

# Plasma Cell Neoplasms and Related Disorders

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Clonal plasma cells • paraprotein biology • organ injury • related entities

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## Learning outcomes

- Distinguish a monoclonal immunoglobulin from a specific plasma cell neoplasm.
- Connect clonal plasma cell biology to bone, kidney and immune complications.
- Recognize myeloma morphology, immunophenotype and core investigations.
- Compare MGUS, smoldering disease, plasmacytoma, AL amyloidosis and IgM-associated lymphoma.

# Plasma cells are terminally differentiated B cells

**Mature B-cell clone**



**Plasma-cell differentiation**



**Immunoglobulin secretion**

- Antigen-experienced B lymphocytes can differentiate into antibody-secreting plasma cells.
- Normal humoral responses are polyclonal, with diverse heavy- and light-chain combinations.
- A neoplastic plasma cell population arises from one clone and typically produces one dominant immunoglobulin species.

**Clonality links a marrow cell population to its secreted paraprotein.**

# The unifying lesion is a monoclonal secretory clone

- Tumor-derived immunoglobulin or immunoglobulin fragments often act as circulating tumor markers.
- Pathology can result from tissue growth, properties of the secreted protein, or loss of normal antibody production.
- A serum monoclonal component is evidence of a clone, not by itself a diagnosis of myeloma.

**Clonal plasma cells**



**M component / free chains**



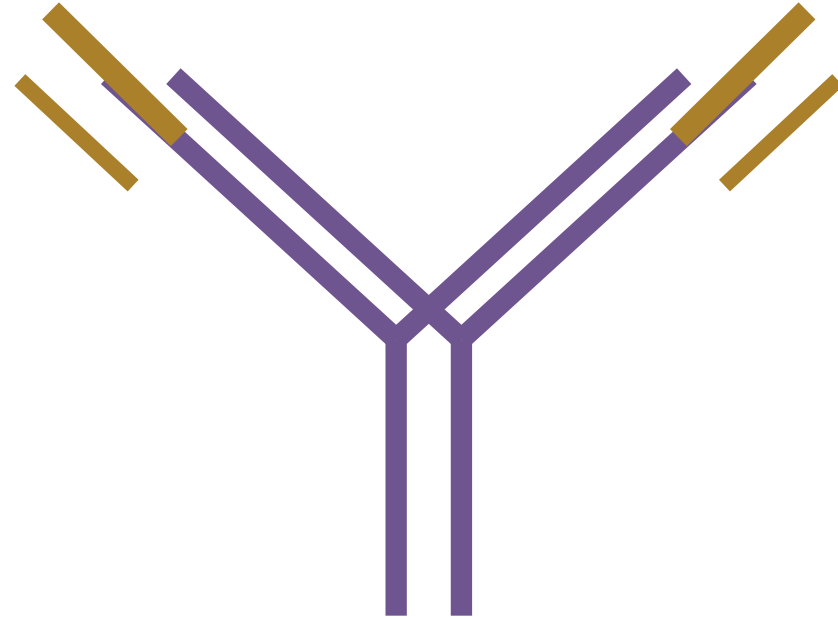
**Variable organ consequences**

## Why the paraprotein matters

- It offers a measurable marker of secretory clone activity.
- Its physical properties can increase viscosity or form tissue deposits.
- Excess free light chains may be filtered and injure renal tubules.
- A monoclonal protein may also be present in a clinically silent precursor state.

# Immunoglobulin architecture explains protein patterns

- An intact antibody consists of two heavy chains and two light chains.
- Neoplastic plasma cells may produce excess unpaired light chains.
- Some tumors secrete only light chains; Rare related disorders secrete heavy-chain fragments.

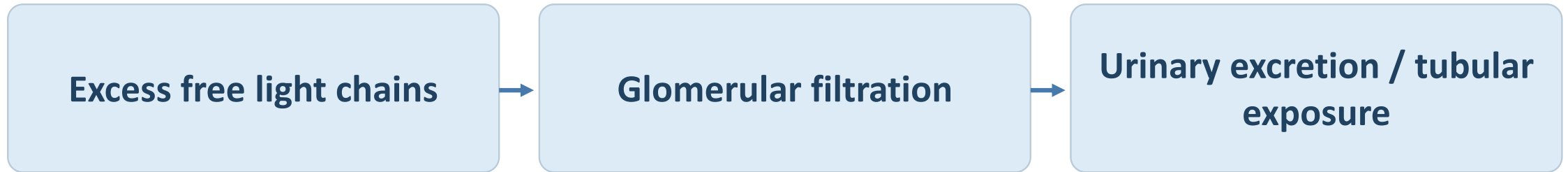


**Stylized intact immunoglobulin: H<sub>2</sub>L<sub>2</sub>**

Violet: Heavy chains | Gold: Light chains

**Secretory imbalance is central to serum, urine and tissue abnormalities.**

# Why free light chains can appear in urine



- Intact immunoglobulins are generally too large for normal glomerular filtration.
- Free  $\kappa$  or  $\lambda$  chains are smaller and may enter urine as Bence Jones proteins.
- Urinary light chains can signal a clone and contribute directly to kidney injury.

# A skewed light-chain ratio indicates clonality

## Polyclonal secretion

- Numerous antibody-producing clones
- Both light-chain classes contribute
- Broad immunoglobulin diversity

## Clonal secretion

- Single dominant secretory population
- $\kappa$  or  $\lambda$  predominance
- Restricted immunoglobulin species

- Normal plasma cell populations collectively produce  $\kappa$  and  $\lambda$  light chains.
- A dominant  $\kappa$ - or  $\lambda$ -restricted clone creates an imbalanced free-light-chain pattern.
- Light-chain restriction supports neoplasia when integrated with marrow morphology and clinical findings.

## M component is not interchangeable with malignancy

- MGUS may have a measurable paraprotein without organ injury.
- Smoldering disease has substantial clonal burden but remains clinically asymptomatic.
- Symptomatic myeloma reflects malignant plasma cells accompanied by characteristic tissue or organ injury.
- IgM paraproteins may arise from a lymphoplasmacytic B-cell lymphoma rather than myeloma.

## The related disorders form a clinical family

### **Precursor**

MGUS / smoldering

### **Plasma cell tumor**

Myeloma /  
plasmacytoma

### **Protein injury**

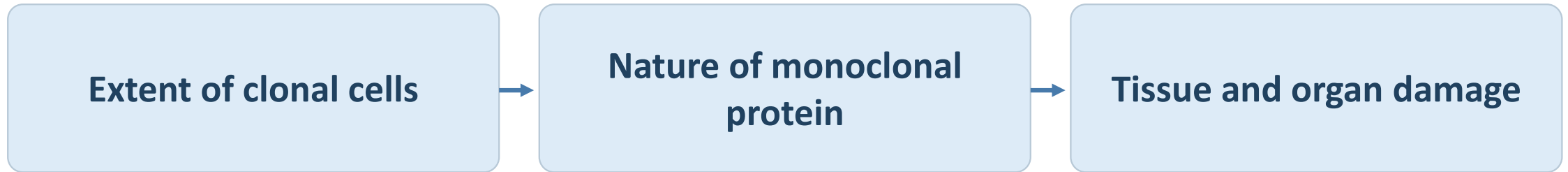
AL amyloidosis

### **IgM lymphoma**

LPL / Waldenström

- Plasma cell myeloma, plasmacytoma and precursor plasma cell proliferations share secretory clonality.
- AL amyloidosis can reflect a small plasma cell clone with disproportionately severe protein-mediated disease.
- Waldenström macroglobulinemia is an IgM-mediated syndrome usually associated with lymphoplasmacytic lymphoma.
- Heavy-chain disease reflects rare secretion of heavy-chain fragments.

# Three axes organize the differential diagnosis



- Clonal burden: Is there a small clone, widespread marrow involvement, or a localized mass?
- Secreted protein: Intact immunoglobulin, free light chain, IgM, or heavy-chain fragment?
- Clinical harm: Lytic bone destruction, renal toxicity, amyloid deposition, or hyperviscosity?

# Multiple myeloma: Systemic plasma cell neoplasm

- The characteristic lesion is multifocal marrow-based plasma cell proliferation.
- Osteolytic skeletal destruction is a major pathologic manifestation.
- Hypercalcemia, renal injury, anemia and impaired humoral immunity explain much of the clinical burden.

**Marrow plasma-cell expansion**



**Osteolytic skeletal lesions**



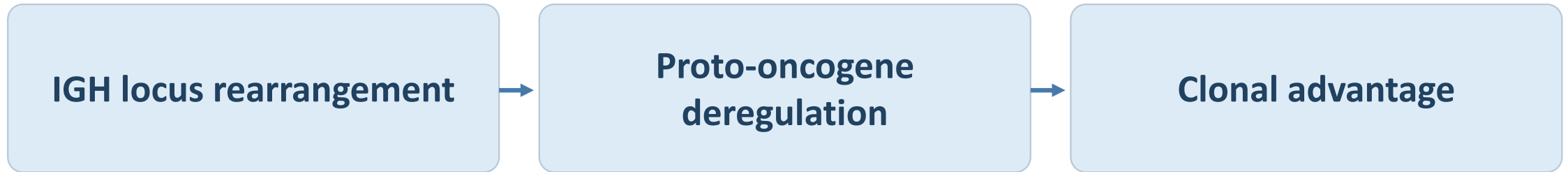
**Organ injury / immune suppression**

# Myeloma is predominantly a disease of older adults

- Maximal incidence around 65–70 years.
- Occurrence is higher in men and in people of African descent.
- Age and epidemiology create clinical suspicion; Diagnosis still depends on clonal and organ-level findings.

**Epidemiologic patterns are context—not diagnostic criteria.**

# IGH rearrangements are recurrent genetic drivers



- Plasma cell myeloma is genetically heterogeneous.
- Rearrangements involving the immunoglobulin heavy-chain locus at 14q32 are frequent.
- Partner genes include cell-cycle regulators such as CCND1 and CCND3.
- Convergent consequences include altered proliferation and tumor persistence.

# Genomic progression is not a single linear pathway

## Growth and survival

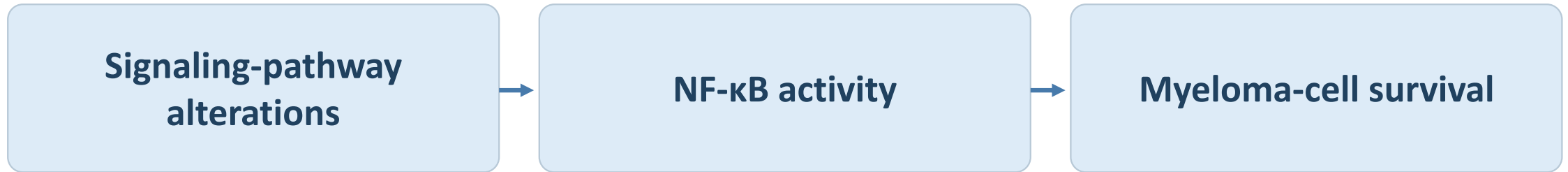
- Cyclin D pathway deregulation
- NF- $\kappa$ B-associated survival changes
- Marrow niche support

## Aggressiveness / risk

- 17p/TP53 loss
- MYC lesions in aggressive disease
- Variable accompanying abnormalities

- Deletion of 17p involving TP53 is associated with an adverse outcome.
- Alterations affecting NF- $\kappa$ B signaling can enhance B-cell survival.
- MYC rearrangements may occur in highly aggressive forms, including plasma cell leukemia.
- Diverse genetic lesions complicate simple one-marker disease classification.

# NF- $\kappa$ B alterations favor plasma cell survival



- NF- $\kappa$ B is a transcriptional network supporting B-cell survival.
- Myeloma genomes frequently harbor mutations in signaling components of this pathway.
- Sustained prosurvival signaling helps maintain the malignant clone.

## IL-6 connects malignant cells to the marrow niche



- IL-6 is an important plasma-cell growth and survival factor.
- Both tumor cells and resident marrow stromal cells may produce IL-6.
- High IL-6 levels in active disease were associated with worse prognosis in the Robbins discussion.

# Bone marrow stroma contributes beyond cytokines

- Direct physical interactions between myeloma cells and stromal cells favor tumor growth and survival.
- Tumor cells also alter the normal balance between bone-forming and bone-resorbing cells.
- Marrow pathology is therefore an interaction between the neoplastic clone and its microenvironment.

**Neoplastic plasma cell**

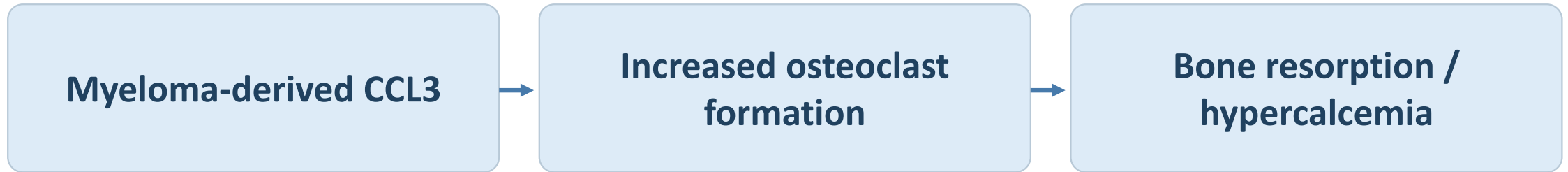


**Stromal-cell contact / cytokines**



**Survival and skeletal injury**

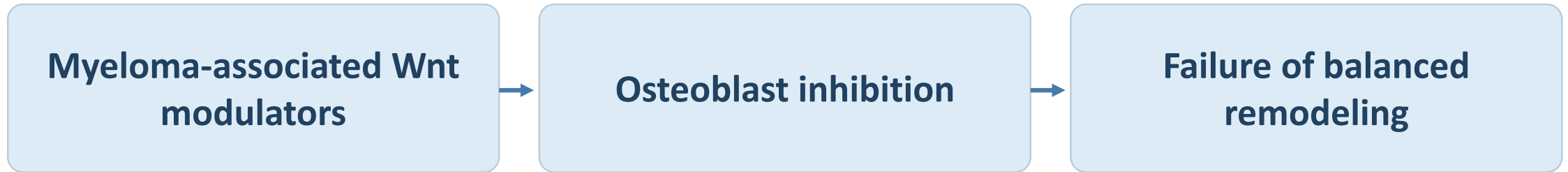
# Osteoclast activation initiates destructive bone disease



- Myeloma-derived CCL3 (MIP-1 $\alpha$ ) augments osteoclast formation through several mechanisms.
- Osteoclast activity increases mineralized-bone resorption.
- Net skeletal loss explains the characteristic osteolytic lesions and contributes to elevated calcium.

**Bone destruction is biologically driven—not merely mechanical tumor expansion.**

## Osteoblast inhibition prevents effective repair



- Tumor-derived regulators of Wnt signaling can strongly suppress osteoblast activity.
- Resorption continues while compensatory bone formation is impaired.
- This coupling defect helps explain persistent, sharply lytic lesions.

# Bone destruction reflects remodeling uncoupling

## Osteoclast side

- CCL3-associated formation
- Increased bone resorption
- Release of calcium

## Osteoblast side

- Wnt pathway modulation
- Reduced new bone formation
- Poor structural repair

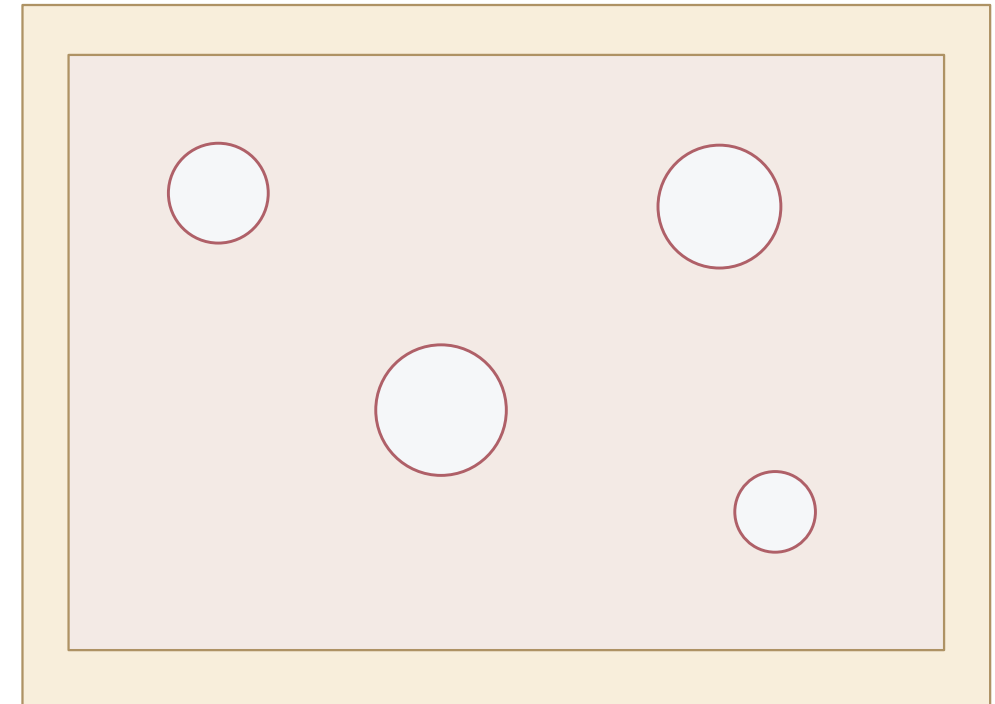
- Heightened osteoclast function removes existing bone.
- Depressed osteoblast function prevents adequate replacement.
- The imbalance produces osteopenia or focal osteolysis and increases fracture risk.

## Skeletal involvement favors the axial skeleton

- The vertebrae, ribs, skull and pelvis among commonly involved sites.
- Long-bone and shoulder-girdle sites can also be affected.
- The distribution contributes to back pain, fractures and neurologic compression syndromes.

# Osteolytic lesions arise within marrow

- Plasma cell masses begin in the medullary compartment and erode cancellous bone.
- Progressive destruction may extend into the cortex.
- Localized defects can coexist with diffuse demineralization.



Schematic cortical / marrow bone destruction

**This is a simplified anatomical schematic, not a radiograph.**

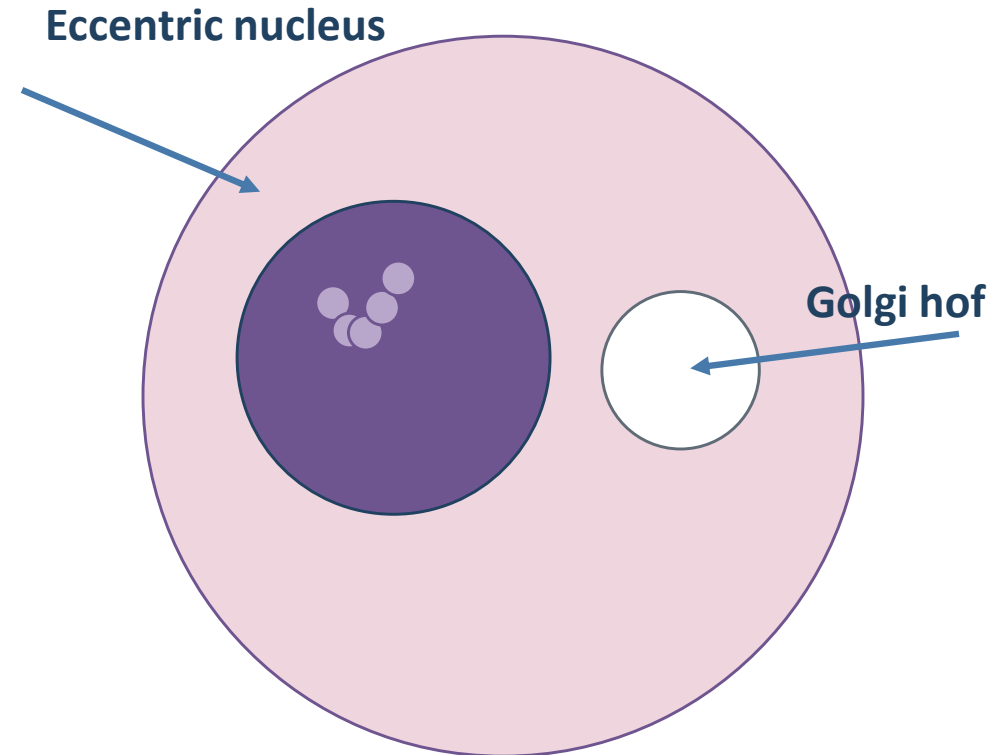
# Structural failure explains pain and fractures



- Loss of cancellous and cortical bone reduces load-bearing capacity.
- Vertebral fractures are particularly frequent in myeloma.
- A fracture, spinal lesion or severe focal pain can be the clinical clue to marrow disease.

# Myeloma plasma cells retain recognizable features

- Many tumor cells preserve an eccentrically located nucleus.
- A pale perinuclear zone represents a prominent Golgi apparatus.
- Morphology may resemble normal plasma cells despite biologic malignancy.



Schematic — not a histologic specimen

# Cytologic atypia varies substantially

## Relatively mature morphology

- Eccentric nucleus
- Perinuclear clearing
- Variable atypia

## Immature or pleomorphic morphology

- Prominent nucleolus
- Vesicular chromatin
- Occasional bizarre or multinucleated forms

- Some clones contain relatively mature plasma cells with coarse chromatin.
- Plasmablasts show more open chromatin and prominent nucleoli.
- Bizarre or multinucleated forms may also be present.
- Appearance alone cannot determine systemic organ injury or replace clonality assessment.

# Intracellular immunoglobulin creates inclusion variants

## Cytoplasmic changes

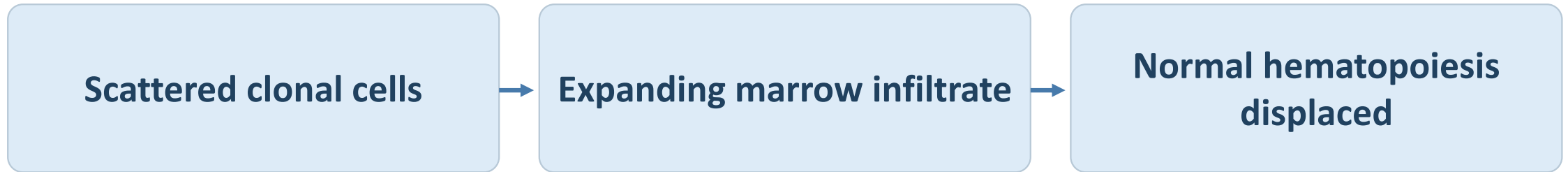
- Flame cells
- Mott cells
- Russell bodies

- Flame cells exhibit conspicuously reddish cytoplasm.
- Mott cells contain multiple grape-like cytoplasmic immunoglobulin accumulations.
- Russell bodies are intracytoplasmic globular inclusions.
- Dutcher bodies are intranuclear-appearing immunoglobulin inclusions.

## Nuclear-appearing inclusion

- Dutcher bodies
- Associated with secretory protein accumulation
- Not unique to myeloma

## Marrow infiltration may be subtle or extensive



- Clonal plasma cells may occupy scattered interstitial positions.
- In advanced infiltration they can replace normal hematopoietic elements.
- Marrow suppression contributes to anemia and affects diagnostic sampling.
- The degree of infiltration must be assessed alongside the whole clinical syndrome.

## Myeloma can become extramedullary

- Advanced disease may infiltrate lymph nodes and soft tissue organs.
- Spleen, liver, kidney and lung involvement are described.
- Rarely, circulating tumor cells become sufficiently prominent to produce plasma cell leukemia.

**The usual presentation remains marrow-centered; Extramedullary spread changes the disease pattern.**

# CD138 and light-chain restriction support lineage

## Plasma-cell identification

- CD138 (syndecan-1)
- Cytoplasmic immunoglobulin
- Marrow morphologic context

## Clonal / aberrant features

- $\kappa$  or  $\lambda$  restriction
- Often CD56 expression
- Must integrate with clinical context

- Myeloma plasma cells express CD138 (syndecan-1).
- They often express CD56, which can help recognize an abnormal plasma cell population.
- Cytoplasmic  $\kappa$  or  $\lambda$  light-chain restriction supports monoclonality.
- Immunophenotype is interpreted with morphology, protein tests and clinical injury.

# Three processes account for myeloma manifestations

## **Tumor mass**

Bone and marrow effects

## **M protein**

Light chains / viscosity

## **Immune deficit**

Reduced normal Ig

- Tissue growth: Skeletal damage and replacement of marrow.
- Paraprotein toxicity: Renal tubular injury, deposits and altered blood flow.
- Suppression of normal humoral immunity: Susceptibility to infections.

# CRAB organizes characteristic end-organ injury

## **C | Hypercalcemia**

Osteoclast-mediated bone resorption

## **R | Renal impairment**

Light chains plus additional insults

## **A | Anemia**

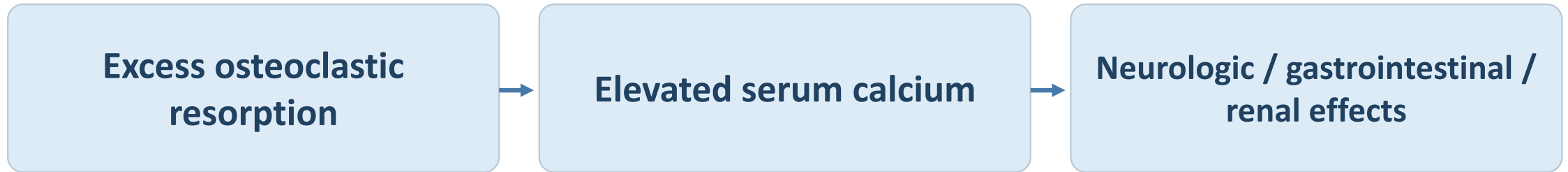
Marrow replacement and other factors

## **B | Bone lesions**

Lytic lesions, pain and fractures

**CRAB is a clinicopathologic framework; Abnormalities need attribution to the plasma cell disorder.**

# Hypercalcemia is a consequence of bone resorption



- Increased osteoclastic activity releases calcium from bone.
- Neurologic effects include lethargy, weakness and confusion.
- Constipation and polyuria are characteristic systemic manifestations.
- Hypercalcemia can intensify renal impairment.

## Free light chains can be toxic to renal tubules



- Excess light chains are filtered at the glomerulus and delivered to tubular structures.
- Tubular epithelial toxicity is an important mechanism of myeloma kidney.
- Kidney function may decline even when skeletal findings do not dominate.

# Renal dysfunction is multifactorial

## Protein-associated injury

- Tubular exposure to free chains
- AL deposits in susceptible cases
- Variable patient-specific effects

## Other contributors

- Hypercalcemia
- Hemodynamic and additional factors
- Often more than one process

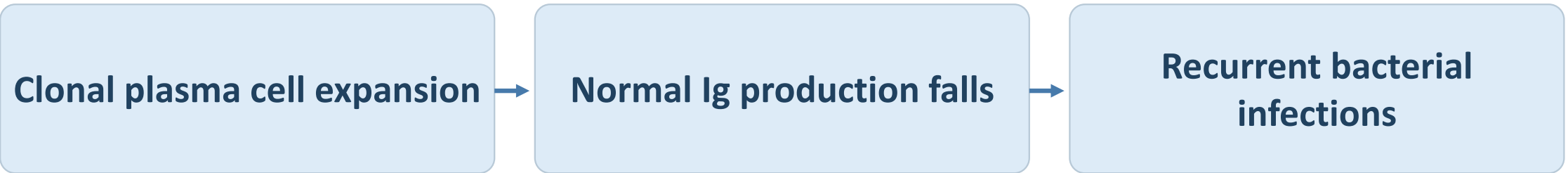
- Bence Jones light-chain excretion is emphasized as a major contributing factor.
- Hypercalcemia further compromises renal physiology.
- AL amyloid deposition may also involve the kidney.
- Clinical evaluation should not attribute every elevation in creatinine to a single mechanism.

# AL amyloidosis represents toxic protein deposition



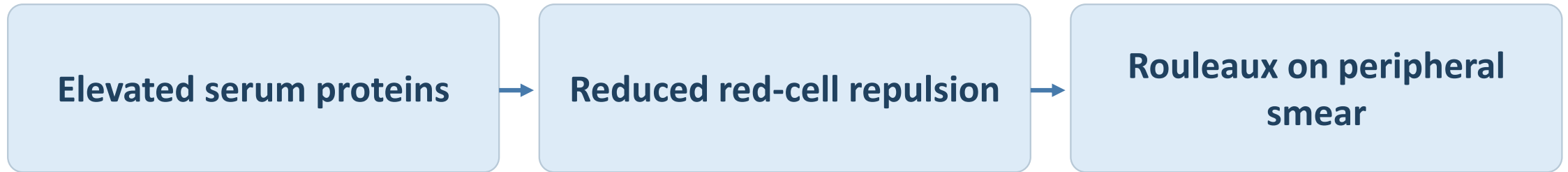
- A monoclonal plasma cell proliferation may secrete amyloidogenic light chains.
- A predominance of  $\lambda$ -associated chains in AL disease.
- Some patients have overt myeloma; Others harbor only a relatively small marrow clone.
- Clinical phenotype follows the distribution of tissue deposits.

# Suppression of polyclonal immunoglobulin impairs defense



- Myeloma often reduces normal immunoglobulin production.
- Loss of humoral protection increases susceptibility to bacterial infections.
- Cellular immunity is relatively less affected description.
- Recurrent infection can dominate morbidity despite a demonstrable serum paraprotein.

# Rouleaux reflects altered plasma protein composition

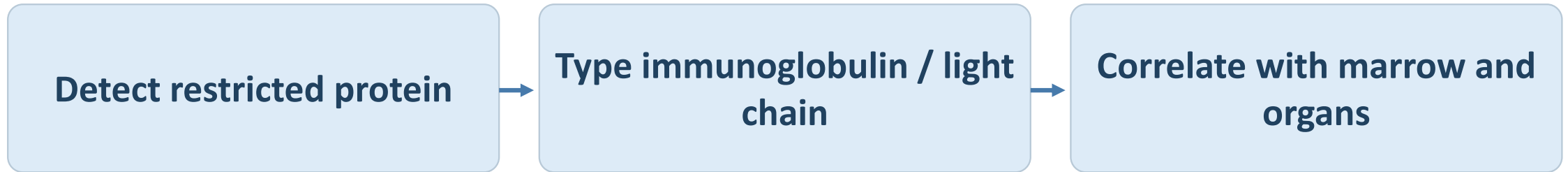


- High immunoglobulin concentrations favor red cell stacking in linear arrays.
- Rouleaux may be noted on blood smears in multiple myeloma.
- It is not specific: Other causes of elevated immunoglobulin can produce the same finding.

# Hyperviscosity is possible but not universal in myeloma

- Abundant paraprotein can increase serum viscosity.
- IgA or IgG3 aggregates in selected patients.
- Clinical hyperviscosity is more characteristic of high-IgM lymphoplasmacytic disease.
- Protein subtype and physical behavior matter in addition to paraprotein quantity.

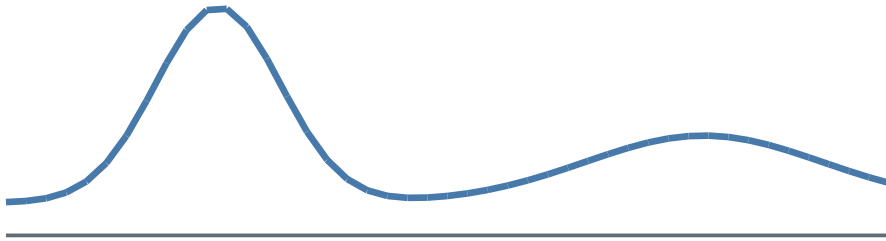
# Monoclonal-protein evaluation uses complementary tests



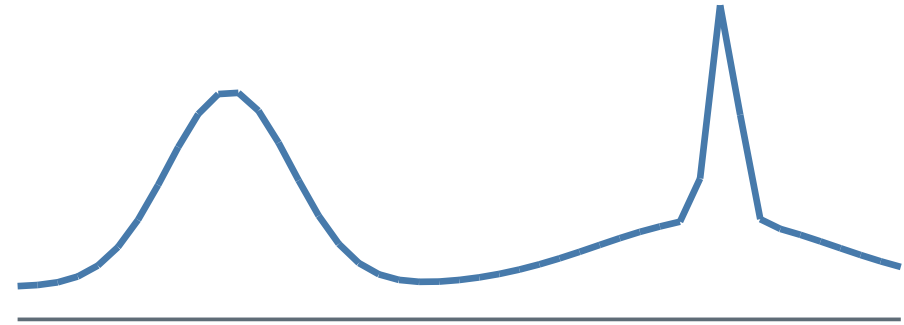
- Serum and urine protein electrophoresis screen for abnormal restricted proteins.
- Immunofixation identifies the heavy-chain class and  $\kappa/\lambda$  identity.
- Free-light-chain testing identifies light-chain predominance, including cases without intact M protein.
- Interpretation requires bone marrow and organ-damage assessment.

# Electrophoretic patterns: Narrow versus broad

**Broad polyclonal pattern**



**Monoclonal band / spike**



Qualitative schematic only — not patient data, quantified electrophoresis or a diagnostic result

- A polyclonal immunoglobulin distribution forms a broader background pattern.
- A predominant monoclonal immunoglobulin often creates a sharp restricted band or spike.
- Protein electrophoresis detects a possible M component; It does not identify the complete disease entity.

# Immunofixation determines the paraprotein isotype

**Restricted serum/urine band**



**Heavy-chain assignment**



**κ or λ light-chain typing**

- Antisera recognizing IgG, IgA or IgM identify the heavy-chain class.
- Separate κ and λ antisera reveal the restricted light-chain component.
- An example such as IgG-κ describes the monoclonal molecule, not disease stage or organ risk.
- Suppression of unrelated immunoglobulins may be detected concurrently.

# Secretory patterns create diagnostic blind spots

## Detectable secretion

- Intact immunoglobulin
- Free light chains
- Both may coexist

## Little or no conventional M protein

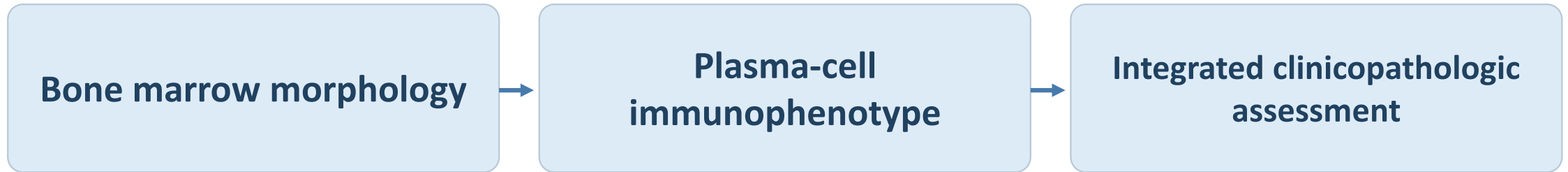
- Occasional nonsecretory myeloma
- Protein studies may be unrevealing
- Marrow and organ assessment remain important

- Common myeloma clones secrete intact immunoglobulin, often with excess free light chains.
- Other clones produce light chains alone.
- Rare tumors are nonsecretory: A missing conventional M spike does not completely rule out myeloma.
- Marrow findings and tissue consequences remain essential.

## IgG and IgA predominate among myeloma M proteins

- The Robbins description identifies IgG as the leading secreted isotype.
- IgA is the next most common intact immunoglobulin class.
- IgM-, IgD- and IgE-associated myelomas are described as uncommon.
- Protein isotype alone does not distinguish myeloma from every related clonal disorder.

# Marrow testing establishes the cellular component



- Bone marrow examination documents plasma cell infiltration and cytology.
- CD138 staining and  $\kappa/\lambda$  studies help identify and characterize the clone.
- Genetic assessment can reveal recurrent structural abnormalities.
- The final diagnosis integrates cell findings with laboratory and organ-level evidence.

# Do not interpret a CRAB feature in isolation

- Anemia may coexist with a monoclonal gammopathy for unrelated reasons.
- Kidney impairment is not automatically caused by a paraprotein.
- Bone symptoms require demonstration of characteristic skeletal pathology.
- Clinical attribution depends on the combined patient findings.

**Identify abnormality**

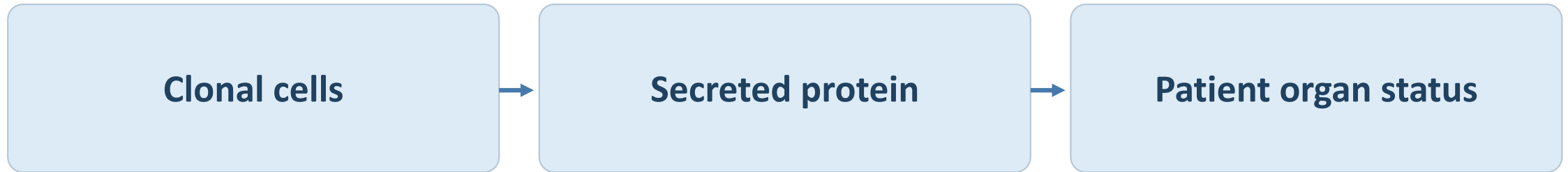


**Evaluate alternate causes**



**Link to clonal disorder if supported**

# Myeloma evaluation is a multi-domain process



- Identify clonal marrow plasma cells and characterize the immunoglobulin product.
- Assess blood counts, serum calcium and renal function.
- Investigate characteristic skeletal disease.
- Integrate findings instead of relying on one positive test.

**No single laboratory test is an adequate stand-alone diagnosis.**

## A plasma cell clone has several important mimics

| Finding                    | Supports                    | Must distinguish from            |
|----------------------------|-----------------------------|----------------------------------|
| Clonal marrow cells        | Plasma cell proliferation   | Clinically silent precursor      |
| Bone lytic lesions         | Symptomatic myeloma pattern | Other destructive bone disorders |
| IgM paraprotein            | Monoclonal B-cell process   | Lymphoplasmacytic lymphoma       |
| Localized plasma cell mass | Plasmacytoma                | Systemic myeloma                 |

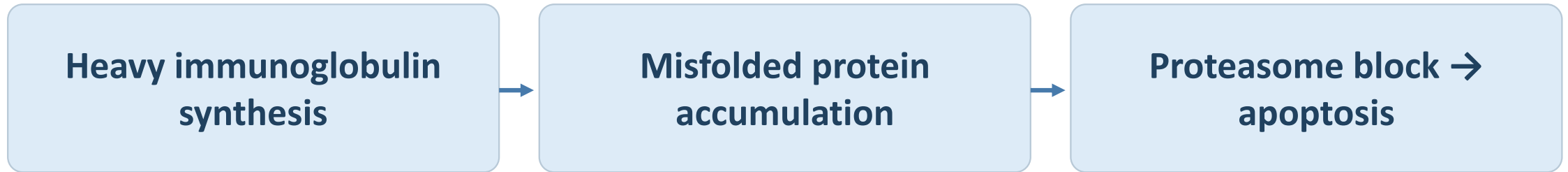
Reactive plasmacytosis can accompany chronic immune stimulation. • MGUS and smoldering states may exhibit clonality without myeloma-type symptoms. • IgM lymphoplasmacytic lymphoma is a B-cell neoplasm with plasmacytic differentiation. • An isolated mass needs distinction from generalized marrow disease.

# Chromosomal abnormalities influence prognosis

| Genetic feature                    | Robbins interpretation           |
|------------------------------------|----------------------------------|
| Cyclin D1-associated translocation | Relatively favorable association |
| 17p loss involving TP53            | Adverse outcome                  |
| 13q deletion                       | Adverse association              |
| t(4;14)                            | More aggressive course           |

Translocations involving cyclin D1 are described as associated with a relatively favorable outcome. • Deletion 17p, deletion 13q and t(4;14) are associated with more aggressive behavior in the source. • Genetic associations modify risk but require interpretation with the clinical disease state.

# Proteasome inhibition exploits protein-synthesis stress



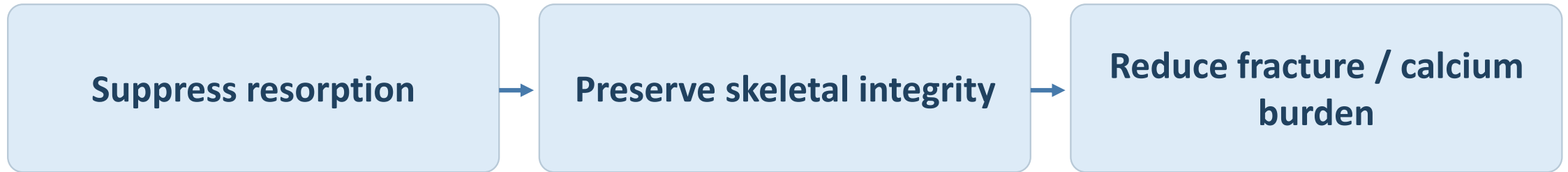
- Plasma cells synthesize large amounts of immunoglobulin.
- Heavy-/light-chain imbalance increases the burden of misfolded protein.
- Proteasome inhibition prevents degradation of unwanted proteins.
- Accumulation of damaged proteins can trigger tumor-cell apoptosis.

# Immunomodulatory drugs also alter protein turnover



- Thalidomide-related compounds such as lenalidomide as active therapies.
- Lenalidomide can redirect selected ubiquitin ligase activity.
- Growth-essential proteins become targeted for degradation.
- The biological explanation differs from direct inhibition of proteasome catalytic function.

# Bone-directed treatment targets skeletal complications



- Bisphosphonates suppress bone resorption.
- Reducing osteoclast-mediated loss decreases fracture and hypercalcemia complications.
- This supportive mechanism is distinct from eradication of the malignant clone.

# BCMA-directed CAR-T represents targeted immunotherapy

## Mechanism and potential

- BCMA-directed T-cell targeting
- Deep responses in selected patients
- Immunologic attack on malignant clone

## Major toxicities

- Cytokine release syndrome
- Neurotoxicity
- Hypogammaglobulinemia-associated infection

- B-cell maturation antigen (BCMA) provides a target on plasma cells.
- CAR-T approaches can induce deep remissions in many patients.
- The Robbins discussion emphasizes cytokine release syndrome, neurologic toxicity and infection risk.
- Benefit and complications both follow potent immune activation and plasma-cell targeting.

# MGUS: Monoclonality without symptomatic neoplasm

- Monoclonal gammopathy of undetermined significance is common in older adults.
- By definition in the Robbins discussion, patients are asymptomatic with a relatively small serum M component.
- There is no clinical evidence of a symptomatic plasma cell neoplasm at the time of classification.
- Its relevance is the possibility of later progression.

**Small plasma-cell clone**

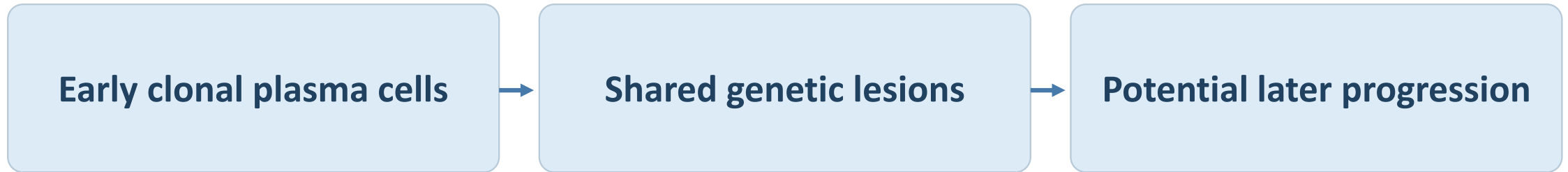


**Monoclonal component**



**No attributable symptomatic disease**

# MGUS is a biologic precursor, not simply a lab artifact



- Clonal cells can contain chromosome rearrangements also seen in myeloma.
- This overlap supports a multistep model of plasma cell tumor development.
- Most clinically detected MGUS does not immediately become symptomatic myeloma.
- A clonal marker must be interpreted over time.

## MGUS requires longitudinal interpretation

- Progression to a symptomatic plasma cell neoplasm in approximately 1% of MGUS patients per year.
- The course of an individual clone remains unpredictable.
- Periodic surveillance of the M component and urinary free light chains is discussed.
- The presence of a clone should not be equated with immediate tissue damage.

# Smoldering myeloma is an asymptomatic intermediate

## **MGUS**

Clinically silent, smaller clone

## **Smoldering myeloma**

Higher clonal burden, no symptoms

## **Myeloma**

Clonal disease with injury

- It occupies a clinical middle ground between MGUS and symptomatic myeloma.
- There is a greater clonal disease burden than in typical MGUS.
- Patients lack the characteristic symptomatic end-organ manifestations at presentation.
- Meaningful long-term risk of progression.

# Progression is possible—not inevitable on a timetable



- MGUS and smoldering myeloma represent different baseline burdens and risks.
- Biologic progression involves acquired changes and altered tumor-host interactions.
- Clinical transformation is recognized by the disease phenotype, not merely elapsed time.
- The source reports uncertainty in predicting individual evolution.

# Solitary plasmacytoma is a localized plasma cell tumor

## Solitary bone lesion

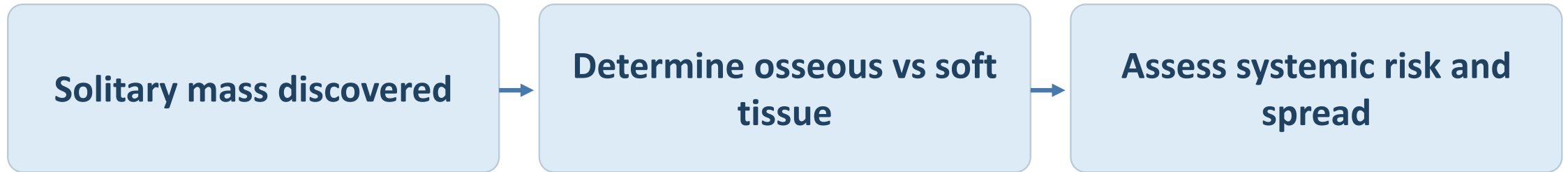
- Plasma-cell mass in bone
- May share sites with myeloma
- Progression to systemic disease is common

## Extraosseous lesion

- Often upper aerodigestive tract
- Local presentation
- Local treatment can be curative

- A single bone or soft-tissue mass may contain neoplastic plasma cells.
- Some patients have a small detectable circulating M component.
- Extent-of-disease evaluation distinguishes a solitary lesion from disseminated myeloma.
- Natural history differs markedly by osseous versus extraosseous site.

# Osseous and extraosseous plasmacytomas diverge



- Bone plasmacytomas frequently evolve into multiple myeloma over long follow-up.
- Upper respiratory tract extraosseous lesions often behave more locally.
- Anatomic localization and careful staging are therefore clinically consequential.

# A small plasma cell clone can cause systemic AL disease

## Clonal burden

- Sometimes limited plasma cell population
- M component may be present
- No requirement for diffuse bone lesions

## Tissue damage

- Misfolded light chains
- Amyloid fibril deposition
- Organ-specific dysfunction

- AL amyloidogenic protein may arise even when marrow infiltration is minor.
- Organ damage results from abnormal light-chain deposition, rather than solely tumor bulk.
- The extent of symptoms can be disproportionate to measured marrow tumor burden.
- This distinguishes protein-mediated disorders from a purely mass-effect model.

## Heavy-chain disease is a rare paraprotein disorder

- The defining secretory feature is a free immunoglobulin heavy-chain fragment.
- It may accompany different B-cell lymphoproliferative diseases.
- Lymphoplasmacytic lymphoma and small-bowel marginal zone disease among associations.
- It is a secretory category, not a synonym for plasma cell myeloma.

# Lymphoplasmacytic lymphoma differs from myeloma

## Myeloma

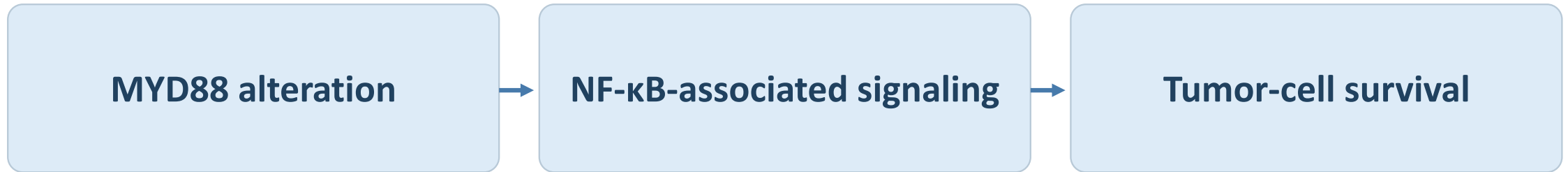
- Plasma cell neoplasm
- Marrow and lytic skeletal pathology
- Often IgG / IgA or free chains

## Lymphoplasmacytic lymphoma

- Mature B cells plus plasma cells
- Frequently IgM secretion
- Hyperviscosity and systemic lymphoid spread

- It is a mature B-cell neoplasm with substantial plasmacytic differentiation.
- The typical monoclonal product is IgM.
- Generalized lymphoid-organ infiltration and IgM-mediated symptoms are characteristic.
- Unlike typical myeloma, destructive skeletal lesions are not a characteristic feature.

# MYD88 mutation is central to LPL biology



- Acquired MYD88 mutations in virtually all cases.
- MYD88 is an adaptor involved in signals activating NF-κB.
- Prosurvival signaling provides a mechanistic basis for B-cell persistence.
- The molecular association supports understanding but must be interpreted with phenotype.

# LPL marrow combines lymphoid and plasma cell forms

## Marrow composition

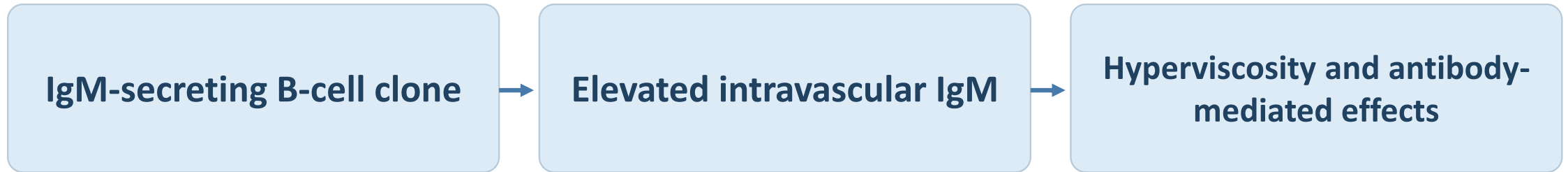
- Small B lymphocytes
- Plasmacytoid cells / plasma cells
- Often accompanying mast cells

## Useful phenotype

- B-cell population expresses CD20
- Surface immunoglobulin on B cells
- Matching secreted Ig from plasma cells

- Marrow infiltrates contain small lymphocytes, plasmacytoid lymphocytes and mature plasma cells.
- Mast cell hyperplasia is often present.
- Russell and Dutcher inclusions can accompany immunoglobulin production.
- CD20-positive lymphoid cells and the immunoglobulin-producing plasma cell component are clonally related.

# Waldenström macroglobulinemia is an IgM syndrome



- High intravascular IgM can markedly increase plasma viscosity.
- The syndrome most commonly develops in lymphoplasmacytic lymphoma.
- Circulatory symptoms reflect the high concentration and large molecular size of IgM.
- IgM excess also produces cold-related antibody effects in selected patients.

# IgM hyperviscosity has characteristic organ effects

## Eyes

Venous congestion

## Brain

Headache / dizziness

## Hemostasis

Mucosal bleeding

- Retinal venous congestion can cause visual impairment.
- Sluggish circulation contributes to headache, dizziness and altered alertness.
- Interactions with platelets or clotting factors can produce bleeding.
- Severe symptoms may require urgent reduction of circulating IgM.

# Cold IgM may cause immune-mediated complications

## Cold agglutinin activity

- IgM binds red cells in the cold
- May lead to hemolysis
- Antibody-mediated effect

## Cryoglobulinemia

- Cold-dependent protein precipitation
- Raynaud phenomenon
- Cold urticaria

- Cold agglutinins are IgM antibodies capable of binding red cells at low temperatures.
- Autoimmune hemolysis may occur in a subset of LPL patients.
- Cryoglobulins precipitate at reduced temperatures and can cause Raynaud phenomena or urticaria.
- These effects differ mechanistically from simple hyperviscosity.

# IgM reduction and lymphoma control are distinct goals

## Immediate protein effect

- Plasmapheresis removes circulating IgM
- Relieves hyperviscosity manifestations

## Underlying neoplasm

- CD20-directed and other lymphoma therapies
- BTK pathway inhibition
- Requires ongoing clinical management

- Plasmapheresis can rapidly reduce predominantly intravascular IgM and its rheologic effects.
- Lymphoma-directed therapies reduce the clone producing the protein.
- Responsiveness to anti-CD20 therapy and BTK inhibition.
- This distinction separates urgent syndrome management from long-term clone control.

## Key contrast: Myeloma versus Waldenström syndrome

| Characteristic     | Multiple myeloma                      | LPL / Waldenström               |
|--------------------|---------------------------------------|---------------------------------|
| Dominant clone     | Plasma cells                          | B lymphocytes with plasma cells |
| Typical M protein  | IgG, IgA or free chains               | IgM                             |
| Bone destruction   | Characteristic lytic lesions          | Not characteristic              |
| Major protein harm | Tubular light chains / AL / viscosity | Viscosity / cold IgM effects    |
| Tumor compartment  | Marrow, skeletal sites                | Marrow, nodes, spleen, liver    |

# Clinicopathologic vignette: Bone pain and proteinuria

An older adult has persistent back pain, a destructive skeletal lesion, anemia and urinary monoclonal free light chains.

## DISCUSSION

- Which mechanism explains focal bone loss?
- Why might the kidney be affected through a second mechanism?
- What three categories of investigations are needed before concluding myeloma?

# Clinicopathologic vignette: Asymptomatic M component

An asymptomatic adult has a newly discovered monoclonal serum band but no identified myeloma-type organ injury.

## DISCUSSION

- Why does an M component alone not establish symptomatic myeloma?
- Which tissue and organ findings would change classification?
- Why is longitudinal reassessment justified?

# Clinicopathologic vignette: Visual and bleeding symptoms

An older adult presents with blurred vision, headaches and mucosal bleeding; Investigations identify a marked monoclonal IgM component.

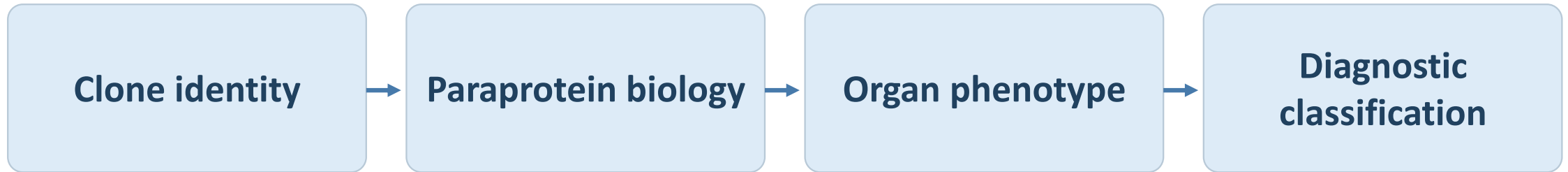
## DISCUSSION

- Which paraprotein is most closely linked to this syndrome?
- What cellular neoplasm should be considered?
- Why can reducing circulating protein help before tumor burden changes?

## Common diagnostic reasoning errors

- Calling every M spike “multiple myeloma.”
- Assuming all renal dysfunction in monoclonal gammopathy is cast-related.
- Treating IgM paraproteinemia and IgG/IgA myeloma as identical mechanisms.
- Inferring histologic malignancy from cytologic atypia alone.
- Using a single older textbook threshold as a complete contemporary diagnostic algorithm.

## Integrative framework: Clone → protein → tissue injury



- Identify the cellular clone and its differentiation stage.
- Determine the type, quantity and physicochemical effects of monoclonal protein.
- Assess marrow, skeleton, kidney, circulation and immune competence.
- Classify the disorder by its combined morphologic and clinical phenotype.

## Core distinctions to retain

- MGUS and smoldering disease are clinically silent at recognition, but differ in clonal burden.
- Myeloma often causes lytic bone disease, renal toxicity and loss of normal immunoglobulin.
- Localized plasmacytoma requires staging to exclude systemic involvement.
- AL damage may be severe despite modest clonal burden.
- Waldenström syndrome reflects large IgM-mediated rheologic and immune effects.

## Source, terminology and interpretation

- Primary reference: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), Chapter 13, pp. 552–556.
- Topic coverage incorporates the adjacent textbook sections for MGUS, smoldering myeloma, plasmacytoma and lymphoplasmacytic lymphoma.
- Diagnostic and prognostic frameworks are presented as described in this textbook; they are not substitutes for a current IMWG or WHO/ICC clinical classification consultation.
- Original diagrams are native PowerPoint schematics, not patient specimens or reproduced textbook figures.