Lab Tests for Multiple Myeloma

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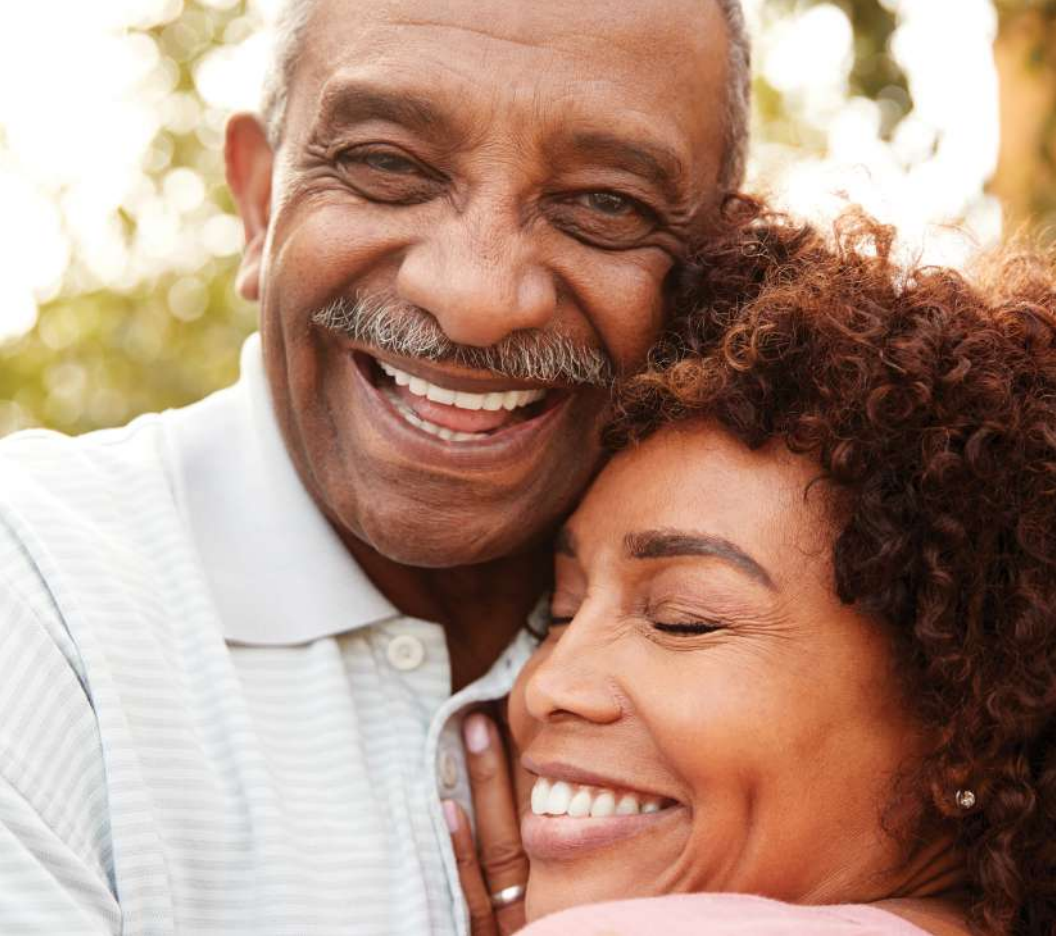

This guide is designed for patient care teams as a quick reference tool of common laboratory tests used for diagnosing and monitoring multiple myeloma.

You'll have access to lab values for blood tests, urine tests, and imaging studies to support your efforts in evaluating and caring for patients.

This guide is not intended to provide a comprehensive list of lab tests or lab values, and it is not intended to recommend which tests should be performed. Treating physicians are responsible for determining lab tests, as patient cases will vary by age, gender, and medical history.

Industry guidance may change over time. Healthcare professionals should refer to the most recent industry guidance to determine the diagnostic needs for each patient case.

Multiple Myeloma Disease Spectrum

Multiple myeloma (MM) is treatable but incurable.[1]

MM is a plasma cell malignancy, where plasma cells accumulate abnormally within the bone marrow.[2]

Precursor Conditions to Active MM

Monoclonal Gammopathy of Undetermined Significance (MGUS)
This benign condition shows low levels of monoclonal protein in the blood and/or urine, a low level of abnormal plasma cells in the bone marrow, and an absence of myeloma-defining events.[3,4]

Smoldering Multiple Myeloma (SMM)
SMM is an asymptomatic type of MM with a higher risk of progression than MGUS. Patients with SMM need to be monitored for signs of progression to MM.[1]

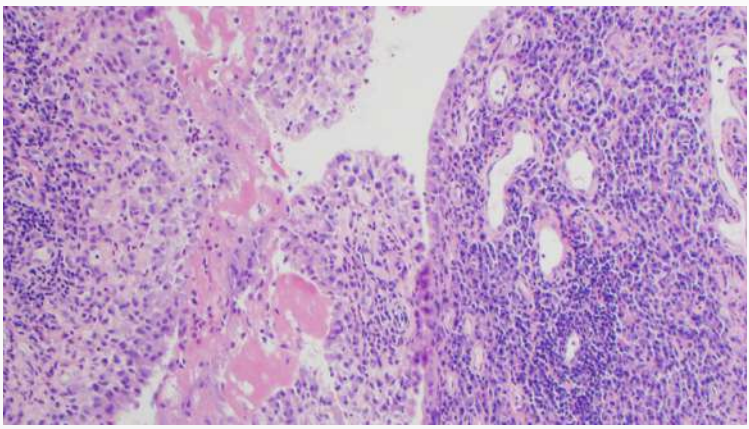

Image above represents a micrograph of myeloma neoplasm from bone marrow biopsy.

MM Diagnostic & Monitoring Considerations

Criteria for Diagnosing Multiple Myeloma (MM)

MM used to be diagnosed when patients presented with signs and symptoms of end-organ damage, but advances in biomarker identification have made it possible to identify the disease earlier in its course.[1]

Identifying where a patient is on the spectrum of MM and monitoring progression are critical aspects of patient care. Research has shown that patients with MM who had a previous diagnosis of MGUS and close monitoring had significantly better overall survival than patients with MM who had no previous MGUS diagnosis.[5]

The current diagnostic criteria for MM include CRAB features that were previously used to diagnose MM. In addition, the IMWG has updated the criteria to also include 3 MM-defining biomarkers known as SLiM features.[3,6] See page 6 for more details and for additional diagnostic criteria.

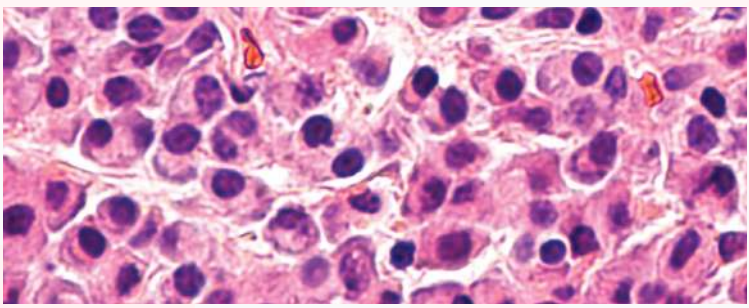

Image above represents a micrograph of myeloma neoplasm from bone marrow biopsy.

CRAB = calcium elevation, renal insufficiency, anemia, bone lesions; IMWG = International Myeloma Working Group; MGUS = monoclonal gammopathy of undetermined significance; SLiM = Sixty, Light chain ratio, MRI.

Diagnostic Criteria for the MM Disease Spectrum[3,6]

NAME	CLINICAL DEFINITION
Monoclonal Gammopathy of Undetermined Significance (MGUS)	• Monoclonal protein (M-protein) (non-IgM type) <3.0 g/dL • Bone marrow monoclonal plasma cells <10%* • No CRAB features or other indicators of active myeloma
Smoldering Multiple Myeloma (SMM)	• Serum M-protein (IgG or IgA) ≥3.0 g/dL or urinary M-protein ≥500 mg/24 hr, and/or clonal bone marrow plasma cells 10%-59% • No CRAB features or other indicators of active myeloma or amyloidosis
Multiple Myeloma	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma AND one or more SLiM-CRAB features

Myeloma-defining Events (MDEs)[3,6] (also known as SLiM-CRAB)

SLiM Features[3,6]

(SLiM = Sixty, Light chain ratio, MRI)

S – Clonal bone marrow plasma cells ≥60%†

Li – Involved:uninvolved serum FLC ratio‡ ≥100 and involved FLC concentration 10 mg/dL or higher

M – > 1 focal lesion (≥5 mm) on MRI

CRAB Features[3,6]

C – calcium elevation (>1 mg/dL higher than upper limit of normal or >11 mg/dL)

R – renal insufficiency (serum creatinine >2 mg/dL or creatinine clearance <40 mL/min§)

A – anemia (hemoglobin <10 g/dL or >2 g/dL decrease from lower limit of normal)

B – bone lesions (one or more osteolytic lesions on skeletal radiography, CT, or PET/CT‖)

* Bone marrow can be deferred in patients with low-risk MGUS (IgG type, monoclonal protein <1.5 g/dL, normal free light-chain ratio) in whom there are no clinical features concerning for myeloma.

† Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow 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.

‡ The involved:uninvolved serum FLC ratio reflects the increase of the monoclonal (involved) free light chain protein and the decrease of the polyclonal (uninvolved) free light chain protein.[7]

§ Measured or estimated by validated equations.

‖ 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.

CT = computed tomography; dL = deciliter; FLC = free light chain; g = gram; hr = hour; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; κ = kappa; λ = lambda; mg = milligram; min = minute; mL = milliliter; mm = millimeter; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron emission tomography; SLiM = Sixty, Light chain ratio, MRI.

Standard Risk Factors for MM and Revised International Staging System (R-ISS)[8]

PROGNOSTIC FACTOR	CRITERIA
ISS Stage	
I	• Serum β2-microglobulin <3.5 mg/L • Serum albumin ≥3.5 g/dL
II	Not ISS stage I or III
III	Serum β2-microglobulin ≥5.5 mg/L
CA by iFISH	
High Risk	Presence of del(17p) and/or t(4;14) and/or t(14;16)
Standard Risk	No high-risk CA
LDH	
Normal	Serum LDH <the upper limit of normal
High	Serum LDH >the upper limit of normal

New Model for Risk Stratification for MM

R-ISS Stage	
I	• ISS stage I • Standard risk CA by iFISH • Normal LDH
II	Not R-ISS stage I or III
III	• ISS stage III • Either high-risk CA by iFISH or LDH >the upper limit of normal

Disease Staging and Risk Stratification Systems for Multiple Myeloma[3]

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)	R2-ISS*
I	Serum β2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH and Serum LDH ≤ the upper limit of normal	Low-risk: 0 points† • Not ISS stage II or III • Serum LDH ≤ the upper limit of normal • del(17p), t(4;14), 1q+: Not detected
II	Not ISS stage I or III	Not R-ISS stage I or III	Low-intermediate risk: 0.5–1 points† • ISS stage II or • Serum LDH > the upper limit of normal or • del(17p) or t(4;14) or 1q+: Detected
III	Serum β2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH or Serum LDH > the upper limit of normal	Intermediate-high risk: 1.5–2.5 points† • Any combination of high-risk features that equals a score of 1.5–2.5
IV			High-risk: 3–5 points† • Any combination of high-risk features that equals a score of 3–5

* R2-ISS is only validated for newly diagnosed multiple myeloma.
† For R2-ISS classification a numerical value is assigned to each risk factor based on their influence on OS: ISS-III is 1.5 points, ISS-II is 1 point, del(17p) is 1 point, t(4;14) is 1 point, 1q+ is 0.5 points, and serum LDH > the upper limit of normal is 1 point.

β2 = beta-2; CA = chromosomal abnormalities; del = deletion; dL = deciliter; FISH = fluorescence in situ hybridization; g = gram; iFISH = interphase fluorescent in situ hybridization; ISS = International Staging System; L = liter; LDH = lactate dehydrogenase; mg = milligram; MM = multiple myeloma; R-ISS = revised International Staging System; t = translocation.


0/0.65
60/0.17

Lab Test Overview

The following laboratory tests are recommended by the National Comprehensive Cancer Network® (NCCN®) for an initial diagnostic workup to help differentiate patients with symptomatic vs asymptomatic MM.[3]

A medical history and physical examination should also be included.[3]

See pages 11-17 for more information about each test.

Lab Test Overview for Diagnosing & Monitoring MM[3]

BLOOD TESTS	PAGE
• Complete blood count (CBC) with differential and platelets	11
• Comprehensive metabolic panel (CMP)	12
• Serum quantitative immunoglobulins	13
• Serum free light chains (sFLC)	13
• Serum protein electrophoresis (SPEP)	13
• Serum immunofixation electrophoresis (SIFE)	13
• Serum β2-microglobulin*	13
• Serum lactate dehydrogenase (LDH)*	13
• Serum uric acid	13
• Peripheral blood smear	14
• Unilateral bone marrow aspirate and biopsy with IHC and/or multi-parameter flow cytometry	14
• FISH panel on bone marrow†	14

URINE TESTS	PAGE
• Creatinine clearance	15
• 24-hour urine for total protein	15
• Urine protein electrophoresis (UPEP)	15
• Urine immunofixation electrophoresis (UIFE)	15

IMAGING STUDIES	PAGE
• Whole-body low-dose CT scan‡	17
• FDG PET/CT scan§	17
• Whole-body MRI without contrast‖	17
• Skeletal survey‡	17

* β2M, LDH, and FISH panel are used for R-ISS staging.
† CD138 positive selected sample is highly recommended for optimized yield.
‡ Skeletal survey is not needed if whole-body low-dose CT and FDG PET/CT has been performed, as skeletal survey is significantly less sensitive.[3]
§ FDG PET/CT can be used instead of whole-body CT if the CT part of PET/CT fulfills the criteria of a diagnostic whole-body CT.[9]
‖ If whole-body low-dose CT or FDG PET/CT is negative, consider whole-body MRI without contrast to discern SMM from MM.[3]

β2 = beta-2; β2M = beta-2 microglobulin; CD138 = transmembrane heparin sulfate proteoglycan syndecan-1; CT = computed tomography; FDG = F-fluorodeoxyglucose; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron emission tomography; SMM = smoldering multiple myeloma.

Blood Tests

Complete Blood Count With Differential and Platelets[3,10,12]

TEST	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Red blood cell (RBC) count (erythrocytes)	4.2–5.9 million/µL[11]	Abnormal results may be signs of a type of anemia (a CRAB feature – see page 6), liver disease, or kidney disease.[6,10]
Hemoglobin (Hgb)	Female: 12–16 g/dL[11] Male: 14–18 g/dL[11]	
Hematocrit (Hct)	Female: 37%–47%[11] Male: 42%–50%[11]	
White blood cell (WBC) count (leukocytes)	4000–11,000/µL[11]	<Normal range = leukopenia >Normal range = leukocytosis[10]
Absolute neutrophil count (ANC)[10,12]	2000–8250/µL[11]	Lower-than-normal white blood count may indicate neutropenia and risk of infection. Therapeutic use of myeloid growth factors, such as G-CSFs, may be considered.[12]
Platelet (Plt) count	150,000–450,000/µL[11]	Abnormal count may indicate problems in the bone marrow.[10] A platelet count of <150,000 µL (thrombocytopenia[13]) is an adverse event for some MM therapies.[3]

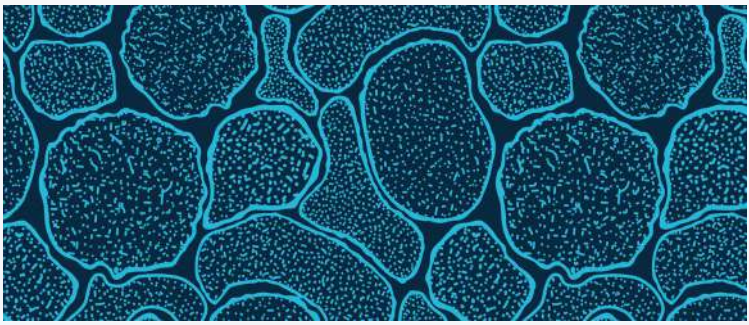

Image above represents healthy human red blood cells.

Reference ranges vary across laboratories based on lab testing methods and may not be applicable to the reference ranges at your center.[14] Interpretation of a particular patient's test result in relation to the reference range depends on the clinical context.[15]

CRAB = calcium elevation, renal insufficiency, anemia, bone lesions; dL = deciliter; g = gram; G-CSF = granulocyte colony stimulating factor; MM = multiple myeloma; µL = microliter.

Comprehensive Metabolic Panel (CMP)[3,16]

TEST	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Blood urea nitrogen (BUN), serum or plasma	8–20 mg/dL[11]	Levels >20 mg/dL indicate decreased kidney function.[11]
Serum creatinine (SCr)	Female: 0.50–1.10 mg/dL[11] Male: 0.70–1.30 mg/dL[11]	Levels >2 mg/dL indicate renal insufficiency.[6]
Serum electrolytes	Sodium: 136–145 mEq/L[11] Potassium: 3.5–5.0 mEq/L[11] Chloride: 98–106 mEq/L[11] Bicarbonate: 23–28 mEq/L[11]	Used to assess kidney function. Electrolyte imbalances may cause kidney disease.[17]
Liver function tests[16]	Identifying levels of protein and enzymes in the blood help in the diagnosing and monitoring of liver disease or damage, which are potential indicators of MM.[16]	
Serum alanine transaminase (ALT, SGPT[18])	10–40 U/L[11]	Higher-than-normal levels may indicate liver damage.[16]
Serum aspartate transaminase (AST, SGOT[19])	10–40 U/L[11]	Higher-than-normal levels may indicate liver damage, liver disease, or muscle damage to the liver.[16]
Serum alkaline phosphatase (ALP)	30–120 U/L[11]	Higher-than-normal levels may indicate liver damage or disease.[16]
Serum albumin	3.5–5.5 g/dL[11]	Lower-than-normal levels may indicate liver damage or disease.[16]
Total serum protein	5.5–9.0 g/dL[11]	Lower-than-normal levels may indicate liver damage or disease.[16]
Total serum bilirubin	0.3–1.0 mg/dL[11]	Higher-than-normal levels may indicate liver damage or disease or certain types of anemia.[16]
Serum calcium	8.6–10.2 mg/dL[11]	Hypercalcemia (calcium elevation >1 mg/dL higher than ULN or >11 mg/dL) suggests evidence of end organ damage that may be attributed to underlying MM.[6]
Plasma glucose (fasting)	70–99 mg/dL[11]	Elevated levels could indicate pre-diabetes or diabetes.[20] For MM patients with diabetes, serum glucose levels should be monitored to reduce the risk of infection and decrease the risk and severity of diabetic microvascular complications. The impact of MM treatments on glucose levels should be considered.[21]

Reference ranges vary across laboratories based on lab testing methods and may not be applicable to the reference ranges at your center.[14] Interpretation of a particular patient's test result in relation to the reference range depends on the clinical context.[15]

dL = deciliter; g = gram; L = liter; mEq = milliequivalent; mg = milligram; MM = multiple myeloma; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; U = unit; ULN = upper limit of normal.

Blood Tests[3]

TEST	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Serum quantitative immunoglobulins (Igs)	IgA: 90–325 mg/dL[11] IgG: 800–1500 mg/dL[11] IgM: 45–150 mg/dL[11]	Monoclonal increase in one class with or without decrease in the other 2 classes may indicate MM.[22]
Serum free light chains (sFLC)	FLCκ: 3.3-19.4 mg/L[11] FLCλ: 5.7- 26.3 mg/L[11] κ/λ ratio: 0.26-1.65[11]	An involved:uninvolved serum FLC ratio* ≥100 and involved FLC concentration 10 mg/dL or higher is an MDE.[3,6]
Serum protein electrophoresis (SPEP)	Electrophoresis test that separates serum proteins into 5 bands: albumin, α1, α2, β, and γ globulins[23]	SPEP is used to quantitatively detect M-protein found in the gamma region and to differentiate MGUS and MM.[23]
Serum immunofixation electrophoresis (SIFE)	SIFE qualitatively identifies M-proteins and is a factor in classifying response to MM treatment.[24]	SIFE is the "gold standard" method to confirm the presence of M-protein and to distinguish its heavy and light chain type.[24]
Serum β2-microglobulin	0.54–2.75 mg/L[11]	Serum β2-microglobulin is a factor in MM staging; it is necessary for prognostic purposes and reflects tumor burden.[24]
Serum LDH	80–225 U/L[11]	LDH is a biomarker used in R-ISS staging.[8] Levels above the ULN denote an increased disease aggressiveness and suggests high proliferation rate and/or the presence of tumor mass.[8] At relapse, elevated LDH is predictive of poor prognosis in MM.[24]
Serum uric acid	3.0–7.0 mg/dL[11]	MM can cause an increased production of uric acid, while chronic kidney disease may cause decreased elimination of uric acid.[25]

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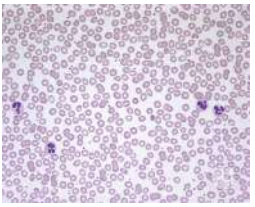
Reference ranges vary across laboratories based on lab testing methods and may not be applicable to the reference ranges at your center.[14] Interpretation of a particular patient's test result in relation to the reference range depends on the clinical context.[15]

* The involved:uninvolved serum FLC ratio reflects the increase of the monoclonal (involved) free light chain protein and the decrease of the polyclonal (uninvolved) free light chain protein.[7]

α1 = alpha-1; α2 = alpha-2; β = beta; β2 = beta-2; dL = deciliter; FLC = free light chain; Ig = immunoglobulin; κ = kappa; λ = lambda; L = liter; LDH = serum lactate dehydrogenase; MDE = myeloma-defining event; mg = milligram; MM = multiple myeloma; M-protein = monoclonal protein; R-ISS = revised International Staging System; U = unit; ULN = upper limit of normal; γ = gamma.

Blood Tests[3] (cont.)

TEST	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Peripheral blood smear	Normal peripheral blood smear with circulating granulocytes.  Reproduced with permission from ASH Image Bank. 2022. © The American Society of Hematology.	A manual, visual analysis is performed to determine any abnormalities in appearance of red blood cells, white blood cells, and platelets.[26] Abnormal red blood cells may indicate liver disease, renal failure, or a form of anemia.[27] Abnormal white blood cells may indicate infection or bone marrow disorders, such as MM.[26]
Unilateral bone marrow aspirate and biopsy with IHC and/or multi-parameter flow cytometry	Evaluation of bone marrow, where MM originates.[28]	≥10% of clonal bone marrow plasma cells is a major criterion for MM diagnosis.[3]
FISH panel on bone marrow*	Chromosomal analysis on the plasma cells obtained from bone marrow aspiration: del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/amplification, 1p deletion.[3]	Essential for R-ISS staging.[3]

Reference ranges vary across laboratories based on lab testing methods and may not be applicable to the reference ranges at your center.[14] Interpretation of a particular patient's test result in relation to the reference range depends on the clinical context.[15]

* CD138 positive selected sample is highly recommended for optimized yield.

del = deletion; dL = deciliter; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; mg = milligram; MM = multiple myeloma; R-ISS = revised International Staging System; t = translocation.

Urine Tests

TEST[3]	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Creatinine clearance (calculated or measured directly)	90-140 mL/min/1.73 m^2 [11]	Clearance of <40 mL/min indicates renal insufficiency, which is a myeloma-defining event (see page 6).[6]
24-hour urine for total protein	<100 mg/24 hr[11]	For suspected or confirmed MM, calculates the amount of proteinuria.[24]
Urine protein electrophoresis (UPEP)	M-protein may appear as a homogeneous peak in the densitometer tracing. The size of the peak and amount of total protein from the 24-hr urine specimen determine the concentration of M-protein.[24]	Looks for M-protein,[24] a marker for MGUS, SMM, and MM.[6]
Urine immunofixation electrophoresis (UIFE)	One or more immunoglobulins may appear as abnormal bands or peaks.[29]	Identifies type of M-protein.[29] UIFE should be performed even if there is no peak in the UPEP test and no measurable protein.[24]

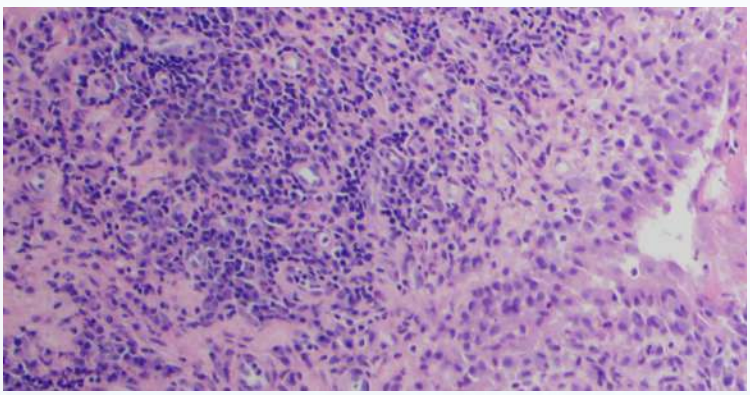


Image above represents a urine sample.

Reference ranges vary across laboratories based on lab testing methods and may not be applicable to the reference ranges at your center.[14] Interpretation of a particular patient's test result in relation to the reference range depends on the clinical context.[15]

hr = hour; m^2 = meter squared; mg = milligram; MGUS = monoclonal gammopathy of undetermined significance; min = minute; mL = milliliter; MM = multiple myeloma; M-protein = monoclonal protein; SMM = smoldering multiple myeloma.

Imaging Studies

TEST[3]	REFERENCE RANGE OR DESCRIPTION	RELEVANCE IN MM
Whole-body low-dose CT scan*	Series of X-rays using a low dose of radiation to detect bone lesions.[30]	First-choice imaging technique to identify and assess the extent of osteolytic lesions[9] (a CRAB feature[3] – see page 6) and paramedullary or extramedullary plasmacytomas.[6]
FDG PET/CT scan†	Sequential studies detect bone lesions and tumor activity.[30] FDG PET detects areas where myeloma is growing outside and inside bone marrow. A tracer injection (FDG) identifies actively growing cancer cells, which are followed up with CT scan.[30]	Recommended for newly diagnosed solitary extramedullary plasmacytoma.[9] The preferred imaging method to create a baseline for response assessment.[9] Highly accurate for diagnosis, therapy assessment, and prognosis of MM.[30]
Whole-body MRI without contrast‡	Two- or three-dimensional imaging detects marrow infiltration by myeloma, such as focal lesions and plasmacytomas.[30]	Recommended for patients with newly diagnosed solitary bone plasmacytoma.[9] Helps to exclude focal lesions as myeloma-defining events.[9] Provides prognostic information based on the presence and number of focal lesions and diffuse infiltrations of the bone marrow.[9]
Skeletal survey*	A series of X-rays to identify bone damage, such as osteopenia, lytic lesions, or fractures.[30] The least sensitive method to detect bone damage caused by MM.[30]	A skeletal survey including long bones is acceptable when advanced imaging is not available (eg, in low resource settings).[3]

This guide is not intended to provide a comprehensive list of lab tests or lab values, and it is not intended to recommend which tests should be performed.

* Skeletal survey is not needed if whole-body low-dose CT and FDG PET/CT have been performed, as skeletal survey is significantly less sensitive.[3]

† FDG PET/CT can be used instead of whole-body CT if the CT part of PET/CT fulfills the criteria of a diagnostic whole-body CT.[9]

‡ If whole-body low-dose CT or FDG PET/CT is negative, consider whole-body MRI without contrast to discern SMM from MM.[3]

CRAB = calcium elevation, renal insufficiency, anemia, bone lesions; CT = computed tomography; FDG = F-fluorodeoxyglucose; MM = multiple myeloma; MRI = magnetic resonance imaging; PET = positron emission tomography; SMM = smoldering multiple myeloma.

Response Criteria for Multiple Myeloma[3]

Revised based on the new criteria by International Myeloma Working Group (IMWG)

Response Category*	Response Criteria
IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF] or next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG-PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue.‖
Standard IMWG response criteria¶	
Stringent complete response	Complete response as defined below plus normal FLC ratio# and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).**
Complete response††	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)‡‡ of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD‡‡ of soft tissue plasmacytomas is also required.
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.

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Standard IMWG response criteria[1] (cont.)	
Progressive disease[§§‖‖]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL) Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL Urine M-protein (absolute increase must be ≥200 mg/24 h) In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%) Appearance of a new lesion(s), ≥50% increase from nadir in SPD[‡‡] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[‡‡] of the measurable lesion Hypercalcemia (>11 mg/dL) Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non–myeloma-related conditions Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis[††] Development of ≥5% plasma cells in the bone marrow Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above)
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma) Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ≥5% clonal plasma cells in the bone marrow Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

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* All response categories require 2 consecutive assessments made any time before starting any new therapy; for MRD there is no need for 2 consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/autologous stem cell transplants (ASCT), consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG-PET if imaging MRD-negative status is reported.

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† Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡ Bone marrow MFC should follow NGF guidelines. The reference NGF method is an 8-color 2-tube approach, which has been extensively validated. The 2-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The 8-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete 8-color method is most efficient using a lyophilised mixture of antibodies, which reduces errors, time, and costs. Five million cells should be assessed. The Flow Cytometry Method (FCM) method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Español de MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood* 2012;119: 687-691.

§ DNA sequencing assay on bone marrow aspirate should use a validated assay.

‖ Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma Criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least 2 consecutive slices. Alternatively, an SUVmax = 2.5 within osteolytic CT areas >1 cm in size, or SUVmax = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. *Clin Cancer Res* 2015;21:4384-4390.

¶ Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. Durie BG, Harousseau JL, Miguel JS, et al, for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. *Leukemia* 2006; 20:1467-1473.

All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated serum FLC assay.

** Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ /L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

†† Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

‡‡ Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

§§ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

‖‖ In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

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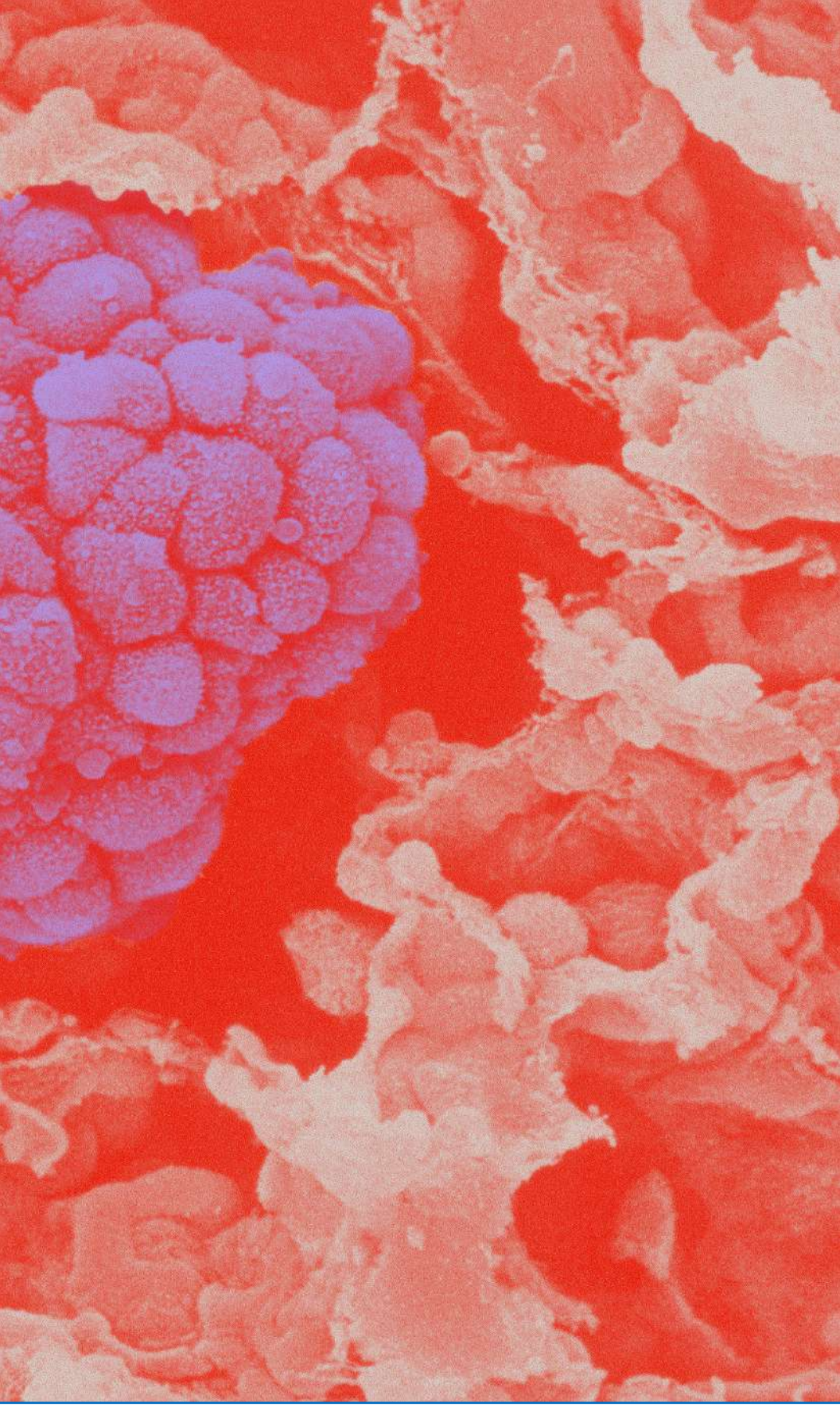

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