Consensus Guidelines on the Diagnosis of Multiple Myeloma and Related Disorders: Recommendations of the Myeloma Canada Research Network Consensus Guideline Consortium

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Abstract

Multiple myeloma (MM) is a plasma cell (PC) malignancy of terminally differentiated B lymphocytes that is typically associated with the secretion of partial and/or complete monoclonal immunoglobulins and a constellation of particular symptoms and signs. MM is a treatable condition, and timely diagnosis is essential to limit or avoid irreversible target-organ damage and to prolong survival. The Myeloma Canada Research Network Consensus Guideline Consortium (MCRN-CGC) proposes national consensus recommendations for the diagnosis of MM and associated PC neoplasms. The focus is on widely available tests but also highlights recent advancements that are important to include in the diagnostic paradigm. By clarifying and updating the required laboratory, radiographic, and bone marrow investigations, the MCRN-CGC hopes to address the needs of Canadian physicians and people living with MM across the country through accurate and timely diagnosis of MM, as well as appropriate initial stratification to improve treatment selection and outcomes. The MCRN-CGC will periodically review the recommendations herein and update as necessary. Recommendations on the therapeutic approaches and associated monitoring of MM will follow.

Introduction

Multiple myeloma (MM), a plasma cell (PC) neoplasm caused by the proliferation of malignant cells in the bone marrow, accounts for approximately 1.8% of all new cancer cases and 2.1% of all cancer deaths in the United States.1 According to the 2019 Canadian Cancer Statistics report, there are approximately 3300 new cases of MM diagnosed annually in Canada (1950 in men and 1400 in women), representing an annual incidence of 9.6 in 100,000 for men and 6.0 in 100,000 for women.2

MM is generally considered incurable; however, with recent therapeutic advancements, survival rates have significantly increased over the past 20 years. Age-adjusted 5-year relative survival has increased from 35.6% in 1998 to 2001 to 44% in 2006 to 2009.3 More recently, high rates of deep remissions have been achieved with novel therapies,4 which are expected to translate into further...
improvements of outcomes going forward. That said, the clinical course of MM is heterogeneous, and outcomes correlate with disease stage and the presence of prognostic indicators and early treatment of symptomatic disease to limit or avoid irreversible target-organ damage – emphasizing the importance of timely, accurate, and complete diagnosis.

PC neoplasms are classified according to the World Health Organization (WHO), and at the time of this publication, the diagnostic criteria for MM are based on updated 2014 International Myeloma Working Group (IMWG) recommendations that identified target-organ damages associated with the development of CRAB (hyperCalcemia, Renal failure, Anemia and Bone lesions) features as well as validated biomarkers associated with very high-risk development of symptomatic MM.

This document provides an overview of the commonly used investigations and criteria for the diagnosis of MM and other related PC disorders. The focus is on relevance, applicability, and the use of the various tests available in routine Canadian practice. The objective is to provide Canadian clinicians with concise diagnostic recommendations upon which therapeutic decisions can be made.

Methodology

The development of the consensus recommendations began with a review of clinical evidence, daily practice, existing guidelines, and availability of diagnostic tools. Members of the Myeloma Canada Research Network Consensus Guideline Consortium (MCRN-CGC) were assigned specific topics to be discussed and reviewed by the entire group during a meeting that took place on April 27, 2018, in Toronto, Ontario. The group reconvened on May 3, 2019, in Toronto, to review and finalize the consensus recommendations. Subsequently, other MCRN members (MCRN contributors) were given the opportunity to review the consensus recommendations prior to its submission for publication. The development of these guidelines was solely supported by Myeloma Canada without funding from the pharmaceutical industry.

To ensure more widespread acceptance of the guidelines, the MCRN-CGC decided against the grading of the recommendations herein. Level A evidence was sought, where available; however, the group did not want to discount clear practice-changing data of lesser quality.

Interpretation and Use

When interpreting the recommendations, clinicians should bear in mind that each recommendation is based on clinical evidence, as well as clinical experience and knowledge gained through daily practice, as well as national and international collaboration with experts in the field of MM. Although the recommendations are intended to be a flexible tool to assist with timely and informed decisions, they should not replace sound clinical judgment or be used as a legal resource.

Spectrum of Plasma Cell Neoplasms

Overview

MM evolves from a clinically silent state termed monoclonal gammopathy of undetermined significance (MGUS). MGUS is a condition with low risk of conversion to overtly symptomatic disease requiring therapy (~ 1% per year). The risk of evolution to symptomatic disease rises with increasing clonal PC burden and is defined as smoldering MM (SMM), an intermediate stage associated with a higher risk of progression to overt MM (~ 10% per year).

Both MGUS and SMM are, by definition, asymptomatic and are differentiated by the amount of secreted monoclonal protein (M-protein) and/or the extent of clonal PC involvement on bone marrow examination. The IMWG diagnostic criteria for MGUS and related plasma-cell disorders (Table 1) are primarily characterized by serum M-protein (IgG or non-IgG) < 30 g/L, urinary M-protein < 500 mg/24 hr, clonal bone marrow PCs (BMPCs) < 10%, and a lack of end-organ damage, as per CRAB criteria.

The revised IMWG diagnostic criteria for SMM and MM are listed in Table 2. Briefly, SMM is characterized by serum M-protein (IgG or IgA) ≥ 30 g/L or urinary M-protein ≥ 500 mg/24 hr, and/or 10% to 60% clonal BMPCs. These criteria must be present in the absence of myeloma-defining events (MDEs) or light-chain (AL) amyloidosis.

Overt symptomatic MM is defined by the presence of a clonal PC population (BMPCs ≥ 10% or biopsy-proven extramedullary plasmacytoma) with any one of the following MDEs: (1) end-organ damage attributed to an underlying PC proliferative disorder, as per CRAB criteria; (2) ≥ 1 biomarker of malignancy (clonal BMPC > 60%, involved:uninvolved serum free light chain ratio [sFLC] ≥ 100, or > 1 focal lesion ≥ 5 mm on magnetic resonance imaging [MRI]).

An MM variant called plasma cell leukemia (PCL) is a very aggressive form of MM characterized by high levels of abnormal PCs circulating in the peripheral blood. PCL is defined as the presence of PCs comprising ≥ 20% of the white blood cell (WBC) differential count or an absolute PC count greater than 2.0 × 10⁹ cells/L in the peripheral blood. PCL can be detected de novo without prior history of MM (primary PCL) or with a known history of MM (secondary PCL).

A recently described group of diseases called monoclonal gammopathy of clinical significance (MGCS) is usually associated with low clonal PC/lymphoplasmacytoid cell burden and involves various tissues, particularly the kidneys (monoclonal gammopathy of renal significance [MGRS]). They are associated with deposition/precipitation of secreted monoclonal immunoglobulins or their fragments, or immune dysfunction through auto-antibodies or complement activation. These disorders are associated with a great deal of morbidity, and even mortality, and their pathologic features should be distinguished from MGUS because treatment is required. A detailed review of MGCS is beyond the scope of this document; however, if MGCS is suspected, confirmation of pathologic monoclonal immunoglobulin deposition in the affected tissue is often required. It is also important to exclude a chance association, especially in the elderly, as there is a relatively high prevalence of monoclonal gammopathy in this population.

Other disorders associated with PC neoplasms include solitary plasmacytoma, AL amyloidosis, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin changes) syndrome, or other MGCS. In amyloidosis and POEMS syndrome, the current understanding is that clonal PCs synthesize immunoglobulin light chain or heavy chain fragments that cannot be completely broken down to their constituent amino acids.
Consensus Guidelines on the Diagnosis of Multiple Myeloma and Related Disorders

Table 1  IMWG Diagnostic Criteria and Classification for MGUS and Related Plasma-cell Disorders

<table>
<thead>
<tr>
<th>Plasma Cell Disorder</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Non-IgM MGUS</td>
<td>• Serum monoclonal protein (non-IgM) &lt; 30 g/L and urinary monoclonal protein &lt; 500 mg/24h&lt;br&gt;• Clonal BMPCs &lt; 10%&lt;br&gt;• Absence of end-organ damage (ie, CRAB) or amyloidosis that can be attributed to the PC proliferative disorder</td>
</tr>
<tr>
<td>IgM MGUS</td>
<td>• Serum IgM-M-protein &lt; 30 g/L and urinary monoclonal protein &lt; 500 mg/24h&lt;br&gt;• Bone marrow lymphoplasmacytic infiltration &lt; 10%&lt;br&gt;• Absence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder</td>
</tr>
<tr>
<td>Light chain MGUS</td>
<td>• Abnormal FLC ratio (&lt; 0.26 or &gt; 1.65)&lt;br&gt;• Increased level of the appropriate FLC (increased ( \kappa ) FLC in patients with ratio &gt; 1.65 and increased ( \lambda ) FLC in patients with ratio &lt; 0.26)&lt;br&gt;• No immunoglobulin heavy chain expression on IFE&lt;br&gt;• Absence of end-organ damage (ie, CRAB) or amyloidosis that can be attributed to the PC proliferative disorder&lt;br&gt;• Clonal BMPCs &lt; 10%&lt;br&gt;• Urinary monoclonal protein &lt; 500 mg/24h</td>
</tr>
<tr>
<td>Solitary plasmacytoma</td>
<td>• Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal PCs&lt;br&gt;• Normal bone marrow with no evidence of clonal PCs&lt;br&gt;• Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)&lt;br&gt;• Absence of end-organ damage (ie, CRAB) that can be attributed to the PC proliferative disorder</td>
</tr>
<tr>
<td>Solitary plasmacytoma with minimal marrow involvement</td>
<td>• Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal PCs&lt;br&gt;• Clonal BMPCs &lt; 10%&lt;br&gt;• Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)&lt;br&gt;• Absence of end-organ damage (ie, CRAB) that can be attributed to the PC proliferative disorder</td>
</tr>
</tbody>
</table>
| POEMS syndrome                          | • Polineuropathy<br>• Monoclonal PC proliferative disorder (almost always \( \lambda \))<br>• Any one of the following major criteria:  <br>  — Sclerotic bone lesions  
  — Castleman disease  
  — Elevated levels of VEGFA<sup>a</sup>  
  • Any one of the following minor criteria:  
  — Organomegaly (spleenomegaly, hepatomegaly, or lymphadenopathy)  
  — Extravascular volume overload (edema, pleural effusion, or ascites)  
  — Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)<sup>b</sup>  
  — Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangioma, plethora, acrocyaranosis, flushing, white nails)  
  — Papilledema  
  — Thrombocytosis/polycythemia |
| Systemic amyloidosis                     | • Presence of an amyloid-related systemic syndrome (eg, renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement)<br>• Positive amyloid staining by Congo red in any tissue (eg, fat aspirate, bone marrow, or organ biopsy)<br>• Evidence that amyloid is light-chain-related established by direct examination of the amyloid using mass spectrometry-based proteomic analysis or immunoelectron microscopy<br>• Evidence of a monoclonal PC proliferative disorder (serum or urine M-protein, abnormal FLC ratio, or clonal BMPCs) |

Adapted from Lancet Oncol 2014; 15:e538-48, with permission from Elsevier.

Abbreviations: BMPCs = Bone marrow plasma cells; CRAB = hypercalcemia, renal failure, anemia, and bone lesion; CT = computed tomography; FLC = free light chain; IFE = immunofixation electrophoresis; IgM = immunoglobulin M; IMWG = International Myeloma Working Group; MGUS = monoclonal gammopathy of undetermined significance; MRI = magnetic resonance imaging; PC = plasma cell; POEMS = polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; VEGFA = vascular endothelial growth factor A.

*VEGFA measured in the serum or plasma should be at least 3 to 4 times higher than the normal reference range for the laboratory that is doing the testing to be regarded as a major criterion.

*To regard endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required because these 2 disorders are common in the general population.

AL amyloidosis, target organ dysfunction is the result of misfolded immunoglobulin light chain fragments that are deposited in tissues.<sup>18</sup>

Solitary plasmacytomas, localized proliferation of neoplastic monoclonal PCs, are an uncommon type of PC neoplasm that account for approximately 2% to 5% of all PC disorders.<sup>17</sup> There are 2 types of solitary plasmacytomas: (1) medullary plasmacytoma arising from the marrow and (2) extramedullary plasmacytomas originating from soft tissues.<sup>17,19</sup> Both are characterized by no radiologic evidence of additional skeletal lesions, absence of signs and symptoms of MM, and bone marrow examinations that are morphologically normal or with very low clonal PC infiltrations (< 10%).<sup>6,17</sup> Although solitary plasmacytomas with \( \geq 10\% \) clonal PCs may be regarded as MM,<sup>4</sup> the majority of patients with extramedullary plasmacytoma have localized disease that is potentially curable with irradiation.<sup>20</sup> It is important to recognize, however, that a majority of patients with medullary plasmacytoma eventually progress to overt MM.<sup>21</sup> Thus, these patients require close follow-up and monitoring.

The focus of this document is on the spectrum of PC neoplasms ranging from MGUS to symptomatic MM.

**Clinical Presentation of MM**

Owing to the non-specific nature of presenting symptoms, the early detection of MM in the primary care setting is challenging.
The most common presenting signs and symptoms include bone pain and lytic lesions (including pathologic fractures), anemia, fatigue, infections, weight loss, hypercalcemia, and renal dysfunction. Bone pain is the most common symptom at presentation, with the lumbar spine being one of the most frequent sites of pain. The vast majority of patients have more than one site of bony involvement. Often, the diagnosis is suggested by a radiologist who identifies evidence of lytic lesions upon review of radiographs ordered for bony pain or other reasons. Anemia is usually normochromic normocytic, and hypercalcemia can lead to additional presenting symptoms such as confusion, somnolence, constipation, nausea, and thirst. Important consideration should be given to the differential diagnosis of MM — manifestations that may be initially attributed to another disease process. This may include back pain attributed to degenerative spine issues, anemia and renal failure attributed to other systemic comorbidities, bone pain attributed to polynymalgia rheumatica, or bone lesions and hypercalcemia attributed to metastatic cancer of another origin. Conversely, metastatic carcinoma of bone and combinations of conditions that mimic CRAB (hypercalcemia of other origin [eg, hyperparathyroidism], renal failure of other origin [eg, diabetes, vascular disease], anemia of other origin, and diffuse severe osteoporosis with imaging findings mimicking diffuse osteolysis of MM) are often misdiagnosed as MM.

Less common presentations of MM are: (1) plasmacytomas; (2) neurologic symptoms, such as peripheral neuropathy (including paresthesia and sensory loss) and carpal tunnel syndrome (owing to coexistent primary AL amyloidosis); (3) recurrent or atypical infection; (4) features of systemic primary AL amyloidosis, which can manifest as any or all of gastrointestinal symptoms, cardiomyopathy, peripheral neuropathy, organomegaly, or skin infiltration; and (5) hyperviscosity with non-specific features, including malaise, headache, and change in mentation. This latter presentation is much more common, however, in Waldenström macroglobulinemia (10%-30%) than in MM (2%-6%) and more common in MM that secrete IgA rather than those secreting IgG monoclonal proteins.

Physical examination findings across the spectrum of PC neoplasms are broad; therefore, we recommend that the first step in diagnosing suspected PC neoplasms is a complete physical and neurologic examination, with a focus on areas of pain to detect bone fractures, spinal cord compression, and potential plasmacytoma(s) affecting critical structures. Neurologic examinations are useful to diagnose cord or peripheral nerve compressions. Rule out amyloidosis and POEMS syndrome, and conduct a careful analysis of past medical history, including history of recurrent atypical infections.

### Diagnosing and Monitoring of MGUS and SMM

**MGUS**

The incidence of MGUS increases with age, presenting in approximately 3% of the general population over the age of 50. MGUS is characterized by the presence of a clonal population of PCs that is not associated with any clinical disease. The IMWG defines this as serum M-protein < 30 g/L, urinary monoclonal...
Once a monoclonal gammopathy is documented, diagnostic workup should begin with basic bloodwork to identify the serologic criteria for hypercalcemia, renal impairment, and anemia. Based on risk stratification, we recommend whole-body low-dose computed tomography (WB-LDCT) in patients with MGUS with >1 risk factor present. If WB-LDCT is not available, skeletal survey by conventional radiography or whole-body MRI are acceptable alternatives. Bone imaging in IgM MGUS is typically not useful or recommended.36,37 If findings are equivocal, consider MRI or 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) to add further clarity to the nature of the lesions observed. Further consideration should also be given for imaging if there is a clinical suspicion of either a higher burden of disease or based on symptomatology. Such imaging may include skeletal survey by conventional radiography, WB-LDCT, MRI, or 18F-FDG-PET/CT to better characterize disease burden.

The rate of reclassification of MGUS to MM based on detection of bone lesions or plasmacytomas by advanced imaging is low (less than 5%).38,39 Although WB-LDCT and MRI have similar sensitivities in detecting bony lesions in the chest, pelvis, humeri, and femori, MRI is superior for detecting extramedullary and spinal lesions, and WB-LDCT is more sensitive for detecting osteolytic lesions in the skull.38,39

Bone marrow examination should be considered in intermediate-risk patients when results may have an impact on diagnosis, long-term management, and/or therapy. At the time of biopsy and aspiration, a bone marrow sample should be drawn for cytogenetic testing with fluorescence in situ hybridization (FISH); however, the diagnostic test should only be processed if the BMPC count is >10% and/or the diagnosis of MM has been clearly established. Additional testing may be required in select patients to rule out other diseases or PC disorders. Such tests can include, but are not limited to, lactate dehydrogenase (LDH), beta-2 microglobulin (β2M), B-type natriuretic peptide (BNP), or N-terminal pro-BNP (NT-pro-BNP).

The purpose of MGUS follow-up is to detect early transformation in order to initiate timely treatment, minimize major complications and prolong survival.36 Given the seriousness of certain complications and the relative ease with which testing for M-proteins can be added to other routine medical tests, regular follow-up is recommended for the vast majority of patients with MGUS.

### Table 3: Risk-Stratification Model to Predict Progression of MGUS to MM or Related Disorders

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Relative Risk</th>
<th>Absolute Risk of Progression (20 Years), %</th>
<th>Absolute Risk of Progression (20 Years), Accounting for Death as a Competing Risk, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low — no risk factors present (39% of patients)</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low-intermediate — 1 risk factor present (37% of patients)</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High-intermediate — 2 risk factors present (20% of patients)</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High — all 3 risk factors present (4% of patients)</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>

Adapted from Blood, 2005;106:812-817, with permission from the American Society of Hematology.

Table 4: Differences in the Risk of Progression Between IgM MGUS and Non-IgM MGUS

<table>
<thead>
<tr>
<th>MGUS Type</th>
<th>Risk Factors</th>
<th>Risk of Progression (20 Years), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM MGUS</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>Non-IgM MGUS</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: MGUS = Monoclonal gammopathy of undetermined significance; MM = multiple myeloma; M-protein = monoclonal protein; sFLCr = serum free light chain ratio.

*Risk factors for the progression of MGUS to MM or related disorders: Abnormal involved/uninvolved sFLCr; Non-IgG MGUS (excluding light chain MGUS); and Serum M-protein level ≥ 15 g/L.
Baseline investigations should be repeated in all patients at 6 months. If findings remain stable, most patients can be followed-up annually thereafter. More frequent monitoring may be indicated in intermediate- to high-risk patients, particularly if there is evidence of disease progression. Low-risk patients do not necessarily require monitoring with bone marrow biopsy or skeletal survey, except if confounding factors are recognized.

Although the greatest focus is put on the progression of MGUS to MM, it is important to remain mindful of the risk of development or co-presentation of a gammopathy-related condition (ie, AL amyloidosis, MGRS, and other MGCS). As such, screening serologic investigations should include examining for unexplained albuminuria (including protein/creatinine ratio), with more detailed investigations determined by a patient’s clinical presentation. Owing to the risk of cardiac AL amyloidosis in light-chain MGUS, baseline investigation should also examine for elevated cardiac biomarkers (ie, BNP, NT-pro-BNP, or highly sensitive troponin [hsTrop] T/L depending on availability). If found to be elevated, prompt referral to hematology is recommended to guide workup.

### Consensus Recommendations: Diagnosing and Monitoring MGUS

#### Diagnosing MGUS

Baseline investigations: CBC, WBC differential count, peripheral blood smear, serum calcium with albumin, creatinine clearance (and/or serum creatinine), total serum protein, SPEP with IFE, sFLC assay, 24-hr total urine protein with UPEP and IFE, quantitative immunoglobulins (IgA, IgG, IgM), and general assessments of hepatic and renal parameters.

**Imaging based on risk stratification (Tables 3 and 4):**

- Low intermediate-, high intermediate-, and high-risk MGUS: > 1 risk factor present: WBLDCT is recommended. If unavailable, skeletal survey by conventional radiography or MRI may be acceptable. Further consideration should be given for imaging by WBLDCT if not used for initial imaging, MRI or 18F-FDG-PET/CT if initial imaging findings are equivocal or if there is a clinical suspicion of either a higher burden of disease or based on symptomatology.

- Low-risk MGUS (no risk factors present): Consider skeletal survey by radiography, WBLDCT, MRI, or 18F-FDG-PET/CT

**Additional tests:** Based on risk stratification and clinical presentation, additional tests may be appropriate to rule out other diseases or PC disorders. If unexplained albuminuria and abnormal FLC ratio is noted, examination for elevated cardiac biomarkers (ie, BNP, NT-pro-BNP, or hsTrop T/L depending on availability) to rule out cardiac AL amyloidosis is recommended.

### Monitoring MGUS

Laboratory assessment should include general assessments of hematologic, hepatic, and renal parameters to examine for features that are: (1) MM-defining; and (2) associated with related conditions (eg, AL amyloidosis & development of albuminuria).

**Low intermediate-, high intermediate-, and high-risk MGUS: > 1 risk factor present:**

- Repeat CBC, calcium with albumin, SPEP, sFLC, and creatinine in 6 months
  - If stable, repeat annually

- Bone marrow examination, imaging, and more frequent monitoring may be clinically indicated based on suspicion of progression

**Low-risk MGUS (no risk factors present):**

- Repeat CBC, calcium with albumin, SPEP, sFLC, and creatinine in 6 months
  - If stable, repeat annually

- Bone marrow examination and skeletal survey are not required in the absence of symptoms

**All MGUS:**

Periodic assessment of osteoporosis and related bone features to initiate timely and appropriate treatment as per clinical practice guidelines published by Osteoporosis Canada.

### SMM

SMM is characterized by higher clonal PC burden than MGUS with 10% to 60% clonal BMPCs and/or a serum M-protein ≥ 30 g/L, a urinary monoclonal protein ≥ 500 mg/24h, but an absence of any CRAB features (Table 2). Unlike MGUS, SMM is a relatively uncommon clinical entity. Although the majority of patients with MM have been found to have pre-existing MGUS, according to the Swedish Myeloma Registry, only 19% of patients with MM were...
Consensus Guidelines on the Diagnosis of Multiple Myeloma and Related Disorders

classified as having a preceding diagnosis of SMM.59 Because SMM is asymptomatic, newly diagnosed patients are typically detected when elevated M-proteins are discovered incidentally on laboratory testing as part of the workup for other disorders.2,50 Owing to the higher rate of transformation of SMM to MM (vs. MGUS to SMM), patients with SMM spend less time in this state and come to clinical attention only once symptoms become apparent.

In SMM, the risk of progression to malignancy is the highest (10% per year) for the first 5 years, then decreases to 3% per year for the next 5 years, and to 1% per year thereafter.8 In fact, 50% of patients with newly diagnosed SMM progress within the first 5 years. On the other hand, approximately one-third of patients with newly diagnosed SMM will not progress in the first 10 years after diagnosis. These patients may have disease biology similar to MGUS, yet with more clonal BMPCs or a higher M-protein count than that specified in the clinical definition of MGUS. Risk-stratification models may help distinguish between these 2 classes of patients with SMM.

A diagnostic workup for SMM should include a complete blood count (CBC), WBC differential count, peripheral blood smear, serum calcium with albumin, creatinine clearance (and/or serum creatinine), total serum protein, serum protein electrophoresis (SPEP) with serum immunofixation electrophoresis (IFE), sFLC assay, 24-hour total urine protein with electrophoresis (UPEP) and IFE, quantitative immunoglobulins (IgA, IgG, IgM), and bone marrow examination with FISH for detection of high-risk cytogenetics (although earlier intervention is not indicated if high-risk FISH results are noted). Patients should also undergo general assessments of hepatic and renal parameters. Additional tests that may be appropriate, based on risk stratification and clinical presentation, include LDH, β2M, BNP, or NT-proBNP. These can help rule out other disorders, including other PC disorders as with the MGUS workup above.

To exclude osteolytic lesions, we recommend that all patients undergo WBLDCT. If WBLDCT is unavailable, skeletal survey by conventional radiography or whole-body MRI are acceptable alternatives. If WBLDCT is unavailable or if results are negative or equivocal, 18F-FDG-PET/CT whole-body MRI (or MRI of the spine and pelvis, if whole-body MRI is not available) is required to exclude focal lesions as MDEs. When performing an MRI of the spine and pelvis, clinicians should note that 10% of lesions might be missed.

Two prognostic models for SMM have been well-studied in prospective trials: the Mayo Clinic model and the model proposed by the Spanish Myeloma Group.31 More recently in 2018, a model that incorporates the revised IMWG diagnostic criteria was proposed by Lakshman et al.32

The Mayo Clinic model uses the quantity of the serum M-protein and extent of bone marrow involvement. These variables classify SMM into 3 risk groups: (1) serum M-protein ≥ 30 g/L and ≥ 10% clonal BMPCs; (2) M-protein < 30 g/L and ≥ 10% clonal BMPCs; and (3) M-protein ≥ 30 g/L and clonal BMPCs < 10%. The median time to progression (TTP) to MM is significantly different among the 3 groups, at 2, 8, and 19 years, respectively.9 The probability of progression at 15 years is 87%, 70%, and 39%, respectively.

The model developed by the Spanish Myeloma Group utilizes the presence of 2 risk factors in patients with SMM who have ≥ 10% clonal BMPCs: (1) presence of an aberrant PC immunophenotype in > 95% of clonal PCs; and (2) immunoparesis (reduction in ≥ 1 uninvolved immunoglobulin by > 25% compared with normal).31 Patients with both risk factors have a median TTP of 23 months, compared with 73 months when only 1 risk factor is present.51 TTP is not calculated when neither risk factor is present. The Spanish model is, however, not easily applicable to Canadian practice, as many centers do not use the next-generation flow cytometry technique used by the Spanish to detect an aberrant PC immunophenotype.

The third model takes 3 risk factors into account: (1) BMPCs > 20%; (2) sFLCr > 20; and (3) M-protein > 20 g/L.52 The risk-stratification system is based on the presence of no (low), 1 (intermediate), and ≥ 2 (high) risk factors. Median TTP was 110, 68, and 29 months, respectively (P < .0001).32

All 3 of these models enable initial risk stratification of SMM. The risk stratification can then be further refined using additional prognostic factors. For example, the prognostic value of the initial Mayo Clinic model can be improved by adding sFLCr as a variable.53

Evidence-based consensus on how frequently to follow-up patients with SMM is lacking. As a result, our follow-up recommendations are based on the best evidence of the likelihood of progression and the presence of risk factors. As the classification of high-risk SMM is of particular relevance for further follow-up and therapeutic approaches, it should be based on all available data on a given patient rather than a restricted set of variables. Revised criteria for high-risk SMM that incorporate both the Mayo Clinic and Spanish Myeloma Group criteria, as well as other risk factors are listed in Table 5.54

Patients defined as having high-risk SMM should be followed closely and re-evaluated 2 to 3 months after the initial diagnosis.54 If findings are stable, testing should be repeated every 4 to 6 months for 5 years and, if they continue to be stable, the period between evaluations can be lengthened to every 6 months. Patients with low-risk SMM should be seen every 3 to 4 months for the first year, followed by every 6 months, if clinically stable, for life or until progression.54

Patients with SMM do not require repeat imaging, but it should be performed if clinically indicated.45,55 In patients with baseline MRI abnormalities, an increase in the number and/or size of lesions has diagnostic and prognostic value.56 Therefore, in patients with MRI showing a solitary focal lesion, diffuse infiltration, or equivocal findings, follow-up examination is recommended in 3 to 6 months.5

Diagnosing Multiple Myeloma
Initial Laboratory Investigation

Overview. The initial laboratory investigation for MM should include CBC to assess for anemia, thrombocytopenia, or leukopenia. In the case of anemia, the reticulocyte count in MM is typically low and, by definition, no alternative cause should be present. Peripheral blood smears may show rouleaux formation (red cells taking on appearance of a stack of coins) owing to elevated total serum protein and/or circulating PCs.
Serum analysis should include quantitative immunoglobulin levels (IgG, IgA, and IgM), SPEP, IFE, as well as sFLC assay with kappa (κ) to lambda (λ) ratio to obtain specific information about the type(s) and quantities of M-protein present. Urinalysis for initial workup should include a 24-hour urine for total protein and UPEP, which remains a part of the IMWG criteria for the diagnosis of PC disorders, and can provide valuable information — particularly in patients with light-chain only disease. Additionally, UPEP is also used to examine for features indicative of related renal diseases falling in the category of MGRS. Of particular importance is the presence of albuminuria that might indicate glomerular disease, a feature of AL amyloidosis and other conditions falling under the MGRS umbrella.

A baseline metabolic panel should be performed to assess coagulation factors and renal and liver function, as well as levels of serum calcium, total serum protein, albumin, beta-2 microglobulin (β2M), LDH, and blood glucose. Although not required, assessment of uric acid can provide additional information, such as high cell turnover or dehydration.

**Glucose Testing.** Corticosteroids can cause blood glucose levels to rise, lead to diabetes, and complicate disease management.

Baseline blood glucose levels should be established prior to the initiation of treatment and monitored carefully during treatment.

**Renal Function.** As part of disease assessment and to guide treatment, renal function assessments should include creatinine clearance (and/or serum creatinine) and electrolytes (sodium, potassium, chloride, bicarbonate). Measured sodium levels in the blood may be decreased in the presence of a paraproteinemian.

**Liver Function.** Following the kidney, the liver is the second most common organ affected by light chains; however, the majority of patients with MM remain asymptomatic or have only mild elevation of liver enzymes. Liver dysfunction owing to PC infiltration has been reported, however, and manifestations such as hepatomegaly, ascites, and jaundice are uncommon but possible. MM presenting as jaundice has been reported owing to hepatic amyloid deposition.

Liver function assessment should include bilirubin (total and direct), alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and prothrombin time (PT). ALP is often elevated in hepatic amyloidosis.

**Urinalysis.** For initial workup should include a 24-hour urine for albumin, creatinine clearance (and/or serum creatinine), total serum protein, SPEP with IFE, sFLC assay, 24-hour total urine protein with UPEP and IFE, quantitative immunoglobulins (IgA, IgG, IgM), and bone marrow examination with FISH for detection of high-risk cytogenetics, in addition to general assessments of hepatic and renal parameters. Based on risk stratification (Table 5) and clinical presentation, additional tests† that may be appropriate to rule out other diseases or PC disorders.

**Imaging.** WBLDCT should be done to exclude osteolytic lesions. If WBLDCT is unavailable, skeletal survey or whole-body MRI are acceptable alternatives. If WBLDCT is unavailable or if initial imaging results are negative or equivocal, 18F-FDG-PET/CT or whole-body MRI (or MRI of the spine and pelvis, if whole-body MRI is not available) is required to exclude focal lesions as MDEs.

**Baseline investigation:** CBC, WBC differential count, peripheral blood smear, serum calcium with albumin, creatinine clearance (and/or serum creatinine), total serum protein, SPEP with IFE, sFLC assay, 24-hour total urine protein with UPEP and IFE, quantitative immunoglobulins (IgA, IgG, IgM), and bone marrow examination with FISH for detection of high-risk cytogenetics, in addition to general assessments of hepatic and renal parameters. Based on risk stratification (Table 5) and clinical presentation, additional tests† that may be appropriate to rule out other diseases or PC disorders.

**Lab work should include general assessments of hematologic, hepatic, and renal parameters to examine for features that are: (1) MM-defining; and (2) associated with related conditions (eg, AL amyloidosis and development of albuminuria)**

- Repeat baseline investigation in 2 to 3 months first year and, if stable, repeat every 4 to 6 months for 5 years or until progression
- If stable, evaluation can be lengthened to every 6 months, for life or until progression
- Consider periodic specialized imaging to rule out asymptomatic progression to MM

**High-risk SMM:**

- Repeat baseline investigation in 2 to 3 months first year and, if stable, repeat every 4 to 6 months for 5 years or until progression
- If stable, evaluation can be lengthened to every 6 months, for life or until progression
- Consider periodic specialized imaging to rule out asymptomatic progression to MM

**Low- and intermediate-risk SMM:**

- Repeat baseline investigation in 3 to 4 months for 1 year
- If stable, repeat testing every 6 months, for life until progression
- Annual serologic and clinical assessments without imaging are sufficient in the majority of cases
- If MM or related condition is suspected, additional investigations are required for diagnosis

**All SMM:**

- Periodic assessment of osteoporosis and related bone features to initiate timely and appropriate treatment as per clinical practice guidelines published by Osteoporosis Canada

**Abbreviations:**

- BNP = B-type natriuretic peptide; β2M = beta-2 microglobulin; CBC = complete blood count; CT = computed tomography; 18F-FDG-PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; FISH = fluorescence in situ hybridization; IFE = immunofixation electrophoresis; LDH = lactate dehydrogenase; MDEs = myeloma-defining events; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-BNP; sFLC = serum free light chain; SMN = smoldering multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell; WBLDCT = whole-body low-dose computed tomography (CT skeletal survey).

**High-risk SMM:**

- Repeat baseline investigation in 2 to 3 months first year and, if stable, repeat every 4 to 6 months for 5 years or until progression
- If stable, evaluation can be lengthened to every 6 months, for life or until progression
- Consider periodic specialized imaging to rule out asymptomatic progression to MM

**Monitoring SMM**

- Repeat baseline investigation in 3 to 4 months for 1 year
- If stable, repeat testing every 6 months, for life until progression
- Annual serologic and clinical assessments without imaging are sufficient in the majority of cases
- If MM or related condition is suspected, additional investigations are required for diagnosis

**Abbreviations:**

- BNP = B-type natriuretic peptide; β2M = beta-2 microglobulin; CBC = complete blood count; CT = computed tomography; 18F-FDG-PET/CT = 18F-fluorodeoxyglucose positron emission tomography/computed tomography; FISH = fluorescence in situ hybridization; IFE = immunofixation electrophoresis; LDH = lactate dehydrogenase; MDEs = myeloma-defining events; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-BNP; sFLC = serum free light chain; SMN = smoldering multiple myeloma; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell; WBLDCT = whole-body low-dose computed tomography (CT skeletal survey).

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- Annual serologic and clinical assessments without imaging are sufficient in the majority of cases
- If MM or related condition is suspected, additional investigations are required for diagnosis

**All SMM:**

- Periodic assessment of osteoporosis and related bone features to initiate timely and appropriate treatment as per clinical practice guidelines published by Osteoporosis Canada
**M-protein Assessment.** Monoclonal immunoglobulins are markers of proliferative clonal PC diseases and have been described as the best serologic and urine-based tumor markers.\(^{62}\) They vary in their molecular weight between 24,000 (FLC) and 900,000 (IgM) Daltons.\(^{62}\) The unique structure of each M-protein makes them highly specific for each PC clone; however, diverse disease presentations and the broad range of serum protein concentrations and molecular weights can pose some unique challenges. Thus, no single test can confidently diagnose or monitor all patients with MM.\(^{62}\) As single tests, sFLC, SPEP, and serum IFE can detect 74%, 79%, and 87% of monoclonal immunoglobulins, respectively, and the 3 tests combined can detect 98.6% of monoclonal immunoglobulins.\(^{62}\) Patients with light chain MM cannot be followed by SPEP alone owing to the small size and low concentration of serum protein, unless concentrations reach more than 1000 mg/L. Serum FLC testing facilitates the identification and monitoring of these patients. Additional challenges are M-proteins that migrate in the β fraction(s) (ie, 30% of all IgAs may hide under the β fraction peak(s)). The broad peak often observed in such cases can be difficult to accurately quantify. Although rarely posing a challenge in diagnosis, this can be problematic when following the peak over time as a marker of disease burden or response to treatment.

It should be noted that approximately 3% of patients with MM have true non-secretory disease with no detectable M-protein in the serum and urine.\(^{64}\) On the other hand, M-protein may be present even when all fractions are within the reference intervals (may be hidden in other serum fractions on the gel). Thus, if MM is clinically suspected, IFE should be performed, even if SPEP appears normal, as the SPEP is a less sensitive test.

IFE permits the identification of proteins within complex mixtures after separation by conventional electrophoresis and is suitable for localization of discrete protein bands and diffuse zones. Uncomplexed antibodies and other proteins are washed and removed from the gel/membrane, leaving only the immunoprecipitates that are too large and insoluble.\(^{63,64}\) The remaining immunoprecipitates can then be identified by staining. IFE improves SPEP sensitivity by approximately 10-fold (from a limit of detection of 1.0 g/L [SPEP] to approximately 0.1 g/L [IFE])\(^{62}\); therefore, a negative or inconclusive SPEP should be followed by IFE if there is a high index of suspicion for MM or a related PC disease. Although IFE can determine M-protein isotype, it should not be used for its quantitation. In contrast, SPEP is capable of estimating M-protein concentration.\(^{63,64}\)

**FLC Quantitation.** Light chains are normally produced by PC in molar excess to heavy chains. The rapid turnover of FLC (2-6 hours) as compared with IgG (23 days) and other immunoglobulins (ie, Ig: 5.8 days; IgM: 5.1 days; IgD: 2.8 days; IgE: 2.3 days) contribute to FLC lability and thus make it a useful disease burden monitoring tool.\(^{62}\) Quantitative FLC assays use antisera directed against epitopes that are exposed only when the light chains are free (unbound to heavy chain) in solution. Thus, FLC immunoassays can be used to specifically quantitate FLC even in the presence of large concentrations of normal serum immunoglobulins. The approach to diagnosis is to use the involved/uninvolved sFLC ratio to detect unbalanced light chain synthesis. Abnormal sFLC ratios have been detected in 90% to 95% of intact immunoglobulin MM and 40% of MGUS.\(^{65}\)

**Quantitative Total Immunoglobulin Testing.** Quantitative immunoglobulin testing measures normal and monoclonal immunoglobulins. Its utility is largely in diagnosing concomitant hypogammaglobulinemia. It is also useful for monitoring monoclonal proteins that cannot be accurately quantified on SPEP such as IgAs that migrate to the β region of those gels.

**Serum Viscosity.** Increased serum viscosity usually results from increased circulating serum immunoglobulins. The signs of hyperviscosity syndrome include blurred or loss of vision, segmental dilation of retinal veins and flame-shaped hemorrhages, oronasal bleeding, headaches, vertigo, decreased hearing, ataxia, paresthesias, diplopia, somnolence, stupor, or coma.\(^{66}\) Serum viscosity evaluation is recommended if IgM levels are > 40 g/L, IgA > 50 g/L, IgG > 60 g/L, or in symptomatic patients.

**Relevance of β2M Level and LDH.** β2M is a low molecular weight protein (11,800 Daltons) synthesized by all nucleated cells and present in all bodily fluids. Its share a structure similar to immunoglobulin molecules, with 2 β sheets linked by a disulfide bond, and it associates with the alpha chain of class I major histocompatibility complex molecules, among other actions. β2M can accumulate in patients with renal dysfunction and can produce dialysis-related amyloidosis. Levels of β2M correlate with tumor burden in MM and fall with response to therapy.\(^{67}\) It is a key feature of the International Staging System (ISS)\(^{68}\) and the more recent revised ISS (R-ISS)\(^{69}\) and thus, along with albumin and LDH, is an important baseline lab test in MM. Baseline LDH is also important for risk stratification, as part of the R-ISS, and in itself may correlate with aggressive disease or PCL.

**Bone Marrow Investigation**

**Bone Marrow Aspiration and Biopsy.** Bone marrow aspiration and core biopsy are required for the quantification of PC and are necessary as part of the baseline workup for MM. PC quantification is expressed as the percentage of PC-to-total nucleated cells examined. Clonality is determined by in situ hybridization (ISH) for κ/λ mRNAs or less accurately with immunocytochemistry, on the core (trephine) biopsies or clot sections of the aspirate, if the former is not available. In addition to being another tool to determine clonality, flow cytometry can provide useful information with respect to aberrant immune profiles of the PC.\(^{71}\) That said, it is not widely available and is not necessary for the diagnosis if a bone marrow biopsy is performed.

**Chromosomal Aberrations and FISH.** Myeloma cells typically divide at a low rate; therefore, standard cytogenetics are often unsuccessful and may reflect background hematopoiesis. Moreover, as...
Consensus Recommendations: Initial Laboratory Investigation for MM

We recommend the following minimally required baseline for laboratory investigation:
- CBC, WBC differential count, peripheral blood smear, serum calcium, total serum protein, albumin, β2M, and LDH and blood glucose
- Creatinine clearance (and/or serum creatinine), electrolytes, and liver function tests
- Serum quantitative immunoglobulins (IgG, IgA, IgM)
- SPEP with IFE
- sFLC assay and sFLC
- 24-hour UPEP with IFE and M-protein quantification

Following the diagnosis of MM, serial evaluation (as above) is recommended, regardless of therapy.

Abbreviations: β2M = Beta 2 microglobulin; CBC = complete blood count; IFE = immunofixation electrophoresis; LDH = lactate dehydrogenase; MM = multiple myeloma; M-protein = monoclonal protein; sFLC = serum free light chain; sFLC = serum free light chain ratio; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; WBC = white blood cell.

Many MM-associated translocations in the PC fraction cannot be detected by standard G-banding karyotyping, other techniques have supplemented it and it is not a required test.

Specific chromosomal aberrations identified in patients with MM involve deletions (del), translocations (t), and amplifications (gain). Aneuploidy analysis segregates patients into 4 subcategories: hypodiploid (up to 44-45 chromosomes), pseudodiploid (44/45 to 46/47 chromosomes), hyperdiploid (> 46/47 chromosomes), and near tetraploid (the last also referred to as the hypotetraploid > 75 chromosomes). It is not clear whether IGH translocations or aneuploidy occurs first in the PC neoplasms, as both aberrations are seen in the very early stages without a clear pattern.

Although chromosomal aberrations are not included in the diagnostic criteria for MM, cytogenetic evaluations by techniques such as FISH are required for all newly diagnosed patients with MM because they can provide important prognostic information, such as duration of remission and overall survival (OS).

In newly diagnosed MM, high-risk disease is minimally defined as the presence of at least one of the following chromosomal aberrations: del(17p), t(4;14)(p16q32), or t(14;16)(q32;q23). A 2009 publication that compared high-risk versus standard-risk cytogenetics showed that the presence of one of these aberrations results in an inferior OS (median OS of 24.5 months vs. 50.5 months). Pending additional data, other adverse cytogenetic profiles that may confer high-risk include gain(1q) with R-SS III, with or without del(1p), and t(14;20). Some of these genomic aberrations are included in the R-SS for MM.

FISH targeted to the myeloma cells following either plasma cell staining or cell sorting is considered the standard technique for analysis of chromosomal aberrations in MM. A PC isolation step is integral to accurately capture aberrations found in the disease cell population. This greatly increases the sensitivity of detection and ensures that only MM-specific mutations are noted rather than germline anomalies potentially unrelated to the disease process. FISH testing includes t(4;14)(p16q32), t(14;16)(q32;q23), del(17p13), and a marker for aneuploidy. FISH testing may also include gain(1q) and del(1p). Translocation t(11;14) results in upregulation of cyclinD1 and was identified as favorable in some studies, whereas it had no impact in others. This translocation is associated with CD20 expression and lymphoplasmacytic morphology. In general, t(11;14), (6;14), gain(5q), and hyperdiploidy do not confer poor prognosis.

Other Techniques. FISH does not detect single-nucleotide variants (ie, in TP53 on chromosome 17p) that may influence prognosis and would only be detected by sequencing. Although standard karyotyping lacks the sensitivity to detect the important aberrations in PCs, it is highly sensitive for the detection of numerical chromosomal aberrations. For example, it is reliable for the detection of chromosome 13 aberrations, including interstitial deletion and monosomy.

Other promising techniques being used in research settings include single-nucleotide polymorphism, comparative genomic hybridization, and gene expression profiling; however, they are yet to be incorporated in clinical practice.

Cytogenetic Risk Stratification. Cytogenetic aberrations can be classified as primary or secondary — events that either contribute to PC immortalization or disease progression, respectively. The common primary and secondary cytogenetic aberrations in MM, MGUS, and SMM are listed in Table 6. The IMWG proposed a model where high-risk MM is defined as at least one of the following determined by FISH: del17p, t(4;14), or t(14;16). The Mayo Clinic classification added hypodiploidy and t(14;20) to the definition of high-risk MM. Later classifications attempted to separate MM into several risk groups. The Medical Research Council IX trial identified 3 groups: favorable risk [no adverse IgH translocation, del(17p), or gain(1q)]; intermediate risk (1 adverse chromosomal abnormality), and high-risk (> 1 adverse chromosomal abnormality). Median progression-free survival (PFS) and OS of patients in the favorable-, intermediate-, and high-risk groups were 23.5, 17.8, and 11.7 months and 60.6, 41.9, and 21.7 months, respectively. Ultra-high-risk was defined as ≥ 3 chromosomal aberrations (2% of patients). Median OS in the ultra-high-risk group was 9 months. More recently, as part of the Myeloma Genome Project, Walker et al described and validated a Double-Hit MM population characterized by poor outcome (median PFS, 15.4 months; OS, 20.7 months). Double-Hit MM is defined by bi-allelic loss of TP53 or by 2 extra copies of 1q together with ISS3.
When attempting to stratify patients according to their prognostic risk based on cytogenetic analysis, it is important to keep in mind that, although there are many single-center studies and publications to provide some guidance, there is an overall lack of consensus. Currently, the stratification suggested by the IMWG is considered to be the gold standard and should be used to guide therapeutic decision-making.

### Consensus Recommendations: Bone Marrow Investigation for MM

- **Bone marrow trephine biopsy to determine:**
  - PC quantification
  - Clonality

- **Bone marrow aspirate:**
  - FISH\(^a\) analysis must be sent and must include:\(^b\)
    - t(4;14)(p16;q32), t(14;16)(q32;q23), del(17p13)\(^c\)
  - To determine cytomorphology
  - For flow cytometry

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### Imaging Investigation

Conventional radiography has been the gold standard for the detection of bone lesions in MM owing to its widespread availability, low cost, and coverage of almost the entire skeletal system. However, it has low sensitivity, and lytic lesions are only detectable if > 30% of the bone cortex is destroyed.\(^{88,89}\) Furthermore, conventional radiography cannot detect or quantify diffuse bone marrow infiltration or extraosseous lesions. Despite these downsides, skeletal survey remains an imaging option. However, the IMWG no longer recommends skeletal survey as the primary modality to determine the presence or absence of MM bone disease, and, if available, newer imaging techniques are preferred.\(^{37}\)

In the past 10 years, advances have been made in imaging technology, and there has been more widespread use of MRI, WBLDCT (CT skeletal survey), and 18F-FDG-PET/CT for assessing lytic bone lesions and to detect early stages of bone marrow infiltration. Table 7 summarizes the pros and cons of the different imaging modalities in MM.

WBLDCT is increasingly used and is replacing conventional radiography at many centers. It has higher sensitivity for the detection of osseous lesions and has the capacity to detect extraosseous lesions. Based on a study by the IMWG, WBLDCT identifies significantly more sites of bone destruction than conventional skeletal survey.\(^{90}\) Of 66 patients with SMM and a negative skeletal survey, 22.2% had lesions on WBLDCT. Based on these results, the investigators suggested WBLDCT as the preferred imaging technique for the detection of osteolytic lesions in MM\(^{37,90}\); if available, we recommend performing WBLDCT as initial imaging for SMM. However, given that WBLDCT is not always available in the Canadian setting, skeletal survey is a reasonable alternative. If WBLDCT is unavailable or if initial imaging results are negative, 18F-FDG-PET/CT or whole-body MRI (or MRI of the spine and pelvis, if whole-body MRI is not available) is required to exclude focal lesions as MDEs.

As of 2014, MRI findings have been included in the IMWG diagnostic criteria.\(^6,88\) Compared with other radiographic methods, MRI has high sensitivity for the early detection of marrow infiltration by MM cells and can detect bone involvement in patients with MM prior to bone destruction, without radiation exposure. MRI is the gold standard for the imaging of the axial skeleton for the evaluation of back pain and for distinguishing benign versus malignant osteoporotic vertebral fractures.\(^{88}\) MRI also has the ability to detect spinal cord or nerve compression and soft tissue masses, and whole-body MRI (or MRI of the spine and pelvis if whole-body MRI is not available) is recommended for the workup of solitary bone

### Consensus Recommendations: Imaging Investigation for MM, SMM, and Plasmacytomas

**MM**

- WBLDCT should be the initial imaging procedure
  - If WBLDCT is unavailable, skeletal survey can replace WBLDCT
  - If initial imaging results are negative or equivocal, whole-body MRI\(^a\) is required:
    - Whole-body MRI is the published standard\(^{88}\)
    - If whole-body MRI is unavailable, MRI of the spine and pelvis should be used
    - If MRI is unavailable: 18F-FDG-PET/CT is widely available in most Canadian centers
      - Provides functional assessment of both medullary and extramedullary disease

**SMM**

- WBLDCT should be the initial imaging procedure to exclude osteolytic lesions
  - If WBLDCT is unavailable, skeletal survey or whole-body MRI can be used in its place
  - If WBLDCT is unavailable or if results are negative or equivocal, 18F-FDG-PET/CT or whole-body MRI is required to exclude focal lesions as MDEs
    - If whole-body MRI is unavailable, MRI of the spine and pelvis can be used in its place

**Solitary Medullary Plasmacytoma**

- Whole-body MRI should be done to rule out other sites of active MM
  - If whole-body MRI is unavailable, MRI of the spine and pelvis is recommended
  - If MRI is unavailable, 18F-FDG-PET/CT is recommended

**Extramedullary Plasmacytoma**

- 18F-FDG-PET/CT should be done to rule out other sites of active MM
  - If 18F-FDG-PET/CT is unavailable, WBLDCT is recommended

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Abbreviations: FISH = Fluorescence in situ hybridization; MM = multiple myeloma; PC = plasma cell.
\(^{a}\)Cytogenetic analysis of high-risk chromosomal aberrations by FISH testing can be substituted by next-generation sequencing-based genomic profiling. If FISH analysis is not available at your local laboratory, consider sending the sample to the nearest/partner tertiary care center.
\(^{b}\)The above recommendations are the minimum requirements for FISH testing. Testing may also include other chromosomal aberrations [ie, gain(1q) and del(1p)]; therefore, laboratories that include other chromosomal aberrations should continue with enhanced testing.
\(^{c}\)Assessment for other translocations could be of further prognostic value.

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**Clinical Lymphoma, Myeloma & Leukemia**

**July 2020**
If MRI is unavailable, 18F-FDG PET/CT can be used in its place.\(^3\) As per the IMWG criteria, patients presenting with >1 focal lesion with a diameter <5 mm should be considered to have symptomatic disease that requires therapy.\(^6\) In cases of equivocal small lesions, a second MRI should be performed in 3 to 6 months. If progression is noted on the second MRI, the patient should be treated for MM.

Although conventional spin-echo T1- and T2-weighted MRI sequences provide sensitive assessment of bone marrow morphology, the addition of dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted imaging (DWI-MRI) can provide additional functional information on tumor-driven angiogenesis and cellularity, respectively. Including functional imaging not only improves sensitivity, but may be useful for response assessment following therapy.\(^9\) DWI-MRI, unlike DCE-MRI, does not require contrast and is the functional modality included in the Myeloma Response Assessment and Diagnosis System core clinical protocol for whole-body MRI in myeloma.\(^9\)

A systematic review that included 6 studies (published from 2008 to 2016) and 147 patients suggested that whole-body MRI may be more sensitive than 18F-FDG PET/CT (68%-100% vs. 47%-100%, respectively), but less specific (37%-83% vs. 62%-85.7%, respectively); however, studies have not yet assessed its impact on initial management.\(^9\) A major strength of 18F-FDG PET/CT is its ability to distinguish between metabolically active and inactive sites of disease.\(^9\) A key limitation is low sensitivity for detection of small lytic lesions.\(^5\)

Several studies have shown that 18F-FDG PET/CT can have prognostic value. The number of 18F-FDG avid bone lesions, the intensity of uptake based on maximum standardized uptake value (SUV\(_{\text{max}}\)), and the presence of extramedullary disease have been

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### Table 5  Definition of High-risk SMM\(^4\)

<table>
<thead>
<tr>
<th>Clonal BMPCs ≥ 10% and Any One or More of the Following:</th>
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<tbody>
<tr>
<td>- Serum monoclonal protein ≥ 30 g/L</td>
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<tr>
<td>- IgA SMM</td>
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<tr>
<td>- Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes</td>
</tr>
<tr>
<td>- Involved: uninvolved sFLCr ≥ 8 and &lt; 100</td>
</tr>
<tr>
<td>- Reductions in 1 or 2 uninvolved immunoglobulins &gt; 25%, compared with normal values(^6)</td>
</tr>
<tr>
<td>- Progressive increase in serum monoclonal protein level (≥ 25% on 2 successive evaluations within a 6-month period)</td>
</tr>
<tr>
<td>- 50%-60% clonal BMPCs</td>
</tr>
<tr>
<td>- Abnormal PC immunophenotype (≥ 95% clonal BMPCs) and reduction of ≥ 1 uninvolved immunoglobulin isotypes</td>
</tr>
<tr>
<td>- One of the following chromosomal aberrations: t(4;14) or del(17p) or gain(1q)</td>
</tr>
<tr>
<td>- Increased circulating PCs</td>
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<tr>
<td>- MRI with diffuse abnormalities or 1 focal lesion</td>
</tr>
<tr>
<td>- PET/CT with focal lesion with increased uptake and no underlying osteolytic bone destruction</td>
</tr>
</tbody>
</table>

Adapted from Blood 2015; 125:3069-75, with permission from the American Society of Hematology. Abbreviations: BMPCs = bone marrow plasma cells; MRI = magnetic resonance imaging; PC = plasma cell; PET/CT = positron emission tomography/computed tomography; sFLCr = serum free light chain ratio; SMM = smoldering multiple myeloma.

### Table 6  Primary and Secondary Cytogenetic Aberrations in MM, MGUS, and SMM\(^8\)

<table>
<thead>
<tr>
<th>Molecular classification of MM on the basis of primary cytogenetic aberrations</th>
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<tbody>
<tr>
<td>- Trisomies (commonly involving odd-numbered chromosomes)</td>
</tr>
<tr>
<td>- Immunoglobulin heavy chain (IgH) translocations and dysregulated oncogenes in the partner chromosome</td>
</tr>
<tr>
<td>- t(4;14); FGFR3 and MMSET</td>
</tr>
<tr>
<td>- t(6;14); CCND3</td>
</tr>
<tr>
<td>- t(11;14); CCND1</td>
</tr>
<tr>
<td>- t(14;16); MAF</td>
</tr>
<tr>
<td>- t(14;20); MAFF</td>
</tr>
<tr>
<td>- IgH translocations with uncommon chromosome partners</td>
</tr>
<tr>
<td>- Trisomies plus any IgH translocation</td>
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<table>
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<tr>
<th>Common secondary cytogenetic aberrations(^8)</th>
</tr>
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<tbody>
<tr>
<td>- Deletion of (del) 13q or monosomy of chromosome 13 (monosomy 13)</td>
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<tr>
<td>- Del 17p or monosomy 17</td>
</tr>
<tr>
<td>- Del 1p</td>
</tr>
<tr>
<td>- Duplication or amplification of 1q</td>
</tr>
</tbody>
</table>

Adapted from Nat Rev Clin Oncol 2018; 15:409-21, with permission from Springer Nature. Abbreviations: MGUS = Monoclonal gammopathy of undetermined significance; MM = multiple myeloma; SMM = smoldering multiple myeloma.

\(^*\)Each secondary cytogenetic abnormality alone or in combination can occur in any primary molecular MM subtype.
shown to predict survival.\textsuperscript{35,36} Like whole-body MRI, 18F-FDG PET/CT provides functional imaging and is sensitive for bone marrow involvement. The IMWG recommends 18F-FDG PET/CT for newly diagnosed solitary extramedullary plasmacytoma.\textsuperscript{37} The IMWG 2017 consensus guideline\textsuperscript{97} recommends 18F-FDG-PET/CT as an option: (1) for suspected solitary plasmacytoma or SMM; (2) in cases where skeletal survey is negative and MRI is unable to be performed; and (3) to monitor effect of therapy on MM-cell metabolism. British Hematology Guidelines for the use of imaging in the management of patients with MM indicates that 18F-FDG PET/CT is superior to skeletal survey and recommends that it be considered in asymptomatic patients with either 10% to 60% PC on a trephine biopsy or bone marrow aspirate or in patients with an M-protein > 30 g/L.\textsuperscript{55} 18F-FDG PET/CT should be considered for patients with newly diagnosed non-secretory or oligosecretory MM and for evaluation of extramedullary disease.\textsuperscript{55}

### Light Chain Only Non-Secretory MM and Oligosecretory Disease

Historically, non-secretory MM was diagnosed in symptomatic patients with clonal BMPCs \(\geq 10\%\) on tissue or bone marrow biopsy without detectable M-protein on UPEP and SPEP with IFE; however, a portion of these patients can now be identified as having light chain only non-secretory MM. If non-secretory myeloma is suspected, sFLC levels and biopsy are required for diagnosis. Moreover, oligosecretory disease is defined as the absence of measurable disease in serum or urine: serum M-protein < 10 g/L and urine M-protein < 200 mg/24h.

### Applying the Updated IMWG Criteria\textsuperscript{6}

The diagnosis of MM has traditionally required evidence of end-organ damage attributable to the neoplastic clone of PCs: hypercalcemia, renal failure, anemia, and osteolytic bone lesions, commonly referred to as CRAB criteria.\textsuperscript{97} Although the criteria clearly distinguish patients with MM, they do not identify those with true early stage malignant disease previously considered to be within the SMM subgroup. Thus, in 2014, the IMWG updated their diagnostic criteria for MM and SMM (Table 2) with the identification of reliable biomarkers that can accurately differentiate patients with high-risk SMM that are at risk of end-organ damage within a short timeframe.\textsuperscript{6}

It is also important to note that the criteria for renal failure includes creatinine clearance, allowing for better identification of kidney dysfunction in smaller and older patients, particularly elderly women. In addition, the kidney-related criteria have been updated to only include renal failure caused by light chain cast nephropathy as an MM-defining event. Although other forms of renal damage can occur in MM, they are not characteristic of MM and can be seen in other PC neoplasms or lymphoproliferative disorders.

Based on nephrologic evaluation, cast nephropathy can be proven by biopsy or deemed highly suspicious by other reasonable biochemical tests (ie, the presence of high involved FLC levels, typically > 1500 mg/L in the absence of significant albuminuria and other risk factors for renal failure). This highlights the importance of assessing the underlying causes of renal failure in PC neoplasms in order to recognize AL amyloidosis and other disorders.

According to the updated IMWG criteria, patients with a clonal BMPC burden \(\geq 60\%\) are defined as having active MM, regardless of the presence of CRAB features.\textsuperscript{6} Furthermore, an involved:uninvolved sFLC\textsubscript{r} of \(\geq 100\) is a predictor of imminent progression to MM (from SMM), provided the involved sFLC is 100 mg/L or higher. As such, patients should be regarded as having MM requiring therapy. This recommendation is based on several studies that noted that the majority of patients (60% to 80%) with SMM and an involved:uninvolved sFLC\textsubscript{r} of \(\geq 100\) progress to MM or related disorders within 2 years.\textsuperscript{98-100} This recommendation, however, is not applicable to patients with MGUS.
MM-related bone disease has been traditionally identified on the basis of conventional skeletal radiography. The updated IMWG criteria include more sensitive imaging modalities (ie, WBLDCT, MRI, and 18F-FDG-PET/CT) for detection of bone lesions. According to these criteria, CT and MRI are equally sensitive; therefore, either test can be used, depending on availability and access.6,101 However, as pointed out by the IMWG criteria, increased metabolic uptake on PET without a detected lesion on CT is not adequate for the diagnosis of MM, and evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination.

Lastly, the updated IMWG diagnostic criteria require focal lesions on MRI to be ≥5 mm in size. This is based on the observation that the presence of more than one focal lesion ≥5 mm was associated with a substantial increase in risk of progression (hazard ratio, 4.05; P < .001).101 Thus, according to IMWG criteria, in patients with a solitary focal lesion, lesions <5 mm, equivocal findings, or diffuse marrow infiltration, follow-up examination in 3 to 6 months is recommended to enable an early and accurate diagnosis of MM. Although a diffuse marrow infiltration pattern in SMM is associated with increased risk of progression, it is not adequate for MM diagnosis. In cases of doubt, the 2014 IMWG criteria recommend considering bone lesion biopsy.

Conclusion
The recent and rapid advances in the treatment and management of MM and other PC disorders has led the MCRN-CGC to develop a set of recommendations specific to the investigation of these diseases. The availability of more precise and specific diagnostic tests requires careful consideration for the integration of these tests into the routine diagnostic armamentarium.

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The authors have stated that they have no conflict of interest.

References


