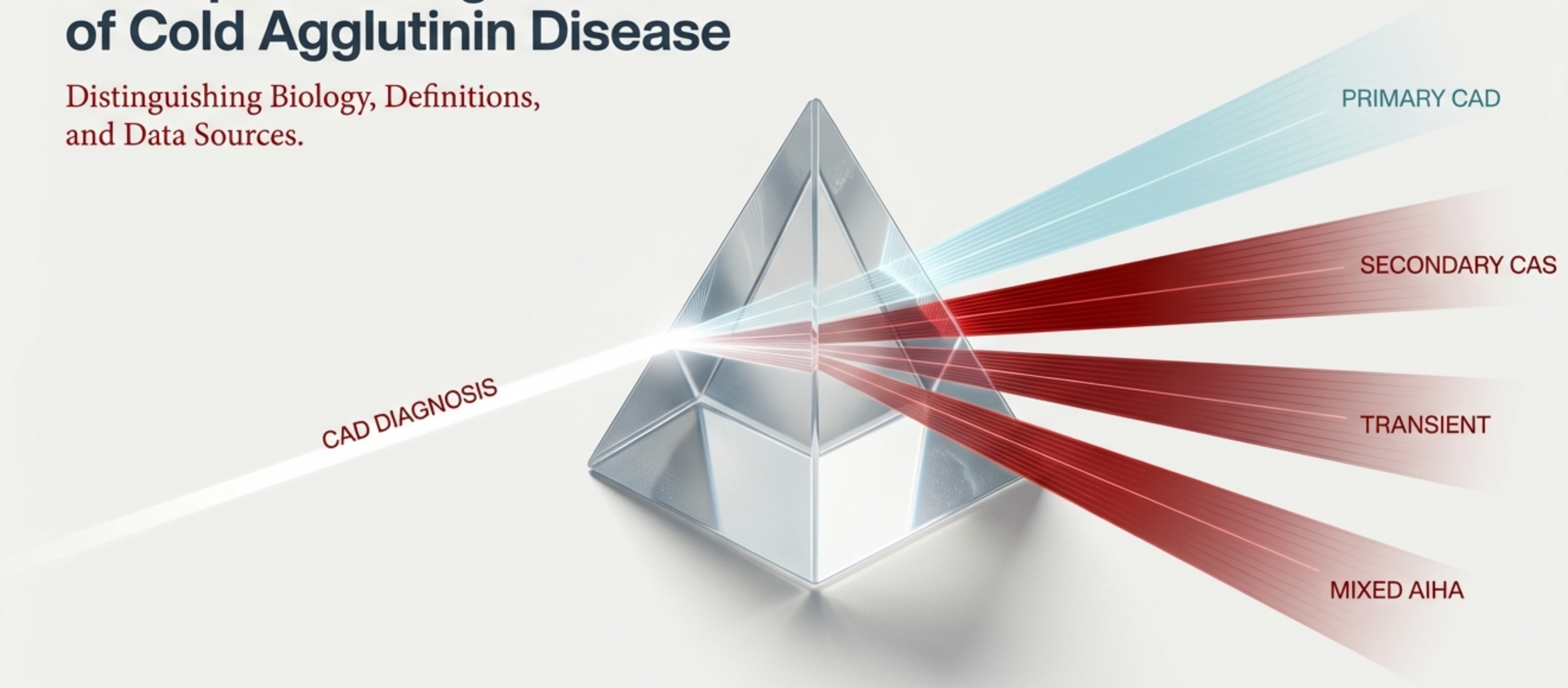
The Epidemiological Prism of Cold Agglutinin Disease

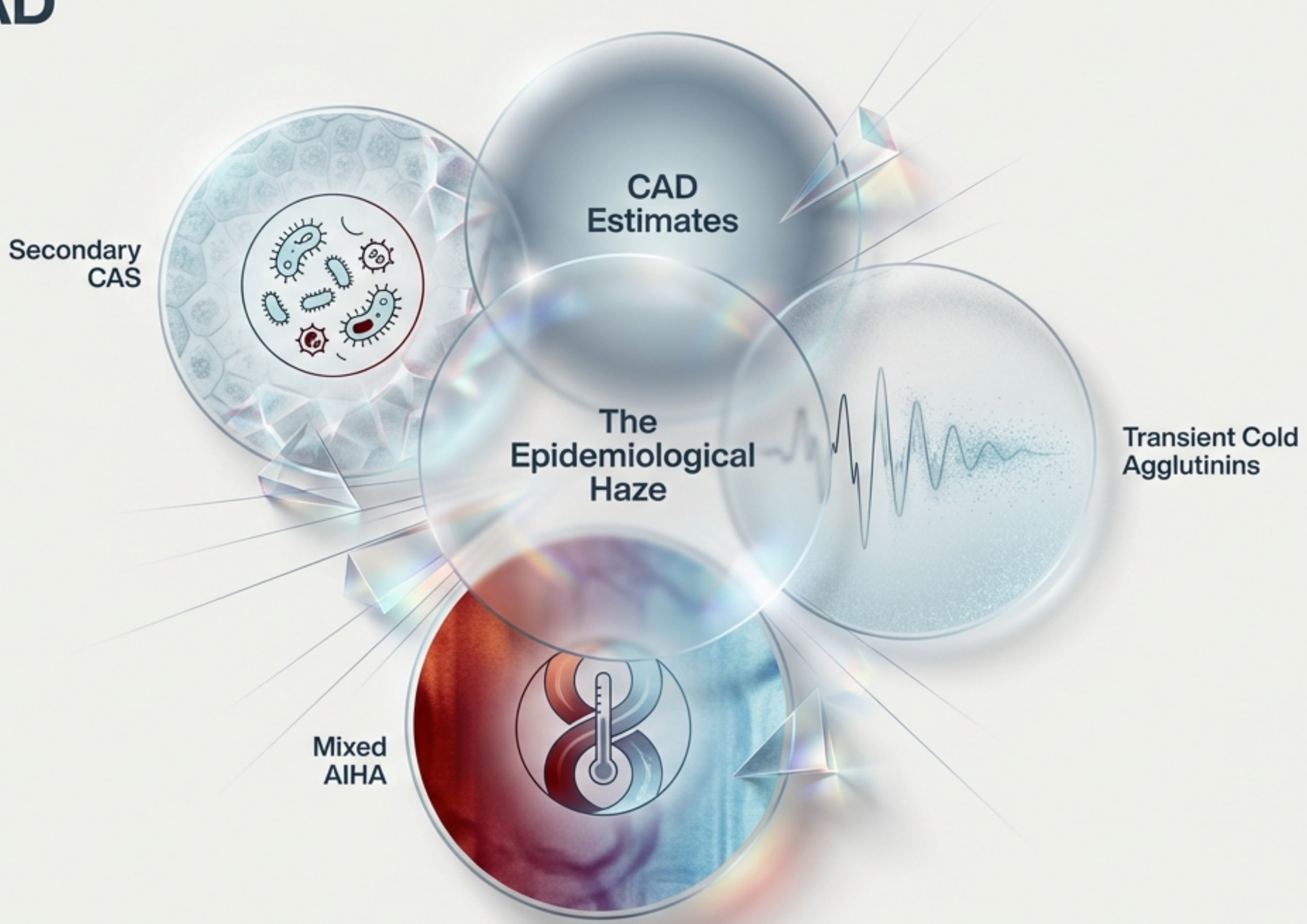
Distinguishing Biology, Definitions, and Data Sources.



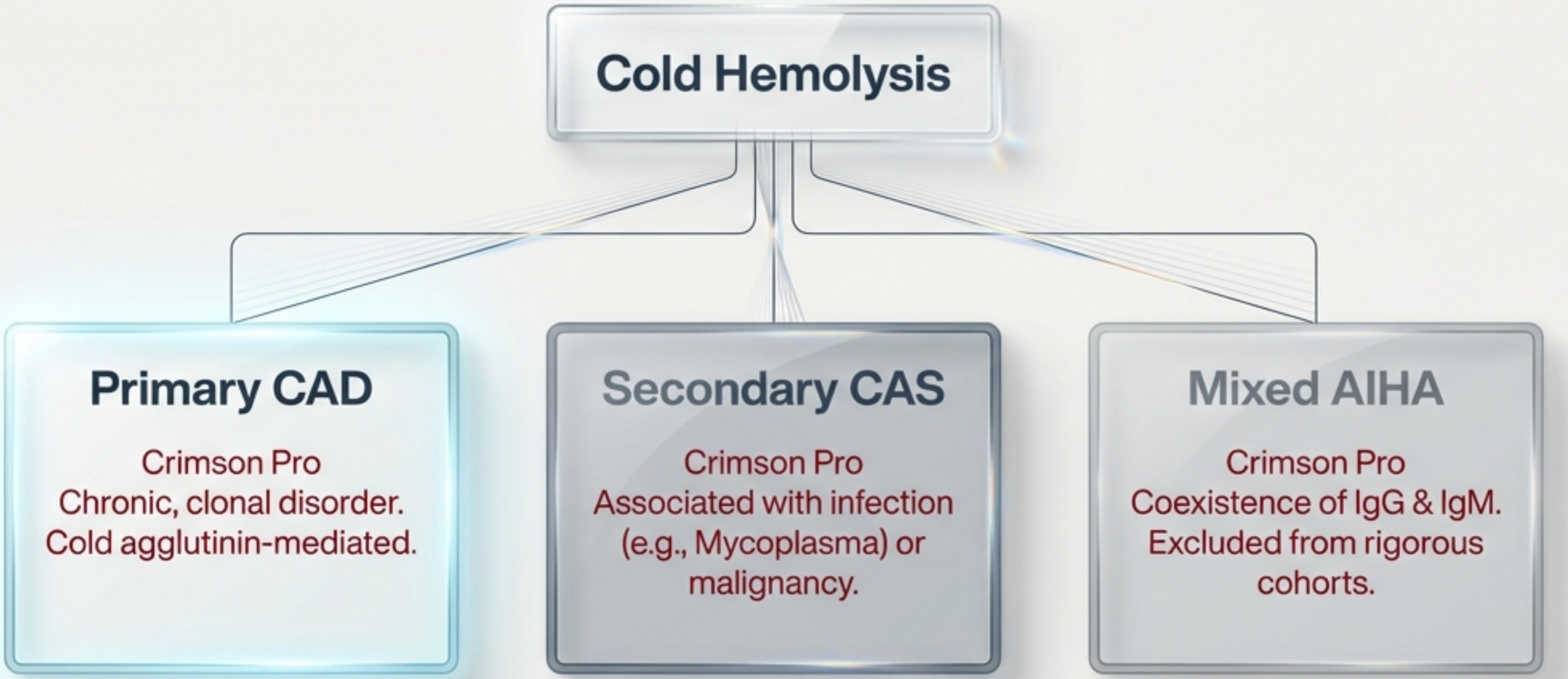
Based on "The Epidemiology of Cold Agglutinin Disease" by William Aird.

Why Counting CAD is Harder Than It Looks

The rarer the condition, the more estimates depe. depend on how cases are defined and found. Many administrative datasets cannot cleanly distinguish among these biologically distinct entities, leading to conflated statistics.

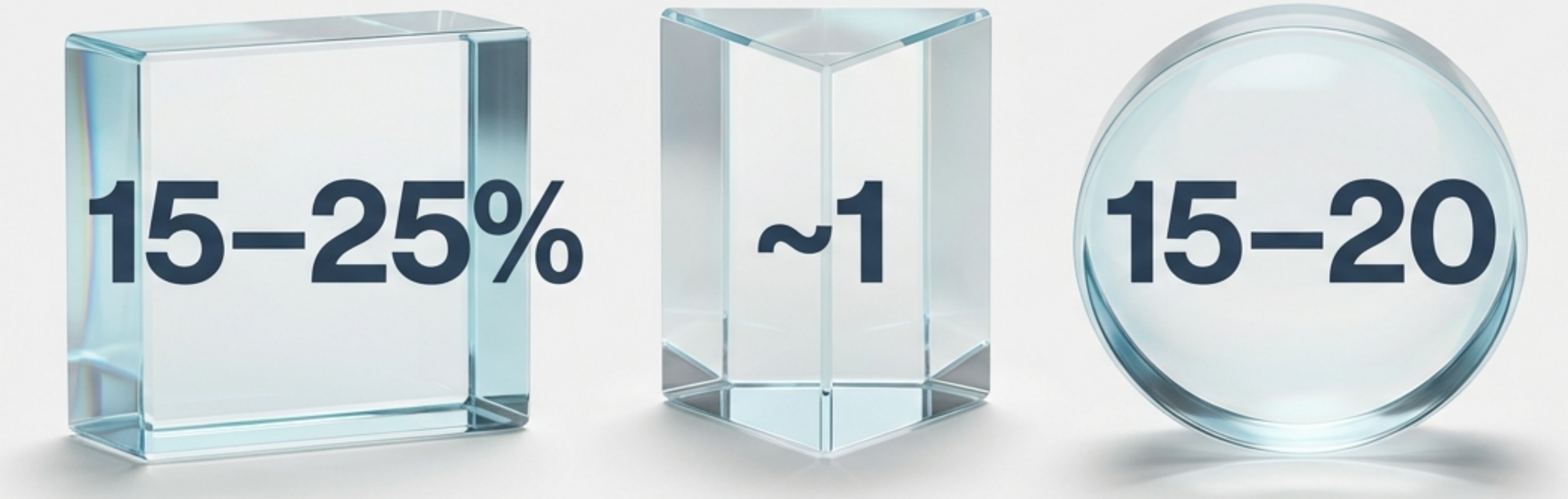


Precision in Phenotype Determines Data Integrity



Note: Administrative datasets often collapse these entities. Rigorous epidemiology requires strict separation.

The Quantitative Anchors (Tier 1 Data)



of all AIHA cases

per million / year
(Incidence)

per million
(Prevalence - N. Europe)

Classic Cohort Data
(Strict Phenotyping)

These figures come from cohorts with careful exclusion of secondary and mixed forms. They represent the “Memory Numbers” for clinicians.

The ‘Real World’ Data Shift (Tier 2 Nuance)

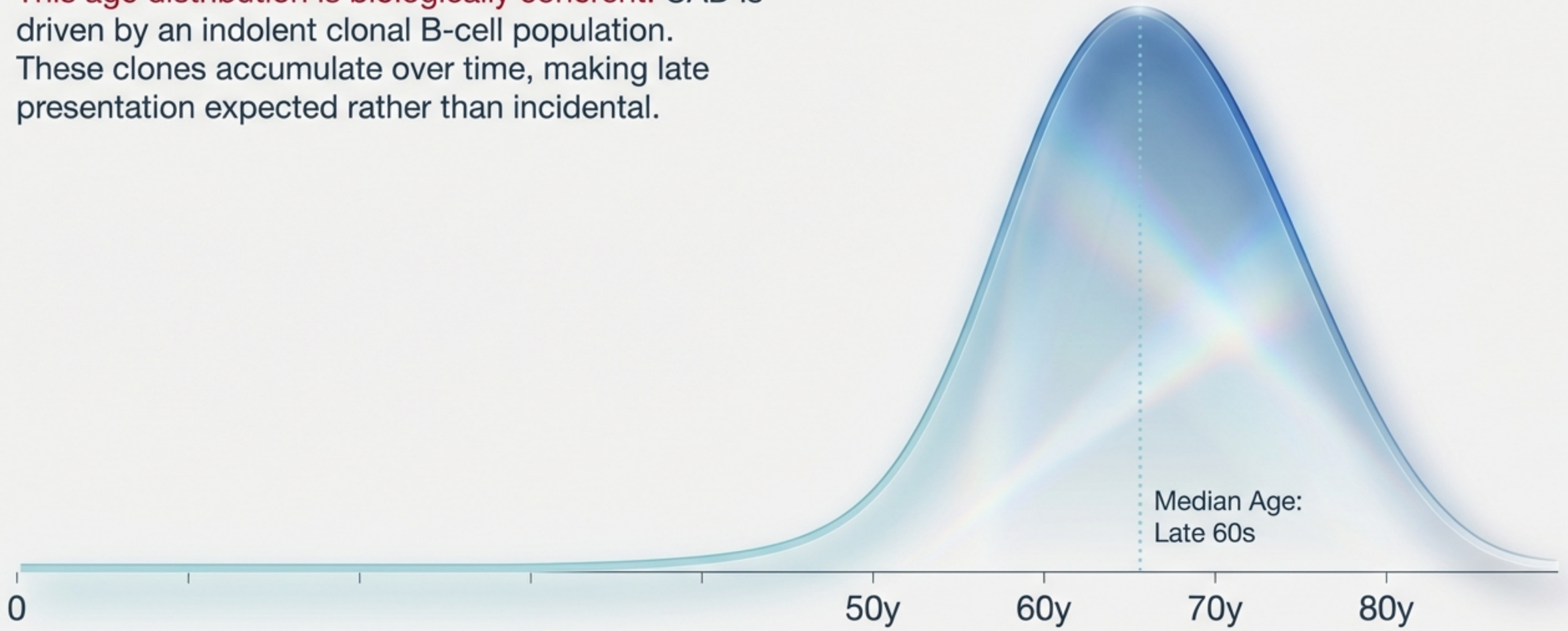
Why the increase?

1. Broader diagnostic coding strategies.
2. Inclusion of mixed or secondary phenotypes.
3. Older insured populations.

Epidemiologic estimates depend strongly on the method (administrative vs. clinical) rather than biology alone.

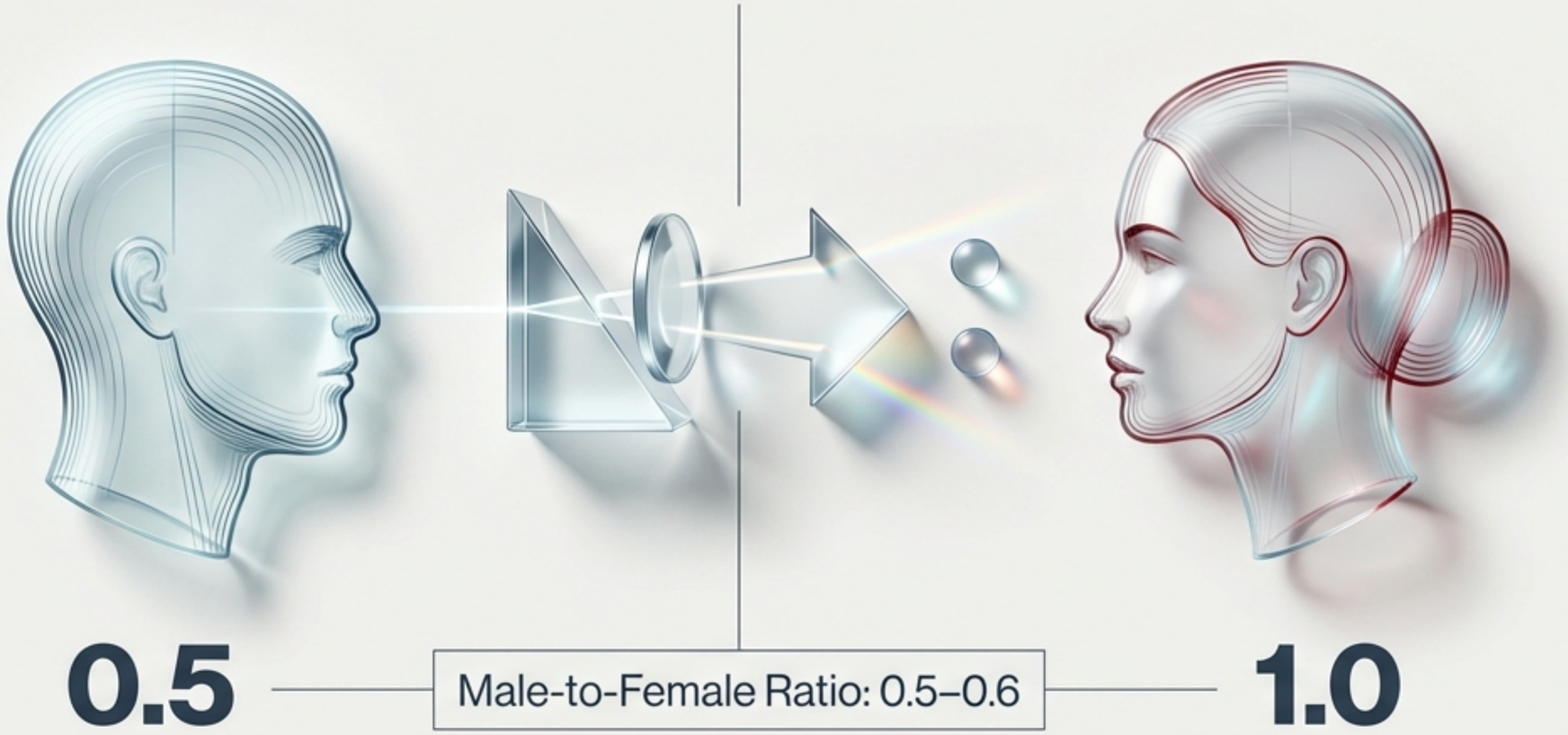
A Disease of Time and Clonal Accumulation

This age distribution is biologically coherent. CAD is driven by an indolent clonal B-cell population. These clones accumulate over time, making late presentation expected rather than incidental.



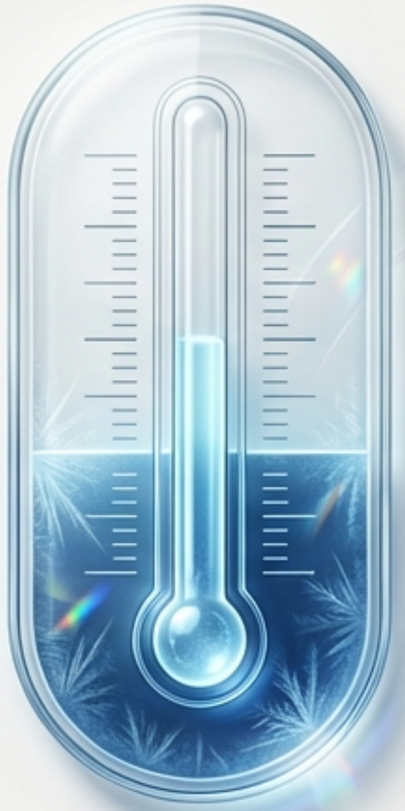
Consistent Female Predominance

This pattern is reproduced in both clinically adjudicated cohorts and administrative data, mirroring broader trends across autoimmune diseases.



The Climate Paradox: Biology vs. Detection

Contemporary datasets do not always show a consistent geographic gradient despite climatic variation. Climate likely influences clinical expression and detection more than true disease incidence.



Ascertainment Bias?

Biology: Cold triggers agglutination.

Epidemiology: Cold regions report higher prevalence.

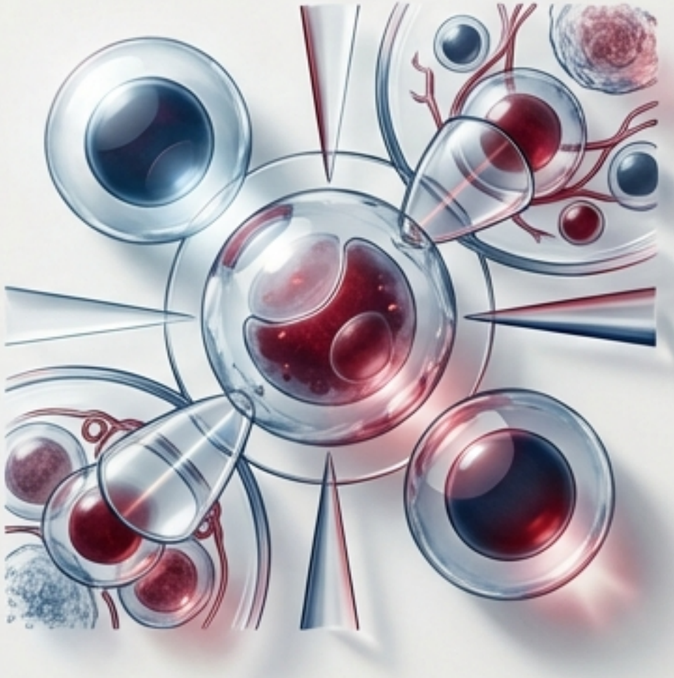
Secondary Cold Agglutinin Syndromes (CAS)

Cold hemolysis triggered by external factors, distinct from Primary CAD.

Infections

Mycoplasma pneumoniae, EBV.
Often transient.

Malignancy



Lymphoproliferative disorders.
Indolent B-cell processes.

Epidemiology is difficult to quantify due to transient cases and inconsistent coding.

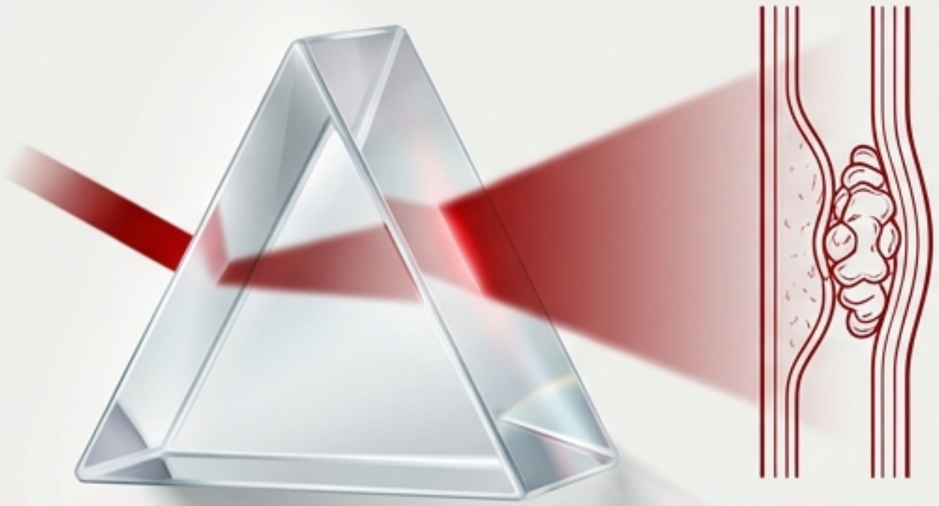
The Diagnostic Dilemma

When cold agglutinin–mediated hemolysis is encountered, epidemiologic literature cannot reliably predict if it is Primary vs. Secondary.

Diagnostic evaluation cannot rely on prevalence assumptions alone; specific testing is required.

Rare Does Not Mean Trivial: Morbidity & Mortality

Thromboembolic Risk



Signals of increase in contemporary analyses.

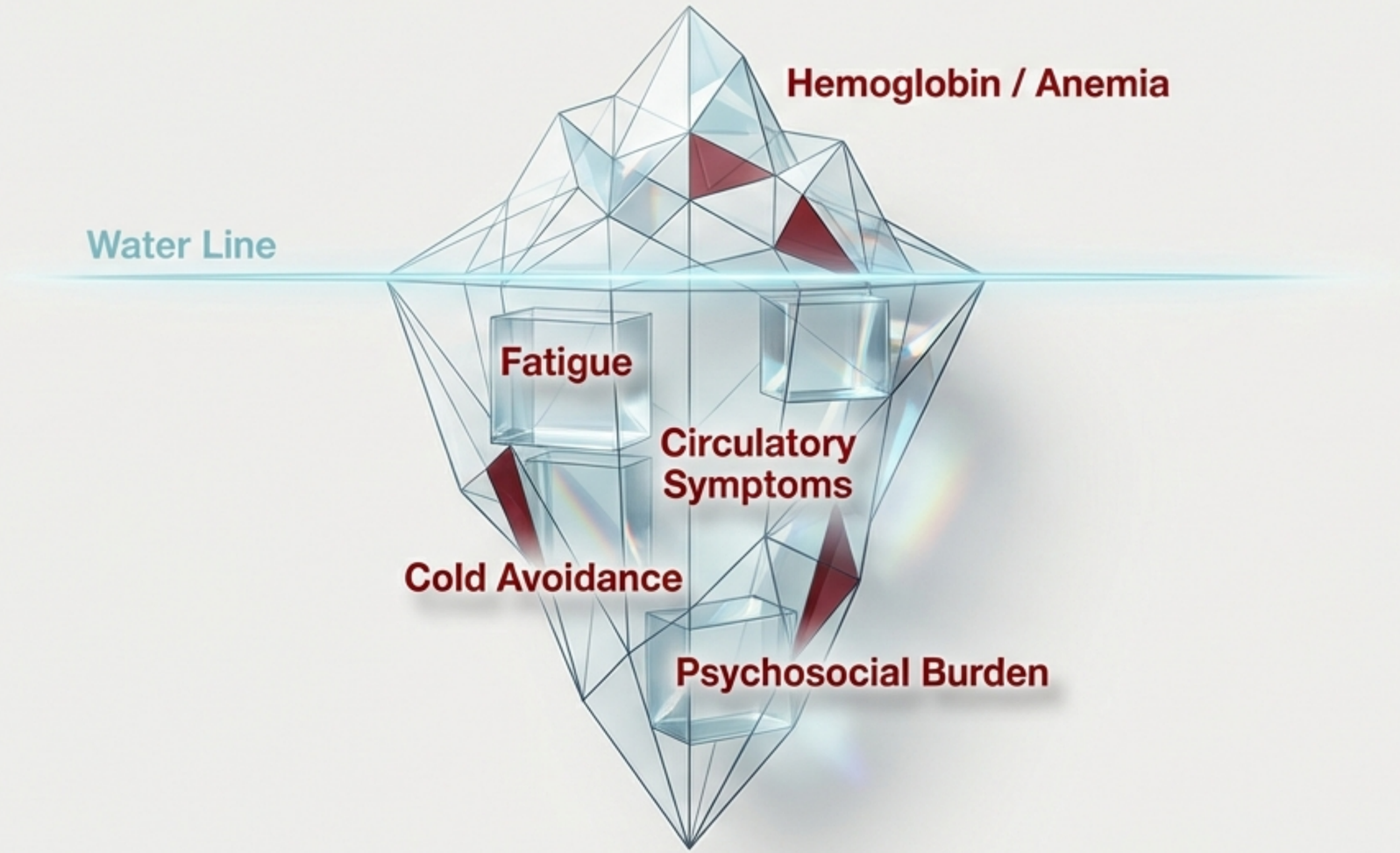
Excess Mortality

Observed in some populations.

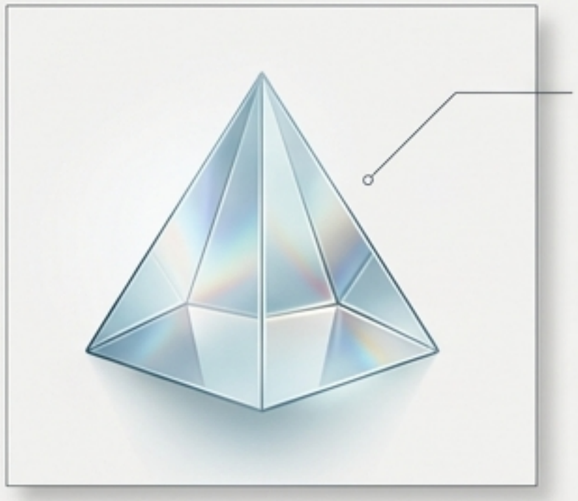
Interpretation depends on comparator selection and disease duration.

The Iceberg of Patient Burden

"Numbers measure one dimension; patients live the whole system."

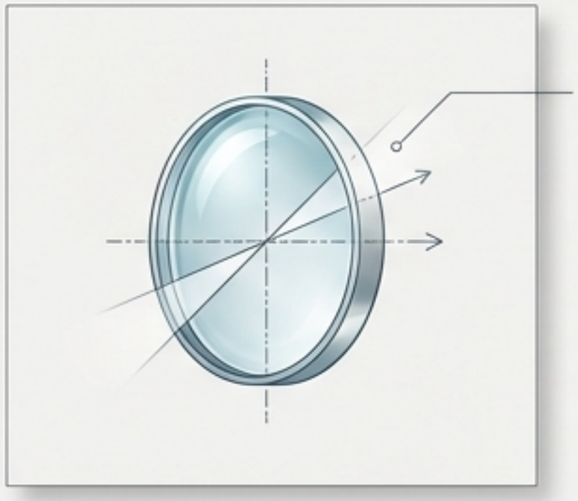


Summary: The Epidemiological Landscape



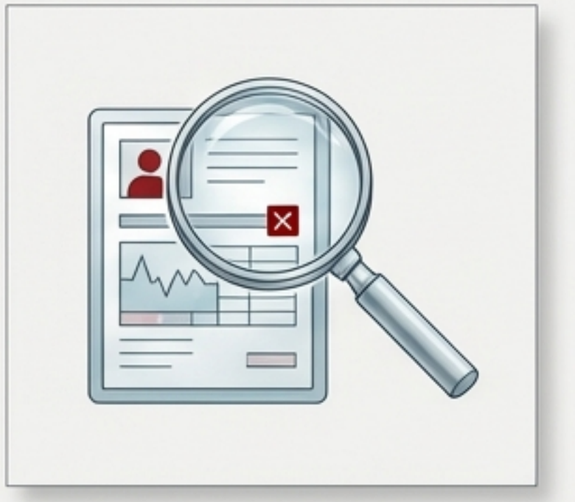
Rarity

15–25% of AIHA. Incidence ~1/million (cohorts) vs. higher in claims.



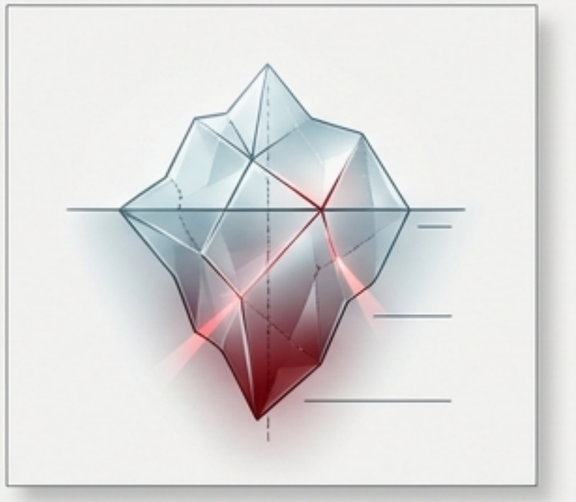
Profile

Disease of older adults (clonal accumulation) with mild female predominance.



Caveat

‘Rare’ depends on definition. Rigorous exclusion of Secondary CAS is vital.



Impact

High symptom burden and QoL impairment often exceed predictions based on hemoglobin.