

ATTR (Transthyretin) Amyloidosis

Protein misfolding, organ tropism, morphology and
clinicopathologic diagnosis

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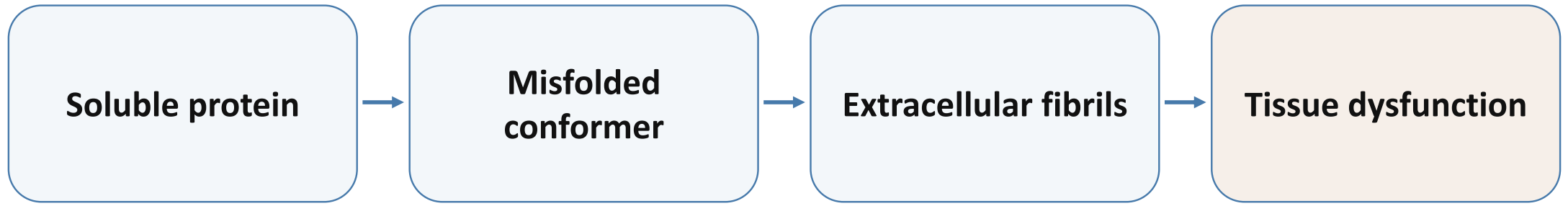
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Learning objectives

- Distinguish ATTRwt from autosomal-dominant ATTRv amyloidosis.
- Trace TTR misfolding to extracellular amyloid accumulation and organ injury.
- Explain cardiac and neuropathic phenotypes from deposit location.
- Separate detection of amyloid from definitive identification of its protein.

A correct diagnosis requires both the amyloid phenotype and its molecular type.

Amyloidosis is a protein-deposition disorder



Schematic

- Amyloid forms when aggregation-prone proteins accumulate as insoluble extracellular fibrils.
- Clinical effects reflect progressive distortion and loss of normal tissue architecture.

Transthyretin has a normal transport role

Normal transthyretin (TTR)

A circulating plasma protein

Transports thyroxine and retinol-associated cargo

In ATTR disease

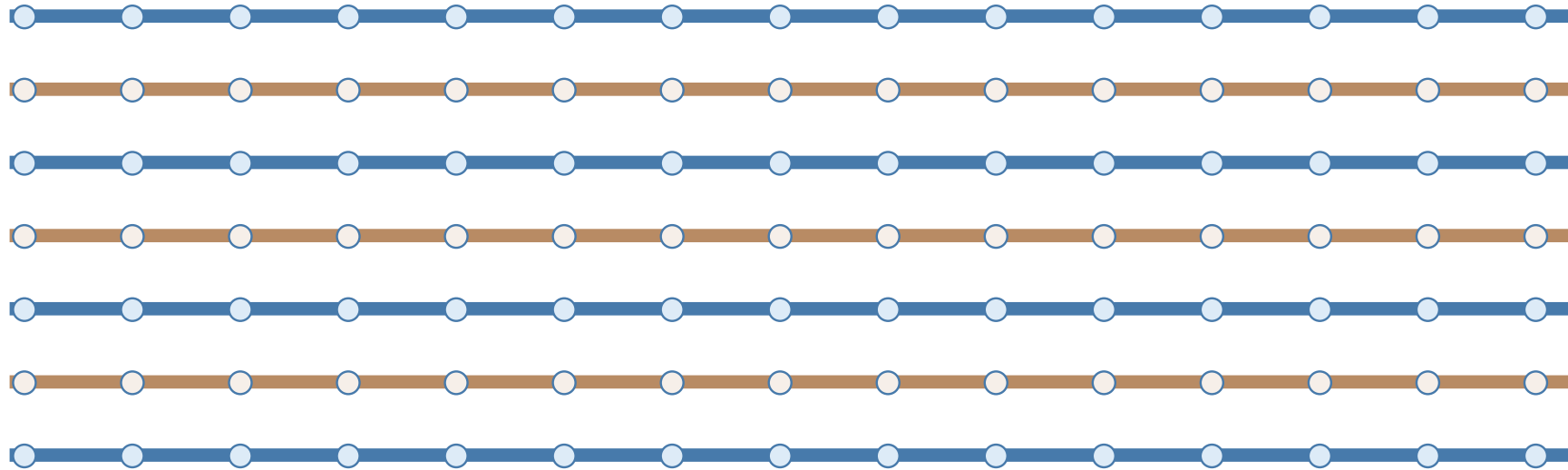
The same precursor becomes amyloidogenic

Fibrils accumulate in susceptible tissues

Amyloid identity depends on the fibril protein

Amyloid type	Precursor protein	Source-supported context
AL	Immunoglobulin light chains	Clonal plasma-cell proliferation
ATTR	Transthyretin	Aging-associated or inherited
AA	Serum amyloid A–derived	Chronic inflammatory states

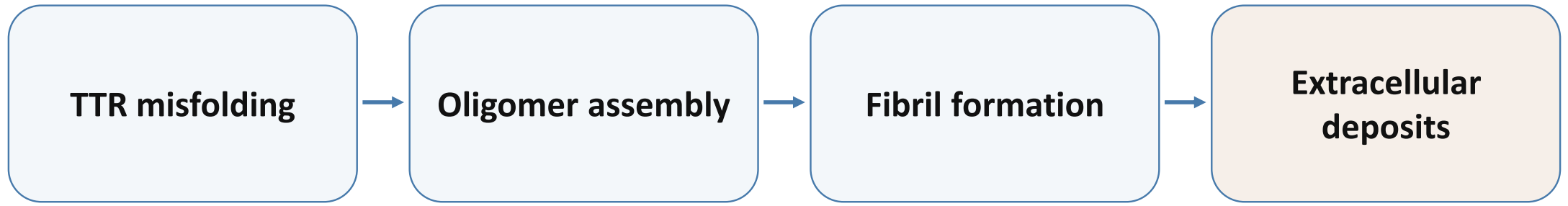
Amyloid has a shared ultrastructural architecture



Continuous, nonbranching fibrils (schematic)

- Nonbranching amyloid fibrils measure approximately 8–10 nm in diameter.
- A cross- β -pleated organization produces a common staining signature across amyloid types.
- Identical architecture does not imply identical precursor proteins.

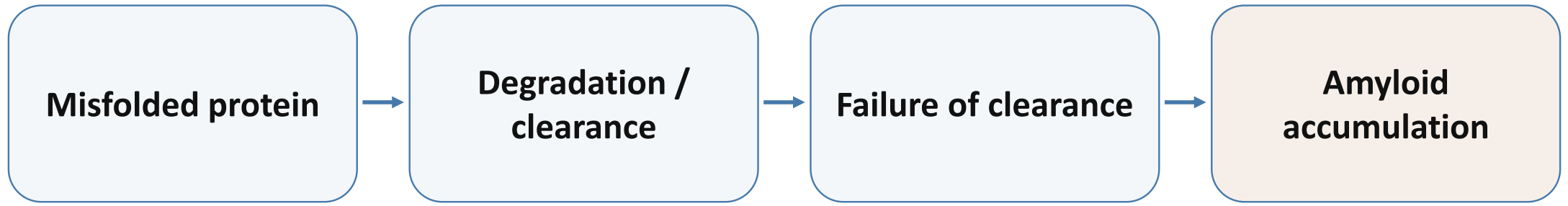
TTR aggregation follows a multistep process



Schematic

- Aging of wild-type TTR or a TTR variant can initiate pathological misfolding.
- Aggregates ultimately form insoluble amyloid fibrils in tissue.

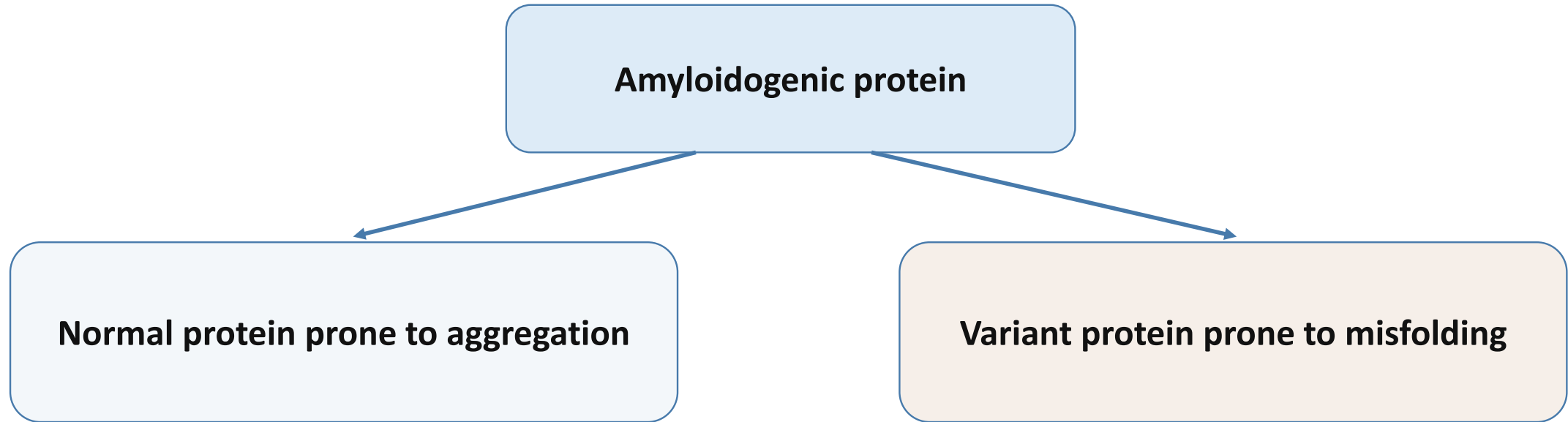
Protein quality control normally limits aggregation



Schematic

- Intracellular proteasomes and extracellular macrophages can remove misfolded proteins.
- Amyloidogenesis reflects escape from these protective mechanisms.

Two routes generate aggregation-prone precursors



Schematic

- Amyloid can arise from a normal protein that misfolds with aging or altered turnover.
- Alternatively, an inherited altered protein may have heightened aggregation propensity.

ATTR is defined by its deposited protein

- ATTR names amyloid fibrils derived from transthyretin.
- TTR may be wild-type or genetically variant.
- ATTR classification refers to protein origin—not just the affected organ.
- Cardiac amyloidosis is a phenotype; ATTR specifies an amyloid type.

Deposit type and clinical phenotype answer different diagnostic questions.

Amyloid can be localized or systemic

Localized deposits

Fibrils accumulate near their site of production

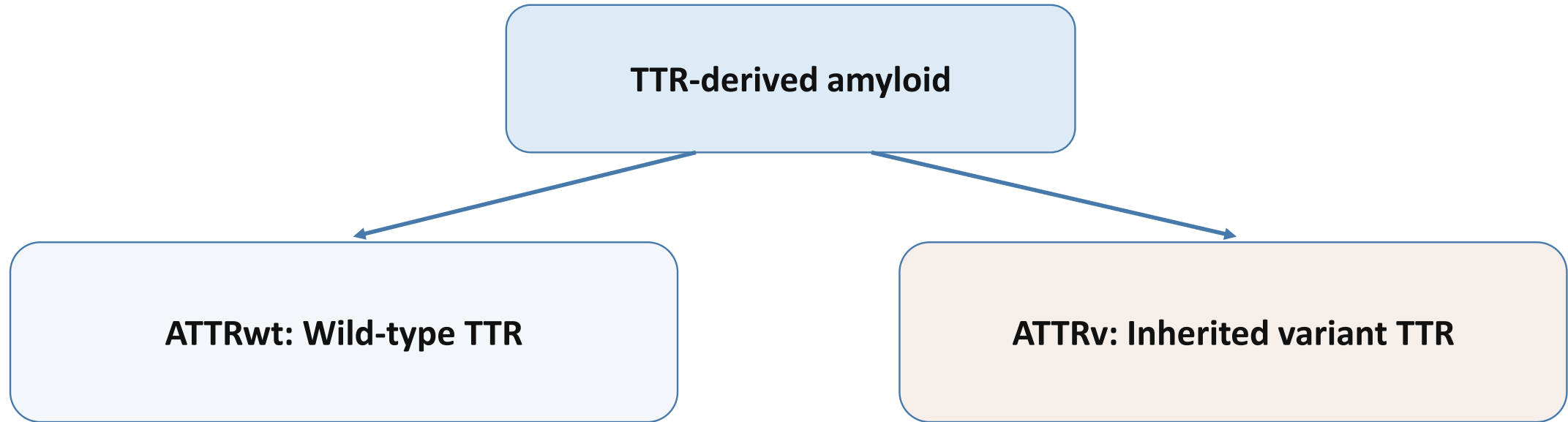
Distribution depends on the precursor

Systemic deposits

Circulating precursor can deposit in distant organs

ATTR commonly involves several susceptible tissues

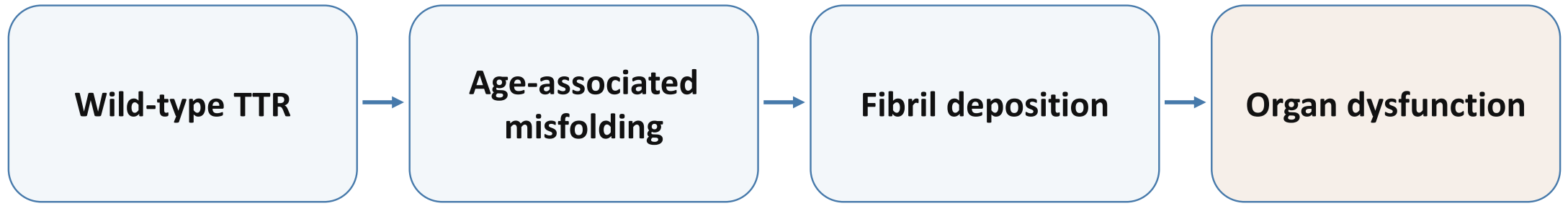
ATTR separates into two etiologic categories



Schematic

- ATTRwt reflects aggregation of otherwise normal transthyretin.
- ATTRv arises from a variant TTR polypeptide and is autosomal dominant.

ATTRwt develops without a TTR sequence variant



Schematic

- ATTRwt is an acquired, age-associated form of TTR amyloidosis.
- Normal TTR can become insoluble and accumulate despite unchanged protein sequence.

ATTRwt primarily affects older adults

- Typical presentation in men older than 70 years.
- The heart is the principal involved organ.
- ATTRwt is described as the second most common form of systemic amyloidosis.
- Increasing prevalence is linked in the text to population aging.

Demographics are a clue, not a definitive biochemical amyloid type.

The heart is the dominant ATTRwt target

Heart

Predominant deposition

Ligaments

Connective-tissue
deposits possible

Other tissues

Site-dependent
distribution

- Wild-type TTR deposits commonly accumulate in myocardium.
- Connective tissues, including ligaments, can also contain deposits.

Ligament deposits broaden the ATTRwt phenotype

Cardiac disease

Amyloid in myocardium and associated structures

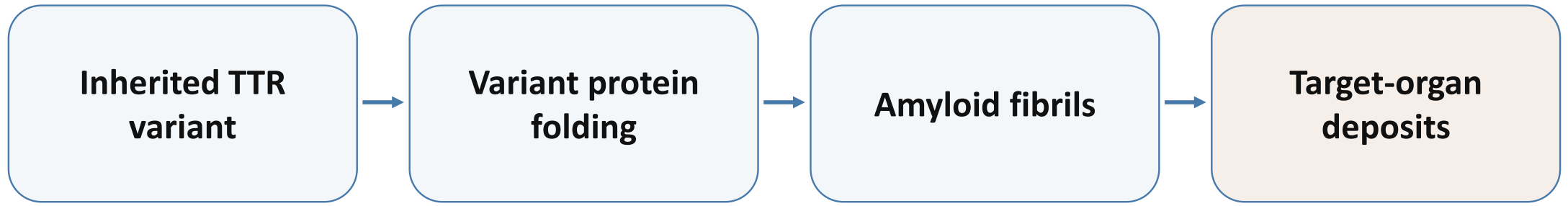
May produce restrictive physiology

Extracardiac involvement

TTR deposits in connective tissue

Organ distribution is not exclusively myocardial

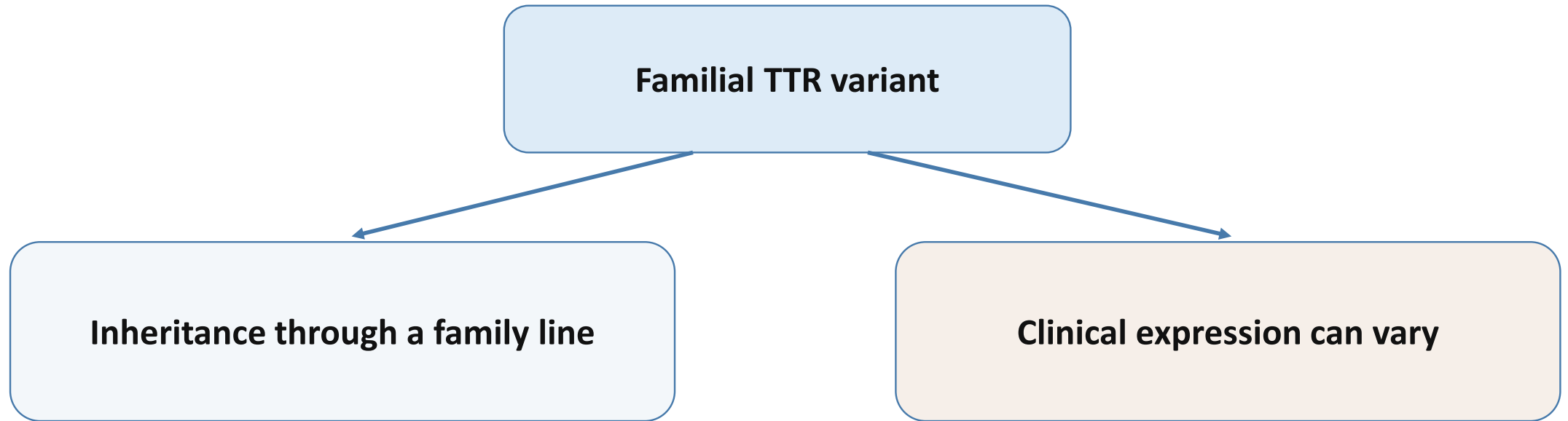
ATTRv reflects a genetically altered precursor



Schematic

- TTR sequence variation can increase the tendency of the protein to misfold.
- Variant-specific properties help determine tissue deposition patterns.

ATTRv follows autosomal-dominant inheritance



Schematic

- The source identifies ATTRv as autosomal dominant.
- Clinical severity cannot be predicted solely from carriage of a variant.

Different TTR variants favor different organs

Peripheral nerves

Polyneuropathy
phenotype

Autonomic nerves

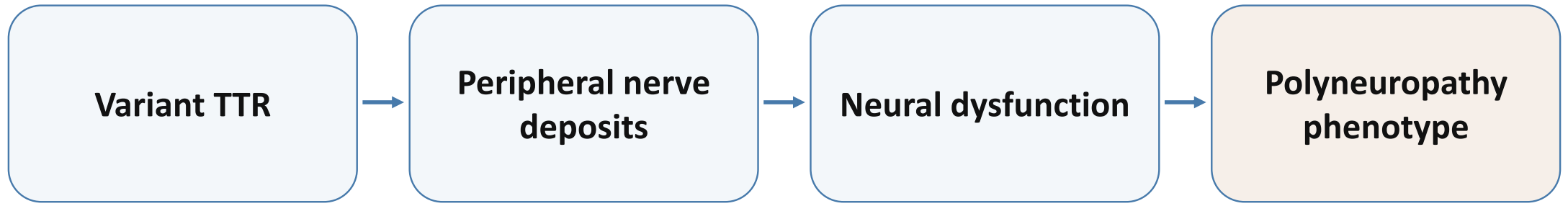
Autonomic neuropathy
phenotype

Heart

Cardiomyopathy
phenotype

- Variant TTR polypeptides are associated with distinct organ tropism.
- Both neurologic and cardiac patterns occur in hereditary families.

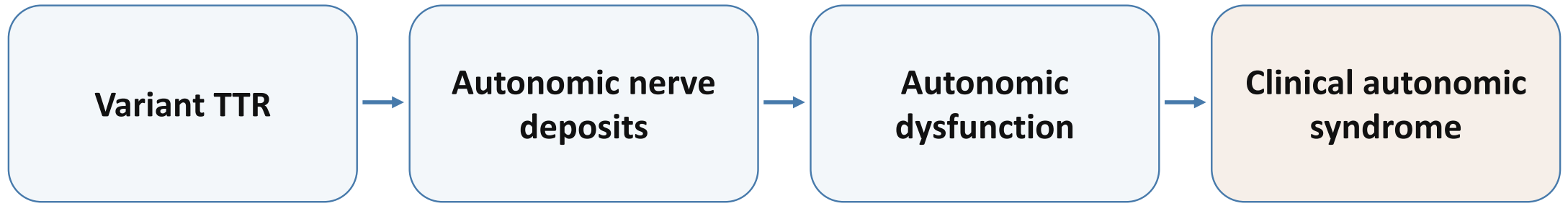
Hereditary polyneuropathy is an ATTRv pattern



Schematic

- Some hereditary ATTR families principally develop peripheral nerve amyloidosis.
- The source calls this phenotype familial amyloid polyneuropathy.

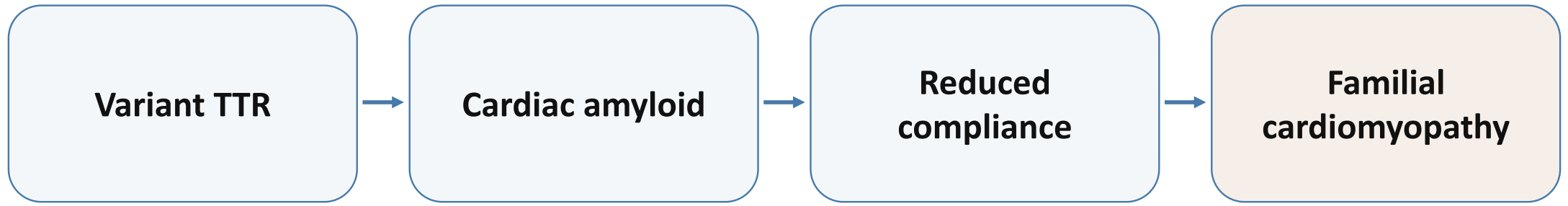
Autonomic nerves can be involved in ATTRv



Schematic

- Autonomic nerve involvement accompanies the neuropathic disease spectrum.
- The anatomical location of deposits explains why manifestations differ across tissues.

Hereditary cardiomyopathy is another ATTRv pattern



Schematic

- In other hereditary families, deposits predominantly accumulate in the heart.
- The designation ATTRv-CM for familial transthyretin cardiomyopathy.

Clinical expression shows incomplete penetrance

Genetic status

The same pathogenic variant may be present in relatives

Autosomal-dominant inheritance

Observed disease

Severity differs substantially between carriers

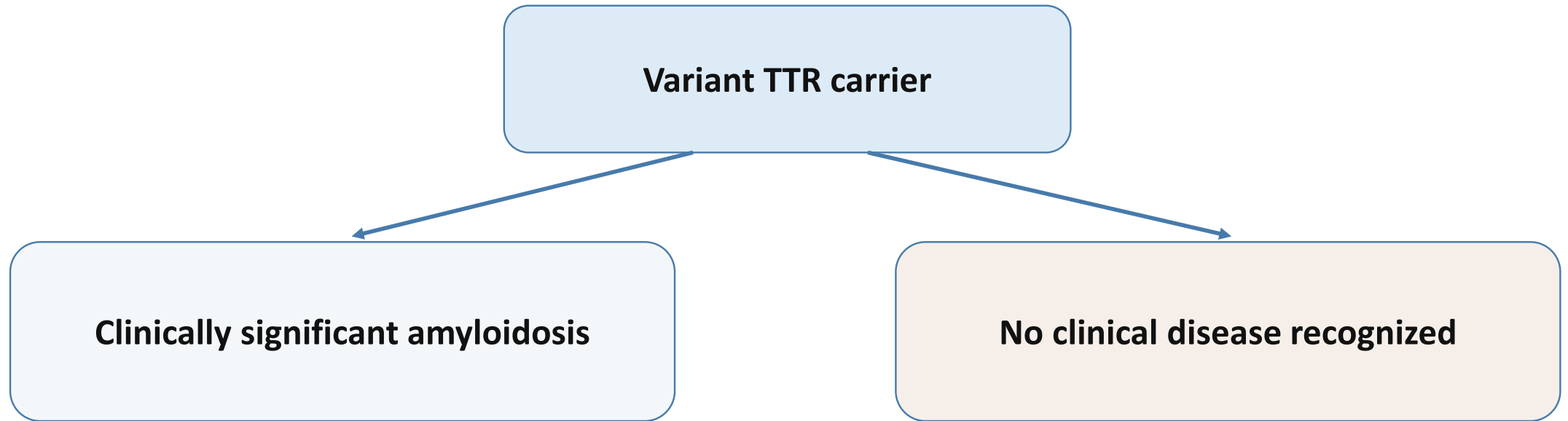
Some develop severe disease; Others remain without disease

Robbins gives a founder-variant example

- The chapter describes a cardiac-amyloid-associated TTR variant linked to West African ancestry.
- It reports carriage in approximately 4% of the African-American U.S. Population.
- Cardiomyopathy has been recognized in heterozygotes and homozygotes.
- Clinical penetrance is variable; Ancestry alone does not establish disease.

The quoted population estimate belongs to this textbook edition—not an individualized risk model.

A TTR variant is not a clinical destiny



Schematic

- The source describes marked variability among carriers.
- Presence of an allele and evidence of tissue injury are distinct observations.

Wild-type and variant ATTR: Essential contrasts

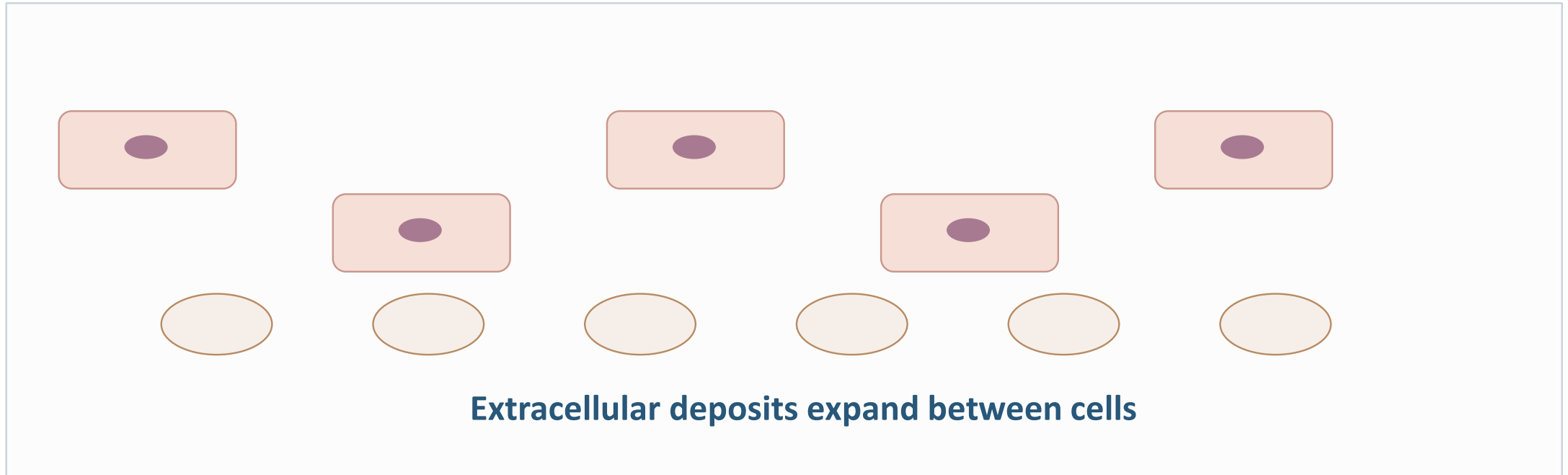
Feature	ATTRwt	ATTRv
Precursor	Wild-type TTR	Variant TTR
Basis	Acquired / age-associated	Autosomal dominant
Characteristic organs	Heart; ligaments possible	Heart; peripheral/autonomic nerves
Phenotypic variability	Cardiac-predominant	Variant-specific tropism and penetrance

Organ phenotype does not establish amyloid type

- Cardiac deposition can arise from more than one amyloid precursor.
- Similar extracellular material is seen with AL, ATTR and AA fibrils.
- Typing the protein is necessary for a subtype-specific diagnosis.

A cardiac phenotype supports suspicion; Amyloid protein identification establishes type.

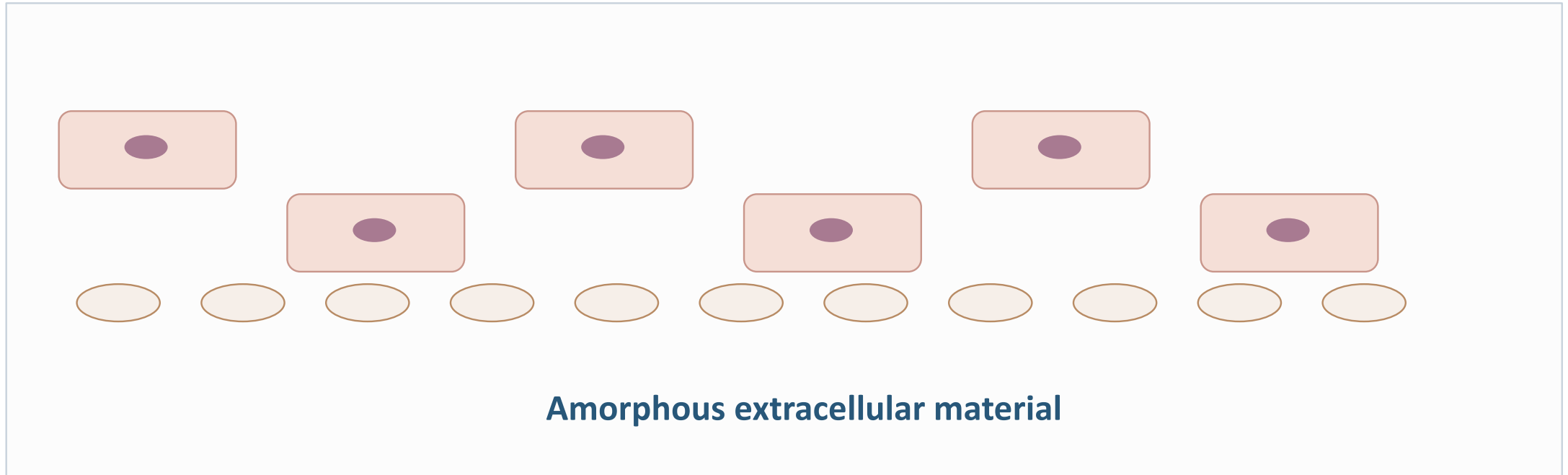
Extracellular deposition distorts tissue architecture



Schematic—not a histologic specimen

- Amyloid first accumulates between cells, often near basement membranes.
- Increasing extracellular material compresses, isolates and may destroy adjacent parenchymal cells.

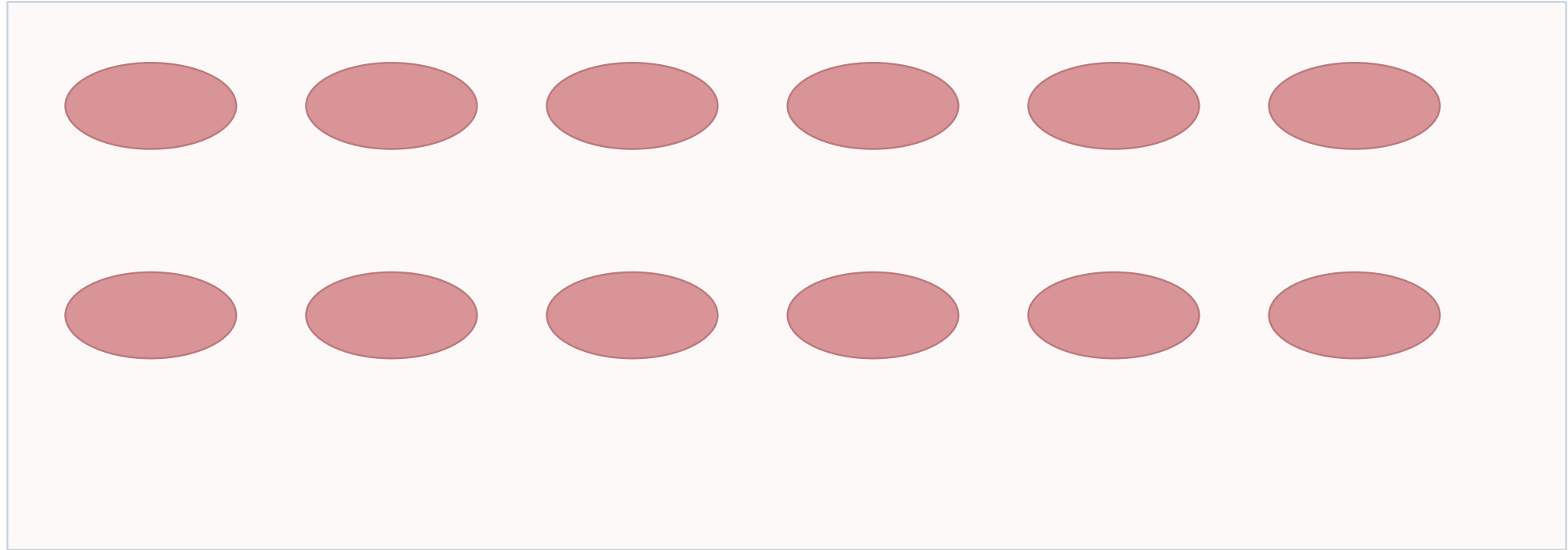
Amyloid is eosinophilic and hyaline on H&E



Schematic—not a histologic specimen

- On H&E, deposits appear amorphous, eosinophilic and extracellular.
- This appearance is not unique to TTR and can resemble other hyaline substances.

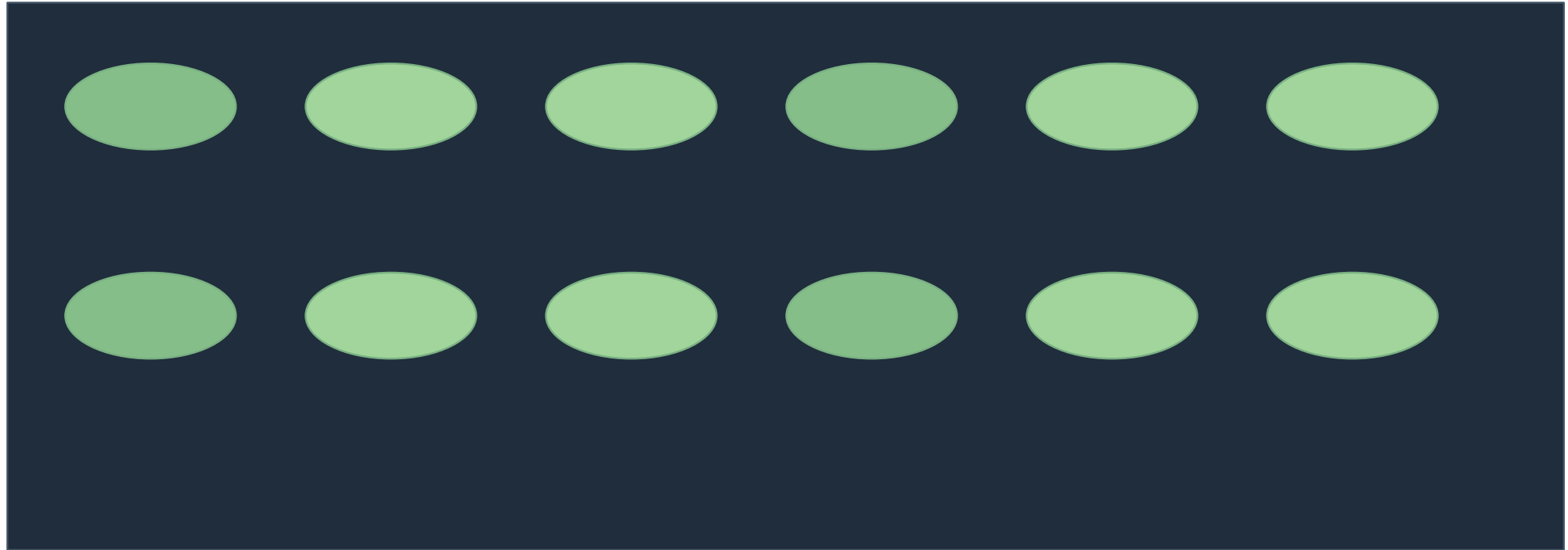
Congo red highlights the amyloid deposit



Pink/red Congo red–positive tissue material

- Congo red stains amyloid pink to red under ordinary transmitted light.
- Staining identifies the material as amyloid but cannot specify ATTR by itself.

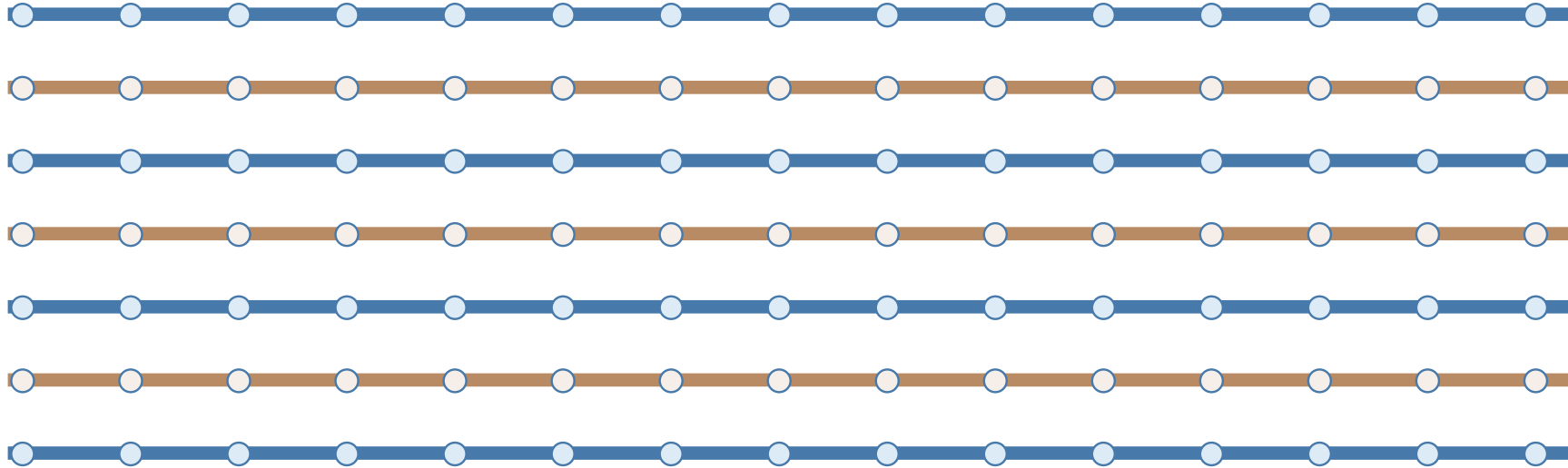
Polarization reveals characteristic birefringence



Optical birefringence after Congo red + polarization

- Congo red–stained amyloid shows characteristic apple-green birefringence under polarized light.
- Its optical properties reflect the shared β -pleated fibril arrangement.

Electron microscopy demonstrates fibrils



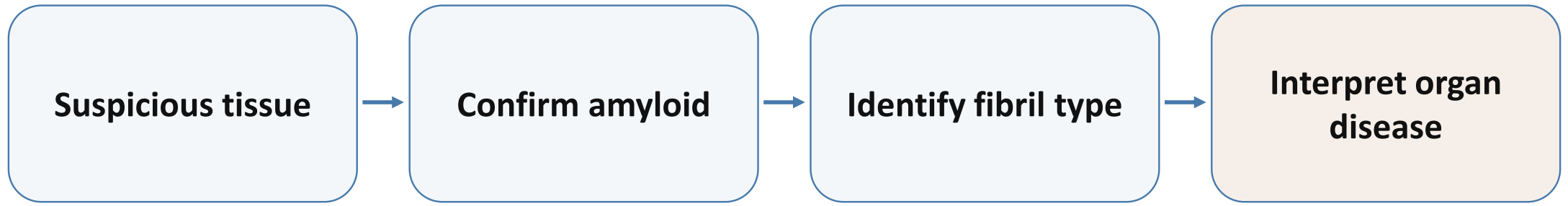
Continuous, nonbranching fibrils (schematic)

- Amyloid consists of continuous, nonbranching fibrils.
- Fibril diameter is about 8–10 nm.
- Ultrastructure demonstrates amyloid architecture—not its unique molecular precursor.

All amyloid types share a morphologic endpoint

Finding	What it supports	What it cannot resolve
Extracellular hyaline	Abnormal deposited material	Which precursor protein
Congo red birefringence	Amyloid fibrils	ATTR versus AL/AA
Nonbranching fibrils	Amyloid ultrastructure	Wild-type versus variant TTR

Histologic confirmation and protein typing are distinct



Schematic

- Morphologic techniques establish the presence of amyloid.
- Biochemical typing is a second, indispensable classification step.

Immunohistochemistry can help distinguish types

Tissue finding

Confirmed Congo red–positive amyloid

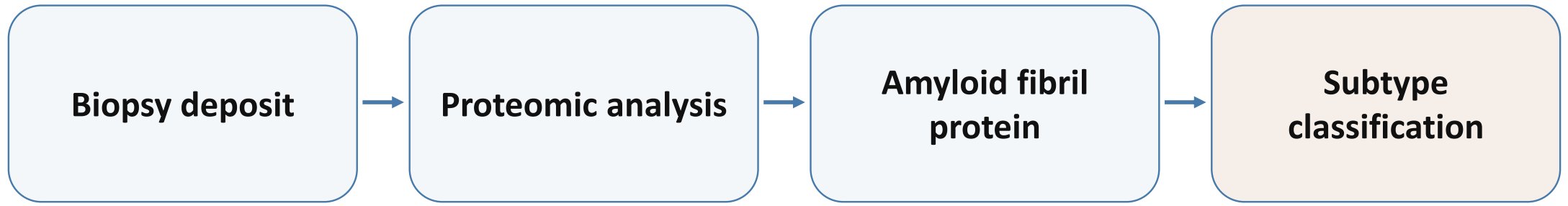
Protein still unidentified

Type-specific assessment

Immunostains can distinguish TTR, AL and AA amyloid

Interpretation requires appropriate controls

Mass spectrometry provides amyloid protein identity



Schematic

- Mass spectroscopy can identify amyloid types in specialized centers.
- Protein-level identification separates the appearance of amyloid from its biochemical source.

Distribution alone is an unreliable amyloid classifier

Clinical distribution

Suggests organs at risk and directs sampling

May raise suspicion of ATTR

Biochemical identity

Requires investigation of fibril protein

Cannot be inferred from the organ map alone

Cardiac amyloidosis may have subtle gross findings

- The heart may appear near normal, firm or rubbery on gross inspection.
- Chambers are usually normal in size but can become dilated.
- Walls may be thickened as amyloid accumulates.
- Absence of dramatic gross change does not exclude myocardial deposits.

Microscopy is often more decisive than gross appearance.

Atrial endocardium may show waxy nodules

Reported gross feature

Small semitranslucent nodules

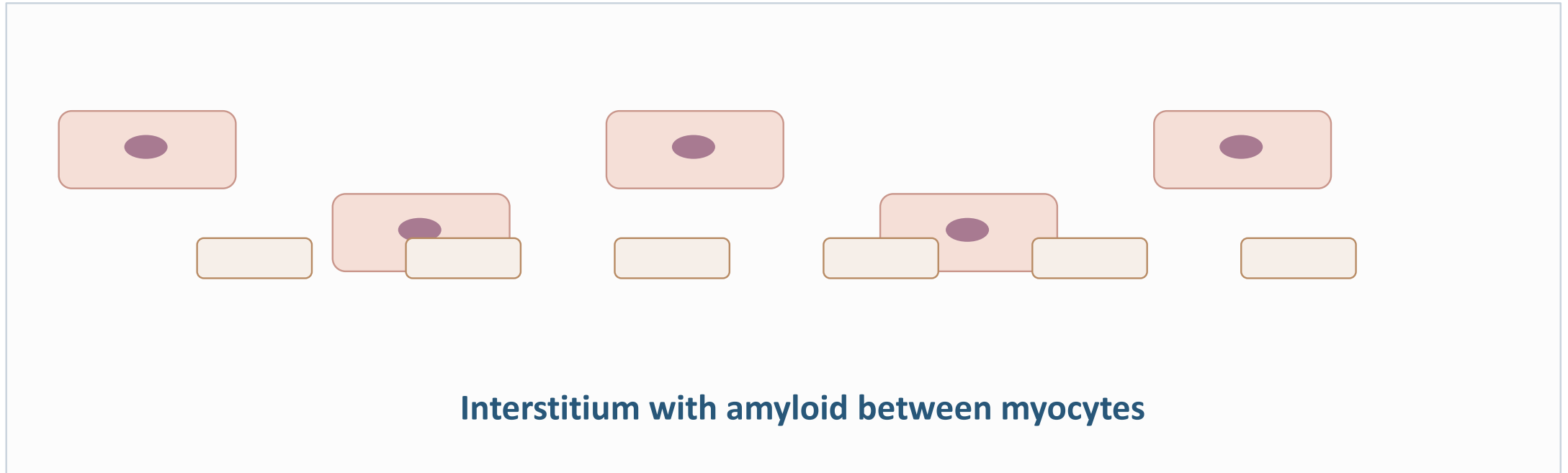
Resemble drops of wax

Anatomic site

Atrial endocardial surface

Especially left atrium in the description

Amyloid occupies the cardiac interstitium



Schematic—not a histologic specimen

- Hyaline eosinophilic material appears between cardiomyocytes.
- Progressive interstitial deposits separate muscle fibers and compromise myocardial architecture.

Cardiac deposits are not confined to myocardium

Interstitial

Myocyte separation

Conduction tissue

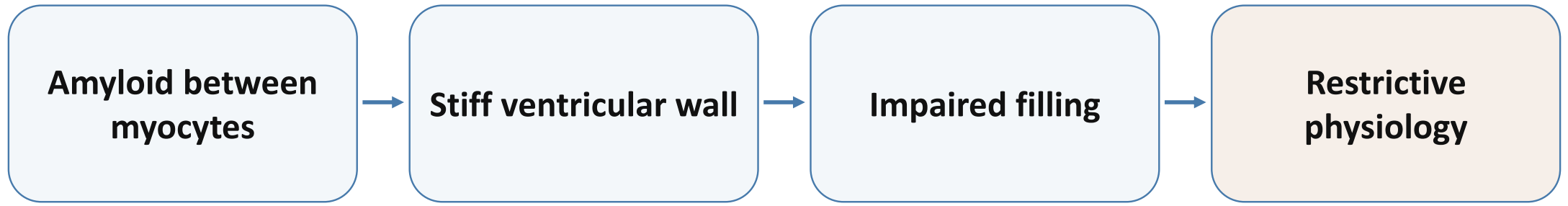
Electrical dysfunction

Small arteries

Luminal narrowing

- Additional deposits may involve valves, endocardium and pericardium.
- The dominant site explains diverse cardiac manifestations.

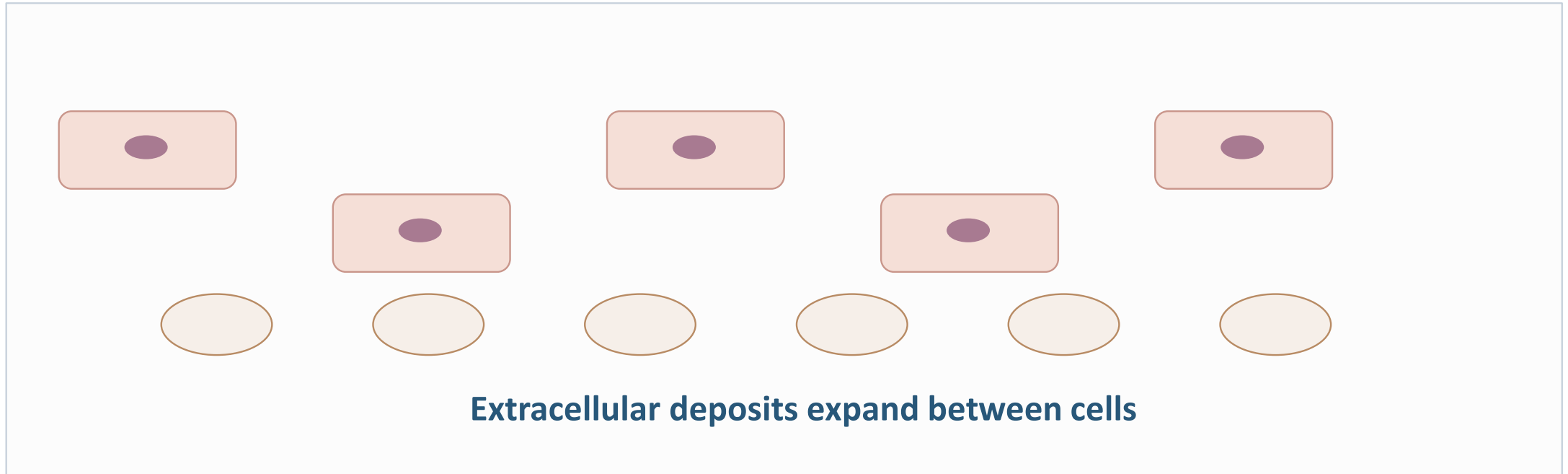
Extracellular infiltration reduces compliance



Schematic

- A growing extracellular burden limits ventricular distensibility.
- Restrictive cardiomyopathy is a common functional expression of cardiac amyloidosis.

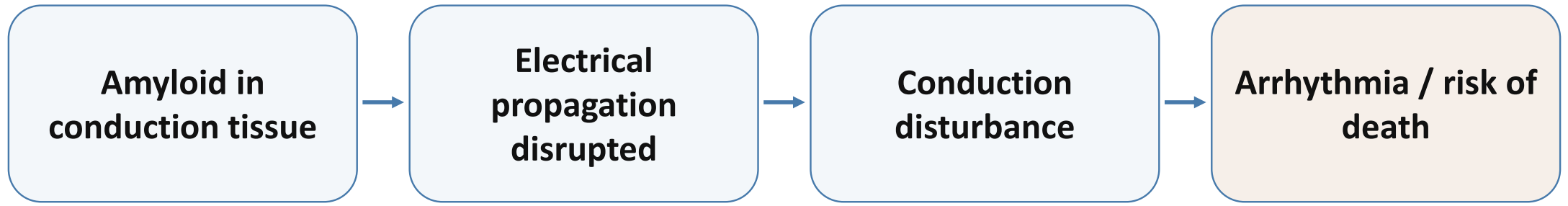
Accumulating amyloid causes myocyte atrophy



Schematic—not a histologic specimen

- Deposits progressively expand between cardiomyocytes.
- Mechanical encroachment and pressure atrophy contribute to loss of viable muscle.

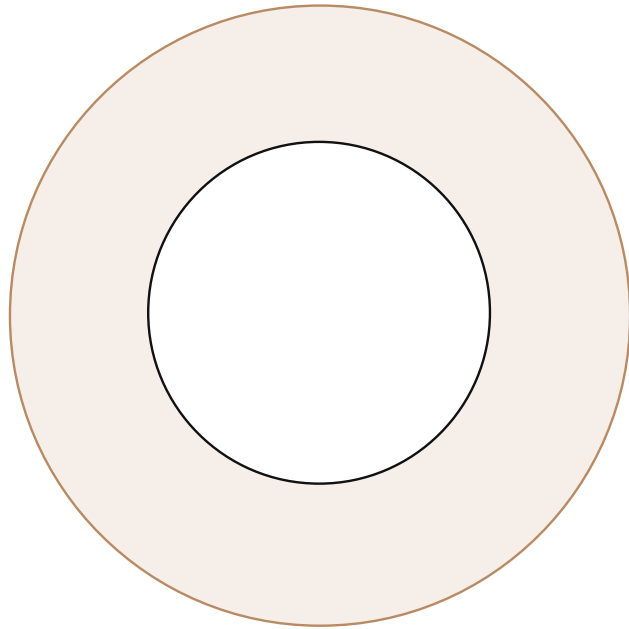
Conduction-system involvement can be dangerous



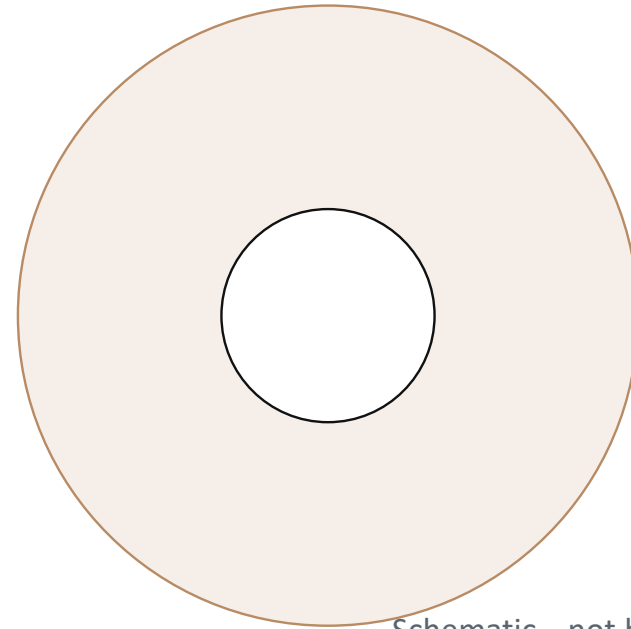
Schematic

- Subendocardial and conduction-system deposits can injure cardiac conduction pathways.
- Conduction abnormalities and arrhythmias as serious cardiac consequences.

Intramural arterial deposits can cause ischemia



Less narrowed vessel lumen



Schematic—not histology

Amyloid-laden vessel wall

- Amyloid may accumulate in the walls of small intramural coronary arteries.
- Progressive vessel narrowing can impair myocardial perfusion even without large-vessel coronary disease.

Cardiac presentation is clinically heterogeneous

Deposit location / burden	Possible expression
Extensive ventricular interstitium	Restrictive cardiomyopathy or heart failure
Conduction system	Rhythm or conduction abnormalities
Small intramural arteries	Small-vessel ischemia
Variable extent / location	Asymptomatic or disease mimicking other cardiac disorders

Why a thick heart can still fill poorly

Morphologic observation

Ventricular walls may be thickened

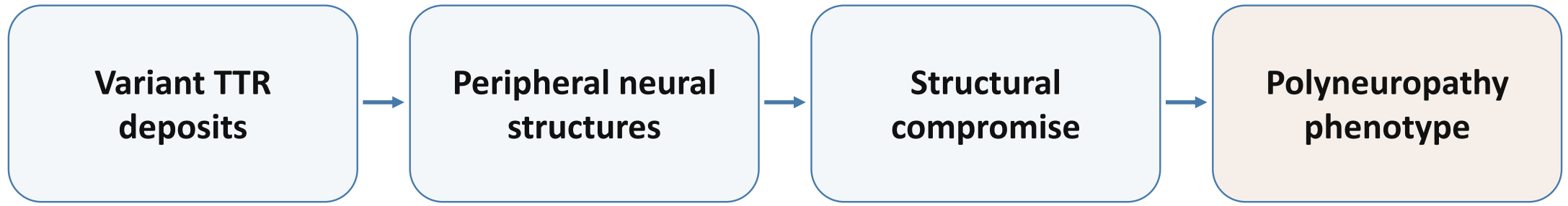
Chamber size may remain normal

Physiologic consequence

Excess interstitial material stiffens myocardium

Filling restriction may dominate function

Peripheral nerve involvement defines another axis



Schematic

- Hereditary ATTR may preferentially involve peripheral nerves instead of the heart.
- The major phenotype is determined by tissue distribution, not by a different stain reaction.

Autonomic and somatic nerve disease can coexist

Peripheral nerves

Familial amyloid polyneuropathy

Peripheral nerve deposits

Autonomic nerves

Autonomic nerve involvement

Visceral regulation may be affected

Connective-tissue deposits require context

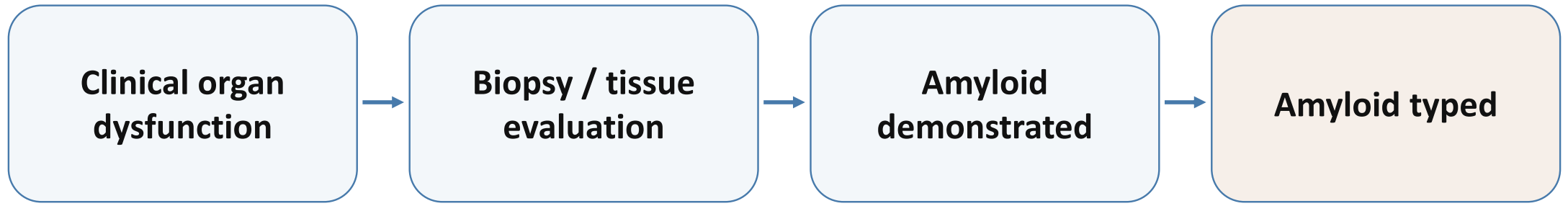
- Wild-type transthyretin deposits may be present in ligaments.
- Finding amyloid outside myocardium is compatible with ATTRwt.
- A particular ligament location alone does not identify the amyloid fibril protein.

Anatomical clues should lead to typing, not replace it.

Variant-specific tropism and penetrance are different

Concept	Question answered	Source finding
Organ tropism	Where does amyloid tend to deposit?	Variant-specific cardiac or neural patterns
Penetrance	Will a carrier manifest disease?	Wide variability, including no disease
Disease severity	How severe is the phenotype?	May differ substantially among carriers

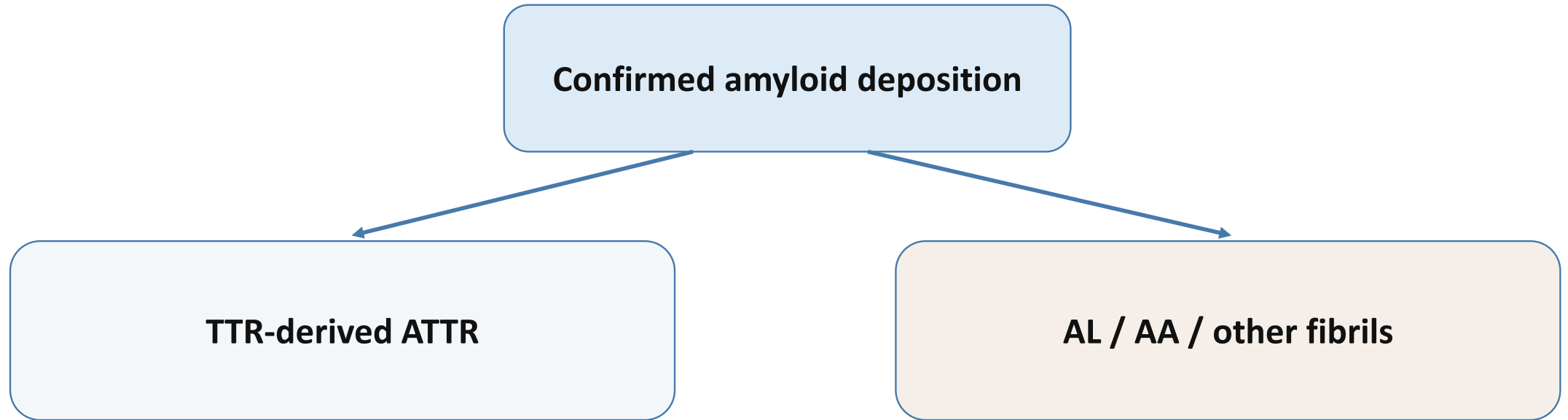
Diagnostic reasoning begins with the tissue finding



Schematic

- The source emphasizes histologic demonstration in appropriate tissue.
- Typing resolves whether deposits are ATTR, AL or another amyloid.

Congo red positivity is not an ATTR diagnosis



Schematic

- Shared staining properties establish amyloid, not its protein of origin.
- The precursor must be identified before a specific amyloidosis label is assigned.

ATTR and AL differ in precursor biology

Property	ATTR amyloidosis	AL amyloidosis
Fibril precursor	Transthyretin	Immunoglobulin light chains
Underlying biology	Age-related or inherited TTR misfolding	Clonal plasma-cell light-chain production
Overlap	Both may involve heart	Both may involve heart
Typing requirement	Demonstrate TTR origin	Demonstrate light-chain origin

ATTR and AA differ in causal setting

Property	ATTR amyloidosis	AA amyloidosis
Precursor	Transthyretin	Serum amyloid A–derived
Major trigger	Wild-type aging / TTR variants	Persistent inflammatory stimulation
Common patterns	Cardiac; neural in ATTRv	Systemic, commonly renal in general AA
Shared feature	Extracellular amyloid fibrils	Extracellular amyloid fibrils

Case: Older patient with a stiff ventricle

Hypothetical case: A man in his late 70s develops a restrictive cardiac phenotype. Tissue examination shows Congo red–positive deposits.

Which subtype is suggested, and what evidence is still missing?

ATTRwt is plausible from the age and phenotype, but Congo red does not establish TTR origin; Amyloid typing remains necessary.

Case: Familial neuropathy with cardiac risk

Hypothetical case: A family has several members with progressive peripheral and autonomic neuropathy; Another relative has cardiomyopathy.

Which amyloidosis pattern best explains this family?

An autosomal-dominant ATTRv phenotype is consistent with variable TTR organ tropism and clinical expression. Confirm the deposited protein.

Case: A positive stain without a protein type

Hypothetical case: A myocardial biopsy shows extracellular eosinophilic material with Congo red birefringence.

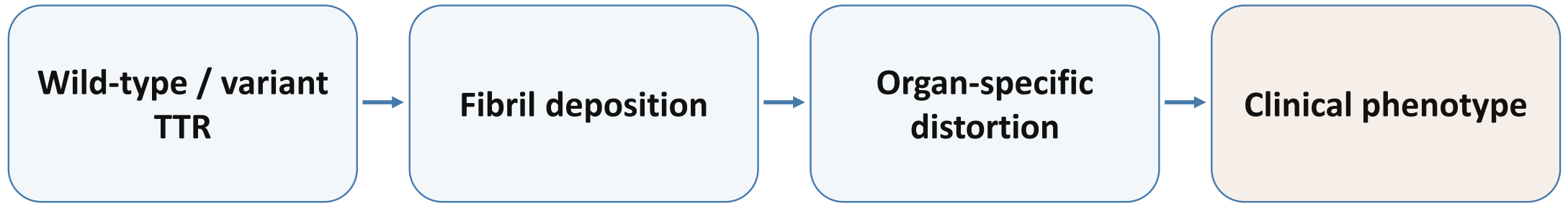
What has the pathologist actually proved?

Amyloid is present. The stain cannot prove ATTR; Type-specific immunohistochemistry or mass spectrometry can establish fibril identity.

Common errors in interpreting ATTR

Potential error	Correct interpretation
“Congo red positive = ATTR”	Congo red confirms amyloid, not its type
“Any thick wall = ATTR”	Cardiac morphology needs amyloid evidence and typing
“Genotype predicts severity precisely”	Penetrance can vary substantially
“ATTRwt is strictly myocardial”	Ligament and other tissue deposition can occur

Integrating precursor, tissue and phenotype



Schematic

- The protein determines the molecular class; Its tissue distribution determines manifestations.
- Amyloid morphology is shared, making subtype identification essential.

Consolidated diagnostic interpretation

- ATTRwt: Age-associated wild-type TTR amyloid, usually cardiac-predominant.
- ATTRv: Autosomal-dominant variant TTR, with variant-specific cardiac or neurologic involvement.
- Congo red and ultrastructure establish amyloid; Protein identification establishes ATTR.
- Cardiac dysfunction follows deposition within interstitium, vessels and conduction structures.

Interpret ATTR by integrating molecular precursor, tissue localization and functional injury.

Primary textbook and internal source scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 6: Diseases of the Immune System, pp. 230–234.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. Chapter 12: The Heart, pp. 522–523.

Primary topic: ATTR (Transthyretin) Amyloidosis; adjacent amyloid protein, morphology and clinical sections used for context.