

Smoldering Myeloma

The asymptomatic clonal plasma cell state between MGUS and active myeloma

Classification • pathology • risk stratification • clinical decisions

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Learning objectives

- Differentiate MGUS, smoldering myeloma, and active myeloma using modern IMWG criteria.
- Interpret marrow clonality, monoclonal protein studies, and whole-body imaging.
- Distinguish diagnostic myeloma-defining events from prognostic risk factors.
- Apply risk stratification to monitoring and high-risk treatment decisions.

A continuum of clonal plasma cell disorders

MGUS
Small clone



Smoldering myeloma
More burden, no defining
event



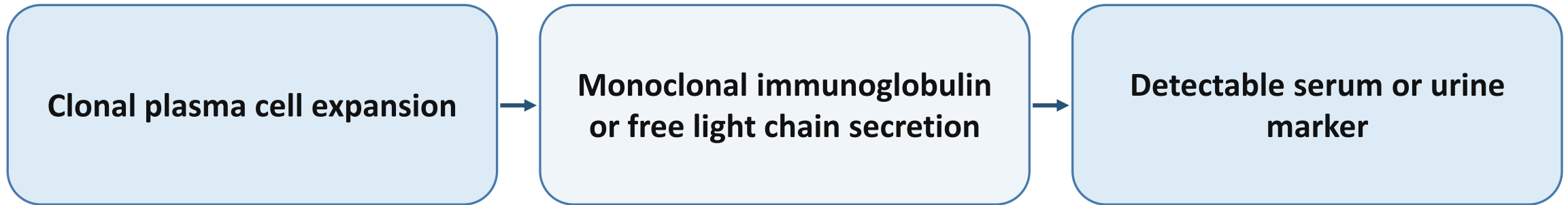
Active multiple myeloma
Myeloma-defining event

These are clinical categories, not guaranteed sequential stages.

The defining paradox of smoldering myeloma

- Clonal plasma cells are already present and may be disseminated.
- Disease burden exceeds the usual MGUS range.
- Patients lack attributable myeloma-defining organ injury or defining biomarkers.
- Risk of progression varies substantially across individuals.

How a plasma cell clone becomes detectable



Protein burden and marrow burden are related but not interchangeable measurements.

M-protein is a measurable marker, not a diagnosis

- An M component reflects monoclonal immunoglobulin synthesized by a clone.
- Its concentration is quantified by serum protein electrophoresis when measurable.
- A high M-protein level does not prove CRAB injury or active myeloma.
- Interpret with marrow findings, free light chains and imaging.

Electrophoresis versus immunofixation

Protein electrophoresis

Detects and quantifies a discrete M component.

Serial peak size tracks secretory tumor burden.

Very small components may be difficult to measure.

Immunofixation

Identifies immunoglobulin isotype and light chain.

Can detect a band not clearly quantified by electrophoresis.

Does not alone classify MGUS versus SMM.

Serum free light chains add a second axis

- Clonal plasma cells may produce excess κ or λ chains.
- Involved/uninvolved FLC ratio estimates relative chain excess.
- Involved FLC concentration is important for the ≥ 100 ratio myeloma-defining event.
- Interpret assay values with renal function and laboratory context.

Why urinary monoclonal light chains occur

Free light chains are small proteins



Glomerular filtration



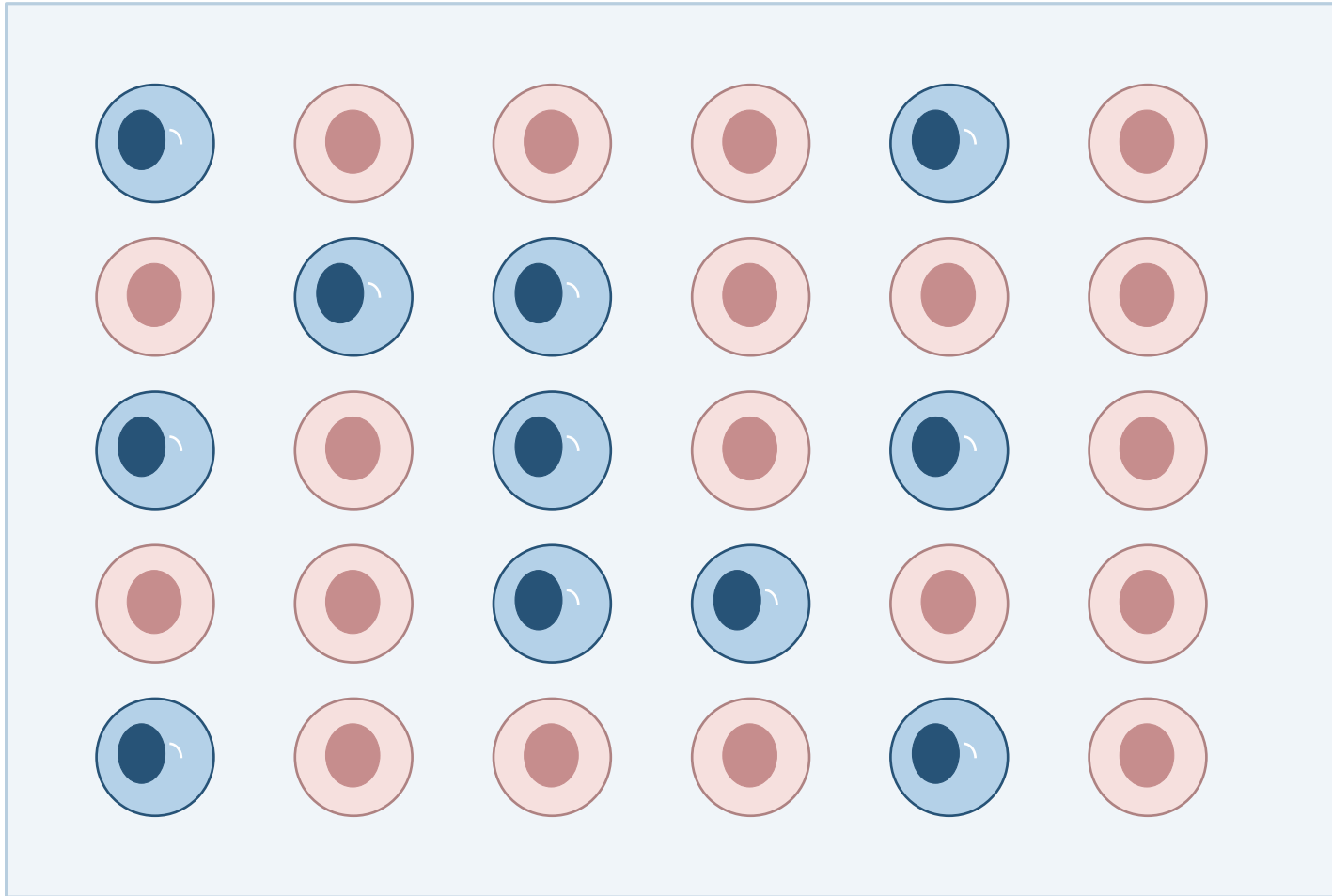
Urinary light chain detection

Filtered monoclonal free light chains are traditionally called Bence Jones proteins.

Marrow burden: Percentage of clonal plasma cells

- Aspirate and trephine biopsy evaluate marrow infiltration.
- The diagnostic percentage concerns clonal plasma cells, not all lymphoid cells.
- Uneven distribution may create discordance between samples.
- $\geq 60\%$ clonal plasma cells is itself an active-myeloma defining biomarker.

Conceptual marrow infiltration in a plasma cell disorder



Clonal plasma cells: Eccentric nuclei and perinuclear pale zone

**Morphology supports lineage;
Clone proof requires light-chain restriction**

Schematic illustration — not histology

The original Robbins description

- Smoldering myeloma occupies the middle ground between MGUS and active myeloma.
- 10%–30% plasma cells and serum M-protein >3 g/dL in asymptomatic patients.
- The text estimates about 75% progress to myeloma over 15 years.
- This textbook summary should not be substituted for current IMWG diagnostic rules.

Modern IMWG definition: Two requirements

Disease-burden condition	Required absence
IgG/IgA serum M-protein ≥ 3 g/dL; And/or	No attributable myeloma-defining event
Urinary monoclonal protein ≥ 500 mg/24 h; And/or	No AL amyloidosis
Clonal marrow plasma cells 10% to $<60\%$	Assess all CRAB and SLiM criteria

The connective logic is OR, then AND

Burden criterion

Any qualifying serum, urine, or marrow threshold can establish the burden condition.

AND

All myeloma-defining events must be absent.

AND

AL amyloidosis must be absent.

A serum M-protein below 3 g/dL does not exclude SMM if marrow burden qualifies.

Asymptomatic does not mean uninvestigated

- SMM is clinically silent with respect to attributable myeloma-defining events.
- A patient may feel well yet have an MRI or FLC biomarker defining active myeloma.
- Assess anemia, kidney dysfunction, hypercalcemia, and bone lesions even without symptoms.
- Evidence of concurrent illness must not automatically be attributed to the clone.

Myeloma-defining events: CRAB and SLiM

CRAB

End-organ injury attributable to the plasma cell disorder.

SLiM

Three high-risk biomarkers that establish active myeloma.

Clinical decision

Any qualifying MDE shifts classification from SMM to active myeloma.

CRAB: Attributable end-organ damage

Domain	IMWG threshold or finding
C — Hypercalcemia	Ca >11 mg/dL or >1 mg/dL above upper normal limit
R — Renal dysfunction	CrCl <40 mL/min or creatinine >2 mg/dL
A — Anemia	Hb <10 g/dL or >2 g/dL below lower normal limit
B — Bone lesions	≥1 osteolytic lesion on radiograph, CT or PET/CT

Hypercalcemia requires attribution

- Myeloma-associated osteolysis may elevate serum calcium.
- IMWG defines the criterion using a measured calcium threshold.
- Hyperparathyroidism, supplements, dehydration, and other cancers are alternatives.
- A borderline elevation without attribution is not sufficient by itself.

Renal impairment requires attribution

- Filtered monoclonal light chains may injure renal tubules.
- IMWG criterion: Creatinine >2 mg/dL or clearance <40 mL/min.
- Diabetes, vascular disease, obstruction, and dehydration may coexist.
- Avoid labeling unrelated chronic kidney disease as a myeloma-defining event.

Anemia is a clinical feature, not merely a number

- Marrow replacement and chronic inflammation can impair erythropoiesis.
- IMWG criterion: Hb <10 g/dL or >2 g/dL below the lower normal limit.
- Blood loss, nutritional deficiency, and renal disease require evaluation.
- Only anemia attributable to the plasma cell disorder is a defining event.

Osteolytic lesions change disease classification

- Myeloma cells perturb bone-remodeling in favor of osteoclast activity.
- A qualifying osteolytic lesion constitutes the “B” in CRAB.
- CT evidence of osteolysis can meet criteria even if plain films are negative.
- Generalized osteopenia alone is not a qualifying lytic lesion.

The three SLiM biomarkers

S — Sixty

Clonal marrow plasma cells
≥60%.

Li — Light chains

Involved/uninvolved serum
FLC ratio ≥100 plus involved
FLC ≥100 mg/L.

M — MRI

More than one focal lesion,
each ≥5 mm.

Each is a myeloma-defining event even in the absence of overt CRAB symptoms.

Marrow plasma cells $\geq 60\%$ is active myeloma

- The percentage threshold is a diagnostic biomarker, not merely a risk score.
- Even without symptoms, clonal plasma cells at $\geq 60\%$ meet an MDE.
- The modern SMM marrow range stops below 60%.
- Check the percentage and clonality on adequate marrow material.

The FLC biomarker has two simultaneous parts

- Serum involved/uninvolved FLC ratio ≥ 100 .
- Absolute concentration of the involved serum free light chain ≥ 100 mg/L.
- Both conditions are needed for this SLiM criterion.
- An FLC ratio of 25 is a risk factor in the 20/2/20 model—not an MDE.

MRI focal lesions require number and size

- More than one focal marrow lesion is required for the SLiM MRI event.
- Each counted lesion should be ≥ 5 mm.
- A single focal lesion prompts clinical assessment but does not meet this MRI MDE.
- MRI signal changes must be interpreted using radiologic expertise.

Diagnostic comparison across the plasma cell spectrum

Feature	Non-IgM MGUS	SMM	Active myeloma
Serum M-protein	<3 g/dL	≥3 g/dL or other qualifying burden	Any level
Clonal marrow PCs	<10%	10%—<60% or qualifying protein	≥10% or plasmacytoma
Myeloma-defining event	Absent	Absent	Present
AL amyloidosis	Absent	Absent	Separate clinically important entity

Localized plasmacytoma versus SMM

Solitary plasmacytoma

Biopsy-proven single bone/soft tissue lesion.

Requires focused systemic marrow and imaging evaluation.

A discrete mass is the organizing finding.

Smoldering myeloma

Systemic monoclonal disease burden without MDE.

No defining focal bone destruction or other end-organ injury.

Monoclonal protein alone cannot distinguish the two.

AL amyloidosis cannot be ignored

- Monoclonal light chains can form tissue-deposited amyloid.
- The contemporary IMWG SMM definition requires absence of AL amyloidosis.
- Proteinuria, cardiomyopathy, or neuropathy may prompt organ-focused investigation.
- Low marrow tumor burden does not rule out clinically important AL amyloidosis.

A practical diagnostic workflow

**Confirm monoclonal
protein**



**Quantify marrow
clonality**



**Evaluate CRAB and
SLiM**



**Classify and stratify
risk**

Do not assign SMM solely from an M-spike or a marrow percentage.

History and examination: Seek organ injury

- Document new bone pain, fractures, infections, fatigue, and neurologic symptoms.
- Assess functional status and previous unexplained laboratory abnormalities.
- Review comorbid causes of anemia, hypercalcemia and kidney impairment.
- A lack of symptoms does not replace dedicated imaging.

Initial routine laboratory panel

- CBC with differential for anemia and other cytopenias.
- Creatinine, eGFR/CrCl and metabolic panel for renal function and calcium.
- Total protein, albumin and quantitative immunoglobulins provide context.
- Repeat or corroborate an unexpected abnormality before attribution.

Serum assays answer different questions

- SPEP: How much monoclonal protein is measurable?
- Immunofixation: Which heavy-chain/light-chain isotype?
- Serum FLC: How asymmetric is κ versus λ production?
- Quantitative immunoglobulins: Is there suppression of uninvolved isotypes?

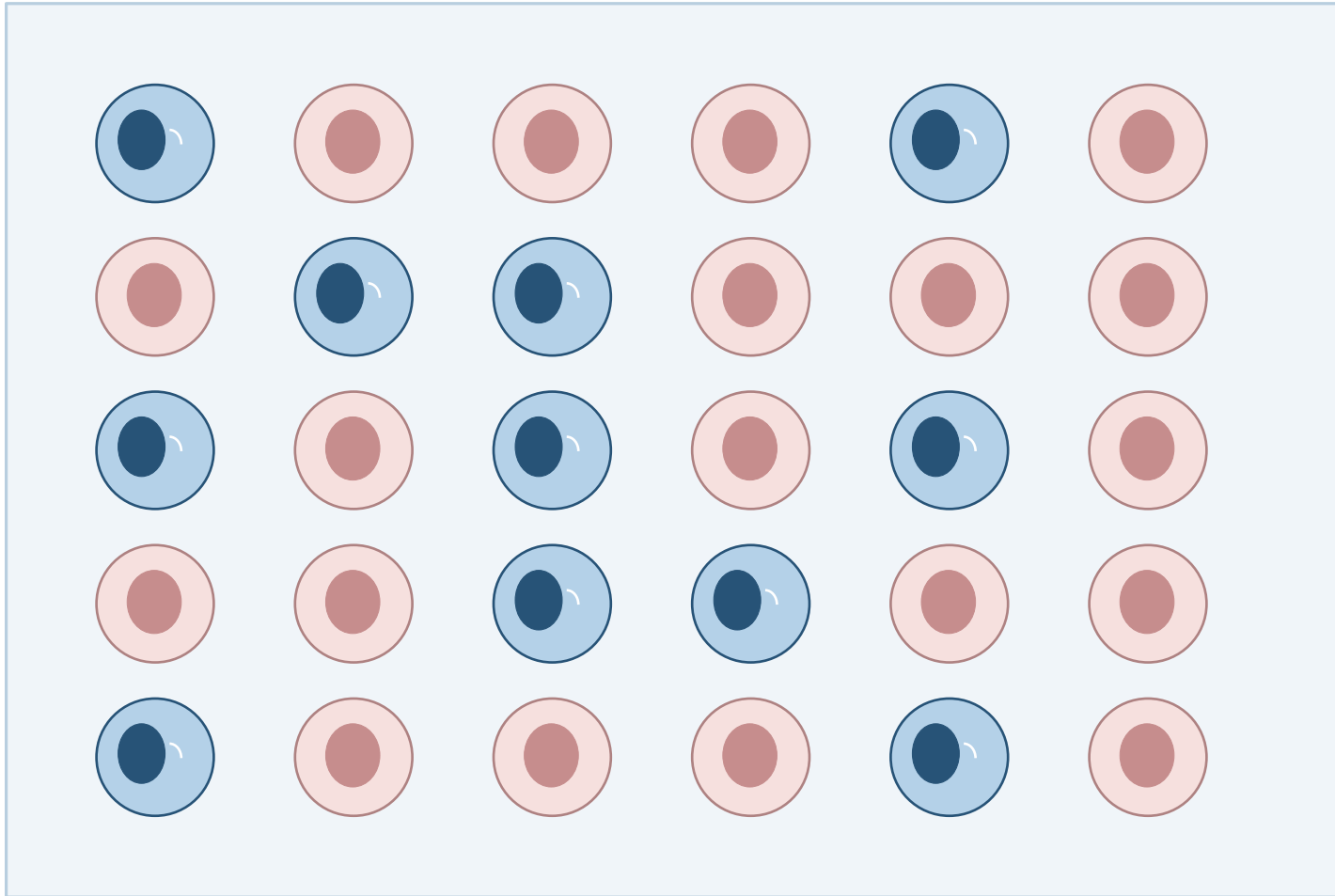
Urine studies remain clinically relevant

- Urine electrophoresis and immunofixation detect monoclonal light chains.
- A timed collection can quantify 24-hour monoclonal protein excretion.
- ≥ 500 mg per 24 h is one accepted SMM burden route in the IMWG criteria.
- Distinguish albuminuria from light-chain predominant proteinuria.

Bone marrow: Aspirate and core are complementary

- Aspirate enables differential count and cellular studies.
- Trephine biopsy evaluates spatial pattern and overall infiltration.
- Discordant estimates require review of adequacy and focality.
- Record the clonal plasma cell estimate and method, not “increased plasma cells” alone.

Plasma cell morphology: What the schematic shows



Clonal plasma cells: Eccentric nuclei and perinuclear pale zone

**Morphology supports lineage;
Clone proof requires light-chain restriction**

Schematic illustration — not histology

Immunophenotyping establishes the clone

- CD138 highlights plasma cells on marrow sections.
- κ/λ restriction helps demonstrate clonality in the appropriate context.
- Flow cytometry characterizes aberrant plasma cell populations.
- No single stain is a substitute for clinical and biochemical integration.

Cytogenetics and FISH are prognostic tools

- FISH can identify adverse genomic features in a clonal plasma cell population.
- The extended IMWG SMM model uses t(4;14), t(14;16), 1q gain and del(13q).
- These findings refine progression risk rather than independently establish MDEs.
- Risk marker and diagnostic marker are different concepts.

Why sampling variation matters

Focal marrow infiltration



**Aspirate and biopsy capture
different locations**



**Different percentages may
result**

Interpret marrow results together with imaging and expert hematopathology review.

Bone imaging in suspected SMM

Low-dose whole-body CT

Sensitive assessment for osteolytic destruction.

Whole-body/spine MRI

Detects marrow focal lesions before cortical destruction.

PET/CT

Combines metabolic activity with CT assessment of bone structure.

Appropriate modality depends on indication and local resources.

CT: Identify structural osteolysis

- Any qualifying osteolytic lesion may establish active myeloma.
- Low-dose whole-body CT is superior to conventional plain films for subtle osteolysis.
- An osteolytic focus on the CT component can matter even when plain films are normal.
- PET avidity without accompanying lysis is not equivalent to a CRAB bone lesion.

MRI detects marrow involvement before lysis

- A focal MRI lesion can represent localized neoplastic marrow replacement.
- More than one focal lesion ≥ 5 mm is an MDE.
- Diffuse marrow signal changes alone require context and follow-up.
- MRI and CT provide complementary biological and anatomical information.

PET/CT: The distinction is metabolic versus structural

- FDG uptake suggests metabolic activity but is not equivalent to osteolysis.
- The CT portion must demonstrate corresponding destructive change for CRAB bone disease.
- False-positive uptake can arise with infection or trauma.
- Interpret focal PET findings with the complete clinical and imaging assessment.

Osteopenia and fractures are not automatically CRAB

- Generalized osteoporosis is common and may be unrelated to a plasma cell clone.
- A vertebral compression fracture alone does not establish myeloma bone disease.
- Seek imaging evidence of an osteolytic lesion and attribution to myeloma.
- Misclassification may lead to unnecessary therapy.

“Smoldering” encompasses widely different risks

- Some patients remain stable for prolonged intervals.
- Other patients progress rapidly despite initially lacking CRAB or SLiM events.
- Single baseline measurements do not fully describe biological tempo.
- Risk models aid surveillance and treatment decisions but do not guarantee outcomes.

Natural history: Interpret estimates in context

- Approximately 75% progression over a 15-year period.
- A specific cohort estimate depends on diagnostic era and selection.
- Modern criteria reclassify some formerly “high-risk SMM” patients as active myeloma.
- Use contemporary risk models for current prognostic counseling.

IMWG 20/20/20: Three measurable predictors

Marrow

Clonal plasma cells >20%

Monoclonal protein

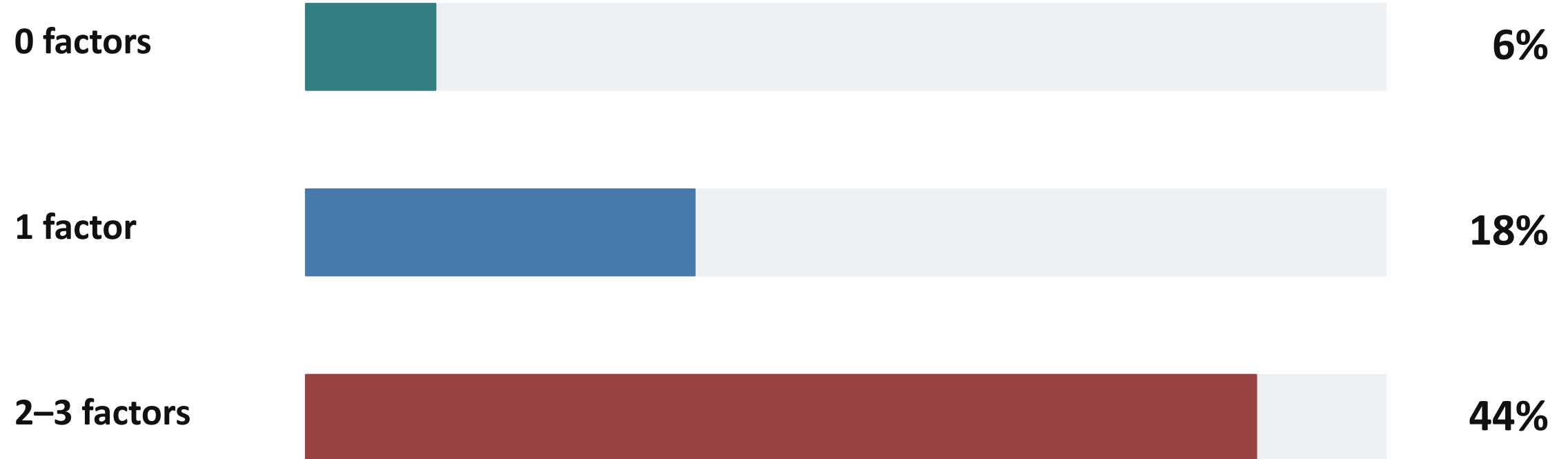
Serum M-protein >2 g/dL

Light chains

Involved/uninvolved FLC ratio
>20

These are prognostic risk-factor cutoffs, not diagnostic MDEs.

IMWG 2020: Two-year progression risk



Observed cohort estimates; Not an individual patient probability.

How to use the 20/2/20 score

- Count one factor for each threshold strictly exceeded.
- 0 factors: Low-risk; 1: Intermediate-risk; 2–3: High-risk in the original model.
- The estimated 2-year progression rates were 6%, 18%, and 44%, respectively.
- Confirm SMM classification before assigning a risk tier.

Extended IMWG model incorporates FISH

Additional cytogenetic factor	Clinical interpretation
T(4;14) or t(14;16)	Adverse disease biology in the IMWG model
1q gain	Adds progression-risk information
Deletion 13q	Adds progression-risk information
Combined factors	The extended model uses risk-group aggregation

Risk models: Strengths and limitations

- 20/2/20 uses accessible baseline measurements.
- Risk categories reflect population estimates, not deterministic trajectories.
- Heterogeneous cohorts, evolving diagnostic criteria and evolving biomarkers affect calibration.
- Serial trends and independent clinical events still matter.

Surveillance: Reassess biology and organ health

- Repeat monoclonal protein measures and serum FLC to detect dynamic change.
- Recheck CBC, kidney function and calcium for new attributable injury.
- Repeat imaging when clinically indicated or when a new lesion is suspected.
- Individualize visit frequency by risk category and evolving findings.

Monitoring frequency: Risk-sensitive approach

SMM group	2025 EHA–EMN guidance
Low-risk	Evaluate approximately every 6 months
Intermediate-risk	Evaluate every 3–6 months
Higher risk / evolution	More intensive specialist reassessment and management discussion

Dynamic progression requires a fresh classification check

- Increasing M-protein or FLC values may suggest clonal evolution.
- New cytopenias, hypercalcemia or kidney abnormalities demand attribution.
- New bone symptoms should trigger review of skeletal disease.
- Re-evaluate CRAB and SLiM before labeling a patient “still smoldering.”

Clinical decision: Surveillance or intervention?

Confirm absence of MDE



Risk stratify



**Discuss surveillance versus
high-risk therapy**

Management decisions depend on current guidelines, indication and patient preferences.

Why immediate treatment was historically deferred

Potential benefit

Prevents or delays end-organ injury.

Can lower risk of progression in selected high-risk SMM.

May reduce irreversible damage from active myeloma.

Potential cost

Adverse events in asymptomatic individuals.

Treatment burden and monitoring requirements.

Possible overtreatment of indolent disease.

AQUILA: Randomized evidence for high-risk SMM

- Open-label randomized trial compared subcutaneous daratumumab/hyaluronidase with active monitoring.
- 390 participants had high-risk smoldering myeloma.
- Primary efficacy measure: Progression to active myeloma or death.
- Trial eligibility/risk criteria should not be conflated with all SMM categories.

AQUILA: Progression-free survival

Trial population

390 patients with high-risk
SMM

Hazard ratio

0.49 (95% CI 0.36–0.67)

Active monitoring

Median PFS: 41.5 months

Median PFS was not reached in the daratumumab arm at the reported analysis.

US regulatory update: November 2025

- FDA approved subcutaneous daratumumab/hyaluronidase-fihj for adults with high-risk SMM.
- It is not an indication for every patient with SMM.
- Risks include infections, cytopenias and administration reactions.
- Therapy should be considered with specialist assessment and shared decision-making.

ASCO 2026: More than one defensible strategy

- In high-risk SMM, ASCO permits active monitoring or daratumumab for up to 36 months.
- Recommendation is conditional, with moderate-quality evidence.
- Lenalidomide is not routinely recommended in the cited ASCO living guideline.
- Patient values and toxicity tolerance inform choice.

Treatment discussion: Benefits versus harms

Possible benefit

Reduce risk of progression to active disease.

Defer myeloma-related organ injury.

Offer an option to selected high-risk patients.

Potential harms

Infections and treatment-related cytopenias.

Hypersensitivity or administration reactions.

Burden of repeated therapy and monitoring.

An individualized high-risk pathway

**Reconfirm SMM and exclusion
of MDEs**



**Check risk factors,
comorbidities and preferences**



**Offer active monitoring or
approved therapy**

An FDA approval does not make treatment obligatory for every high-risk patient.

Case A — incidental small IgG-κ component

- Illustrative case: IgG-κ M-protein 1.5 g/dL.
- Clonal marrow plasma cells 8%.
- Normal hemoglobin, creatinine and calcium; No lytic lesions.
- Question: Is this MGUS, SMM, or active myeloma?

Hypothetical diagnostic teaching vignette; Not patient data.

Case A — classification

Burden

M-protein <3 g/dL and
marrow <10%.

Defining event

No CRAB/SLiM or amyloidosis.

Answer

Non-IgM MGUS, not
smoldering myeloma.

Neither qualifying SMM burden route is met.

Case B — two positive 20/2/20 factors

- Illustrative case: Serum M-protein 2.4 g/dL.
- Clonal marrow plasma cells 22%.
- FLC ratio 13; No CRAB/SLiM event or AL amyloidosis.
- Question: Classification and number of risk factors?

Hypothetical diagnostic teaching vignette; Not patient data.

Case B — classification and risk

Diagnosis

SMM: 22% clonal marrow PCs.

Risk factors

M-protein >2; Marrow >20;
FLC ratio not >20.

Interpretation

2/20/20 high-risk SMM (2 factors).

A high prognostic score does not itself establish active myeloma.

Case C — asymptomatic, but SLiM-positive

- Illustrative case: Clonal marrow plasma cells 12%.
- Involved/uninvolved FLC ratio 115.
- Absolute involved serum FLC concentration 120 mg/L.
- Normal CRAB labs and no reported symptoms.

Hypothetical diagnostic teaching vignette; Not patient data.

Case C — a myeloma-defining biomarker

Marrow

≥10% clonal plasma cells.

FLC

Ratio ≥100 and involved FLC
≥100 mg/L.

Answer

Active myeloma by an IMWG
SLiM event.

“Asymptomatic” alone does not justify an SMM label.

Case D — high M-protein with marrow <10%

- Illustrative case: IgG M-protein 3.2 g/dL.
- Clonal marrow plasma cells 8%.
- No CRAB, SLiM, AL amyloidosis, or plasmacytoma.
- Question: Why can this still be SMM?

Hypothetical diagnostic teaching vignette; Not patient data.

Case D — use the OR condition

Serum

IgG M-protein meets ≥ 3 g/dL threshold.

Marrow

8% does not meet the $\geq 10\%$ route.

Answer

SMM because the serum route qualifies.

Modern SMM burden criteria are not a requirement that BOTH protein and marrow thresholds be high.

Case E — MRI changes the diagnosis

- Illustrative case: Marrow clonal plasma cells 18%.
- Two discrete MRI focal lesions, each ≥ 5 mm.
- No clinically evident CRAB abnormality.
- Question: Remain SMM or reclassify?

Hypothetical diagnostic teaching vignette; Not patient data.

Case E — MRI is a myeloma-defining event

MRI

>1 focal lesion of qualifying size.

Marrow

Clonal plasma cells exceed the 10% requirement.

Answer

Active myeloma by the SLiM MRI criterion.

Radiologic interpretation must establish that the lesions are compatible with myeloma.

Final diagnostic checkpoint

**Evidence of clone and
sufficient burden**



Any CRAB or SLiM event?



**If no: SMM; Then stratify
progression risk**

Amyloidosis and alternate diagnoses must be considered separately.

Core pathology distinctions to retain

- Diagnostic category depends on clone burden AND the presence or absence of a defining event.
- Risk factors >20%, >2 g/dL and >20 FLC ratio are not interchangeable with SLiM criteria.
- Marrow morphology and monoclonal protein detection do not replace imaging and laboratory attribution.
- High-risk management has changed; Confirm dated guidelines before counseling.

Source readings for the lecture

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Ch. 13, plasma cell neoplasms, pp. 552–555.
- International Myeloma Working Group revised diagnostic criteria (2014); International Myeloma Foundation diagnostic resource.
- Mateos et al. IMWG risk model for SMM. Blood Cancer J. 2020;10:102.
- US FDA. High-risk SMM daratumumab approval, 6 November 2025.
- ASCO. Treatment of Multiple Myeloma Living Guideline, Version 2026.1.1.