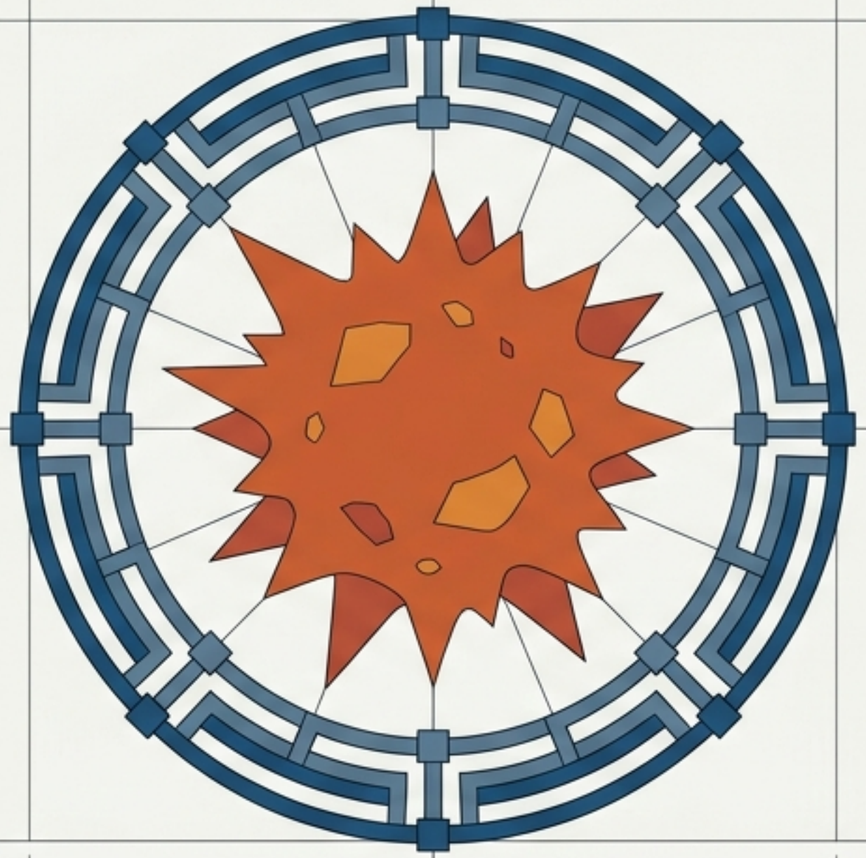
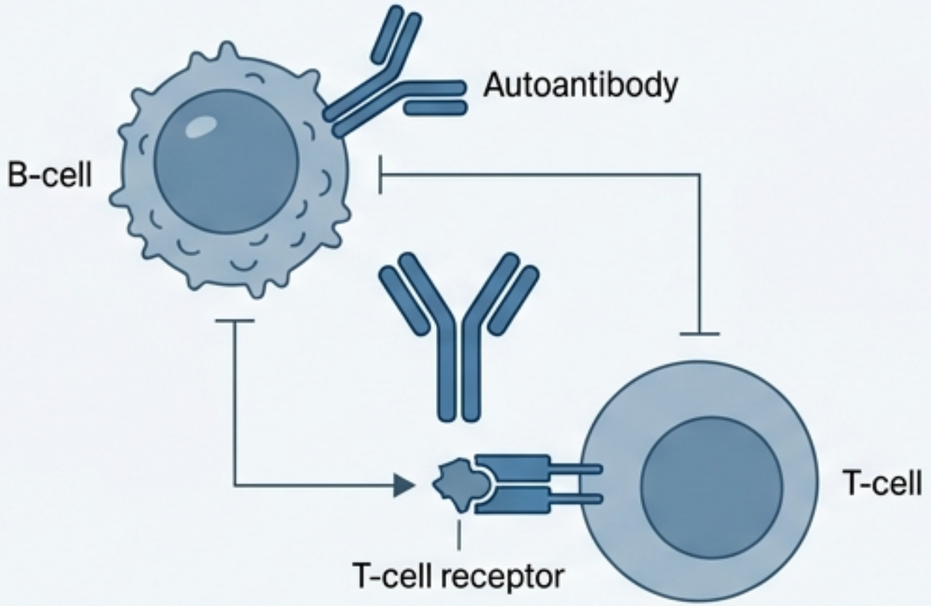


A Clinical Field Guide to Autoinflammatory Diseases

PRECISION IDENTIFICATION AND MANAGEMENT IN THE AUSTRALIAN CONTEXT

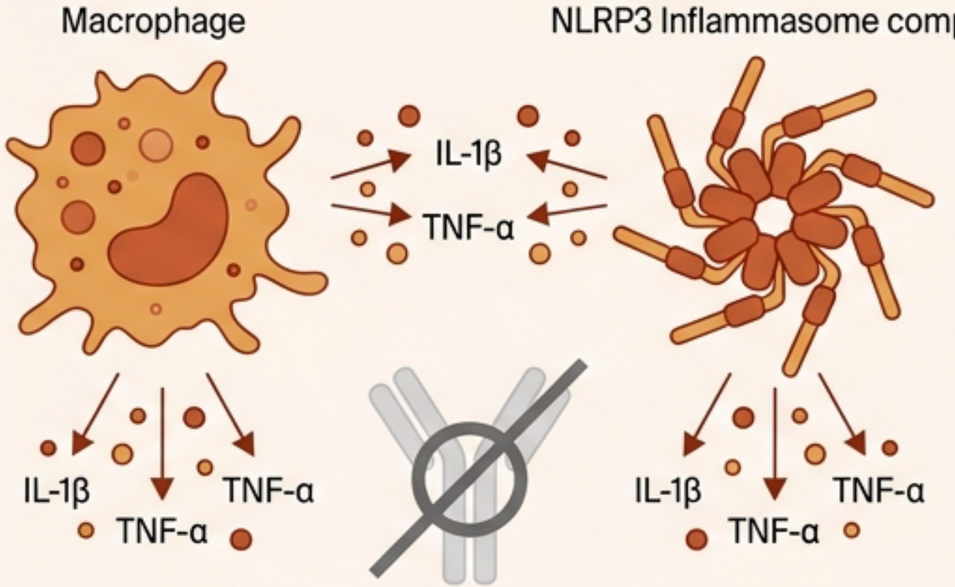
Immune Mechanisms: Adaptive vs. Innate Dysregulation

Adaptive Immunity: Autoimmune.



Driven by antigen-specific T-cells and pathogenic autoantibodies.

Innate Immunity: Autoinflammatory.



Driven by sterile, unprovoked innate immune dysregulation. Absence of high-titre autoantibodies or autoreactive T-cells.

Core Differentiator: **Autoinflammatory diseases lack pathogenic autoantibodies, presenting instead as unprovoked, recurrent systemic inflammation.**

Australian Epidemiology & The Diagnostic Gap

Monogenic Epidemiology

Incidence of 1–3 per 100,000 population.

Higher FMF prevalence in communities with Mediterranean, Middle Eastern, Armenian, Lebanese, Turkish, Jewish, and Arab descent.

AOSD Incidence

Adult-Onset Still Disease affects 0.16 per 100,000 per year, presenting more commonly in adult practice.

5 to 10 Years

Mean Diagnostic Delay for Monogenic Conditions in Australia

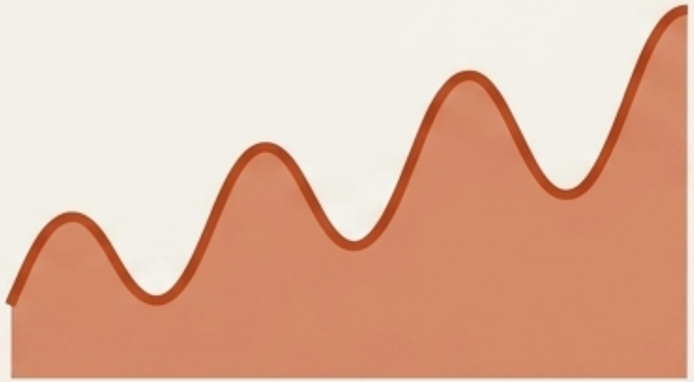
The Unifying Threat: The Race Against Amyloidosis

Clinical Goal:
Target SAA <10 mg/L via 6–12 monthly surveillance

The Trigger

Uncontrolled, recurrent autoinflammatory flares

The Accumulator



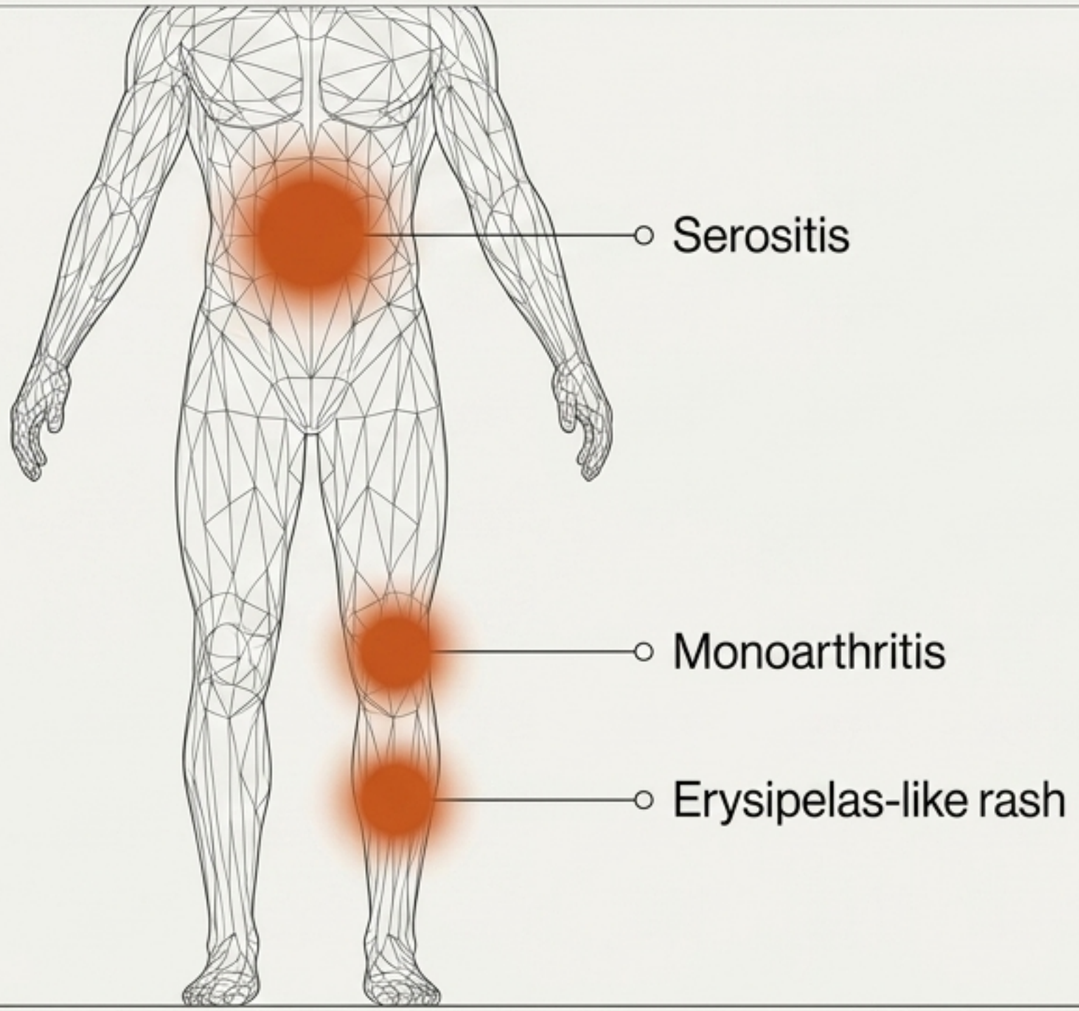
Sustained elevation of Serum Amyloid A (SAA)

The Consequence

AA Amyloidosis. Without prophylaxis, conditions like FMF carry a 60–70% risk of this catastrophic renal outcome.

Familial Mediterranean Fever (FMF)

The most common monogenic autoinflammatory disease



Genetic Profile

MEFV gene (chromosome 16p13.3) encoding pyrin. Autosomal-recessive. Common Australian pathogenic variants: M694V, V726A, M680I.

Clinical Hallmarks

Recurrent 1–3 day febrile episodes, serositis (peritonitis/pleuritis/pericarditis), acute large-joint monoarthritis, erysipelas-like erythema over lower limbs.

Paediatric Note

Episodes may be shorter and more frequent; scrotal oedema is a recognised feature in children.

Diagnostic Standard

Clinical diagnosis via Tel-Hashomer criteria supported by *MEFV* genotyping (MBS-rebated).

Recurrent Fever Diagnostic Matrix

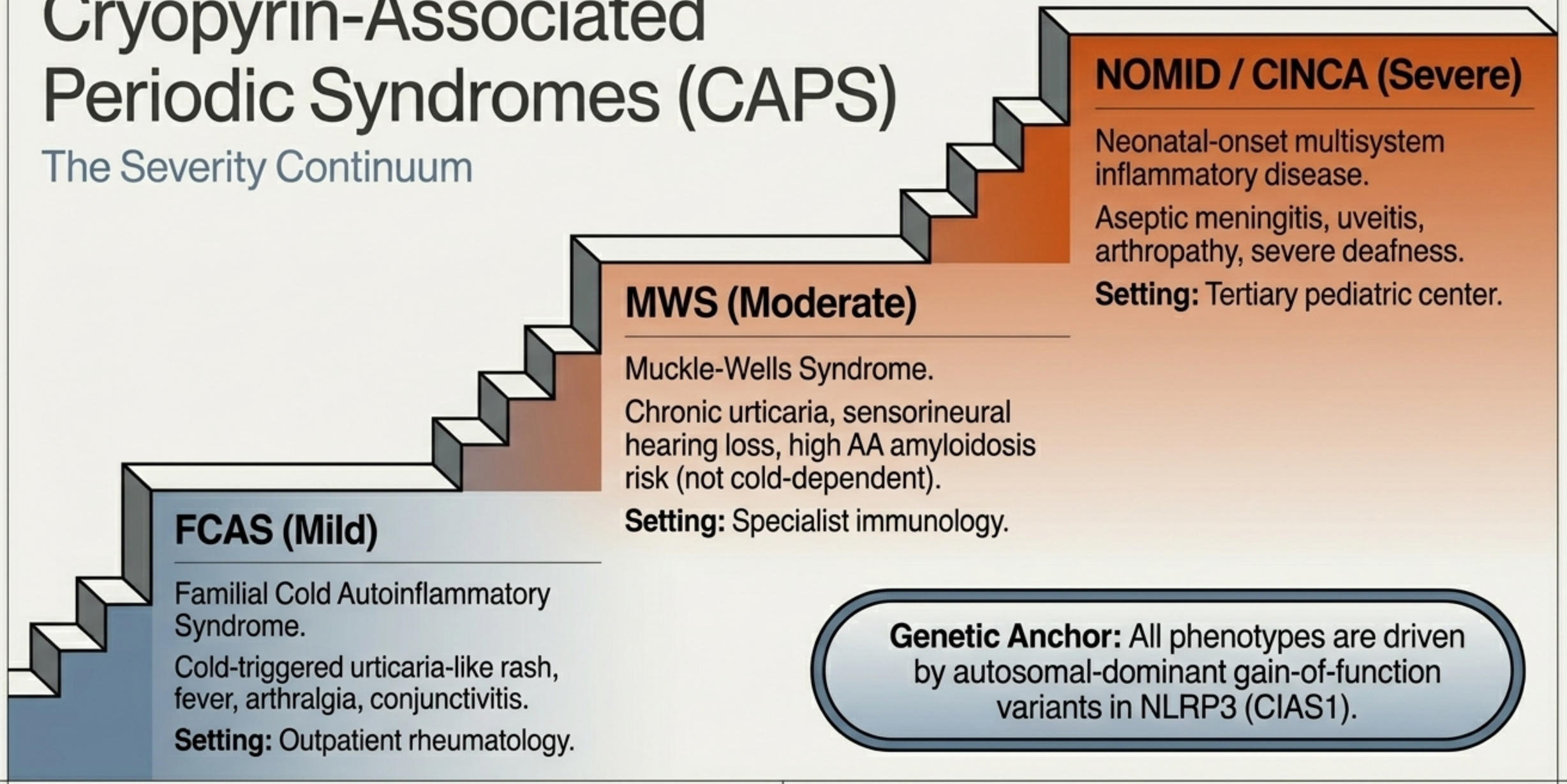
Differentiating the major monogenic febrile syndromes

	FMF	TRAPS	HIDS (MKD)
Gene & Inheritance	*MEFV* (Autosomal Recessive)	TNFRSF1A (Autosomal Dominant)	*MVK* (Autosomal Recessive)
Episode Duration	1–3 days	1–3 weeks (Longest duration)	3–7 days
Hallmark Features	Serositis, erysipelas-like rash, monoarthritis	Migratory myalgia, centrifugal erythematous rash, periorbital oedema	Cervical lymphadenopathy, abdominal pain, elevated IgD >100 IU/mL
Prophylaxis	Colchicine	IL-1 inhibitor or Etanercept	Canakinumab

Note: All targeted biologic therapies listed above require PBS Authority.

Cryopyrin-Associated Periodic Syndromes (CAPS)

The Severity Continuum

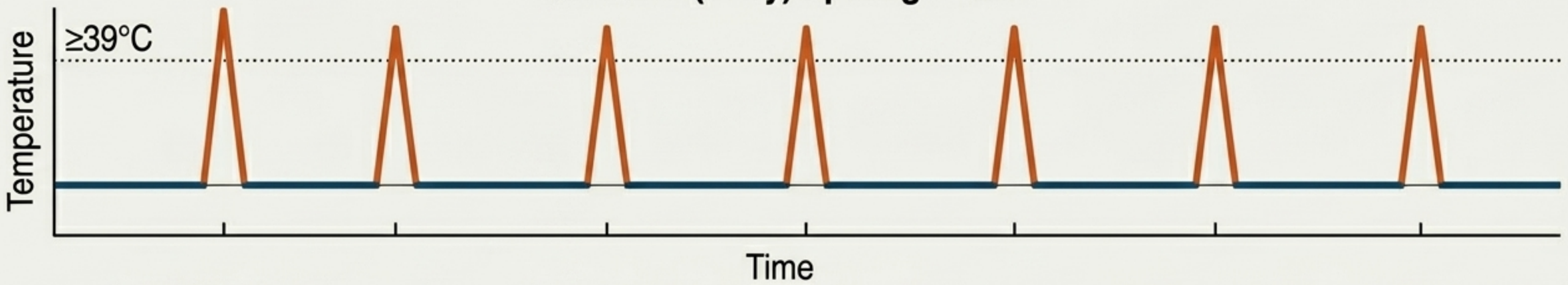


Genetic Anchor: All phenotypes are driven by autosomal-dominant gain-of-function variants in NLRP3 (CIAS1).

Adult-Onset Still Disease (AOSD)

Clinical Presentation of a Polygenic Mimic

Quotidian (Daily) Spiking Fevers



Evanescent Salmon Rash

A characteristic salmon-pink macular rash typically appearing on the trunk and proximal limbs. Crucially, the rash occurs synchronously with the daily fever

Severe Pharyngitis & Arthritis

Severe sore throat is a classic early symptom. Accompanied by arthritis (affecting wrists, knees, ankles) which becomes chronic in approximately 50% of patients.

Marked Hyperferritinaemia

Extreme elevation of serum ferritin is a hallmark feature, often alongside lymphadenopathy, serositis, and hepatosplenomegaly.

AOSD Diagnostic Scorecard

Modified Yamaguchi Criteria

Major Criteria

- ☐ Fever ≥39°C, intermittent, ≥1 week
- ☐ Arthralgia ≥2 weeks
- ☐ Typical salmon evanescent rash
- ☐ Leukocytosis ≥10×10^9/L (≥80% neutrophils)

Requires ≥5 criteria (including ≥2 major)

Minor Criteria

- ☐ Sore throat
- ☐ Lymphadenopathy
- ☐ Hepatomegaly or splenomegaly
- ☐ Abnormal liver function tests
- ☐ Negative RF and ANA

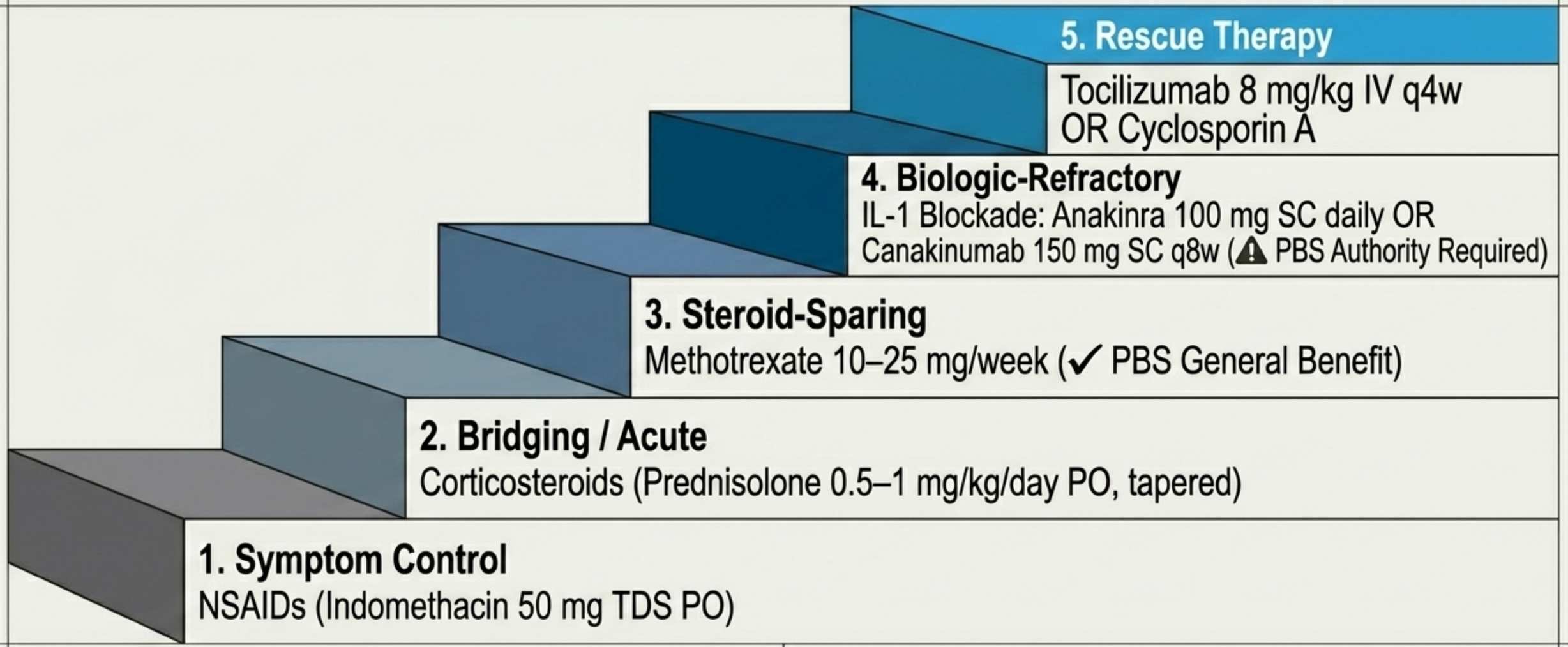
Critical Alert: Macrophage Activation Syndrome (MAS)

Threshold: Ferritin >10,000 µg/L, falling fibrinogen, cytopenias. This is a haematological emergency.

Action: IV methylprednisolone pulse (1 g × 3 days) ± cyclosporin A. Transfer to tertiary center immediately.

AOSD Treatment Ladder

Escalation pathways from symptom control to targeted blockade



Other Inflammasomopathies

Ultra-rare syndromes requiring targeted blockade

PAPA

PSTPIP1

Pyogenic arthritis, pyoderma gangrenosum, acne.

Rx: **Anakinra or IL-6 inhibitor**

DADA2

CECR1 (ADA2)

Livedo, early-onset lacunar strokes, vasculitis, immunodeficiency.

Rx: **Anti-TNF** (etanercept / adalimumab)

DIRA

IL1RN

Neonatal-onset sterile multifocal osteomyelitis, periostitis, pustulosis.

Rx: **Anakinra** (replaces endogenous IL-1Ra)

HA20

OTULIN

Early-onset Behçet-like disease; oral and genital ulcers, fever.

Rx: **Anakinra** or **Anti-TNF**

The Intervention Landscape

Broad antimitotic defense vs targeted biologic precision

Colchicine
(Broad Shield)

Mechanism: Broad antimitotic agent.

Primary Use: First-line prophylaxis for FMF.

Adult Dose: 1–2 mg/day PO.

Renal Adjustment: Reduce dose by 50% if eGFR <30 mL/min.

Access: ✓ PBS General Benefit.

IL-1 Inhibitors
(Precision Key)

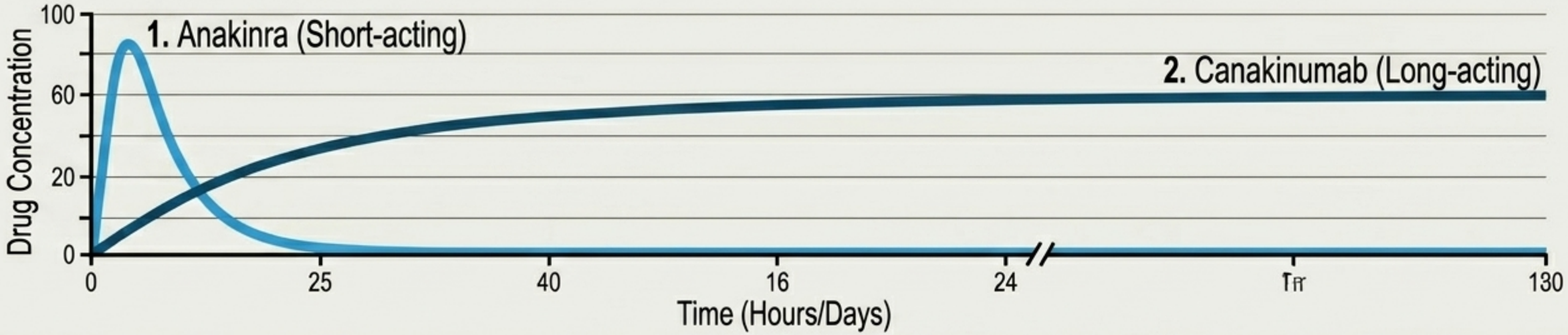
Mechanism: Targeted blockade of the inflammasome cytokine axis.

Primary Use: Cornerstone for CAPS, TRAPS, HIDS, and refractory AOSD/FMF.

Agents: Anakinra (IL-1Ra) and Canakinumab (Anti-IL-1β mAb).

Access: ⚠ PBS Authority Required for all indications.

IL-1 Inhibitors: Pharmacokinetic Profiles



Anakinra / Kineret®

Target: IL-1 receptor antagonist (IL-1Ra).

Dose: 100 mg SC daily.

Half-life: 4–6 hours.

Clinical Utility: Rapid onset. Excellent for diagnostic trials in AOSD.

Adverse Effects: Injection-site reactions (~70%), neutropenia.

Canakinumab / Ilaris®

Target: Anti-IL-1β monoclonal antibody.

Dose: 150 mg SC q8w (CAPS dosing).

Half-life: 26 days.

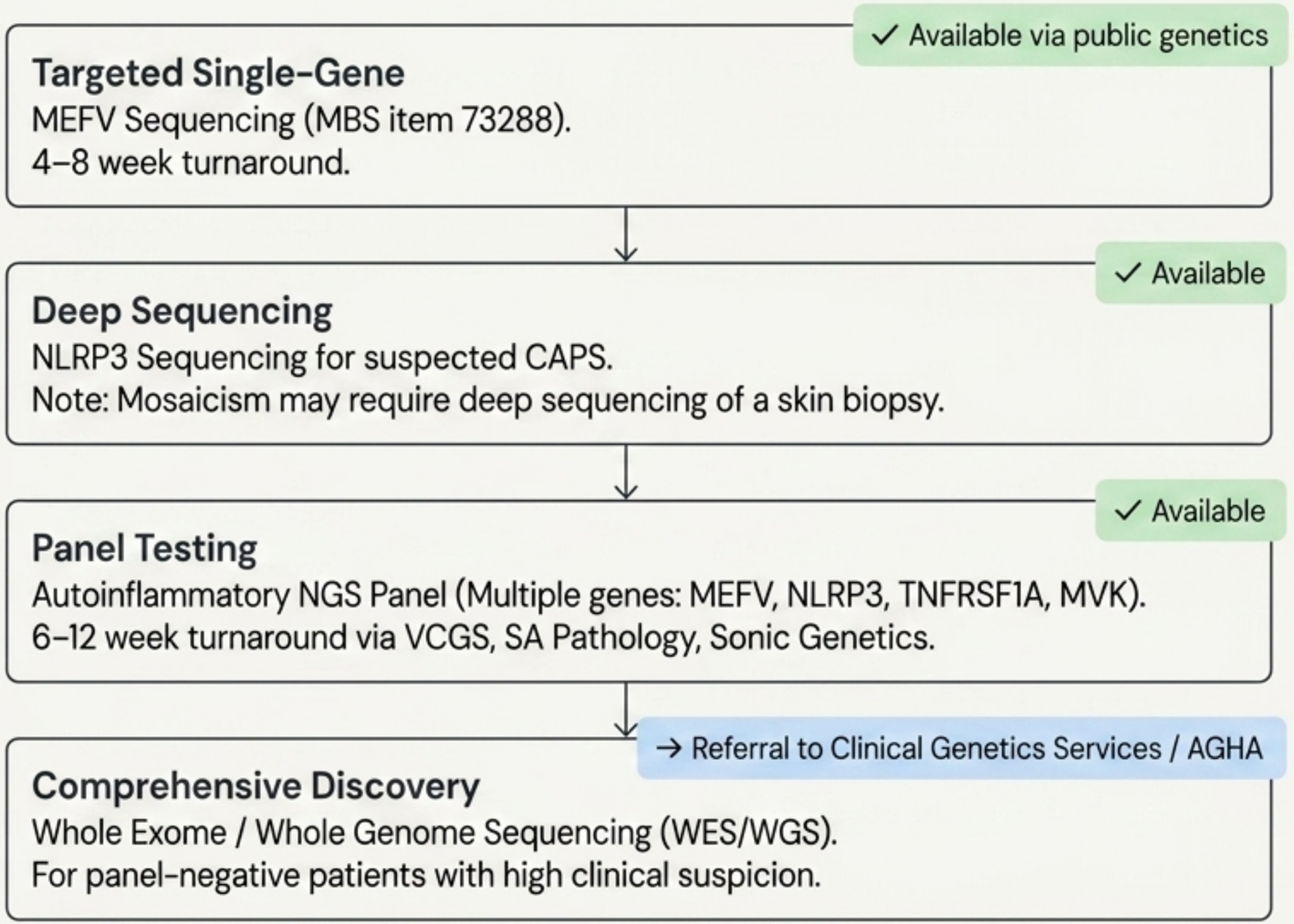
Clinical Utility: Convenient, sustained maintenance dosing.

Adverse Effects: URTI, Hep B reactivation risk.

Pre-Flight Checklist: Screen for TB (Quantiferon-Gold), Hep B/C, and HIV before initiating. Live vaccines contraindicated.

Public Genetics Navigation Flowchart

Diagnostic pathways for Australian clinicians



Vulnerable Populations Matrix

Pharmacological adjustments and considerations

Pregnancy

Colchicine is safe; continue usual dose. Anakinra is Category B3 (continue only if benefit > risk). Canakinumab is generally avoided (stop ≥4 months pre-conception).

Paediatrics

NOMID requires early anakinra from neonatal period. FMF utilizes weight-based colchicine from diagnosis. Canakinumab approved at 2–4 mg/kg.

Renal Impairment

Reduce colchicine dose by 50% if eGFR <30 mL/min; avoid in dialysis if possible.
No formal IL-1 dose adjustment required, but monitor LFTs/FBC due to immunosuppression.

Immunocompromised

High serious infection risk with IL-1 inhibitors. Strictly avoid live vaccines.
Screen for latent TB and Hep B before initiation.
Monitor FBC fortnightly initially.

Aboriginal & Torres Strait Islander Considerations

Equitable Care & Diagnostic Access

Geography & Telehealth

Undifferentiated recurrent fever in remote communities may be misattributed to infection. Maintain high suspicion. Telehealth (MBS 91822–91823) and RFDS coordination are essential for specialist

Supply Logistics

Colchicine is accessible via community pharmacy (PBS General Benefit). IL-1 inhibitors require PBS Authority and strict cold-chain SC coordination with remote nursing staff.

Culture & Consent

Engage Aboriginal Health Workers and ACCHOs. Ensure culturally safe, yarning-based communication and face-to-face genetic consent, respecting family decision-making and carrier implications.

Clinical Anchors & Key References

1. **Suspect monogenic autoinflammation in undifferentiated recurrent fever presenting with serositis or typical rashes.**

2. **Suppress the fire: Treat relentlessly to target SAA <10 mg/L to prevent the catastrophic complication of AA amyloidosis.**

3. **Ferritin >10,000 µg/L in AOSD indicates impending Macrophage Activation Syndrome. Treat as a haematological emergency.**

Federici et al. (Ann Rheum Dis 2015)

Shinar et al. (Ann Rheum Dis 2012)

Ozen S, Bilginer Y. (Nat Rev Rheumatol 2014)

Kuemmerle-Deschner et al. (Ann Rheum Dis 2017)

Gerfaud-Valentin et al. (Autoimmun Rev 2014)