

# The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network

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**Supplemental Table 1. Diagnostic criteria**

	<b>International Myeloma Working Group (IMWG) consensus diagnostic criteria<sup>107</sup> combined with the Mayo Clinic Criteria<sup>6</sup></b>	<b>Consensus Panel Recommendations From the Second International Workshop on Waldenstrom's Macroglobulinemia<sup>5</sup></b>
<b>non-IgM MGUS<sup>†</sup></b>	<ul style="list-style-type: none"> <li>•Serum M-protein &lt;30g/L and</li> <li>•Clonal bone marrow plasma cells &lt;10% and</li> <li>•Absence of end-organ damage<sup>1,2</sup></li> </ul>	-
<b>IgM MGUS</b>	<ul style="list-style-type: none"> <li>•Serum IgM M-protein &lt;30 g/L and</li> <li>•Bone marrow lymphoplasmacytic infiltration &lt;10% and</li> <li>•Absence of end-organ damage<sup>2,3</sup></li> </ul>	<ul style="list-style-type: none"> <li>•Presence of IgM M-protein</li> <li>•Absence of bone marrow infiltration by lymphoplasmacytic lymphoma<sup>5</sup></li> <li>•No symptoms attributable to tumor infiltration<sup>2,6</sup></li> <li>•No symptoms attributable to IgM<sup>7</sup></li> </ul>
<b>IgM-related disorder</b>	-	<ul style="list-style-type: none"> <li>•Presence of IgM M-protein</li> <li>•Absence of bone marrow infiltration by lymphoplasmacytic lymphoma<sup>5</sup></li> <li>•No symptoms attributable to tumor infiltration<sup>2,6</sup></li> <li>•Presence of symptoms attributable to IgM<sup>7</sup></li> </ul>
<b>Light-chain MGUS</b>	<ul style="list-style-type: none"> <li>•Abnormal FLC ratio (&lt;0.26 or &gt;1.65) and</li> <li>•Increased level of the involved light-chain and</li> <li>•No immunoglobulin heavy-chain expression on immunofixation and</li> <li>•Clonal bone marrow plasma cells &lt;10% and</li> <li>•Absence of end-organ damage<sup>1,2</sup></li> </ul>	-
<b>Smoldering MM (or asymptomatic MM)</b>	<ul style="list-style-type: none"> <li>•Serum M-protein ≥30g/L and/or</li> <li>•Clonal bone marrow plasma cells ≥10% and</li> <li>•Absence of end-organ damage<sup>1,2</sup></li> </ul>	-
<b>Smoldering WM (or asymptomatic WM)</b>	<ul style="list-style-type: none"> <li>•Serum IgM M-protein ≥30 g/L and/or bone marrow lymphoplasmacytic infiltration ≥10% and</li> <li>•Absence of end-organ damage<sup>2,3</sup></li> </ul>	<ul style="list-style-type: none"> <li>•Presence of IgM M-protein</li> <li>•Presence of bone marrow infiltration by lymphoplasmacytic lymphoma<sup>5</sup></li> <li>•No symptoms attributable to tumor infiltration<sup>2,6</sup></li> <li>•No symptoms attributable to IgM<sup>7</sup></li> </ul>
<b>Idiopathic Bence Jones proteinuria</b>	<ul style="list-style-type: none"> <li>•Urinary M-protein ≥500 mg/24 h and/or clonal bone marrow plasma cells ≥10%</li> <li>•No immunoglobulin heavy-chain expression on immunofixation</li> <li>•Absence of end-organ damage<sup>1,2</sup></li> </ul>	-
<b>Symptomatic MM</b>	<ul style="list-style-type: none"> <li>•Presence of M-protein in serum and/or urine (except in patients with non-secretory multiple myeloma) and</li> <li>•Clonal bone marrow plasma cells ≥10% and</li> <li>•Evidence of end-organ damage<sup>1,2</sup></li> </ul>	-
<b>Symptomatic WM</b>	<ul style="list-style-type: none"> <li>•Presence of IgM M-protein (regardless of the size of the M-protein) and</li> <li>•Bone marrow lymphoplasmacytic infiltration ≥10%<sup>4</sup></li> <li>•Evidence of end-organ damage<sup>2,3</sup></li> </ul>	<ul style="list-style-type: none"> <li>•Presence of IgM M-protein</li> <li>•Presence of bone marrow infiltration by lymphoplasmacytic lymphoma<sup>5</sup></li> <li>•Presence of symptoms attributable to tumor infiltration<sup>2,6</sup></li> <li>•Presence of symptoms attributable to IgM<sup>7</sup></li> </ul>

<sup>1</sup>End-organ damage includes hypercalcemia, renal insufficiency, anemia, and lytic bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder

<sup>2</sup>Especially in elderly persons other causes should be considered such as deficiencies of vitamin B12, folic acid or iron for anemia; primary hyperparathyroidism for hypercalcemia; diabetes and hypertension for renal insufficiency; metastatic carcinoma for lytic bone lesions<sup>106</sup>.

<sup>3</sup>End-organ damage includes anemia, constitutional symptoms, hyperviscosity, lymphadenopathy or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder

<sup>4</sup>Bone marrow lymphoplasmacytic infiltration by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (eg, surface IgM<sup>+</sup>, CD5<sup>-</sup>, CD10<sup>-</sup>, CD19<sup>+</sup>, CD20<sup>+</sup>, CD23<sup>-</sup>) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma

<sup>5</sup>Patients with unequivocal bone marrow infiltration by lymphoplasmacytic lymphoma will be considered to have WM, while patients without evidence of infiltration will be considered MGUS. However, it is acknowledged that in some patients equivocal evidence of bone marrow infiltration is demonstrable. This may be manifest in a number of ways and includes the detection of clonal B cells by flow cytometry or PCR in the absence of morphological evidence of bone marrow infiltration. Alternatively, patients may have equivocal bone marrow infiltrates without confirmatory phenotypic studies. It is considered that these patients should be classified as MGUS until further data become available.

<sup>6</sup>Symptoms attributable to tumor infiltration include constitutional symptoms, cytopenia(s), or organomegaly.

<sup>7</sup>Symptoms attributable to the IgM M-protein include symptomatic cryoglobulinemia, amyloidosis, or auto-immune phenomena such as peripheral neuropathy and cold agglutinin disease.

<sup>†</sup>Almost all patients have IgG or IgA MGUS. IgD isotype is found in only ~0.04-0.1% of MGUS patients. Very rarely, cases of IgE MGUS have been reported.

**Supplemental Table 2. Grade recommendations for grading levels of evidence**

<b>Grade</b>			
<b>1</b>	Evidence strongly suggests that the benefit of the procedure outweighs potential risks or risks of the procedure outweighs potential benefits	<b>A</b>	Consistent evidence from systematic reviews of high-quality randomized studies or from high-quality randomized studies or from high-quality observational studies
<b>2</b>	Evidence suggests the benefit and risk of a procedure is finely balanced or uncertain	<b>B</b>	Evidence from randomized and observational studies with important methodological flaws
		<b>C</b>	Evidence from randomized and observational studies with major methodological flaws or other sources of evidence (e.g. case series)

Supplemental Table 3. Complication rates at the time of diagnosis for patients with MM, WM, or LPL with or without preceding MGUS follow-up<sup>105</sup>

<b>Complication</b>	<b>Preceding follow-up for MGUS (n=1037)</b>	<b>No preceding follow-up for MGUS (n=16392)</b>
Acute kidney injury (%)	10.1	13.7
Cord compression (%)	1.4	2.4
Dialysis (%)	3.4	5.4
Fracture (%)	11.0	17.0
Hypercalcemia (%)	2.4	5.7
Any complication (%)	20.8	32.6