International Myeloma Working Group (IMWG) Updated Criteria for the Diagnosis of Multiple Myeloma[1] and NCCN Recommended Baseline Diagnostic Workup[2]

About the IMWG Updated Criteria for the Diagnosis of Multiple Myeloma and the Importance of Establishing Baseline Disease Characteristics[1,2,6]

The IMWG updated the disease definition of multiple myeloma in 2014 to include validated markers in addition to existing requirements of CRAB features (hypercalcemia, renal failure, anemia, and bone lesions) attributable to the underlying clonal plasma cell disorder.[1] These changes were based on the identification of biomarkers associated with the near inevitable development of CRAB features in patients who would otherwise be regarded in the past as having smoldering multiple myeloma. The consensus was based on the concern that a delay in the application of the label of multiple myeloma and postponement of therapy could be detrimental to this population of patients. In addition to this change, the IMWG clarified and updated the underlying laboratory and radiographic variables that fulfill the criteria for the presence of myeloma-defining CRAB features, and the histological and monoclonal protein requirements for the disease definition. We urge you to read the consensus statement in its entirety as it represents the standard of care worldwide. Finally, the IMWG provided specific metrics that new biomarkers should meet for inclusion in the disease definition. *Managing Myeloma* recommends the implementation of the IMWG criteria in routine practice. We also recommend that you refer to the following article for additional discussions regarding the rationale that contributed to the changes in the definition of multiple myeloma to include patients at ultra-high risk of progression who otherwise would have been defined as having smoldering multiple myeloma under the previous definition: Dispenzieri A, Stewart AK, Chanan-Khan A, et al. Smoldering multiple myeloma requiring treatment: time for a new definition? *Blood*. 2013;122(26):4172-4181.

The first and largest observational, noninterventional, prospective registry of patients newly diagnosed with multiple myeloma in the United States is known as the MM Connect Registry.[6] It collects longitudinal data on patients within clinical practice including patients in clinical trials. A report of an initial analysis of the Connect MM Registry in 2014 stresses the importance of establishing baseline disease characteristics in multiple myeloma patients.[6] Variations were observed in the percentage of reported baseline data. These results suggest that oncology practitioners who provide care for patients with multiple myeloma are not consistently performing all of the recommended work-up evaluation tests required for the diagnosis and prognosis of multiple myeloma. The MM Connect Registry findings provide the most direct evidence to date that support the conclusions of the *Managing Myeloma* Continuing Education Initiative Advisory Group that there is a gap in practice in performing the required baseline tests while a number of their predictions in anticipated practice changes have been realized through the recent updates to the diagnostic criteria and revisions to the international staging system for multiple myeloma to name only a few.[1,7,8] Practitioners are reminded that creating solid records of baseline patient disease characteristics using suggested NCCN diagnostic work-up[2] and IMWG diagnostic criteria[1] provide a foundation for monitoring both disease progression and response to treatment.[6,7] *Managing Myeloma* has provided this tool as a reference resource and reminder of the importance of these tests and criteria. It is the responsibility of practitioners to proactively seek out updates to the diagnostic criteria and recommended diagnostic workup.

In June 2015, the IMWG issued the Revised International Staging System for Multiple Myeloma.[8] Practitioners who provide care for patients with multiple myeloma should immediately adopt the new R-ISS into practice. Managing Myeloma has developed a separate tool to assist you in navigating the new R-ISS which combines three prognostic factors into one algorithm.

www.ManagingMyeloma.com also reminds practitioners who treat and manage multiple myeloma that the best care for their patients is clinical trial. MGUS and smoldering multiple myeloma patients should not be treated outside of clinical trial.

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NCCN Recommended Initial Diagnostic Workup:[2] Establishing Baseline Patient Disease Characteristics

Initial Diagnostic Workup[5]

- History and physical
- CBC, differential and platelet count
- BUN/creatinine, electrolytes
- Lactate dehydrogenase (LDH)
- Calcium/albumin
- Beta-2 microglobulin
- Serum free light chain (FLC) assay
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Cytogenetics
- Fluorescence in situ hybridization (FISH) [del 13; del 17p13; t(4;14); t(11;14); t(14;16); 1q21 amplification]

Useful Under Some Circumstances[5]

- MRI
- CT scan (avoid contrast)
- PET/CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell labeling index
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

Managing Myeloma

International Myeloma Working Group (IMWG) Updated Criteria for the Diagnosis of Multiple Myeloma[1]

MGUS[3,4,5]

Refer to Clinical Trial or Observe

IgG/A/M MGUS [All criteria must be met]
- Serum monoclonal protein (IgG or IgA or IgM) <3 g/dL AND
- Clonal BM plasma cells <10% AND
- No myeloma defining events (see below)

OR

Light chain MGUS [All criteria must be met]:
- Abnormal sFLC ratio (<0.26 or >1.65) AND
- Increased level of the appropriate involved light chain (increased κ sFLC in patients with ratio >1.65 and increased λ sFLC patients with ratio <0.26) AND
- No immunoglobulin heavy chain on immunofixation AND
- Clonal BM plasma cells <10% AND
- Urinary monoclonal protein <500 mg/24h AND
- No myeloma defining events (see below)

Smoldering Myeloma[1]

Refer to Clinical Trial or Observe

- Serum monoclonal protein (IgG or IgA) ≥3 g/dL
  or
- Urinary monoclonal protein ≥500 mg/24 h
  and/or
- Clonal BM plasma cells 10% - 60%

AND

- No myeloma defining events or amyloidosis (no CRAB and no SLiM as detailed below)

Multiple Myeloma[1]

Refer to Clinical Trial or Treat

- Clonal BM plasma cells of ≥10%
  or
- Biopsy-proven bony or extramedullary plasmacytoma

AND

- 1 or more myeloma defining events as detailed below:

  ≥1 **CRAB** feature(s)
  OR
  ≥1 **SLiM** feature(s)

Myeloma defining events are evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, especially:

C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT). *If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.*

OR, in the absence of **CRAB**, any one or more of the following biomarkers of malignancy, referred to here as the SLiM criteria **SLiM** criteria:

SLiM: S=≥Sixty-percent (≥60%) clonal BM plasma cells; Li=serum free Light chain ratio involved:uninvolved ≥100; M=>1 focal lesion (≥5 mm each) detected by MRI studies

BM=bone marrow; PET-CT (^{18}F-fluorodeoxyglucose PET with CT); FLC=free light chain; MGUS=monoclonal gammopathy of unknown significance; SMM=smoldering multiple myeloma.
Note: Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. BM plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

References

[1]Rajkumar SV, et al. *Lancet Oncol*. 2014;15(12):e538-548. [2]National Comprehensive Cancer Network [NCCN]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Multiple Myeloma. Version 3.2016. Release date 01/15/2016. Accessed at http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf on April 12, 2016. [3]Kyle RA, et al. *Hematol Oncol Clin North Am*. 2014;28(5):775-790. [4]Rajkumar SV, et al. *Mayo Clin Proc*. 2010;85(10):945-948. [5]Kyle RA, et al. *Hematol Oncol Clin North Am*. 1999;13(6):1181-1202. [6]Rifkin RM, et al. *Clin Lymphoma Myeloma Leuk*. 2015;15(6):368-376. [7]Raje N, et al; Managing Myeloma Continuing Education Initiative Advisory Group. *Clin Lymphoma Myeloma Leuk*. 2014;14(5):356-369. [8]Palumbo A, et al. *J Clin Oncol*. 2015 Aug 3. pii: JCO.2015.61.2267. [Epub ahead of print] PubMed PMID:26240224.