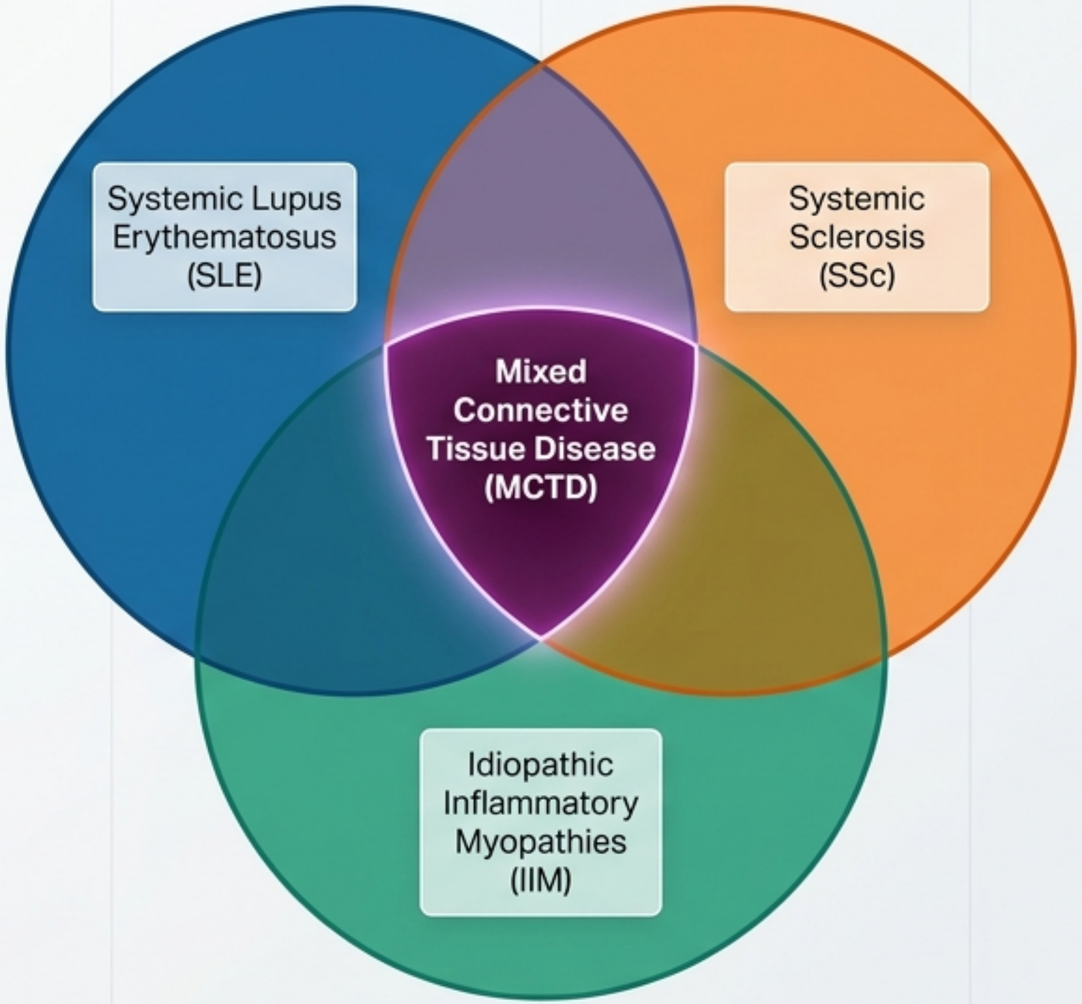
# The Defined Overlap

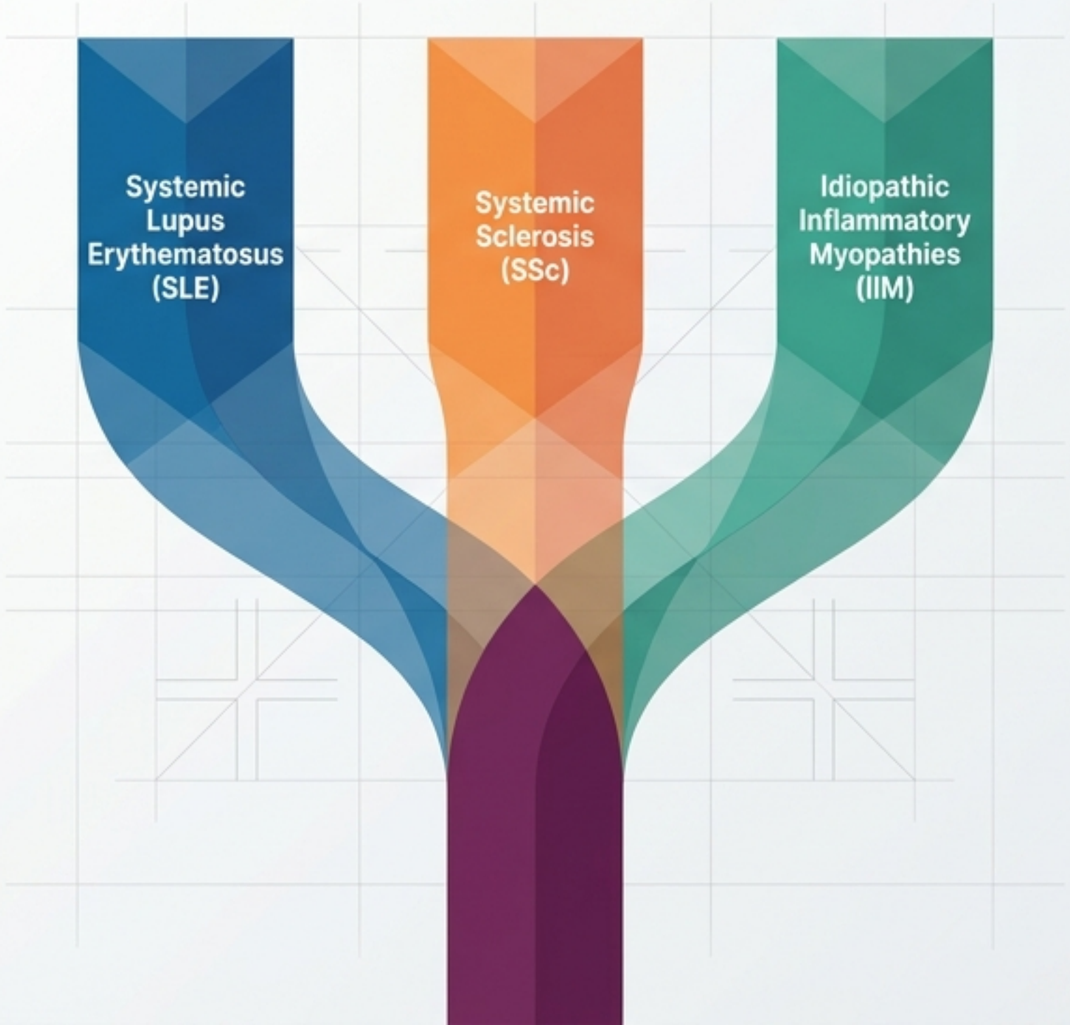
## Diagnosing and Managing Mixed Connective Tissue Disease




Australian Clinical Guideline Synthesis

# A distinct immune-mediated overlap syndrome

MCTD is defined by high-titre anti-U1-RNP antibodies combined with clinical features of SLE, systemic sclerosis (SSc), and polymyositis/dermatomyositis (IIM).




## Demographics Dashboard

1

### Prevalence

**1-2 per 100,000**

(2-3% of systemic autoimmune rheumatic diseases in Australia)

2

### Demographic

**9:1**

Female to Male ratio

3

### Onset

**2nd to 3rd decade**

of life

4

### Outcome

**>80%**

10-year survival (PAH is the primary mortality driver)

# The Sharp Syndrome classical presentation

**High-Titre Anti-U1-RNP**

The Key: Often precedes clinical features.

+

**Sausage Digits**

Puffy hands with non-pitting oedema; distinguishes from pure SSc/SLE.

+

**Triphasic Raynaud's**

Severe vascular response. Present in >95% of patients.

=

Early MCTD

**The Classical Presentation**

# The mandatory serological anchor

## Pathogenesis

Contributes to immune complex formation and interferon-alpha pathway activation.

## Clinical Warning

Isolated low-titre anti-U1-RNP may occur in pure SLE. A high titre in the appropriate clinical context defines MCTD.

**Biomarker: Anti-U1-RNP**
(targets U1 small nuclear ribonucleoprotein complex)

**Threshold: >1:1600**
(by immunofluorescence)

**ANA Pattern:** Speckled
(often the sole extractable nuclear antigen)

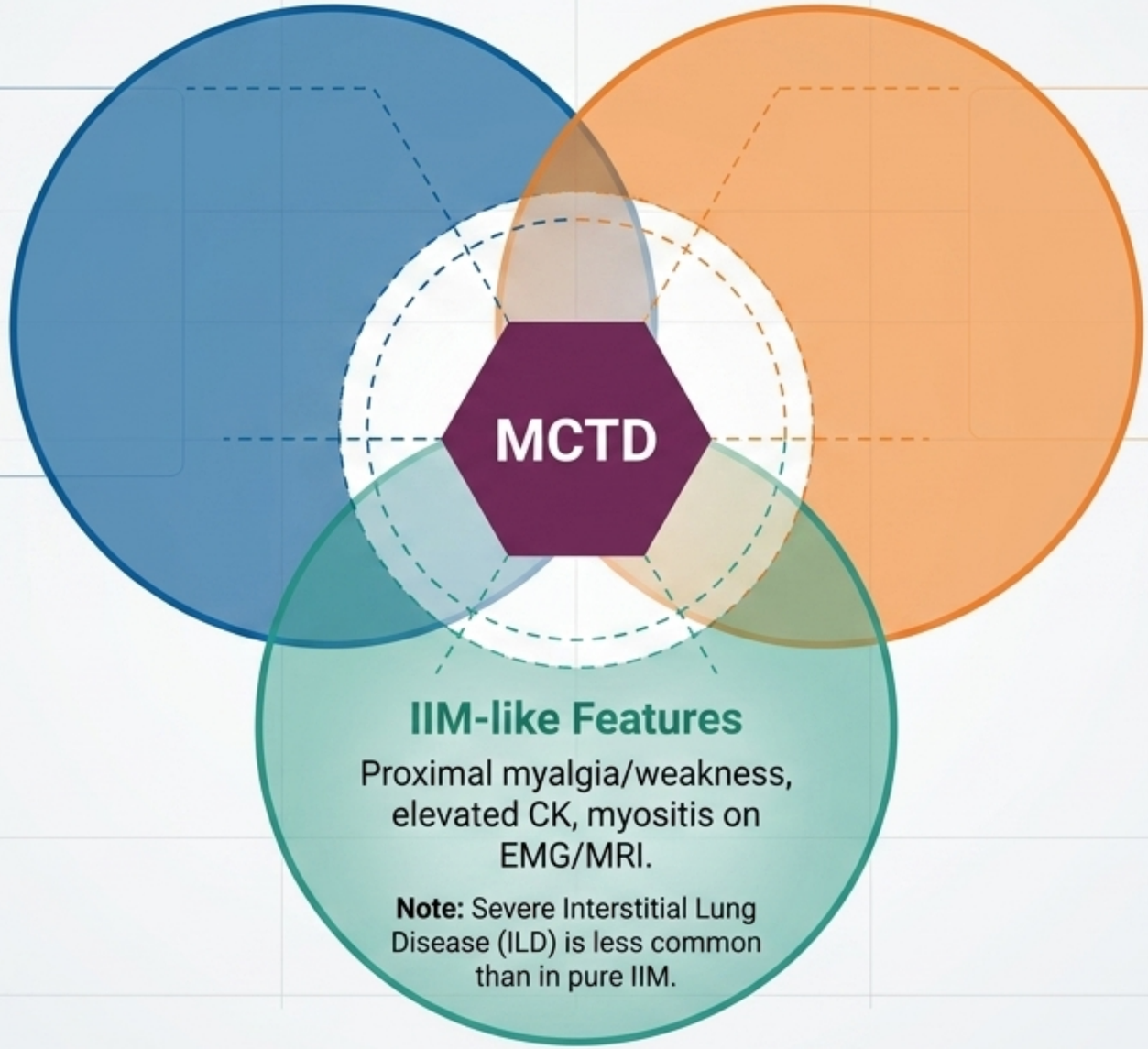

## Prognostic Value

High titres correlate tightly with Raynaud, oesophageal dysmotility, and pulmonary hypertension.

## Australian Testing

Available via major pathology labs. MBS ENA rebate item 69494.

# Mapping the tripartite clinical overlap




## SLE-like Features

Arthritis, serositis, lymphadenopathy, fever, leukopenia.

**Note:** Severe nephritis, CNS lupus, and anti-dsDNA are rare in MCTD.

## SSc-like Features

Raynaud, sclerodactyly, swollen hands, oesophageal dysmotility, PAH.

**Note:** Cutaneous sclerosis is usually limited, not diffuse.

## IIM-like Features

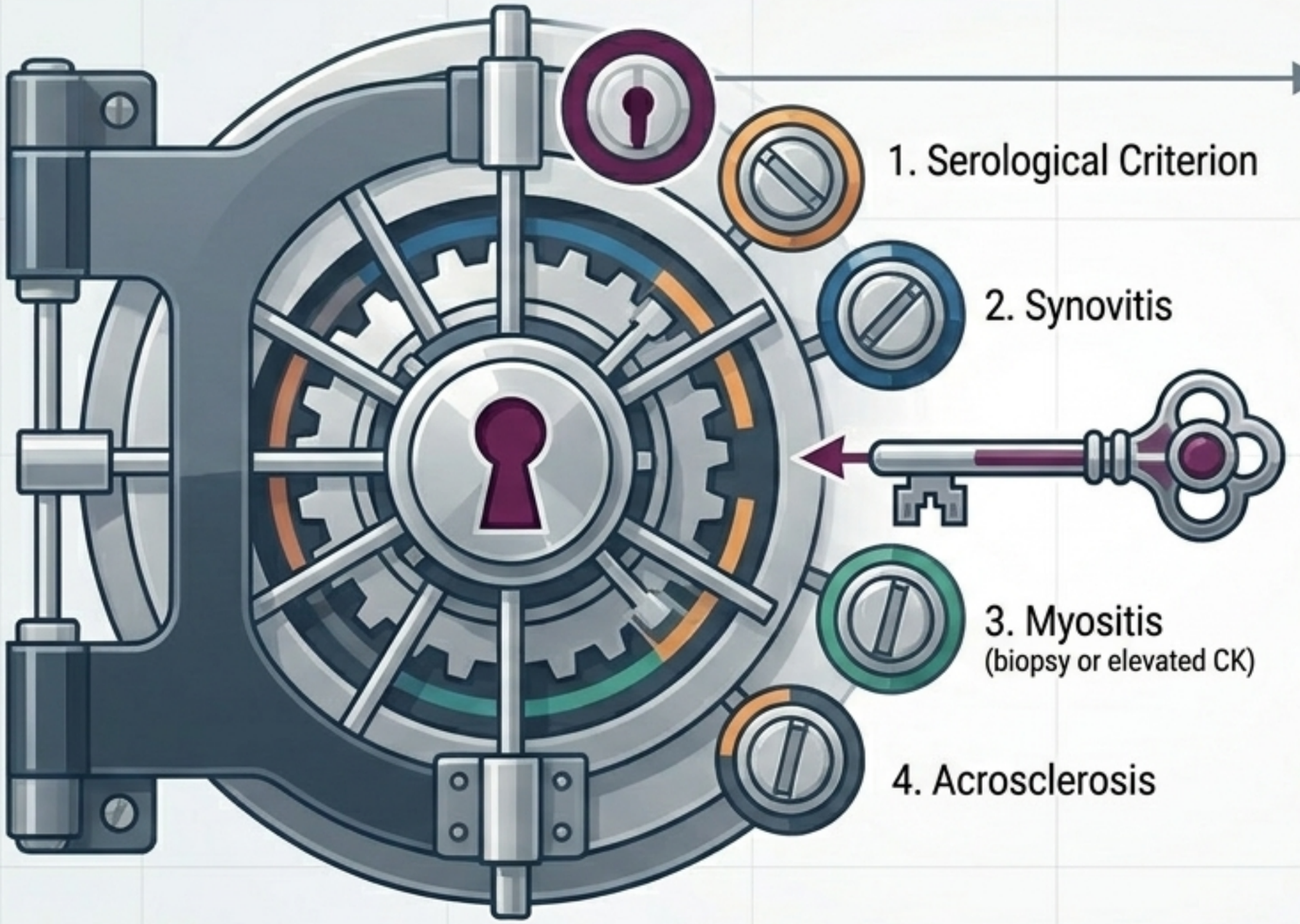
Proximal myalgia/weakness, elevated CK, myositis on EMG/MRI.

**Note:** Severe Interstitial Lung Disease (ILD) is less common than in pure IIM.

# Differentiating from Undifferentiated Connective Tissue Disease

| UCTD | MCTD |
| --- | --- |
| **Required Antibody**<br>ANA often positive; anti-U1-RNP may be low-titre or absent. | **Required Antibody**<br>High-titre anti-U1-RNP (mandatory). |
| **Overlap Features**<br>Non-specific (arthralgia, Raynaud, sicca) without definite pattern. | **Overlap Features**<br>Clear, specific features from ≥2 distinct CTDs (SLE, SSc, IIM). |
| **Diagnostic Criteria**<br>Fails to meet criteria for any specific CTD. | **Diagnostic Criteria**<br>Strictly meets Alarcon-Segovia or Sharp criteria. |
| **Disease Evolution**<br>May evolve into a defined CTD (e.g., SLE) in 30% over 5 years. | **Disease Evolution**<br>Features remain stable or progress strictly within the MCTD phenotype. |

# The Alarcon-Segovia diagnostic architecture



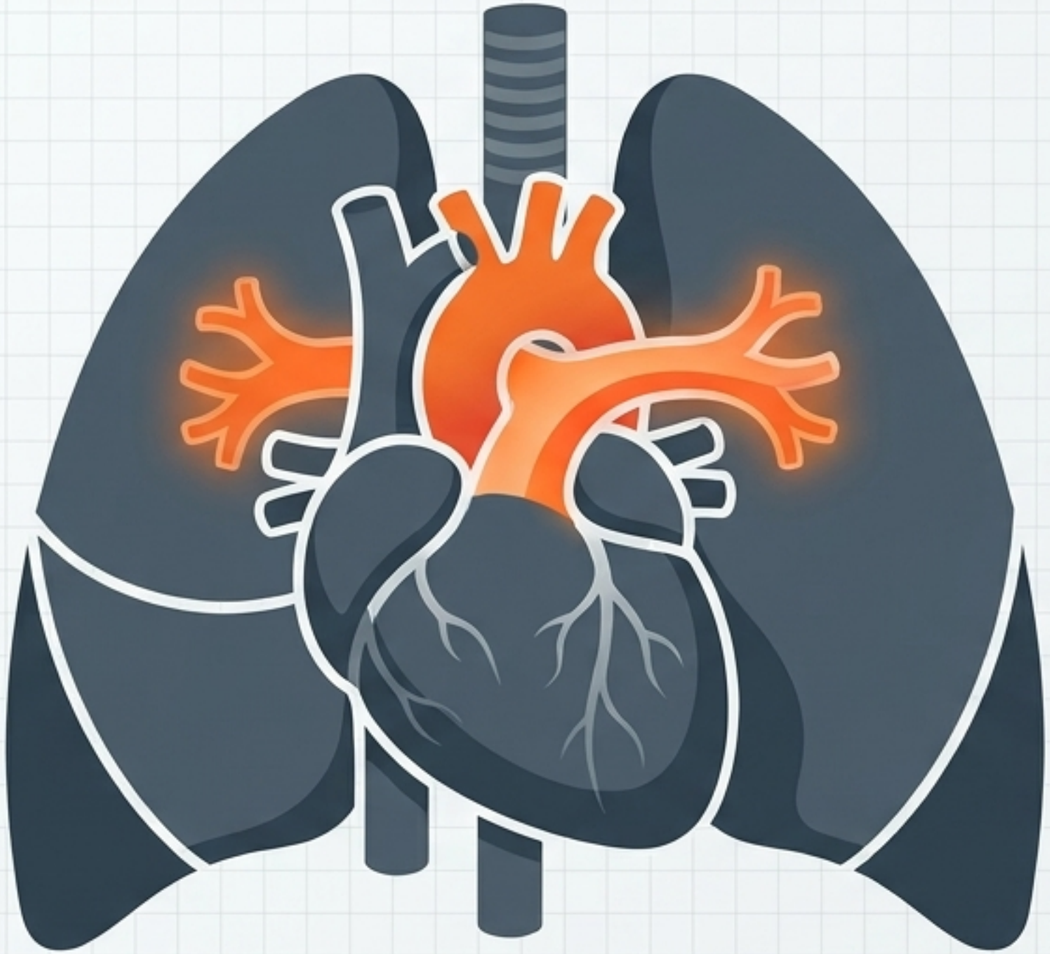

**1. Serological Criterion (Mandatory):**
Anti-U1-RNP antibody positive at titre ≥1:1600.
The vault will not open without this.

**2. Clinical Criteria (Must trigger ≥3 of 6):**

1. Oedema of hands (SSc/SLE)
2. Synovitis (SLE/RA)
3. Myositis (biopsy or elevated CK) (IIM)
4. Raynaud phenomenon (SSc)
5. Acrosclerosis (sclerodactyly) (SSc)
6. DLCO <70% of predicted (SSc/IIM)

**Validation Note:** The triggered clinical features must derive from at least two distinct diseases (SLE, SSc, IIM, RA).

# Pulmonary Arterial Hypertension is the leading mortality driver



**10-30%** **Prevalence** over the disease course

## Mechanism

Predominantly WHO Group 1 PAH arising from severe vasculopathy.

## Clinical Presentation

Exertional dyspnoea (critically, this is often disproportionate to any visible interstitial lung disease).

Syncope and chest pain in advanced stages.

## Clinical Imperative

Because early PAH can be clinically silent, symptom-based screening is insufficient.

# The mandatory annual PAH screening pipeline

## Step 1: Non-Invasive Screening (Annual Requirement)

**Tests:**
Echocardiography (Estimates RVSP) + Pulmonary Function Tests (DLCO). MBS item 11505.

**Trigger Thresholds:**
Systolic PAP >40 mmHg **OR** DLCO <60% predicted.

## Step 2: The Gold Standard Gatekeeper (MCTD)

**Action:**
Referral for Right Heart Catheterisation (RHC).

**Diagnostic Confirmation:**
Mean PAP ≥20 mmHg and PAWP ≤15 mmHg.

## Step 3: Specialist Intervention

**Action:**
Referral to specialized Australian centers (e.g., Royal Adelaide, Alfred, St Vincent's).

**Restricted Therapies:**
Endothelin receptor antagonists (e.g., ambrisentan, PBS Authority), PDE5 inhibitors (sildenafil, PBS Authority), IV prostanoids (epoprostenol).

# Baseline and ongoing diagnostic investigations

## Haematology

**FBC, ESR, CRP**

Expect leukopenia, thrombocytopenia, raised ESR.

## Immunology

**ANA, ENA, anti-dsDNA, complement**

Expect high-titre speckled ANA, negative dsDNA, normal complement.

## Myositis Markers

**Creatine kinase (CK), aldolase**

Elevated in IIM overlap.

## Pulmonary

**High-resolution CT chest**

Check for Non-specific Interstitial Pneumonia (NSIP) pattern if ILD suspected.

## Gastrointestinal

**Barium swallow / manometry**

Reveals reduced motility in distal two-thirds if dysphagia present.

## Renal

**Urinalysis, urine protein/creatinine ratio**

Screen for glomerulonephritis; membranous nephropathy is typical if present.

# Executing phenotype-driven pharmacotherapy


## Dominant SSc-like Pathway

**Features:** Raynaud, Digital Ischaemia.

**First-line:** Amlodipine 5-10 mg daily (PBS General Benefit). Avoid beta-blockers.

**Critical Ischaemia:** IV iloprost (specialist/authority).

## Dominant SLE-like Pathway

**Features:** Arthralgia, fatigue, mild serositis, skin rash.

**Primary Agent:** Hydroxychloroquine (Plaquenil) 200-400 mg daily (≤5 mg/kg actual weight).

## Dominant IIM/Renal Pathway

**Features:** Inflammatory arthritis, myositis, ILD, renal disease.

**Primary Agents:** Methotrexate (7.5-25 mg weekly) OR Mycophenolate (CellCept, 1-1.5 g BD, Authority Required).

# Management considerations in special populations

## Pregnancy

Increased flare risk (arthritis, rash).

**Critical Warning:** Established PAH strictly contraindicates pregnancy.

**Meds:** HCQ is safe. Cease Methotrexate and Mycophenolate at least 3 months pre-conception. Azathioprine/tacrolimus considered safe.

## Paediatrics

MCTD is extremely rare in children (Juvenile dermatomyositis is the much more common presentation).

**Anti-U1-RNP** may be present in other overlap syndromes; requires specialist paediatric rheumatology management.

## Renal Impairment

**Nephritis** is less common than in SLE, but membranous nephropathy can occur.

**Adjustments:** Reduce NSAID use. Adjust Mycophenolate mofetil (MMF) dosing if **eGFR** drops below 25. Treat active nephritis with glucocorticoids + MMF/cyclophosphamide.

# Aboriginal and Torres Strait Islander health context

## Diagnostic Delay

Symptoms like Raynaud and arthralgia are frequently misattributed. A higher index of suspicion and active screening via local Aboriginal Medical Services (AMS) is required.

## Comorbidities

Higher background rates of cardiovascular disease, diabetes, and renal disease complicate baseline MCTD management and drug toxicity monitoring.

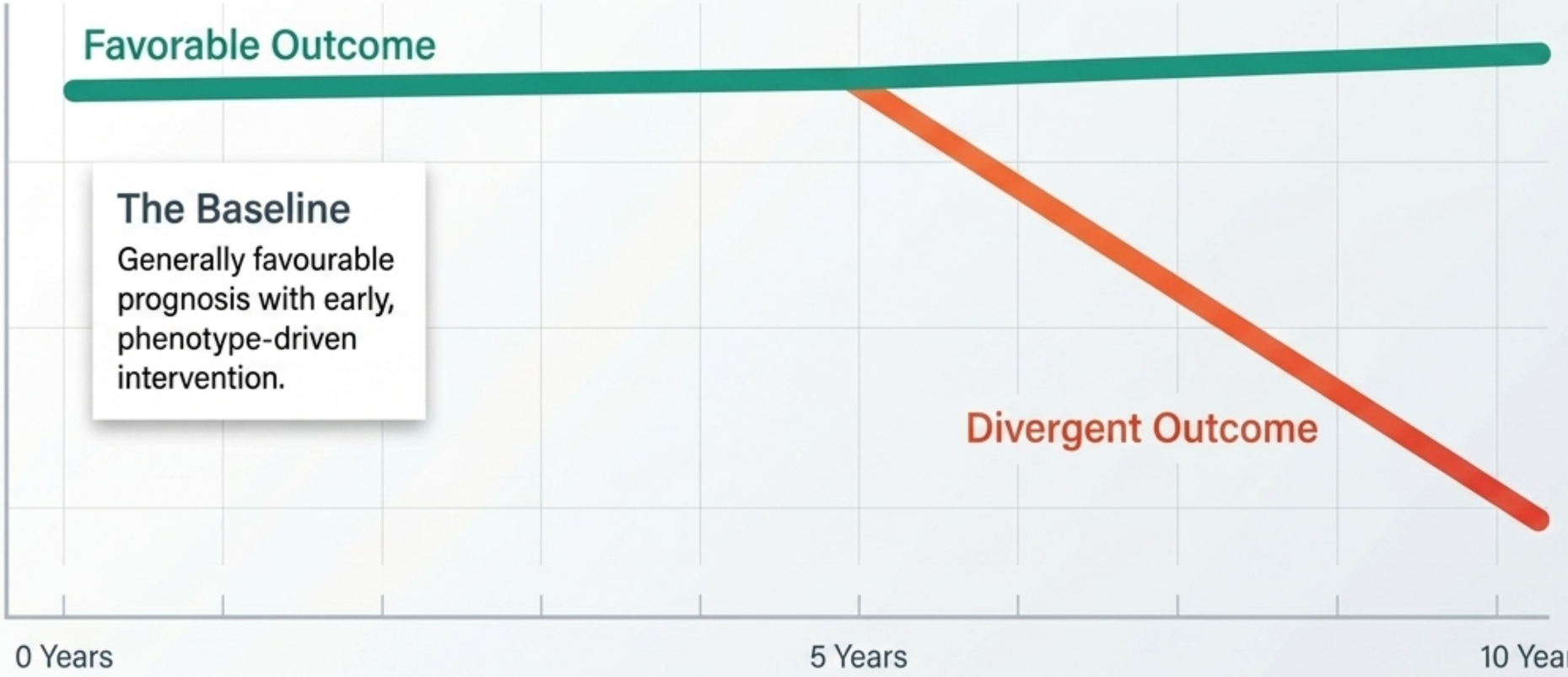
## Access Barriers

Remote communities face severe access limitations. Telehealth for rheumatology/cardiology follow-up and Patient-Assisted Travel Schemes (PATS) are critical structural necessities.

## Cultural Safety

Essential to engage Aboriginal Health Workers/Practitioners to ensure communication about chronic disease evolution and medication adherence is delivered in culturally appropriate formats.

# The long-term clinical trajectory




### The Baseline

Generally favourable prognosis with early, phenotype-driven intervention.

### The Metric

>80% survival rate at 10 years for standard MCTD presentations.

### The Divergence

Unchecked Pulmonary Arterial Hypertension (PAH) and progressive Pulmonary Fibrosis remain the decisive factors that worsen the outcome and drive mortality.

**Rigorous adherence to the Alarcon-Segovia criteria prevents misdiagnosis, while mandatory annual cardiopulmonary screening remains the single most important intervention in long-term MCTD care.**