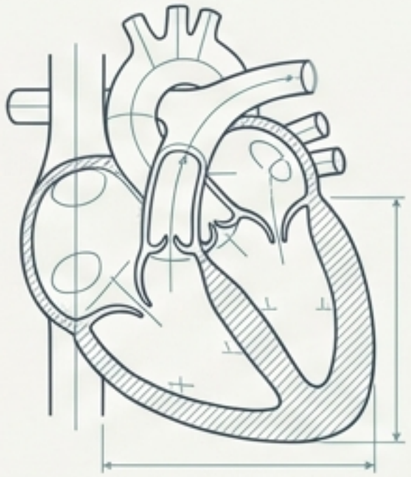

Restrictive and Infiltrative Cardiomyopathies

A Clinical Blueprint for Diagnosis, Subtyping, and Precision Management

Clinical Reference Architecture | Derived from Australian Epidemiological Guidelines | 2026

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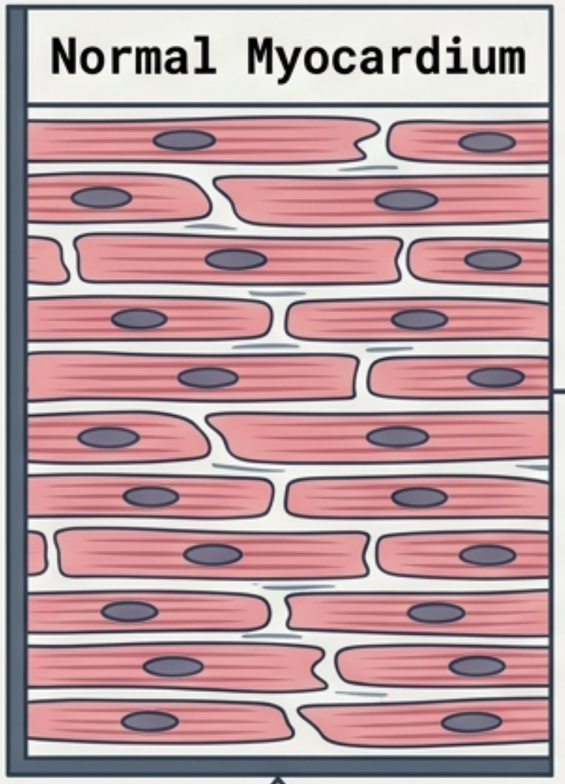
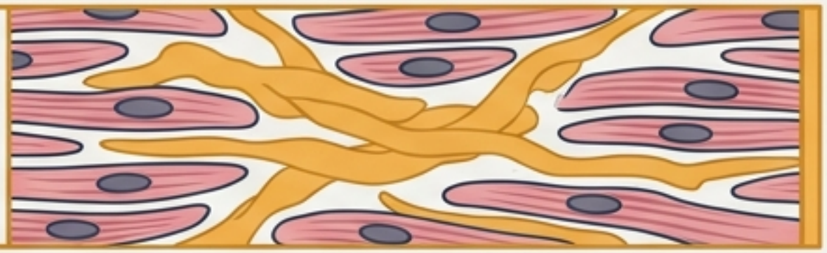
Pathophysiology of the Restrictive Phenotype



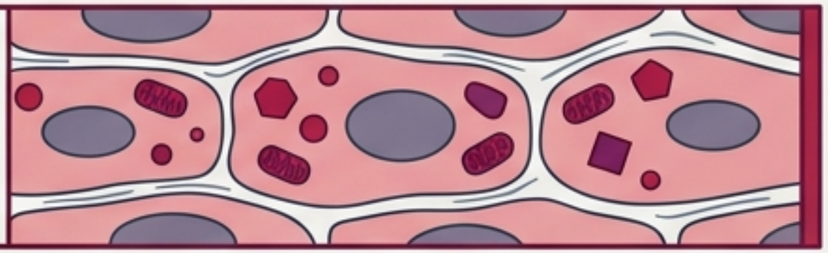
Extracellular Infiltration

Amyloid fibrils (AL/ATTR) or Endomyocardial fibrosis.
Generates a stiff, non-compliant ventricle.



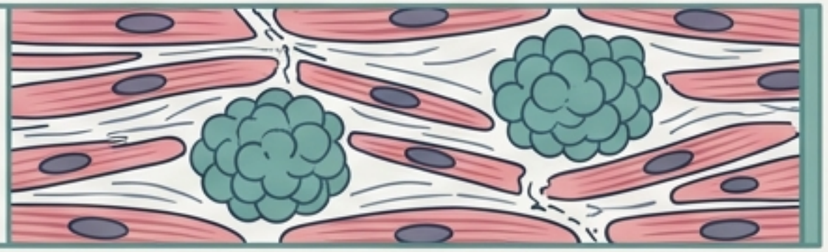
Intracellular Infiltration

Iron (Haemochromatosis) or Glycosphingolipids (Fabry).
Generates oxidative damage and severe LVH.



Granulomatous Infiltration

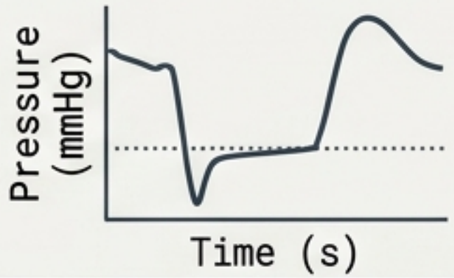
Non-caseating granulomas (Sarcoidosis).
Replaces myocardium, causing fibrosis and conduction disruption.



The Universal Haemodynamic Consequence

Elevated end-diastolic pressures transmit retrogradely → pulmonary and systemic venous congestion.

Hallmark: The ‘dip-and-plateau’ (square root sign) on catheterisation.



Red Flag Diagnostic Matrix

Clinical Clue	Suspected Aetiology	Mandatory First-Line Test
Elderly male + HFpEF + bilateral carpal tunnel + low voltage ECG	Wild-type ATTR	SFLC/IFE then Tc-99m PYP
Heart failure + nephrotic syndrome + macroglossia	AL Amyloidosis	SFLC/IFE then bone marrow biopsy
Young patient + heart block + bilateral hilar lymphadenopathy	Cardiac Sarcoidosis	CMR then FDG-PET/CT
Restrictive CM + bronze skin + diabetes + liver disease	Haemochromatosis	Ferritin/TSAT/HFE then CMR T2*
Young male + LVH mimic + angiokeratomas + proteinuria	Fabry Disease	α-Gal A enzyme activity / GLA sequencing
Migrant from tropical region + HF + eosinophilia	Endomyocardial Fibrosis	Echo apical views / CMR

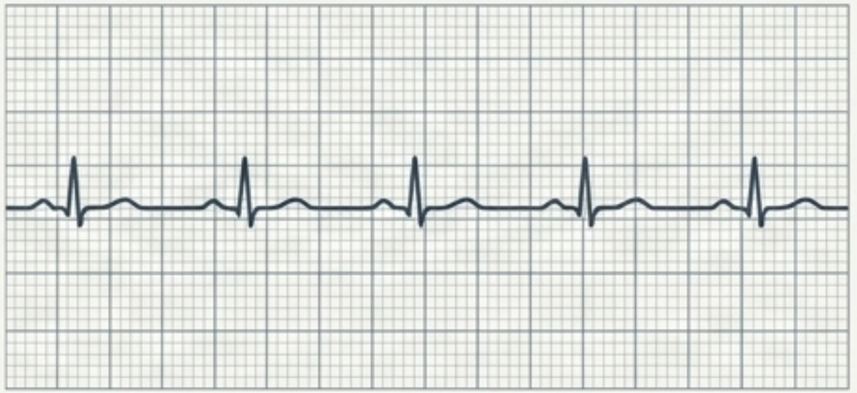
The Amyloid Paradox

Echo Readout

Massive Biventricular Thickening

Echocardiography suggests severe hypertrophy

ECG Readout



Low Voltage QRS Complexes

ECG trace fails to reflect the expected electrical mass of hypertrophied muscle

The Paradox Explained

The thickened wall is NOT muscle—it is inert amyloid protein which generates no electrical signal. Any patient presenting with HFpEF, wall thickness, and an unexpectedly low-voltage ECG must be urgently investigated for amyloidosis

The Amyloid Subtyping Matrix

AL Amyloidosis

- **Precursor:** Immunoglobulin light chains (κ/λ)
- **Age:** 50–70 (M:F 1:1)
- **Triggers:** Monoclonal protein on SFLC/IFE
- **Imaging:** Tc-99m PYP usually negative

ATTR Wild-Type

- **Precursor:** Normal Transthyretin
- **Age:** >65 (M:F 15–50:1)
- **Triggers:** Normal SFLC, negative IFE
- **Imaging:** Strongly positive Tc-99m PYP (Grade 2–3)

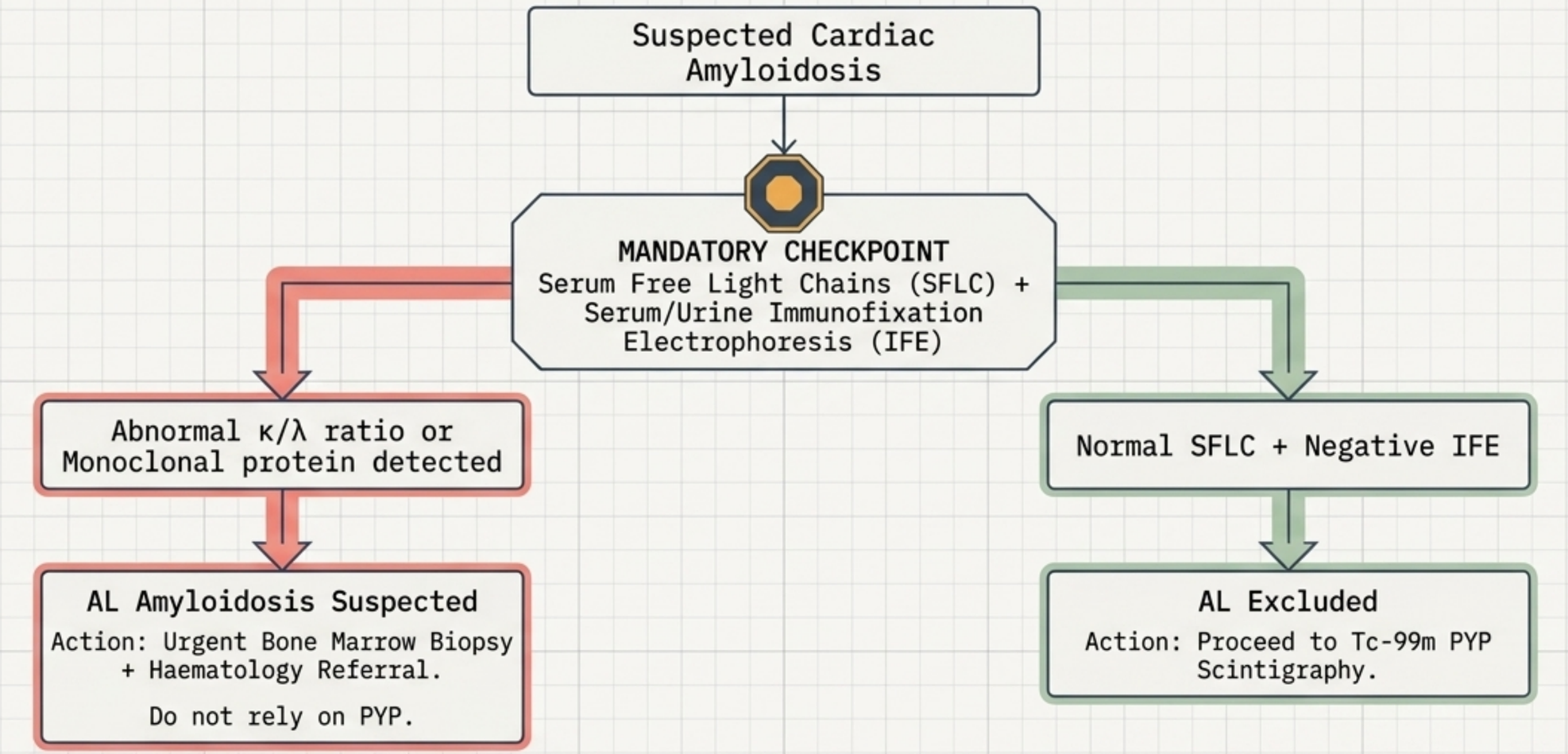
ATTR Hereditary

- **Precursor:** Mutant Transthyretin (e.g., Val122Ile)
- **Age:** 30–60 (variable sex)
- **Triggers:** Neuropathy + Cardiac involvement
- **Diagnosis:** TTR gene sequencing required

Epidemiological Shift

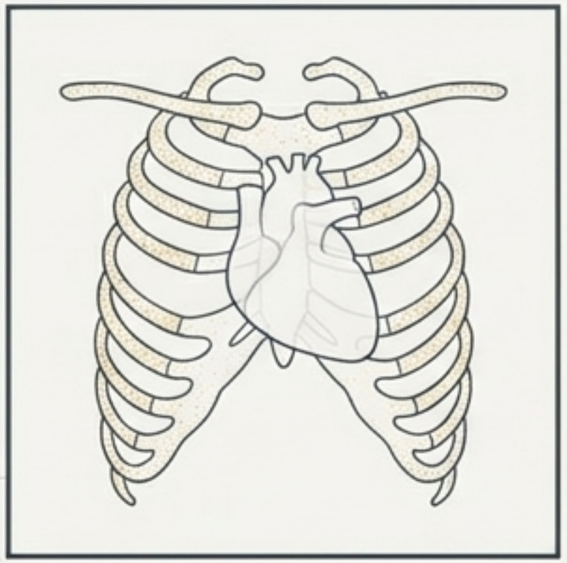
ATTRwt is found in 16–25% of elderly males with HFpEF in autopsy studies. Australian referral rates are rising sharply due to improved advanced imaging access.

The AL Exclusion Workflow

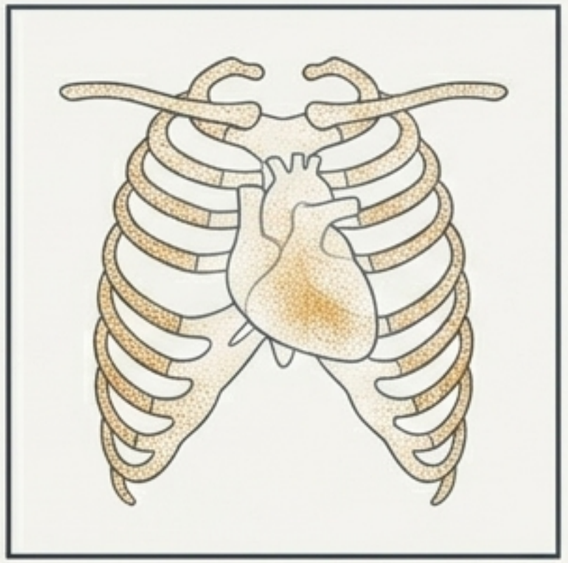


Critical Error Avoidance: Tc-99m PYP scintigraphy can show weak positivity in AL amyloidosis. It is only highly specific for ATTR when AL has been biochemically excluded.

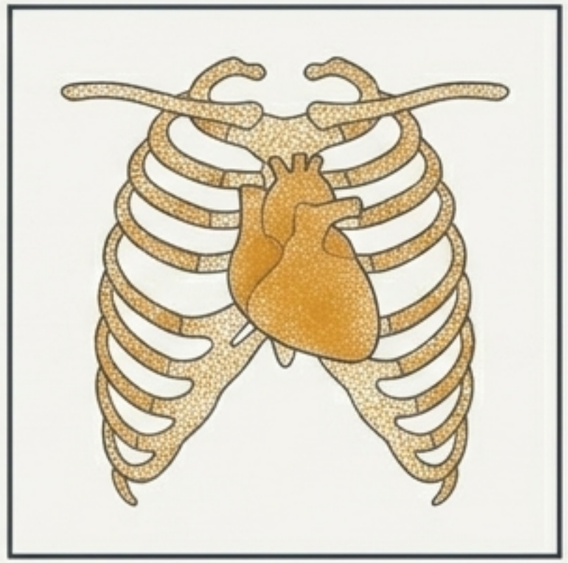
The Scintigraphy Interpretation Scale



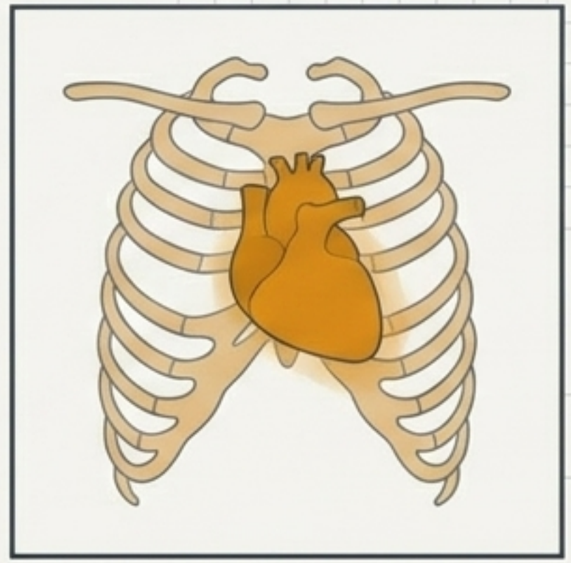
Grade 0
No cardiac uptake.
Equal to bone.
Result: Amyloidosis Unlikely.



Grade 1
Mild uptake.
Cardiac < Bone.
Result: Indeterminate. Needs further workup.



Grade 2
Moderate uptake.
Cardiac = Bone.
Result: Positive for ATTR (if AL excluded).



Grade 3
Strong uptake. Cardiac > Bone with soft tissue uptake.
Result: Highly specific for ATTR.

Quantitative Metric

Heart-to-Contralateral-Lung (H/CL) Ratio:
≥1.5 at 1 hour on planar imaging confirms ATTR diagnosis.

AL Amyloidosis Severity – The 2012 Revised Mayo Clinic Staging

Biomarker Triggers:
NT-proBNP ≥1,800 ng/L
hs-TnT ≥0.025 µg/L
dFLC ≥180 mg/L

Stage I - Low Risk

0 adverse markers.
Setting: Haematology outpatient.
Median Survival: 94 months.

Stage II - Intermediate

1 or 2 adverse markers.
Setting: Specialist centre.
Median Survival: 40 months.

Stage III/IV - High Risk

3 adverse markers (Stage IIIb if NT-proBNP ≥8,500).
Setting: Inpatient/Clinical Trial.
Median Survival: 6–14 months.

Clinical Imperative: AL Amyloidosis is a haematological emergency. Median survival drops precipitously as cardiac involvement progresses.

Divergent Pharmacological Pathways in Amyloidosis

ATTR Therapies (Disease Modifying)

TTR Stabiliser: Tafamidis

Dose: 61 mg PO daily.

Evidence: Reduces all-cause mortality by 30% (ATTR-ACT trial).

Status: PBS Authority Required.

TTR Gene Silencers: Patisiran & Inotersen

Dose: Patisiran 0.3 mg/kg IV q3w.

Evidence: Effective for neuropathy/cardiac subgroup.

Status: Limited Australian PBS availability.

AL Therapies (Haematological Extirpation)

First-Line Regimen: Dara-CyBorD

Components: Daratumumab (Anti-CD38 monoclonal) + Bortezomib + Cyclophosphamide + Dexamethasone.

Evidence: ANDROMEDA trial shows superior complete haematological response (53% vs 18%) over CyBorD alone.

Therapeutic Intent

In ATTR, drugs aim to stabilize the protein.
In AL, drugs aim to eradicate the clonal plasma cell. Both require initiation before irreversible myocardial damage.

Cardiac Sarcoidosis Diagnosis and Imaging

JCS Clinical Diagnosis Criteria

Diagnosis rule: 2 Major OR 1 Major + 2 Minor.

☐ **Major Criteria**
- Advanced AV block
- Basal septal thinning
- Non-coronary LGE on CMR
- FDG myocardial uptake

☐ **Minor Criteria**
- NSVT
- Low LVEF (<50%)
- Abnormal ECG
- Elevated BNP/Trop

(Note: Endomyocardial biopsy has low sensitivity ~20-30% due to patchiness).

FDG-PET/CT Protocol

The Problem:

Normal heart muscle uses glucose, masking sarcoidosis lesions.

The Solution (Patient Prep):

Prolonged fasting (>12h) + High-Fat/Low-Carb diet for 24-48h prior. Suppresses physiological myocardial uptake.

The Target Indicator:

Focal or focal-on-diffuse FDG uptake (SUVmax >2x blood pool) confirms active granulomatous inflammation.

Dual-Track Management of Cardiac Sarcoidosis

Inflammation Track (Immunosuppression)

Phase 1

Prednisolone (0.5 mg/kg/day for 4-8 weeks).

Phase 2

Taper over 6-12 months while repeating FDG-PET.

Phase 3

If active at 3-6 months, add Methotrexate or Mycophenolate Mofetil.

Electrical Track (Arrhythmia Management)

Pacing

Permanent pacemaker for persistent complete heart block (high degree AV block is the most common presentation).

Antiarrhythmics

Sotalol or Amiodarone for VT.

ICD Criteria

Implantation recommended for LVEF <35%, sustained VT, or extensive LGE on CMR (a major predictor of arrhythmic events).

Haemochromatosis: The Cardiac Iron Overload Pathway

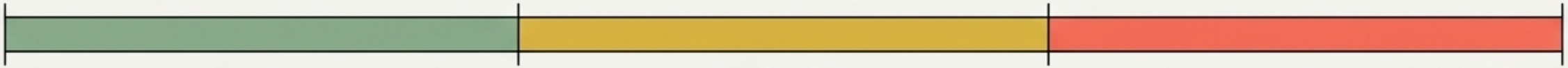
Level 1: Systemic Screening

TSAT >45% and Ferritin >300 µg/L (men) or >200 µg/L (women).

Level 2: Genetic Confirmation

HFE gene analysis. C282Y homozygosity confirms diagnosis (affects 1 in 200 Australians of Northern European descent).

Level 3: The Cardiac T2* Gauge (Gold Standard)



>20 ms.
Normal myocardial iron.
Low risk.

10–20 ms.
Mild-to-moderate overload.
Moderate risk.

<10 ms.
Severe iron overload.
High risk of heart failure, arrhythmia, and sudden death.

Haemochromatosis: T2* Guided Interventions

Therapy 1: Serial Venesection (Phlebotomy)

Indication: Systemic loading, normal cardiac T2* (>20ms).
Regimen: 500mL removed weekly (induction) until ferritin <50 µg/L.
Insufficient for severe myocardial loading.

Therapy 2: Oral Chelation (Deferasirox)

Indication: T2* 10–20 ms (Mild-to-moderate).
Regimen: 20–40 mg/kg/day PO.
Cautions: Contraindicated if eGFR <40 mL/min. Monitor ferritin monthly.

Therapy 3: Intensive Combination Chelation

Indication: T2* <10 ms (Severe/Cardiogenic Shock).
Regimen: Continuous IV Deferoxamine (40–60 mg/kg/day) + Oral Deferiprone.
Outcome: Can completely reverse cardiac dysfunction if initiated before irreversible fibrosis occurs.

Intracellular Storage Cardiomyopathies

Fabry Disease (Lysosomal)

Mechanism:
X-linked α-Gal A deficiency → Gb3 accumulation.

Cardiac Profile:
Severe concentric LVH (often misdiagnosed as HCM), short PR interval, basal infeolateral LGE.

Therapies:
Enzyme Replacement (Agalsidase beta) or oral chaperone therapy (Migalastat - only for amenable mutations).

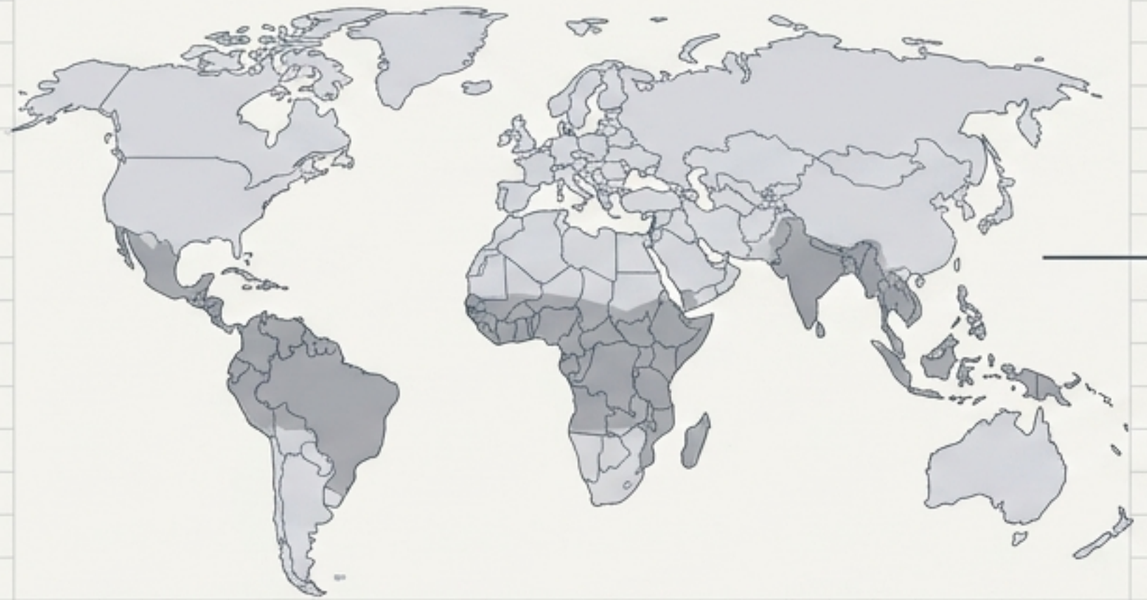
Glycogen Storage Disorders

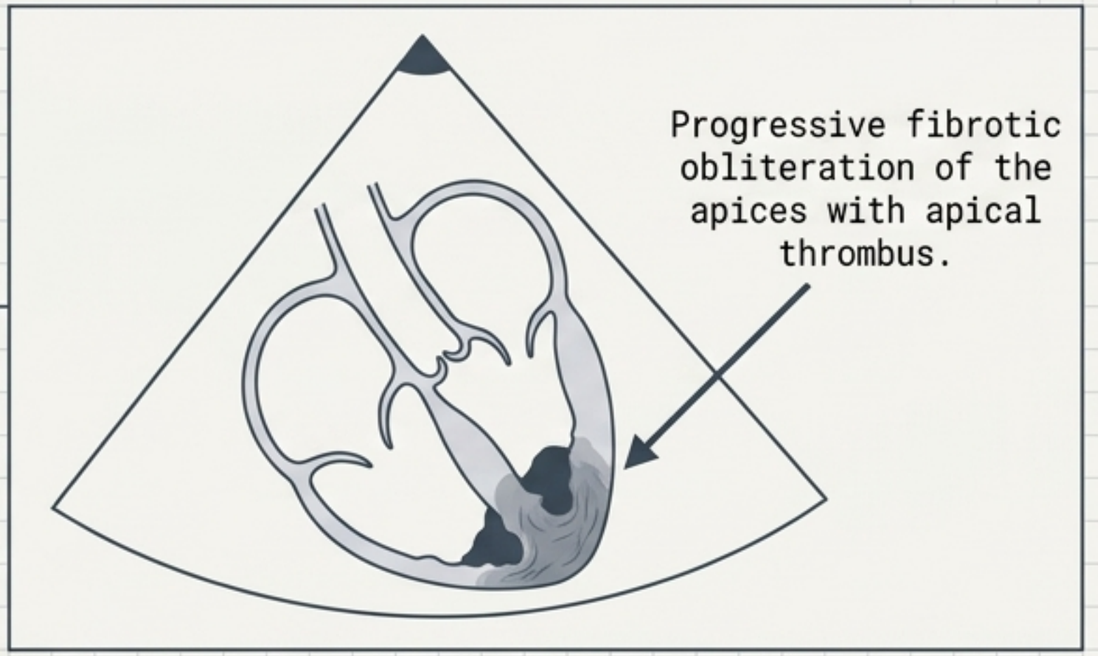
Pompe (GSD II): Infantile massive LVH. Treated urgently with ERT (Alglucosidase alfa).

PRKAG2 Syndrome: LVH + WPW syndrome + progressive conduction disease.

Danon Disease (LAMP2): Severe progression requiring transplant by age 19 in males.

Endomyocardial Fibrosis (EMF)





Epidemiology

Rare in general Australian population. Critical to consider in migrant communities from sub-Saharan Africa, South Asia, and Latin America.

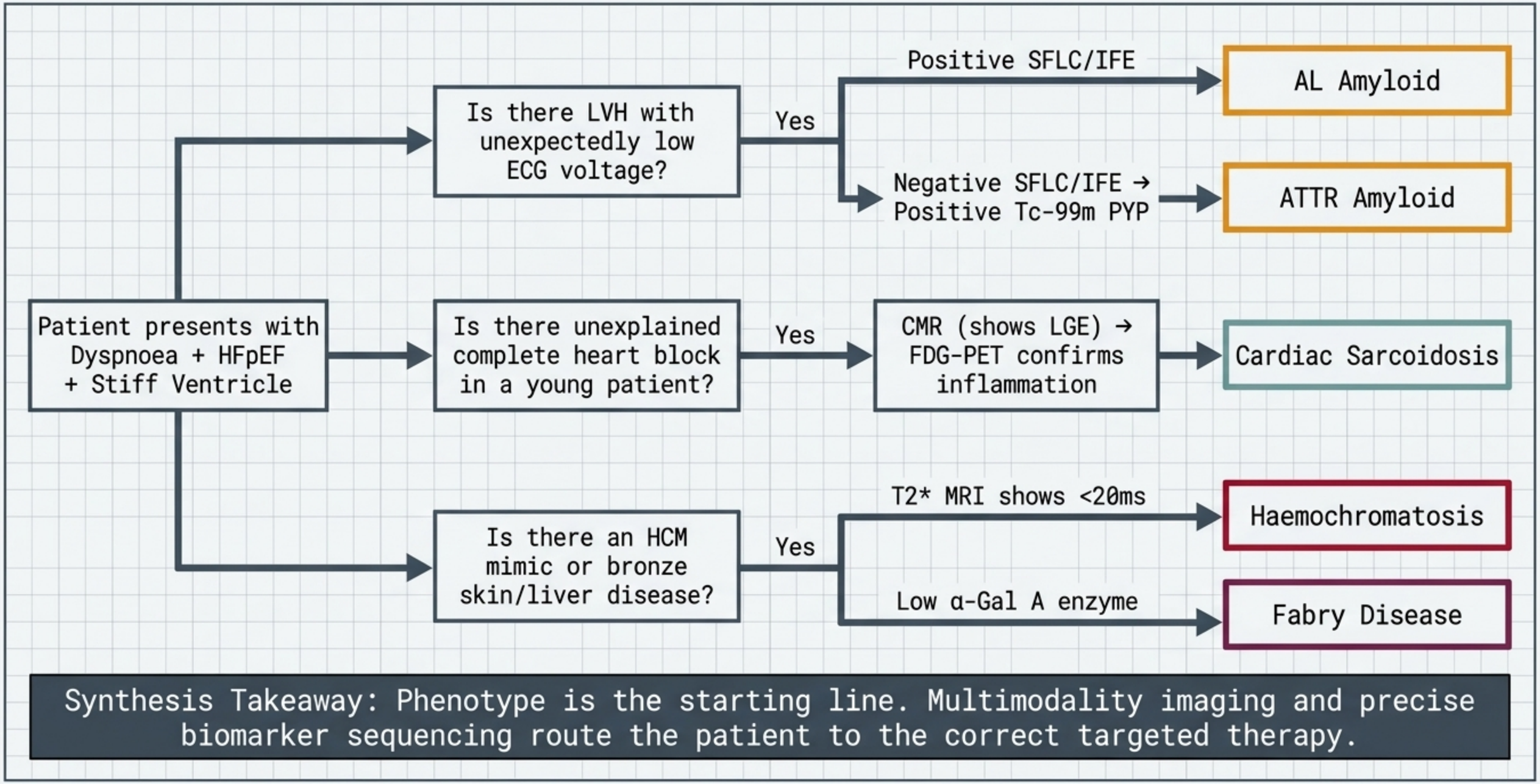
Diagnostic Profile

Presents with heart failure, restrictive physiology, and eosinophilia.

Management

No disease-modifying medical therapy. Treated with diuretics, anticoagulation (for thrombus), and surgical endocardectomy (Davies procedure).

The Cardiomyopathy Crossroads



Synthesis Takeaway: Phenotype is the starting line. Multimodality imaging and precise biomarker sequencing route the patient to the correct targeted therapy.

The Restrictive Heart Failure Toolkit (General Principles)

The Physiologic Problem: Restrictive hearts depend on high filling pressures (preload) and fixed heart rates to maintain cardiac output.

✅ DO

Loop Diuretics. Furosemide or Torsemide. Mainstay of volume management.

Anticoagulation. DOACs preferred. High risk of AF and thrombus due to atrial dilation.

Amiodarone. Preferred antiarrhythmic for AF rhythm control and VT.

❌ DO NOT (CAUTIONS)

Beta-Blockers / ACEi / ARB. Often poorly tolerated (reduces necessary preload and compensatory heart rate). Start very low if needed.

Digoxin. CONTRAINDICATED in AL amyloidosis (binds to fibrils causing severe toxicity).

Calcium Channel Blockers. Bind to amyloid fibrils; avoid in amyloidosis.

The Pharmacopoeia Matrix

Drug Name	Disease Target	Mechanism	PBS Status in Australia
Tafamidis	ATTR Amyloidosis	TTR Stabiliser	Authority Required
Patisiran	hATTR	siRNA Gene Silencer	Not PBS listed (SAS)
Dara-CyBorD	AL Amyloidosis	Clonal Plasma Cell Eradication	Authority Required
Prednisolone	Cardiac Sarcoid	Corticosteroid Immunosuppression	General Benefit
Deferasirox	Iron Overload	Oral Iron Chelator	Authority Required
Agalsidase beta	Fabry Disease	Enzyme Replacement Therapy	Authority Required
Alglucosidase alfa	Pompe Disease	Enzyme Replacement Therapy	Authority Required

Physiological Edge Cases & Special Populations

Pregnancy

- Restrictive physiology is poorly tolerated (NYHA III/IV is WHO Category IV - contraindicated).
- Chemotherapy (AL) and Chelators (Iron) are teratogenic. ERT (Fabry) used with caution.

Renal Impairment

- AL Amyloid: Nephrotic syndrome common. Cyclophosphamide needs dose reduction (eGFR <30).
- Iron: Deferasirox contraindicated if eGFR <40; switch to Deferoxamine.

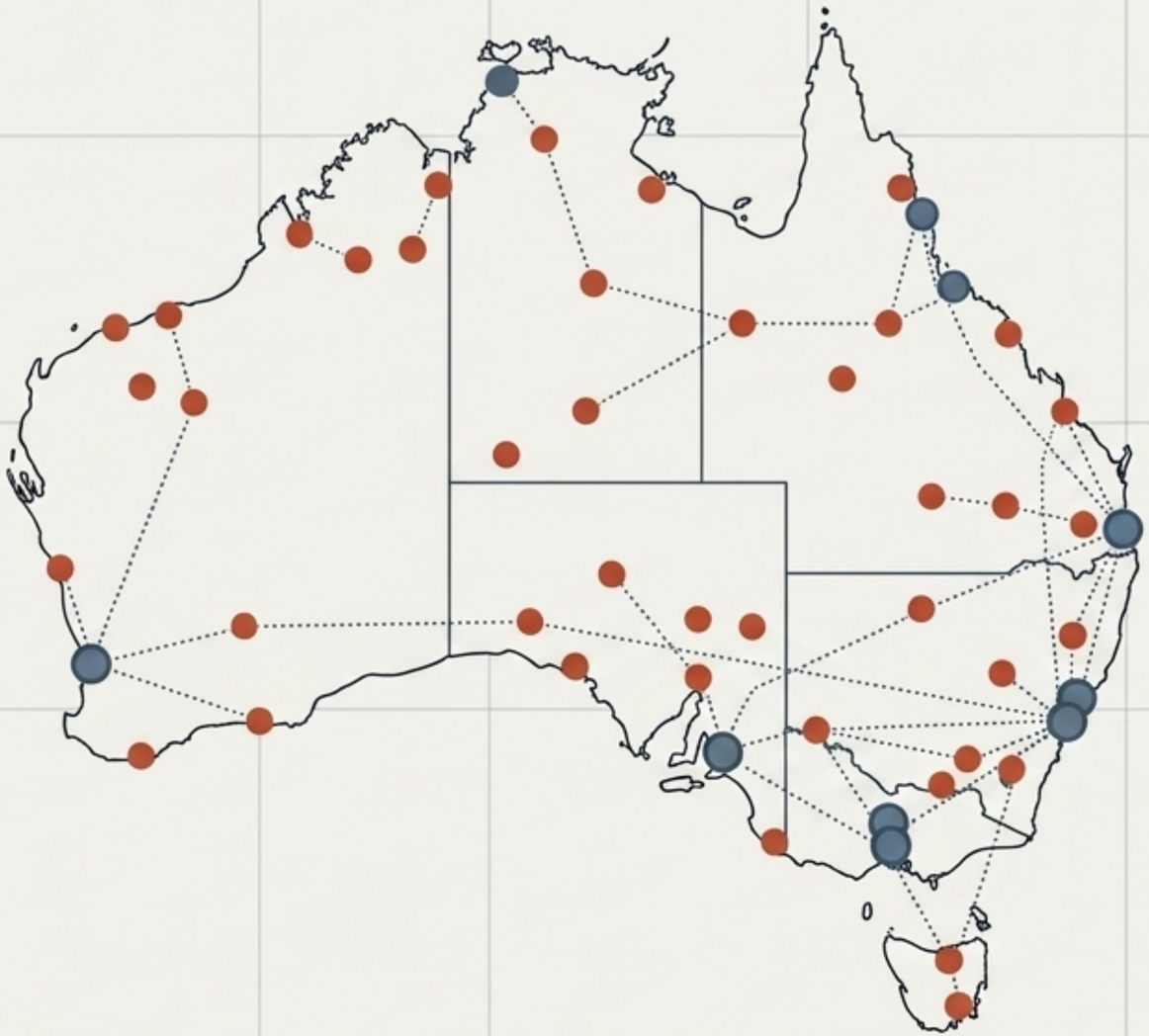
Hepatic Impairment

- Haemochromatosis: Cirrhosis drives HCC risk.
- Deferasirox avoided in Child-Pugh C.

The Elderly (ATTRwt focus)

- Polypharmacy risks. Avoid digoxin/CCBs.
- Tafamidis remains effective regardless of advanced age.

Cultural Safety & Access Map



The Overlap Challenge

High rates of Rheumatic Heart Disease (RHD) in First Nations communities mimic restrictive phenotypes. Distinct from HFE-related iron overload.

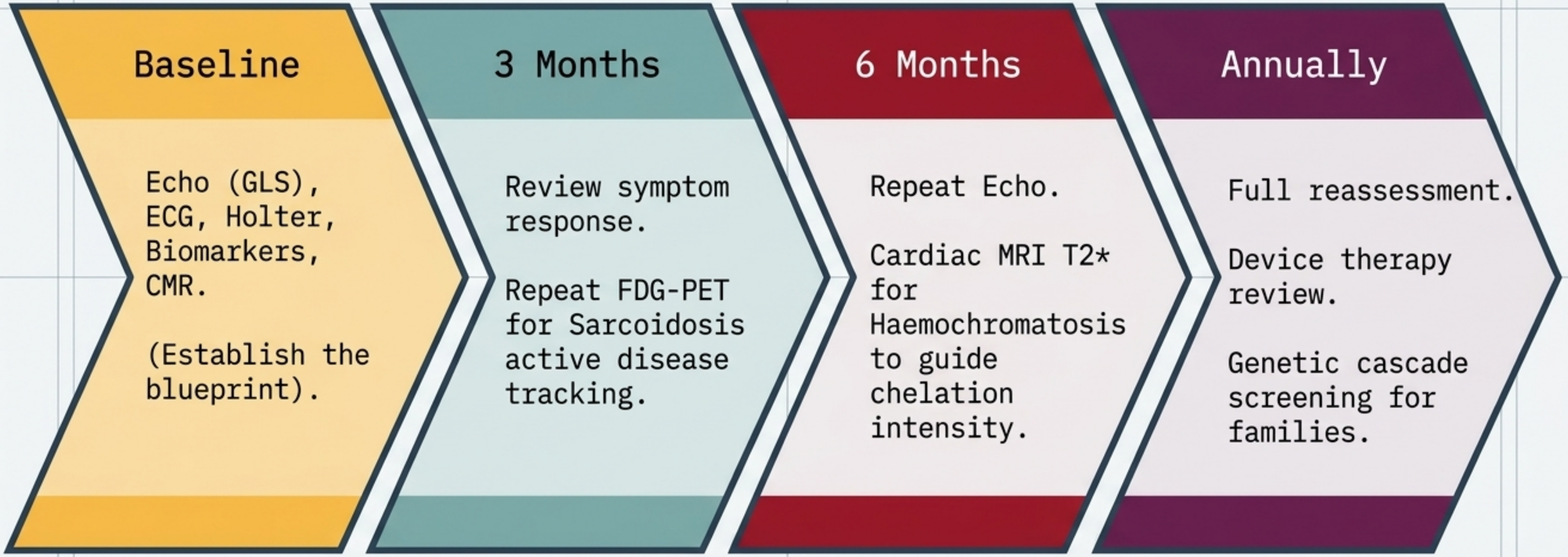
The Access Gap

Advanced imaging (CMR, PYP, PET) is highly concentrated in metropolitan tertiary centers, creating profound geographical and cultural barriers for remote patients.

The Bridges (Solutions)

- **Integration:** Partner with ACCHOs for long-term therapy adherence (e.g., ERT infusions, chelation).
- **Culturally Safe Screening:** Consent processes for genetic testing must consider community implications and kinship structures (men's business).
- **Telehealth:** Expanding fly-in/fly-out and digital cardiology services.

Long-Term Surveillance Timeline



Treatment Targets

Success is disease-specific.
In AL Amyloidosis: Haeromatological complete response + ≥30% NT-proBNP reduction.
In ATTR: Stabilization of wall thickness and Global Longitudinal Strain (GLS) over 12-24 months.