopathy of undetermined significance. J Bone Miner Res. 2004;19(1):25–30. https://doi.org/10.1359/JBMR.0301212
43. Farr JN, Zhang W, Kumar SK, Jacques RM, Ng AC, McCready LK, et al. Altered cortical microarchitecture in patients with monoclonal gammopathy of undetermined significance. Blood. 2014;123(5):647–9. https://doi.org/10.1182/blood-2013-05-505776
44. Thorsteinsdottir S, Lund SH, Lindqvist EK, Thordardottir M, Sigurdsson G, Costello R, et al. Bone disease in monoclonal gammopathy of undetermined significance: results from a screened population-based study. Blood Adv. 2017;1(27):2790–8. https://doi.org/10.1182/bloodadvances.2017010454
45. Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, Raje N, et al. International myeloma working group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol. 2013;31(18):2347–57. https://doi.org/10.1200/JCO.2012.47.7901
46. Terpos E, Dimopoulos MA. Less strength and more fractures for MGUS bones. Blood. 2014;123(5):603–4. https://doi.org/10.1182/blood-2013-11-539973
47. Kristinsson SY, Pfeiffer RM, Björkholm M, Goldin LR, Schulman S, Blimark C, et al. Arterial and venous thrombosis in monoclonal gammopathy of undetermined significance and multiple myeloma: a population-based study. Blood. 2010;115(24):4991–8. https://doi.org/10.1182/blood-2009-11-252072
48. Za T, De Stefano V, Rossi E, Petrucci MT, Andriani A, Annino L, et al. Arterial and venous thrombosis in patients with monoclonal gammopathy of undetermined significance: incidence and risk factors in a cohort of 1491 patients. Br J Haematol. 2013;160(5):673–9. https://doi.org/10.1111/bjh.12168
49. Gregersen H, Madsen KM, Sørensen HT, Schønheyder HC, Ibsen JS, Dahlerup JF. The risk of bacteremia in patients with monoclonal gammopathy of undetermined significance. Eur J Haematol. 1998;61(2):140–4. https://doi.org/10.1111/j.1600-0609.1998.tb01075.x
50. Karlsson J, Andréasson B, Kondori N, Erman E, Riesbeck K, Hogevik H, 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(6):969–77. https://doi.org/10.1128/CVI.00021-11

51. Mishel MH, Braden CJ. Finding meaning: antecedents of uncertainty in illness. Nurs Res. 1988;37(2):98–103. 127.
52. Mishel MH. Reconceptualization of the uncertainty in illness theory. Image J Nurs Sch. 1990;22(4):256–62. https://doi.org/10.1111/j.1547-5069.1990.tb00225.x
53. Neville KL. Uncertainty in illness. An integrative review. Orthop Nurs. 2003;22(3):206–14. https://doi.org/10.1097/00006416-200305000-00009
54. McCormick KM. A concept analysis of uncertainty in illness. J Nurs Scholarsh. 2002;34(2):127–31. https://doi.org/10.1111/j.1547-5069.2002.00127.x
55. Kristinsson SY, Bjorkholm M, Andersson TM, Eloranta S, Dickman PW, Goldin LR, 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(12):1714–20. https://doi.org/10.3324/haematol.2009.010066
56. Atkin C, Richter A, Sapey E. What is the significance of monoclonal gammopathy of undetermined significance? Clin Med (Lond). 2018;18(5):391–6. https://doi.org/10.7861/clinmedicine.18-5-391
57. Tomasson MH, Ali M, De Oliveira V, Xiao Q, Jethava Y, Zhan F, et al. Prevention is the best treatment: the case for understanding the transition from monoclonal Gammopathy of undetermined significance to myeloma. Int J Mol Sci. 2018;19(11):3621. https://doi.org/10.3390/ijms19113621
58. Public Health England. Routes to diagnosis 2015 update: multiple myeloma.
59. Howell D, Smith A, Appleton S, Bagguley T, Macleod U, Cook G, et al. Multiple myeloma: routes to diagnosis, clinical characteristics and survival - findings from a UK population-based study. Br J Haematol. 2017;177(1):67–71. https://doi.org/10.1111/bjh.14513
60. Rögnvaldsson S, Love TJ, Thorsteinsdottir S, Reed ER, Óskarsson JÞ, Pétursdóttir Í, et al. Iceland screens, treats, or prevents multiple myeloma (iStopMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies. Blood Cancer J. 2021;11(5):94. https://doi.org/10.1038/s41408-021-00480-w
61. Kristinsson SY, Rögnvaldsson S, Thorsteinsdottir S, Reed ER, Oskarsson JTT, Petursdottir I, et al. Screening for monoclonal Gammopathy of undetermined significance: a population-based randomized clinical trial. first results from the Iceland screens, treats, or prevents multiple myeloma (iStopMM) study (abstract). Blood. 2021;138:156. https://doi.org/10.1182/blood-2021-152333
62. Ghobrial I. Predicting Progression of Developing Myeloma in a High-Risk Screened Population (PROMISE). Available from: https://www.clinicaltrials.gov/ct2/show/NCT03689595https://www.clinicaltrials.gov/ct2/show/NCT03689595
63. Lodi A, Tiziani S, Khanim FL, Günther UL, Viant MR, Morgan GJ, et al. Proton NMR-based metabolite analyses of archived serial paired serum and urine samples from myeloma patients at different stages of disease activity identifies acetylcarnitine as a novel marker of active disease. PLoS One. 2013;8(2):e56422. https://doi.org/10.1371/journal.pone.0056422
64. Chiu BCH, Zhang Z, Derman BA, Karpus J, Luo L, Zhang S, et al. Genome-wide profiling of 5-hydroxymethylcytosines in circulating cell-free DNA reveals population-specific pathways in the development of multiple myeloma. J Hematol Oncol. 2022;15(1):106. https://doi.org/10.1186/s13045-022-01327-y

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