

Mucopolysaccharidoses

Inherited glycosaminoglycan storage disorders:
from lysosomal dysfunction to skeletal disease

Mechanisms • morphology • clinicopathologic correlations

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Learning objectives

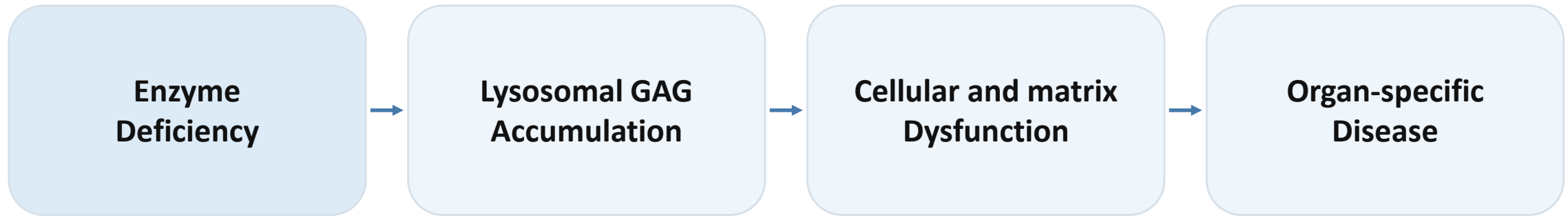
- Explain glycosaminoglycan storage from a deficient lysosomal catabolic step.
- Relate chondrocyte injury and matrix abnormalities to skeletal deformities.
- Recognize the principal histologic, systemic, and syndrome-specific findings.
- Distinguish Hurler from Hunter syndrome using enzyme, inheritance, and corneal findings.

The central clinicopathologic problem

- A lysosomal enzymatic defect prevents normal degradation of glycosaminoglycans.
- The same substrate burden affects connective tissues, viscera, vasculature, and sometimes neurons.
- Bone deformity is one component of a multisystem storage disorder.

Key concept: The skeleton and internal organs share one biochemical defect.

How the biochemical defect becomes a phenotype



Accumulating substrate has different consequences in cartilage, viscera, heart, and CNS.

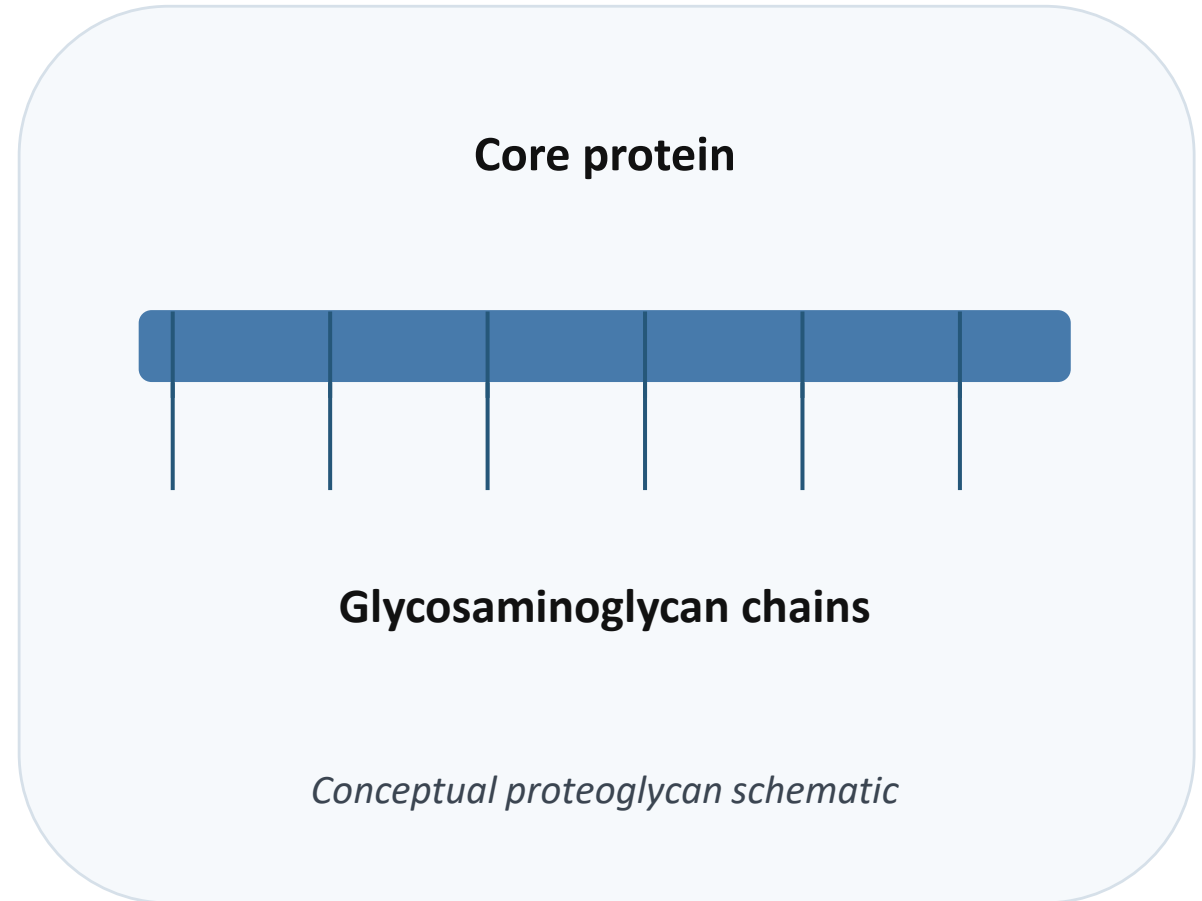
A lysosomal storage disease—not a primary collagenopathy

- Mucopolysaccharidoses are inherited defects of lysosomal substrate degradation.
- The stored substrate is glycosaminoglycan, not type I collagen.
- Skeletal pathology arises largely from altered cartilage development, growth, and joint structure.

Glycosaminoglycans are major matrix constituents

Why the substrate is important in cartilage and connective tissue

- Long, complex carbohydrate chains.
- Linked with core proteins to form proteoglycans.
- Abundant in extracellular matrix, connective tissue, and joint fluid.



The four glycosaminoglycans emphasized in MPS

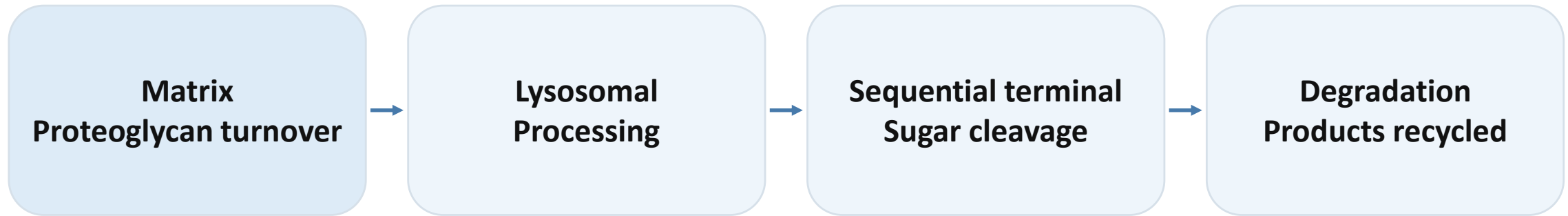
Accumulating glycosaminoglycan	Biologic context
Dermatan sulfate	Proteoglycan-associated connective tissue constituent
Heparan sulfate	Proteoglycan-associated glycosaminoglycan
Keratan sulfate	Contributes to connective tissue and cartilage matrix
Chondroitin sulfate	Component of proteoglycan-rich extracellular matrix

Source lists four storage substrates; Distribution and severity vary across disease types.

Why proteoglycan turnover requires enzymes

- Glycosaminoglycan chains cannot be cleared in a single nonspecific reaction.
- A sequence of lysosomal enzymes normally removes successive sugar residues.
- Loss of one required activity leaves incompletely degraded chains.

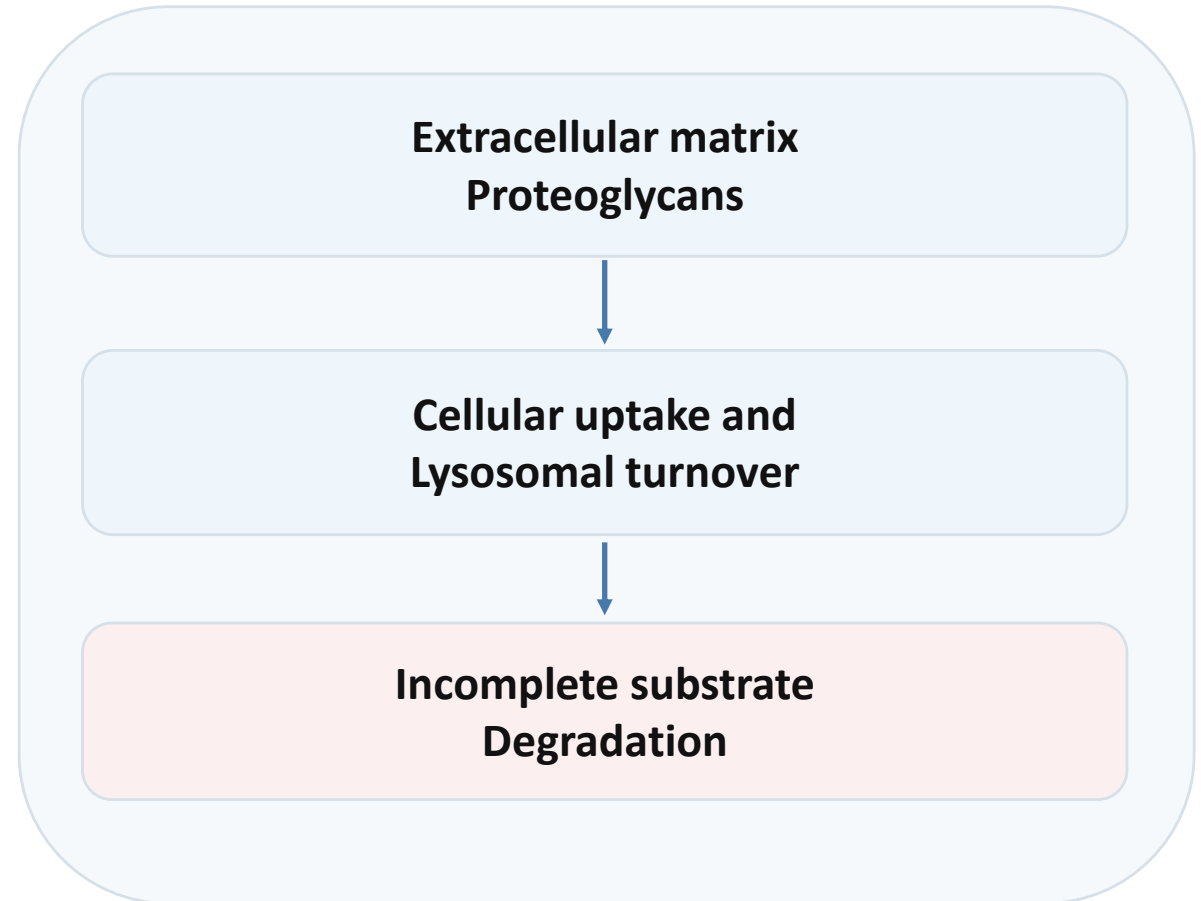
Normal lysosomal glycosaminoglycan clearance



The degradative pathway depends on multiple functioning lysosomal hydrolases.

Deficient acid hydrolase: The biochemical bottleneck

- Many implicated enzymes are lysosomal acid hydrolases.
- One missing or malfunctioning step interrupts GAG catabolism.
- Substrate remains within the lysosomal compartment.



Normal clearance versus the storage state

Functioning degradation

- Enzymatic cleavage proceeds sequentially.
- Products can be processed and recycled.
- Lysosomal substrate does not progressively accumulate.

Enzyme deficiency

- A required cleavage step is blocked.
- Residual GAG fragments persist.
- Lysosomes enlarge with stored material.

Mechanistic comparison—original conceptual schematic.

Primary lysosomal storage is the initiating lesion

- Inherited enzyme deficiency is the primary molecular defect.
- Unmetabolized glycosaminoglycans accumulate within lysosomes.
- Cell enlargement and malfunction follow accumulation across susceptible tissues.

Substrate localization predicts the organs at risk

- MPS affects cells that encounter or degrade GAG-rich material.
- Mesenchymal cells have major roles in extracellular matrix turnover.
- Systemic substrate distribution contributes to multisystem pathology.

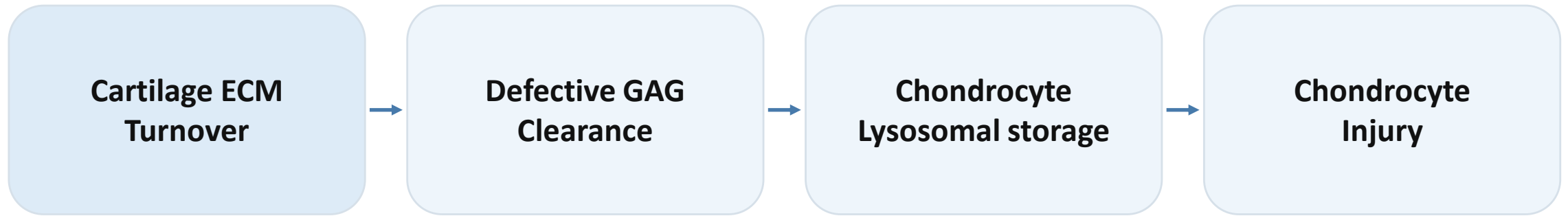
Cartilage and joints

**Vascular / cardiac
tissue**

Liver and spleen

Brain in some variants

Why chondrocytes are a pivotal target



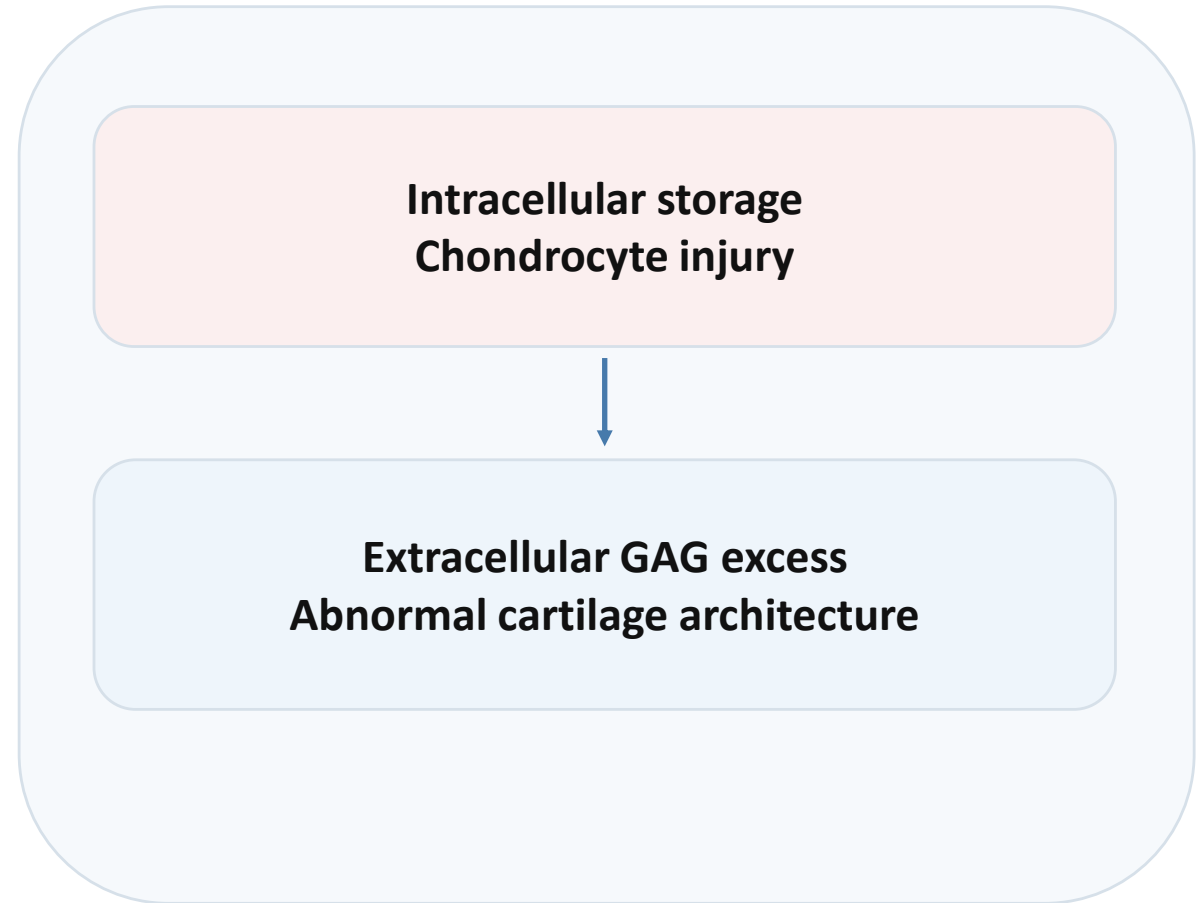
The chapter links storage in chondrocytes to apoptosis and cartilage malfunction.

Chondrocyte apoptosis drives a skeletal component

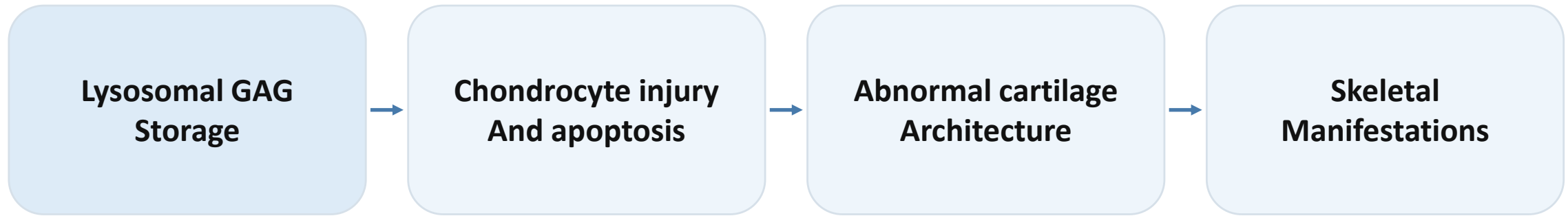
- Glycosaminoglycans accumulate within affected chondrocytes.
- The accumulated material is associated with chondrocyte apoptosis.
- Loss of viable cells compromises cartilage integrity and normal skeletal growth.

Extracellular storage adds structural matrix injury

- Abnormal glycosaminoglycans also accumulate outside cells.
- The extracellular burden produces structural defects in articular cartilage.
- Intracellular toxicity and matrix disruption act together.



Two convergent routes to cartilage pathology

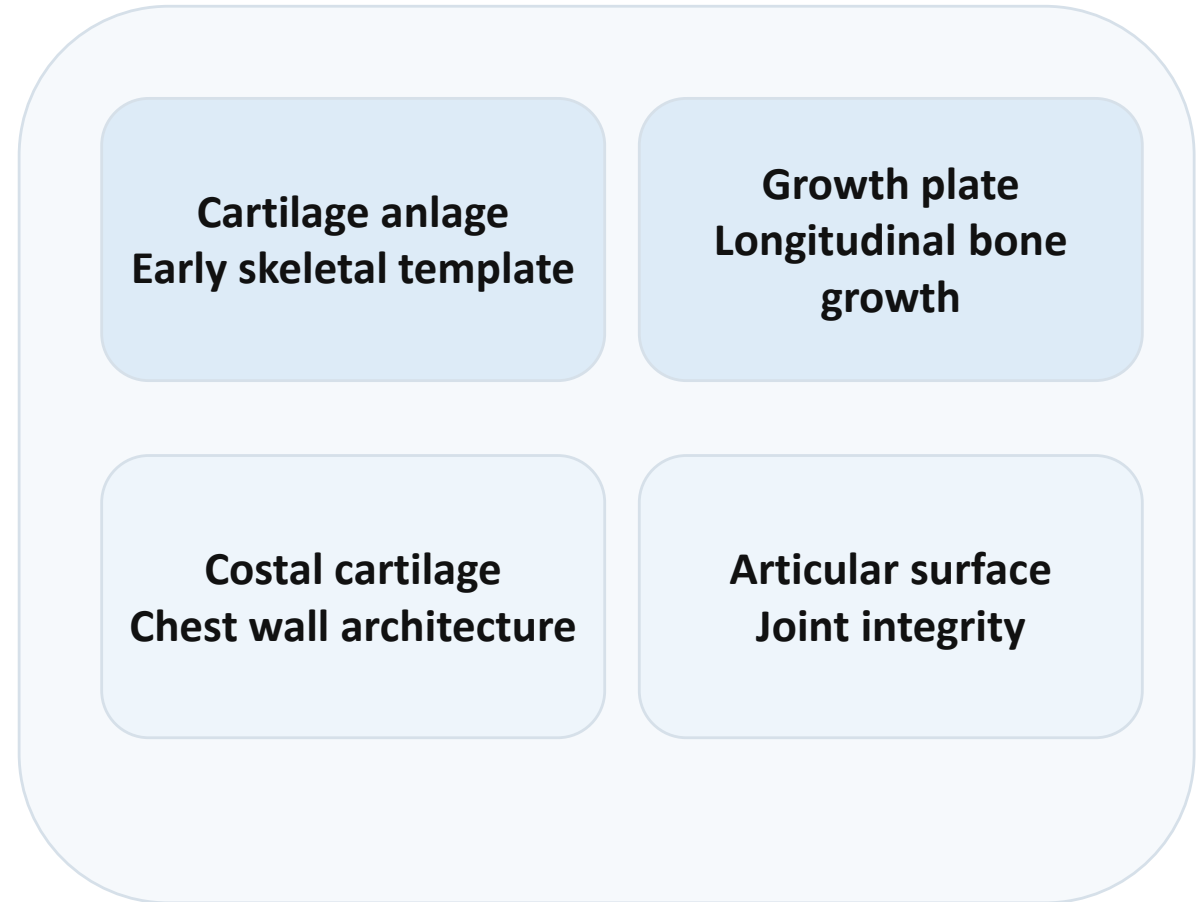


Extracellular substrate accumulation additionally disrupts articular cartilage.

The skeletal sites named by Robbins

Four cartilage-dependent structures explain the skeletal phenotype

- Cartilage anlage: The early skeletal template.
- Growth plates: Normal longitudinal growth.
- Costal cartilages: Chest-wall configuration.
- Articular surfaces: Joint structure.



Cartilage anlage and malformed bones

- The cartilage model guides development of many skeletal elements.
- MPS-related structural abnormalities affect that template.
- Malformed bones can therefore arise during skeletal development.

Growth-plate injury and short stature

- Endochondral bone growth depends on growth-plate cartilage.
- Stored GAGs disrupt the cellular and matrix environment.
- Impaired longitudinal growth helps explain short stature in MPS.

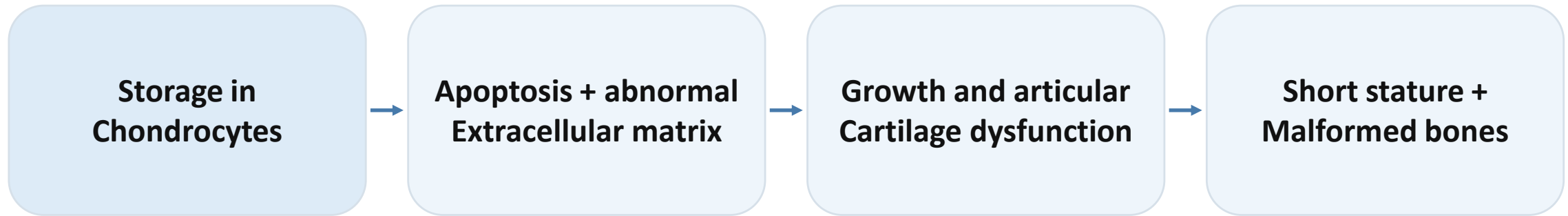
Costal cartilage and chest-wall abnormalities

- Ribs and sternum depend on costal cartilage for normal architecture.
- Disease affects this cartilage compartment.
- Chest-wall abnormalities are among the frequent skeletal manifestations.

Articular cartilage defects and joint disease

- Extracellular GAG accumulation compromises cartilage structure.
- Articular surfaces participate in the skeletal phenotype.
- Joint stiffness is a typical clinical manifestation.

From cartilage dysfunction to recognizable skeletal disease



The combined cellular and extracellular mechanism explains the skeletal phenotype.

Intracellular and extracellular contributions

Inside the chondrocyte

- Accumulated GAGs in lysosomes.
- Chondrocyte injury and apoptosis.
- Reduced maintenance of cartilage.

Within the matrix

- Excess extracellular GAGs.
- Structural defects of articular cartilage.
- Altered mechanical tissue integrity.

Two linked, not mutually exclusive, pathways.

MPS constitutes a genetically heterogeneous group

- Different enzyme defects produce related storage phenotypes.
- 11 clinical variants.
- Phenotypes can overlap because many variants affect GAG metabolism.

One enzyme deficiency can produce variable severity

- Different mutations can alter residual enzyme activity to different degrees.
- Subgroups can arise within a nominal MPS type.
- Clinical severity may therefore differ even when the affected enzyme is the same.

Most MPS variants versus Hunter syndrome

Most MPS disorders

- Autosomal recessive inheritance.
- Disease typically requires pathogenic alleles affecting both copies of the relevant gene.
- Both sexes can be affected.

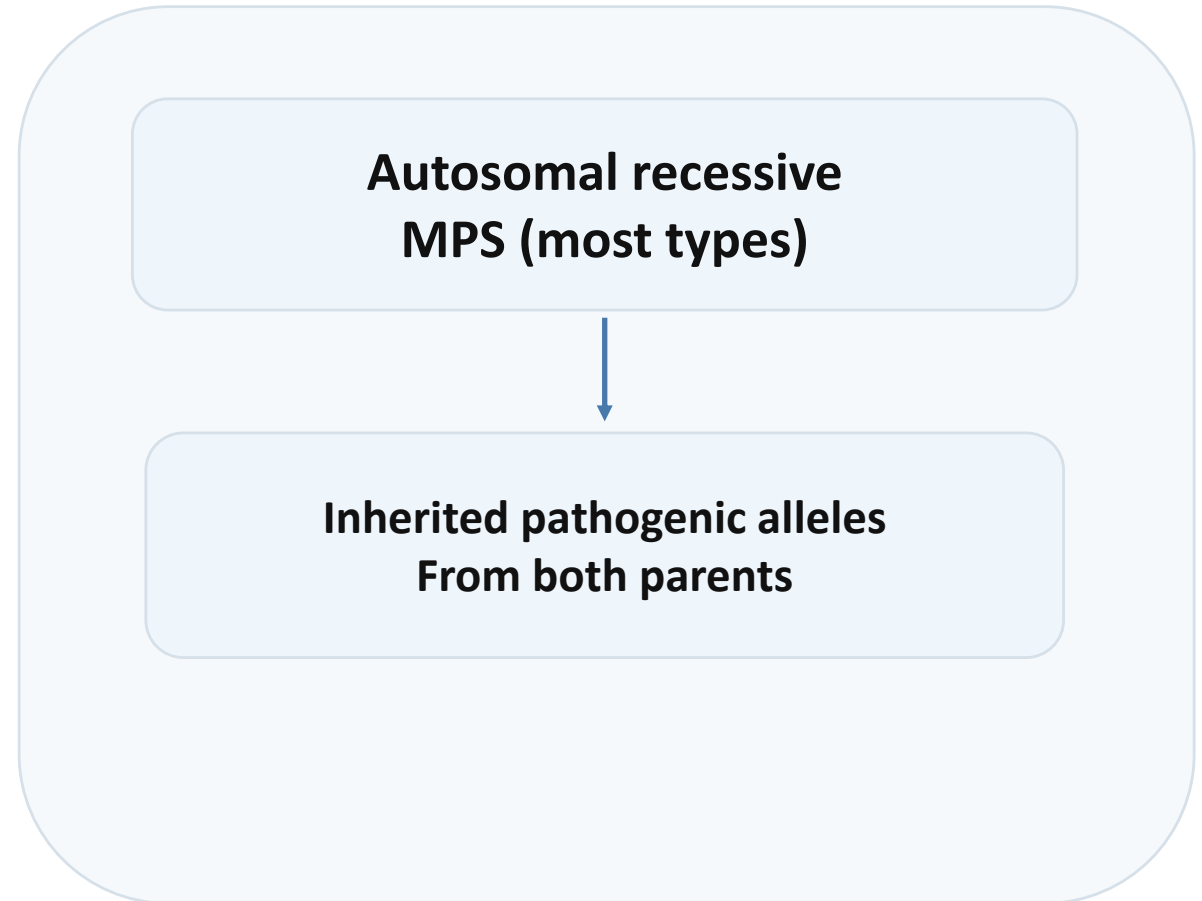
Hunter syndrome (MPS II)

- X-linked recessive inheritance.
- The important inheritance exception in this group.
- Sex-linked pedigree pattern guides suspicion.

Inheritance informs genetic counseling and diagnostic evaluation.

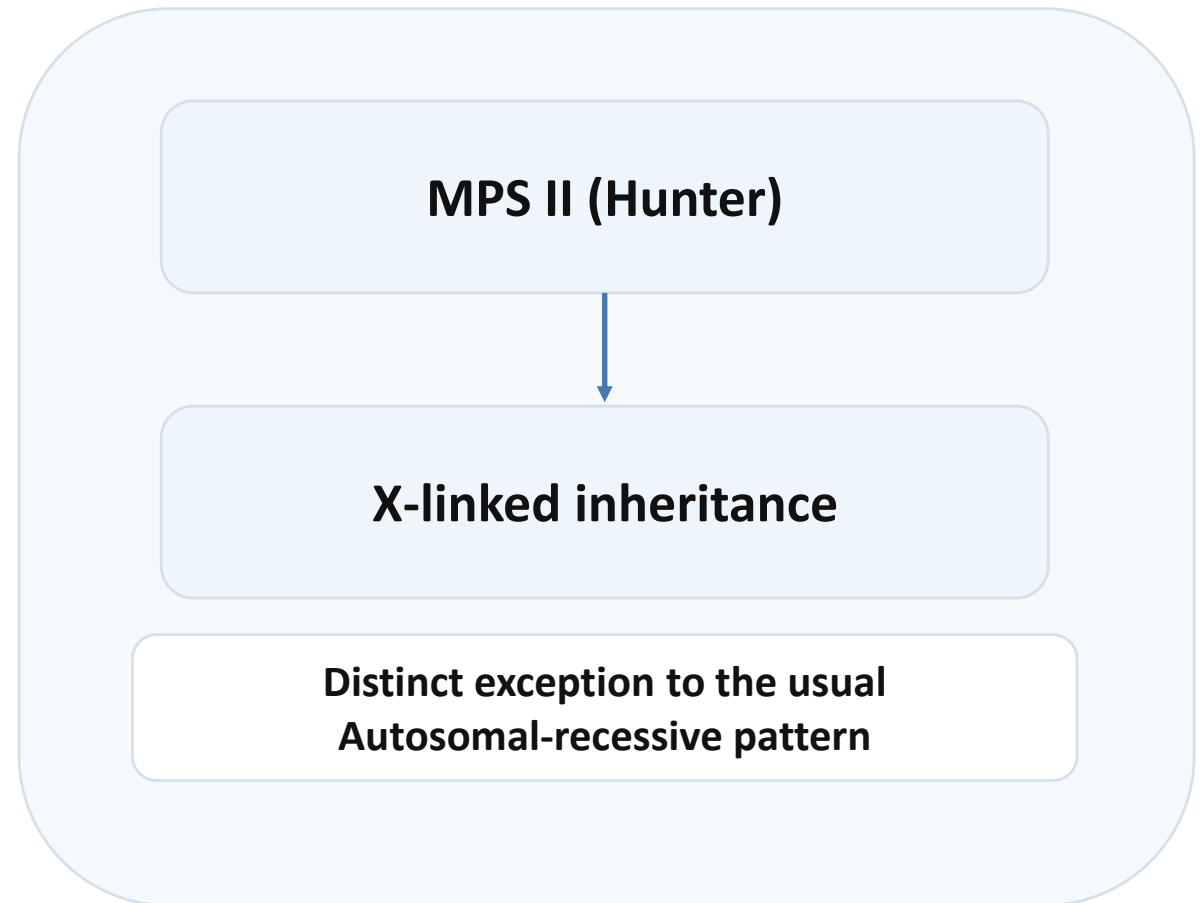
Autosomal recessive inheritance predominates

- All MPS types except Hunter are described as autosomal recessive.
- Carrier parents may be clinically unaffected.
- A positive family history is helpful but not essential for recognition.



Hunter syndrome is the X-linked exception

- MPS II is inherited as an X-linked recessive trait.
- This mode differs fundamentally from most other MPS syndromes.
- The inheritance pattern helps separate related clinical phenotypes.



Clinical variability makes morphology informative

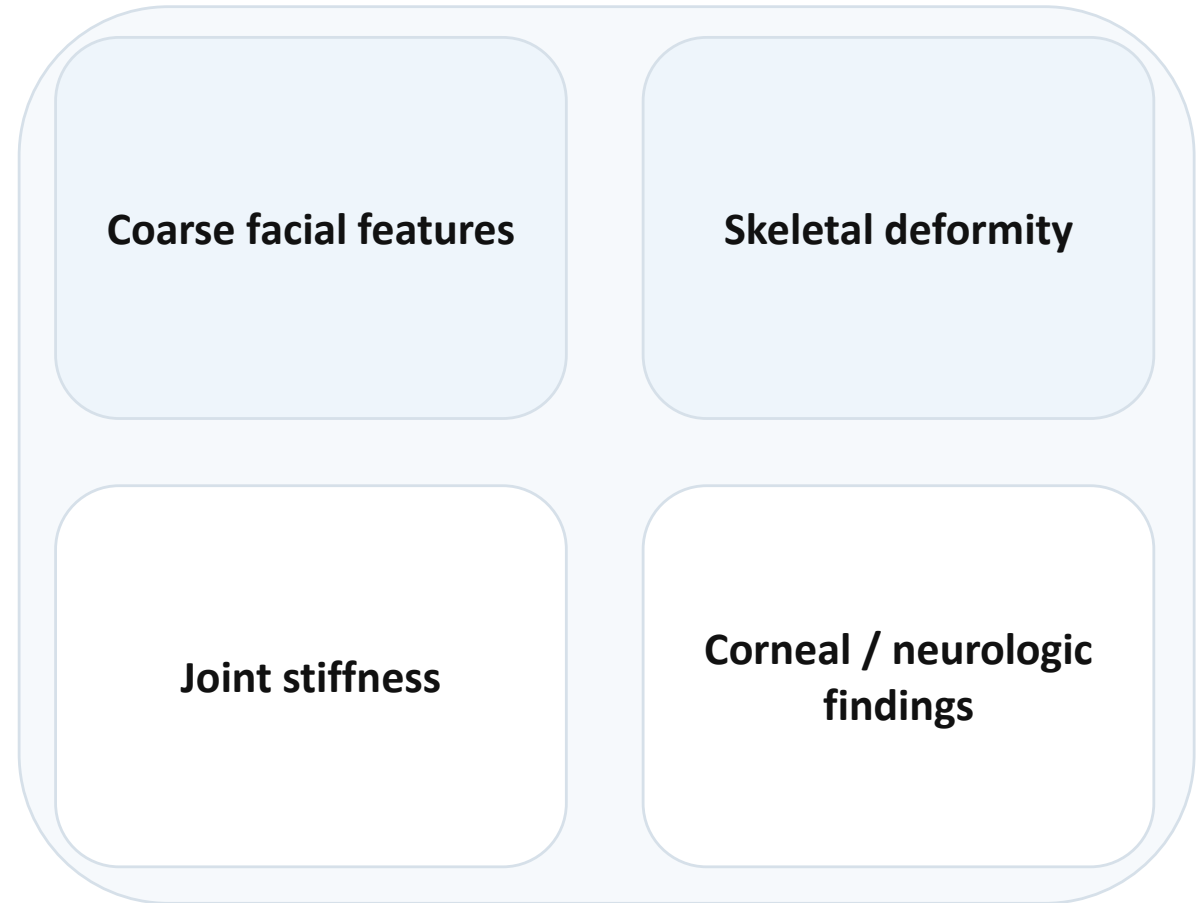
- No single symptom identifies every MPS subtype.
- Systemic storage can affect multiple organs to differing extents.
- Enzyme phenotype, inheritance, ocular findings, and course improve discrimination.

MPS generally follows a progressive course

- Storage is driven by continuing substrate production and impaired clearance.
- Clinical signs become more evident as the disease advances.
- The rate and intensity of progression vary between specific syndromes.

A characteristic clinical constellation

- Coarse facial features occur across the group.
- Joint stiffness and skeletal deformities are common.
- Corneal clouding and intellectual impairment occur in some forms.



Coarse facial features reflect multisystem storage

- A coarse facial appearance is characteristic of the MPS group.
- It is interpreted alongside the skeletal and visceral manifestations.
- Its presence is a clinical clue, not a specific enzyme diagnosis.

Corneal clouding provides a useful clinical discriminator

- Corneal clouding is part of the general MPS phenotype.
- It is highlighted in severe Hurler syndrome.
- Hunter syndrome classically lacks corneal clouding in the Robbins comparison.

Joint stiffness should prompt systemic assessment

- Joint stiffness is included among the recurring manifestations.
- The cartilage defect links joint findings to the metabolic storage process.
- A skeletal presentation alone may miss cardiac or visceral disease.

Intellectual impairment reflects CNS involvement in some forms

- Some MPS syndromes cause storage-related neuronal abnormalities.
- Intellectual disability appears in the general clinical description.
- Neurologic severity is not uniform across all variants.

Hepatosplenomegaly reflects visceral storage

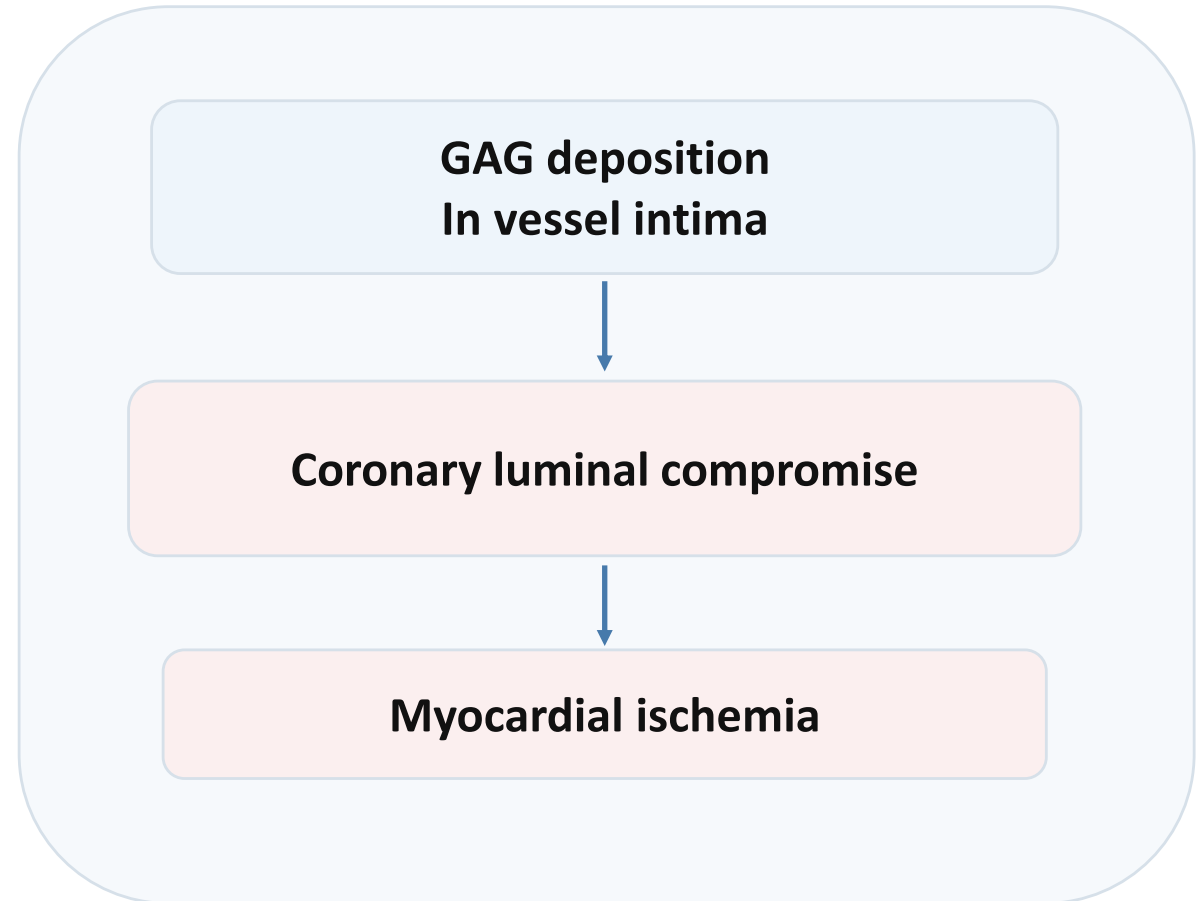
- Liver and spleen are common sites of glycosaminoglycan accumulation.
- Increased cellular substrate burden can produce organ enlargement.
- Hepatosplenomegaly is prominent in the Hurler clinical description.

Skeletal and visceral signs should be integrated

- Short stature and malformed bones identify the skeletal component.
- Coarse facies, hepatosplenomegaly, and joint findings suggest systemic storage.
- Cardiac and neurologic evaluation is important to characterize disease extent.

The heart and arteries are major targets

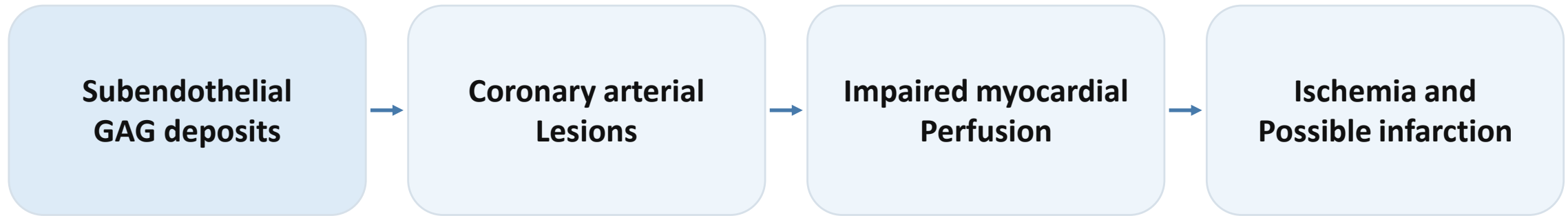
- Valvular lesions are described in the MPS group.
- Arterial subendothelial deposits, especially coronary, may develop.
- Severe involvement produces clinically important cardiovascular complications.



Cardiac valves: A storage-related lesion

- Glycosaminoglycan storage affects cardiac and vascular connective tissues.
- Valvular deposits cause structural valvular lesions.
- Cardiac abnormalities are significant contributors to disease morbidity.

Coronary subendothelial storage and ischemia



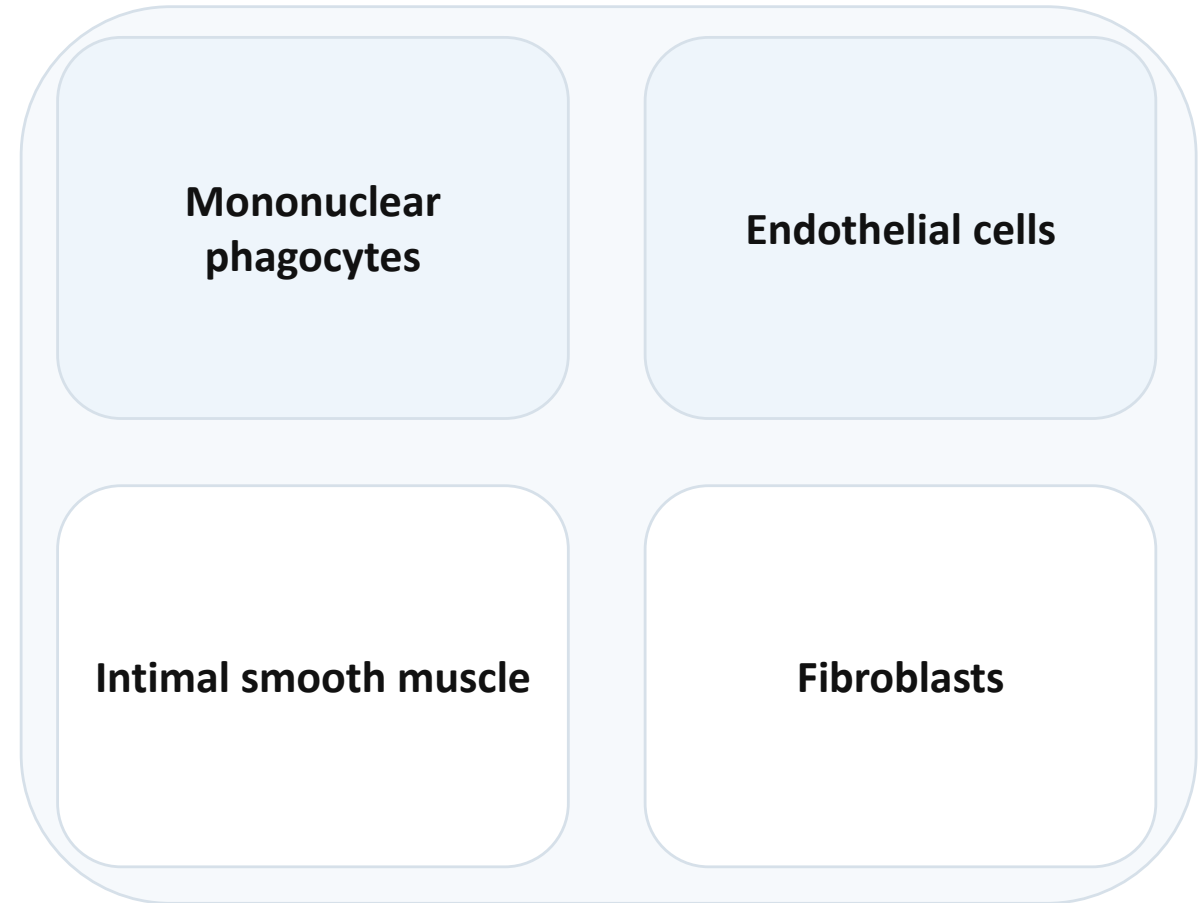
Myocardial ischemia and cardiac decompensation as important causes of death.

Cardiovascular disease can dominate late outcomes

- Coronary lesions occur particularly in more protracted syndromes.
- Myocardial ischemia and infarction may follow subendothelial disease.
- Cardiac decompensation can be fatal.

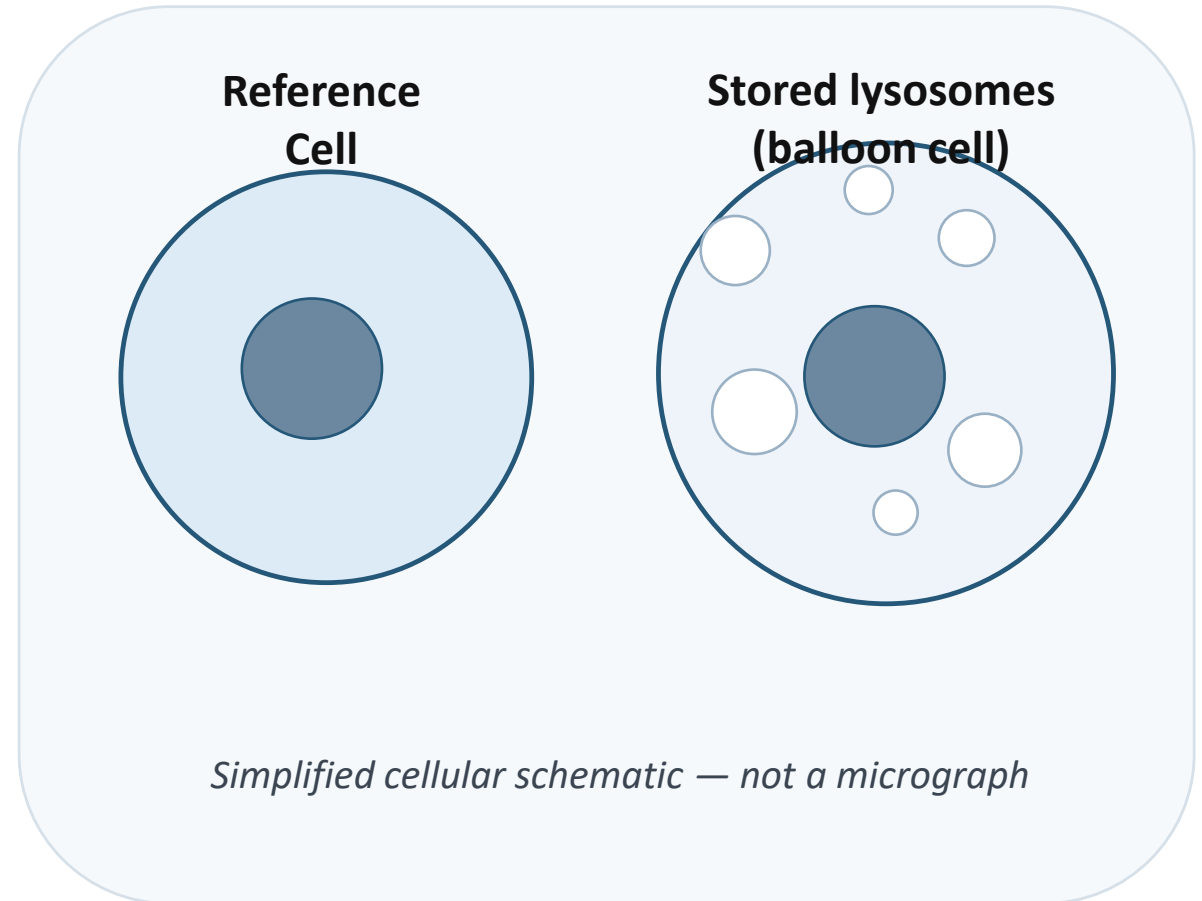
MPS is a systemic histopathologic storage process

- GAG storage occurs in mononuclear phagocytes, fibroblasts, endothelium, and intimal smooth muscle.
- The burden affects multiple tissue compartments rather than a single lineage.
- Affected cells become enlarged by lysosomal distension.



Balloon cells reflect enlarged storage lysosomes

- Microscopically, affected cells may appear distended.
- Cytoplasmic clearing creates the balloon-cell appearance.
- This appearance is linked to storage, not a unique cell lineage.



The vacuolated cytoplasm has an ultrastructural basis

- Clear cytoplasm represents numerous minute vacuoles.
- Electron microscopy identifies distended lysosomal compartments.
- These lysosomes contain the material that failed to undergo normal catabolism.

Stored material has a biochemical identity

- Swollen lysosomes contain finely granular material.
- This material as periodic acid–Schiff positive.
- Biochemical characterization identifies the substrate as mucopolysaccharide.

Light microscopy versus electron microscopy

Light microscopic pattern

- Enlarged cells with pale or cleared cytoplasm.
- Balloon-cell appearance due to intracytoplasmic storage.
- PAS-positive storage material is described.

Ultrastructural correlate

- Numerous minute lysosomal vacuoles.
- Expanded secondary storage compartments.
- Neuronal lamellated inclusions in selected syndromes.

Interpret clearing as a lysosomal-storage finding, not an isolated diagnosis.

Storage is distributed across reticuloendothelial organs

- Common affected sites include liver and spleen.
- Bone marrow and lymph nodes may contain affected cells.
- Distribution helps account for organ enlargement and multisystem manifestations.

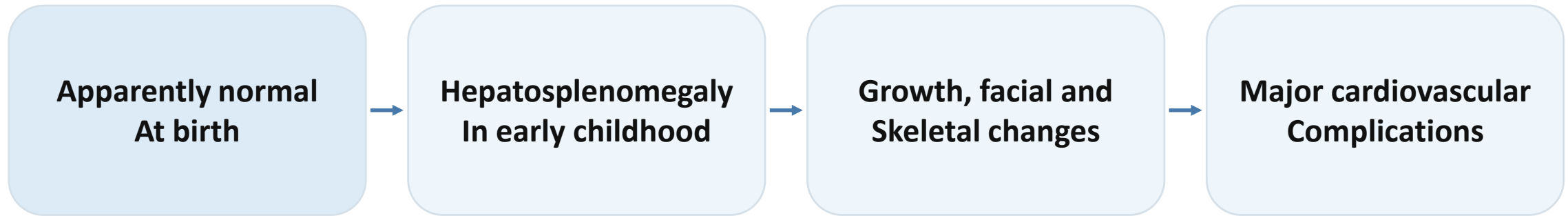
Neuronal involvement changes the clinical phenotype

- Some variants also store GAGs within neurons.
- Neuronal lysosomes may contain lamellated inclusions.
- CNS pathology correlates with cognitive and neurologic involvement.

MPS I: Deficiency of α -L-iduronidase

- Hurler syndrome is a severe form of MPS I.
- The deficient lysosomal enzyme is α -L-iduronidase.
- Dermatan sulfate and heparan sulfate are specified accumulating substrates Table 5.6.

Hurler syndrome: Evolution of the severe phenotype



The source describes hepatosplenomegaly becoming evident by 6–24 months.

Hurler syndrome: Clinically severe childhood disease

- The severe phenotype includes retarded growth and skeletal deformities.
- Coarse facial features and corneal clouding support recognition.
- Childhood mortality, frequently from cardiovascular disease.

MPS II: Hunter syndrome

- Hunter syndrome results from iduronate 2-sulfatase deficiency.
- It has X-linked recessive inheritance.
- Compared with Hurler syndrome, absent corneal clouding and a milder course.

Hurler syndrome and Hunter syndrome compared

Feature	Hurler syndrome (MPS I-H)	Hunter syndrome (MPS II)
Deficient enzyme	α -L-iduronidase	Iduronate 2-sulfatase
Inheritance	Autosomal recessive	X-linked recessive
Corneal clouding	Characteristic	Classically absent
Course in textbook	Severe childhood course	Generally milder than Hurler

The contrast is syndrome-level and does not capture all possible phenotypic variants.

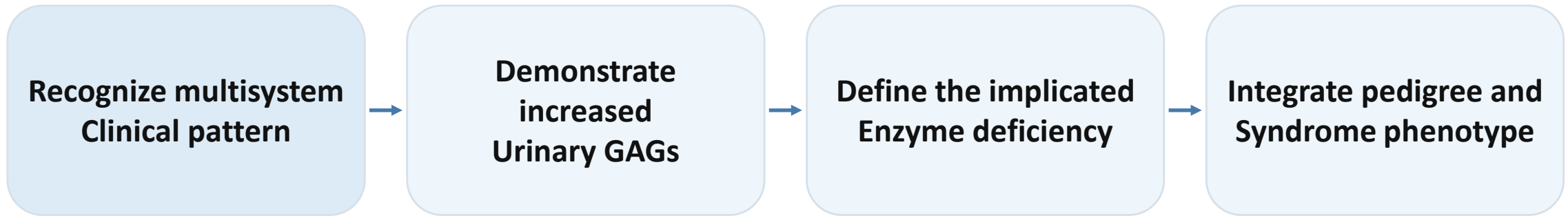
Why phenotypic overlap does not remove diagnostic distinctions

- Coarse facies and skeletal disease may occur in more than one MPS.
- Inherited enzyme deficiencies and substrate accumulation are shared mechanisms.
- Enzyme identity, inheritance, and ocular findings distinguish MPS I-H and MPS II.

Urinary glycosaminoglycan excretion is a diagnostic clue

- Stored mucopolysaccharides are often excreted in increased amounts in urine.
- Urinary GAG testing therefore provides a biochemical diagnostic clue.
- Urinary abnormalities do not, by themselves, identify the precise enzyme defect.

A source-grounded diagnostic reasoning sequence



Clinical suspicion and biochemical specificity answer different questions.

Diagnostic interpretation requires several layers

- Clinical pattern: Skeletal, ocular, visceral, cardiovascular, neurologic features.
- Biochemical level: Accumulating glycosaminoglycans.
- Molecular level: A deficient lysosomal enzyme and its inherited cause.

MPS versus other lysosomal storage diseases

Mucopolysaccharidoses

- Primary accumulation of glycosaminoglycans.
- Cartilage, connective-tissue, and vascular disease.
- Coarse facies and skeletal abnormalities.

Other storage diseases

- May primarily store glycolipids or glycogen.
- Organ distribution follows stored substrate and cell type.
- Certain diseases show neurologic or visceral patterns.

Shared lysosomal mechanism; Different accumulated substrates.

Clinicopathologic application: Case 1

A child appears normal at birth, then develops hepatosplenomegaly, impaired growth, coarse facial features, skeletal deformities, and corneal clouding.

Which MPS syndrome is strongly suggested, and which enzyme is deficient?

Case 1 interpretation

- The constellation strongly suggests the severe MPS I phenotype (Hurler syndrome).
- α -L-iduronidase deficiency underlies this syndrome.
- A biochemical and genetic workup would establish the subtype rather than the phenotype alone.

Clinical phenotype is suggestive—not a substitute for definitive subtype assignment.

Clinicopathologic application: Case 2

A child has coarse facial features, joint stiffness, and skeletal abnormalities. The family history suggests an X-linked trait, and corneal clouding is absent.

Which MPS syndrome should be prioritized, and what biochemical defect is expected?

Case 2 interpretation

- Hunter syndrome (MPS II) is supported by the X-linked inheritance pattern.
- The deficient enzyme is iduronate 2-sulfatase.
- Absent corneal clouding is a classic distinction from Hurler syndrome.

Clinical clues must be integrated with enzyme-based confirmation.

Morphology application: Case 3

A tissue sample contains enlarged vacuolated connective-tissue cells. Stored granular material is PAS positive; Ultrastructure shows multiple swollen lysosomes.

What general mechanism best explains the vacuolated cells?

Case 3 interpretation

- Stored glycosaminoglycans cause lysosomal distension and cell enlargement.
- Clear cytoplasm on light microscopy reflects lysosomal vacuoles.
- Cellular appearance alone is not specific for a particular MPS subtype.

Interpret microscopy in the biochemical and clinical context.

Mechanism application: Case 4

A patient with a glycosaminoglycan degradation disorder has short stature, malformed bones, joint stiffness, and chest-wall abnormalities.

Which cartilage compartments explain this combined skeletal pattern?

Case 4 interpretation

- Growth plates are implicated in impaired longitudinal growth.
- Cartilage anlage abnormalities contribute to malformed bones.
- Articular surfaces and costal cartilage help explain joint and chest-wall findings.

Chondrocyte injury and abnormal extracellular matrix unite the findings.

Integrated clinicopathologic model

- The molecular lesion is an inherited defect in lysosomal GAG degradation.
- The tissue lesion is substrate storage, with chondrocyte apoptosis and matrix dysfunction.
- The clinical phenotype couples skeletal malformation with visceral, cardiac, and sometimes CNS involvement.

Core facts to retain

- MPS is a multisystem lysosomal glycosaminoglycan storage disorder.
- Cartilage injury explains short stature, skeletal deformities, and joint disease.
- Balloon cells contain distended GAG-bearing lysosomes.
- Hurler is α -L-iduronidase deficient; Hunter is iduronate 2-sulfatase deficient and X-linked.

References

Principal textbook sources

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 26: Bones, Joints, and Soft Tissue Tumors. Printed p. 1070.
- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 5: Genes and Human Diseases. Printed pp. 139–140; Table 5.6.
- Lecture schematics are original PowerPoint shapes, not clinical specimens or reproductions of textbook figures.