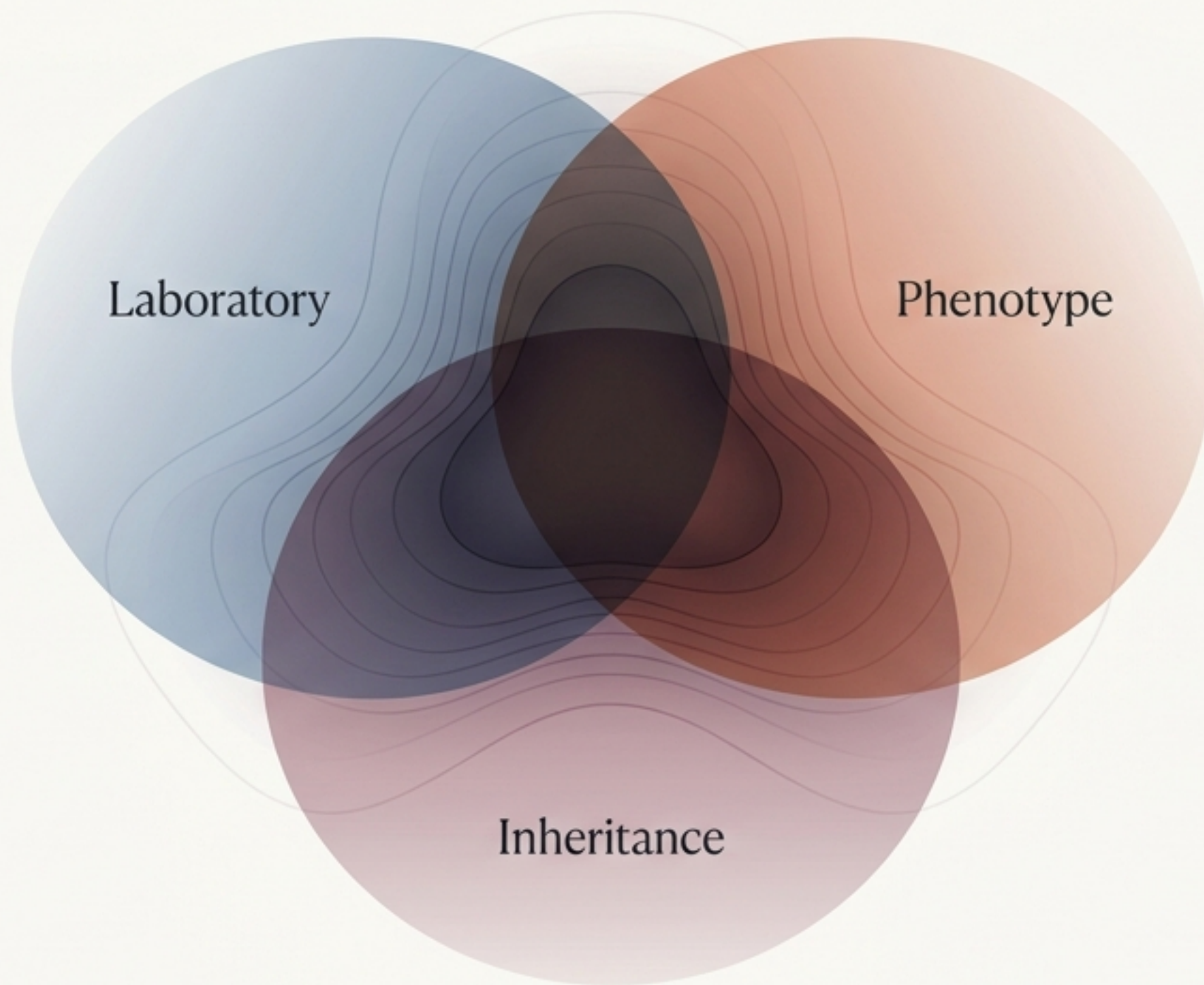


When Numbers and Bleeding Tell Different Stories

A Probabilistic Framework for the Lab-Phenotype Mismatch in Von Willebrand Disease



Two Patients, Opposite Signals

Which patient has stronger evidence for VWD? Which has stronger evidence for clinically important bleeding? VWD forces you to choose neither.

Patient A

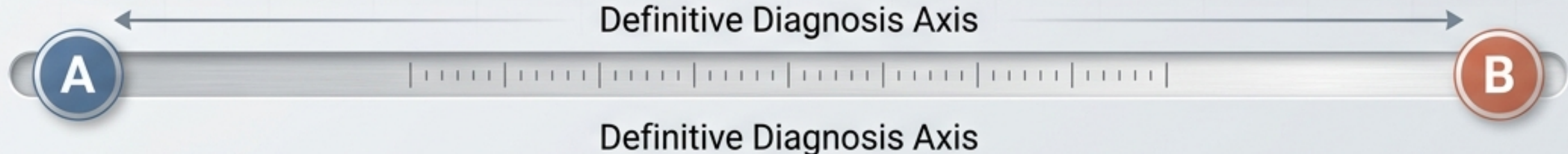
 VWF:Ag: 28 IU/dL

- Bleeding History: Minimal
- Procedural Bleeding: None

Patient B

 VWF:Ag: 62 IU/dL

- Bleeding History: Severe menorrhagia since adolescence
- Procedural Bleeding: Postpartum hemorrhage



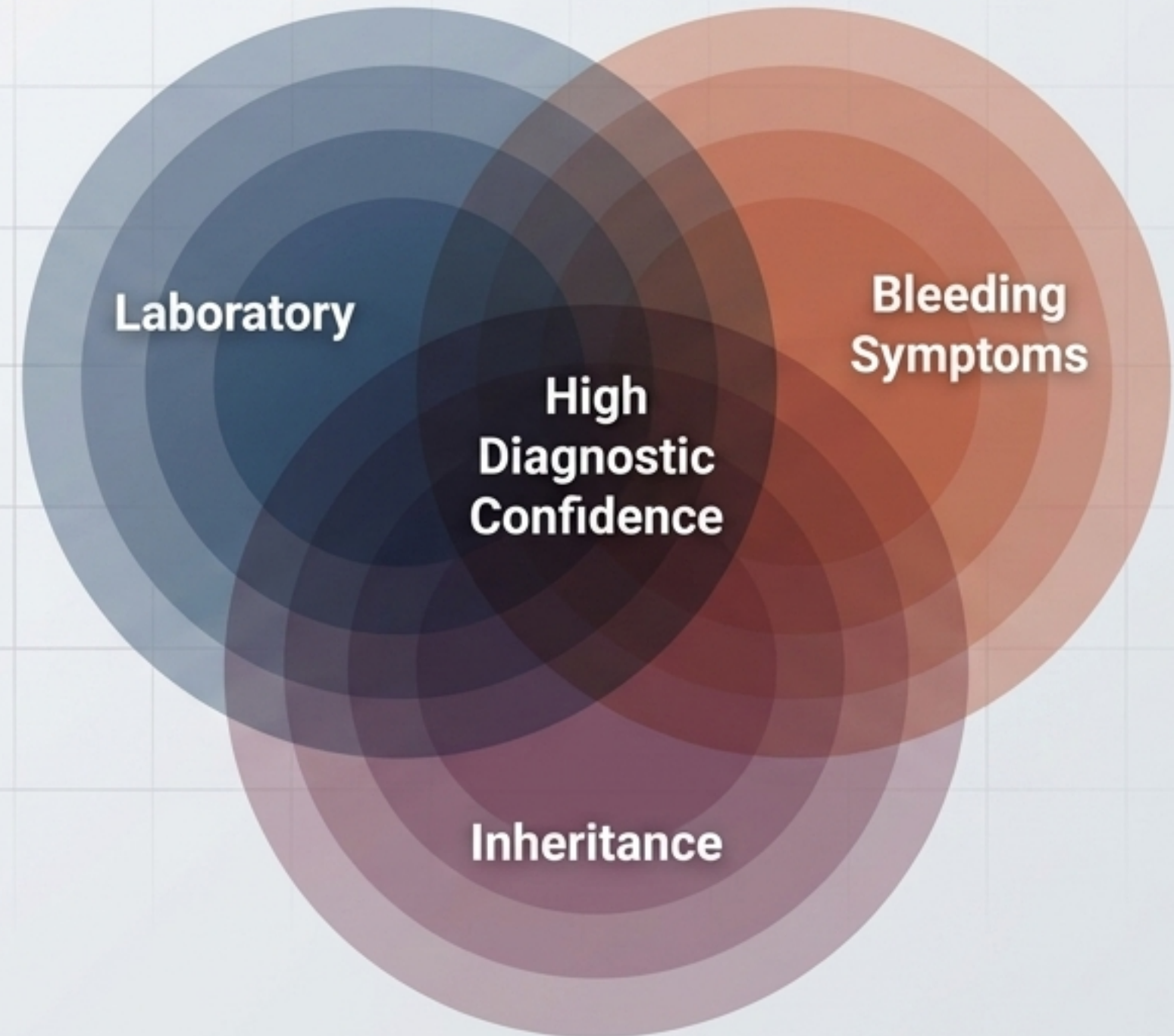
Diagnosis Requires Integration, Not Reduction

Key Takeaways:

- VWD resists reduction to a single number, symptom, or test.
- The diagnostic triad remains central but must be applied probabilistically.
- Family history strengthens confidence when present, but its absence does not exclude VWD.

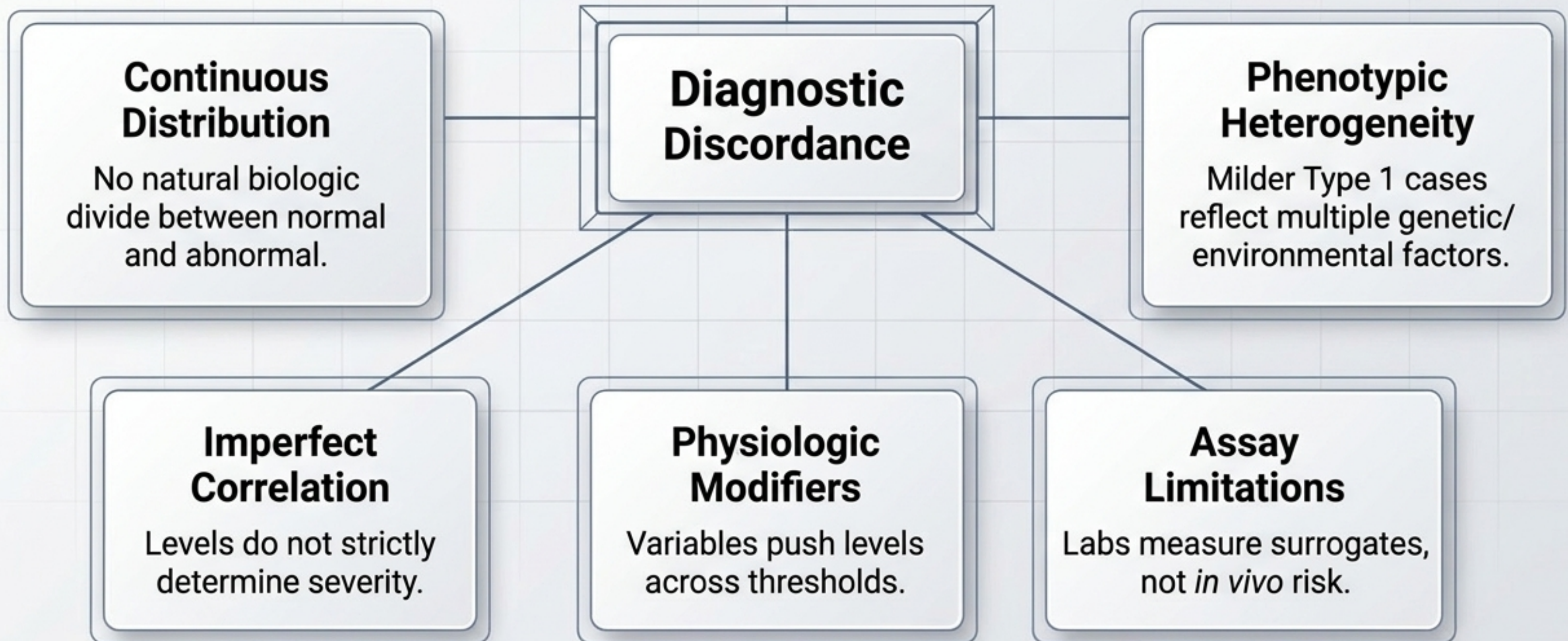
Recognizing mismatch, and **resisting premature resolution, is central to expert care.**

Clinical Triangulation Map



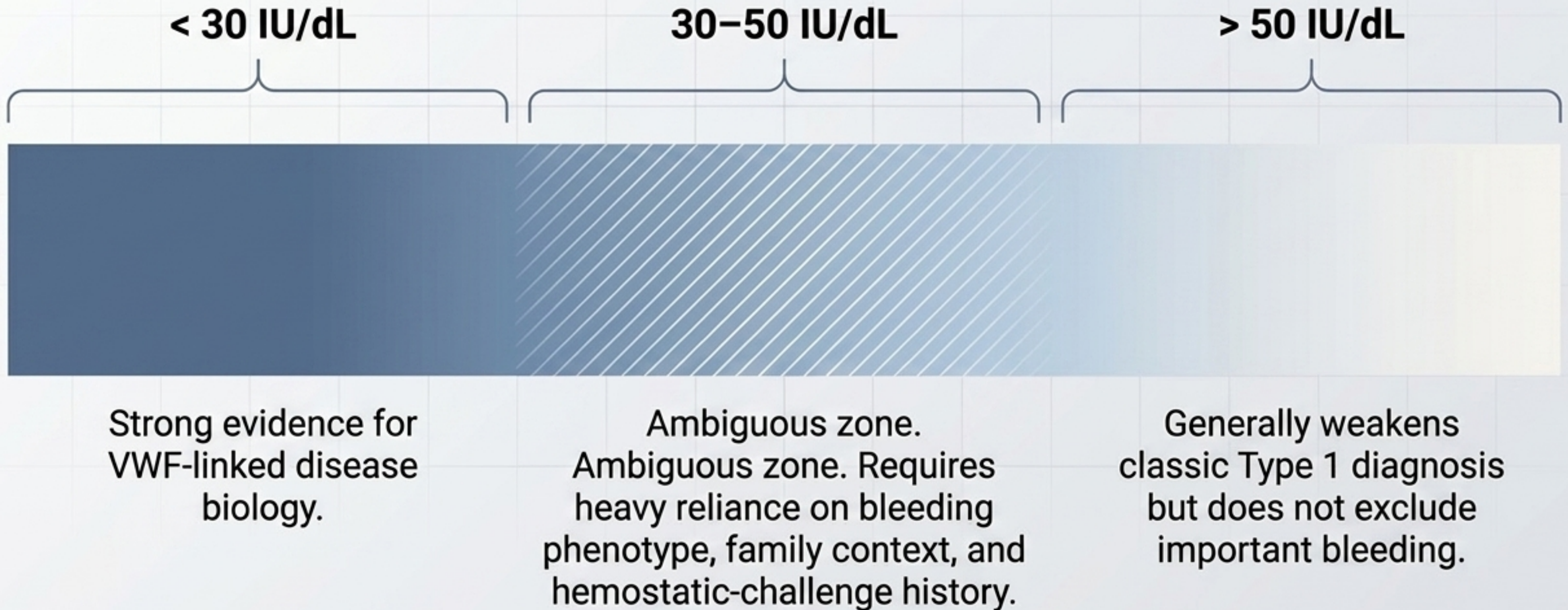
Why the Mismatch Exists: Five Drivers of Discordance

Mismatch is expected, not exceptional. It is a feature of VWF biology.



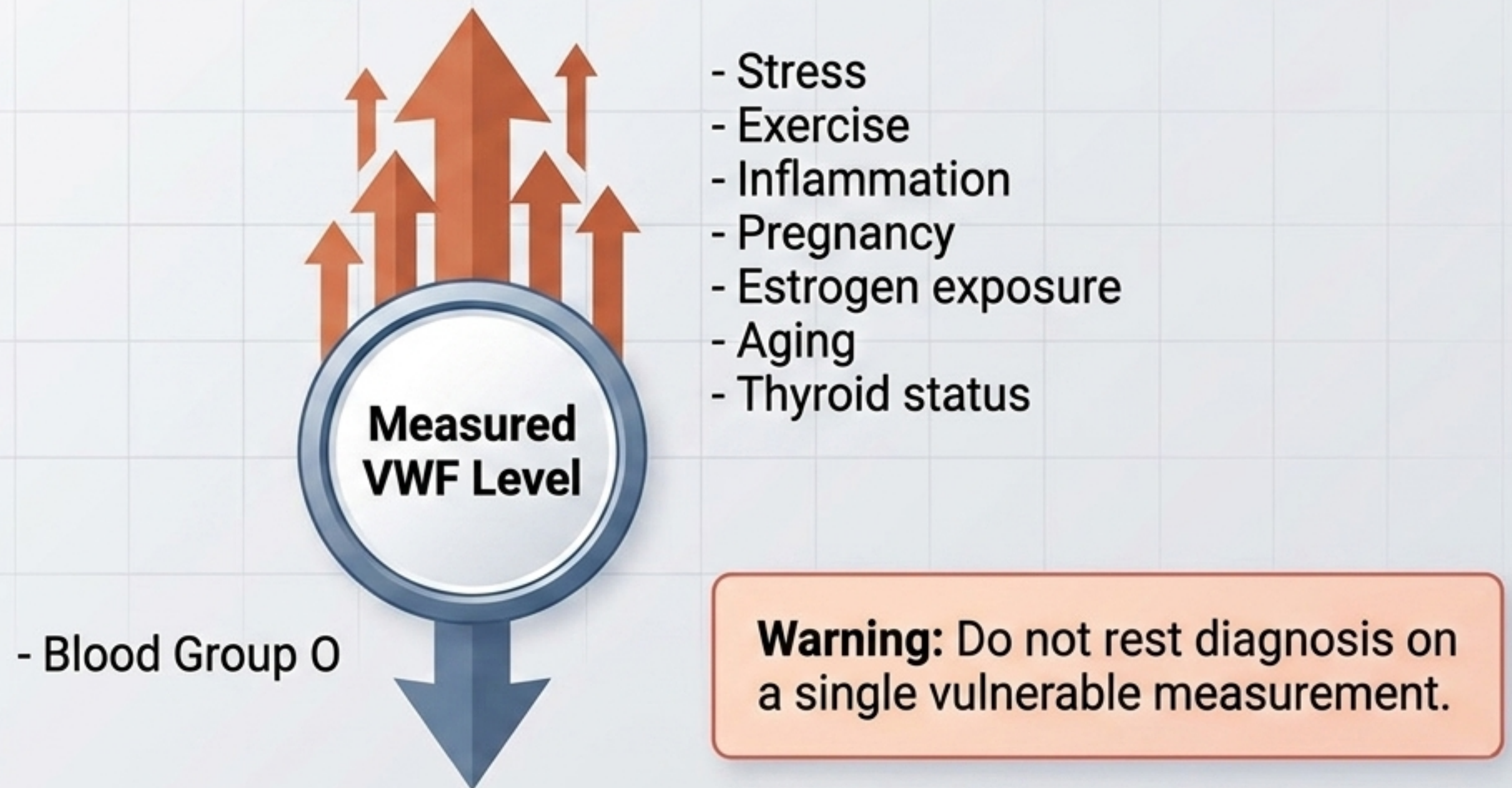
The Threshold Illusion: Biology Has No Sharp Borders

Thresholds help clinicians act. They do not create biological borders.



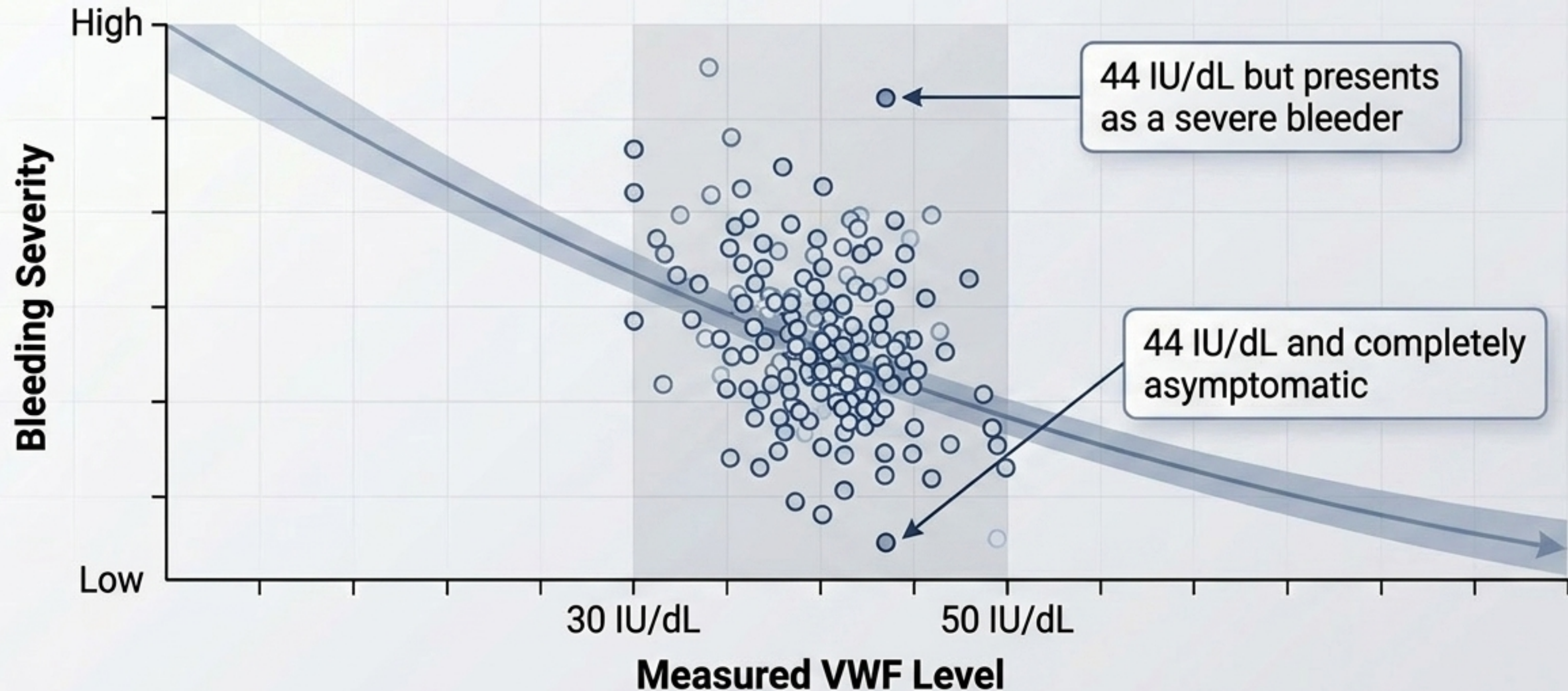
Physiologic Modifiers & The Surrogate Problem

Modifiers can move a patient across a diagnostic threshold without changing the underlying bleeding story.
Assays measure quantity (surrogates), not direct in vivo bleeding risk.



Imperfect Correlation & Phenotypic Heterogeneity

Bleeding risk generally increases as VWF falls, but a given VWF level does not determine the exact bleeding phenotype. Type 1 VWD remains mechanistically heterogeneous.



The Dual Pitfalls of Premature Closure

The reflex is to choose the number or the story. Both choices carry distinct clinical risks.

Privileging the Lab

Result: Patients with important bleeding are incompletely evaluated.

- ⚠ - Heavy menstrual bleeding managed in isolation.
- ⚠ - Delayed diagnosis for women.
- ⚠ - Dismissing clinically important bleeding just because VWF is near-normal.

Privileging the Phenotype

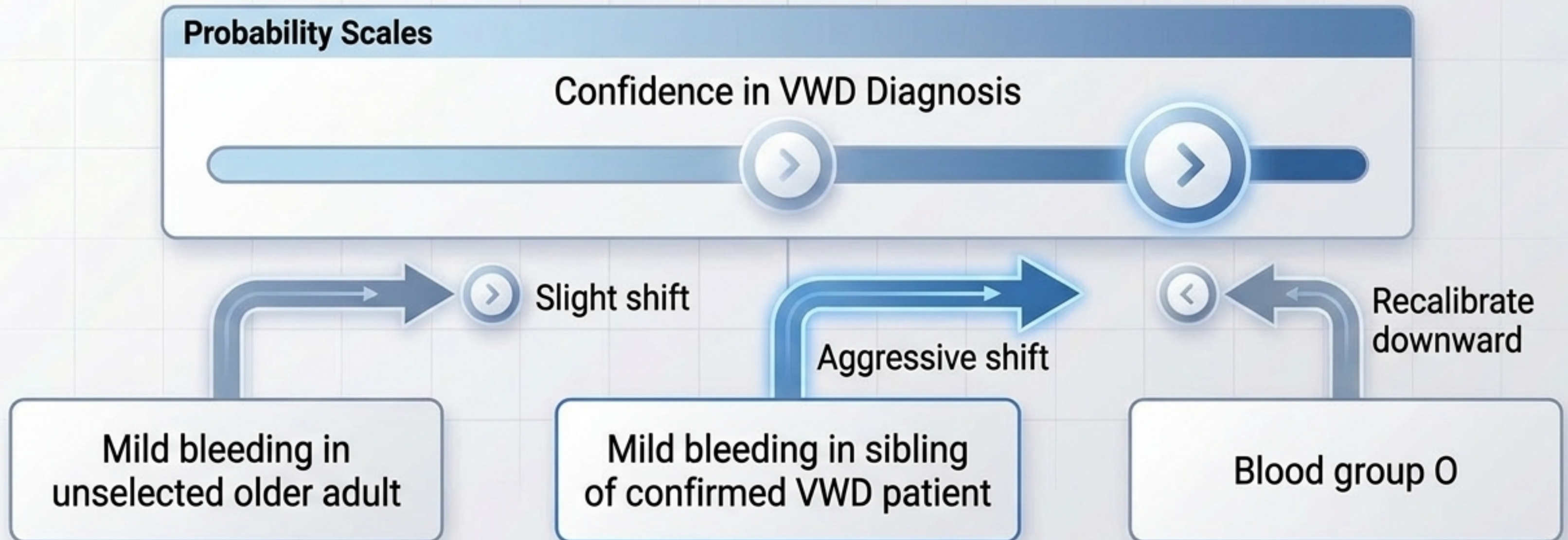
Result: Overattribution and naming disease where biology remains uncertain.

- ⚠ - Procedural anxiety.
- ⚠ - Insurance and documentation burden.
- ⚠ - Unnecessary treatment.
- ⚠ - Ignoring alternative diagnoses (e.g., diagnosing VWD based solely on mild bruising and a 44 IU/dL result).

The Synthesis Pivot: Adopting a Bayesian Frame

VWD diagnosis is evidence integration. The same finding carries different meaning depending on the pre-test setting.

Mismatch does not invalidate diagnosis. It recalibrates probability.



The Four Pillars for Discordant Cases

How experts reason when the laboratory and phenotype misalign.



Phenotypic Severity & Reproducibility

High-signal events?
(Surgical bleeding, dental extractions, recurrent iron deficiency).



Objective Corroboration

Documented proof?
(Transfusion, reoperation, procedural delay).



Laboratory Stability

Consistent across time?
(VWF:Ag, platelet-dependent activity, FVIII:C).

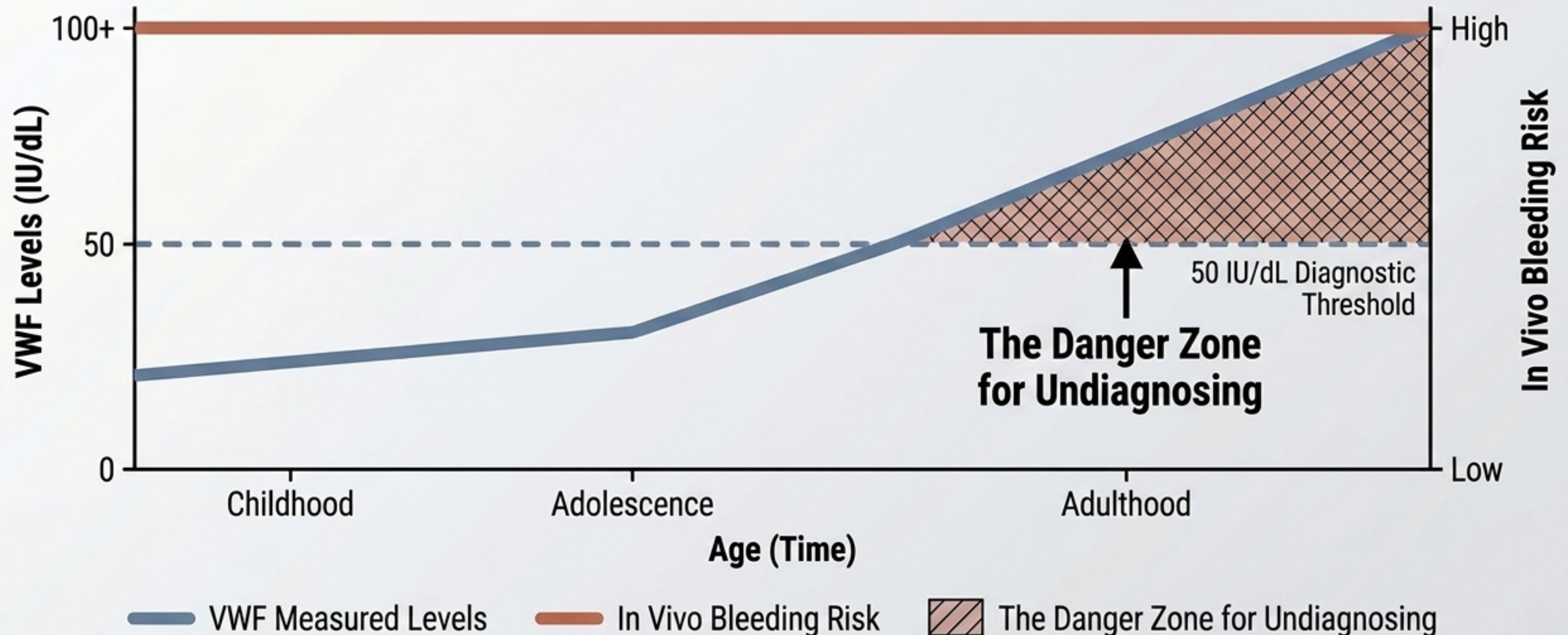


Family Pattern

First-degree relative with similar bleeding, low VWF, or confirmed VWD?

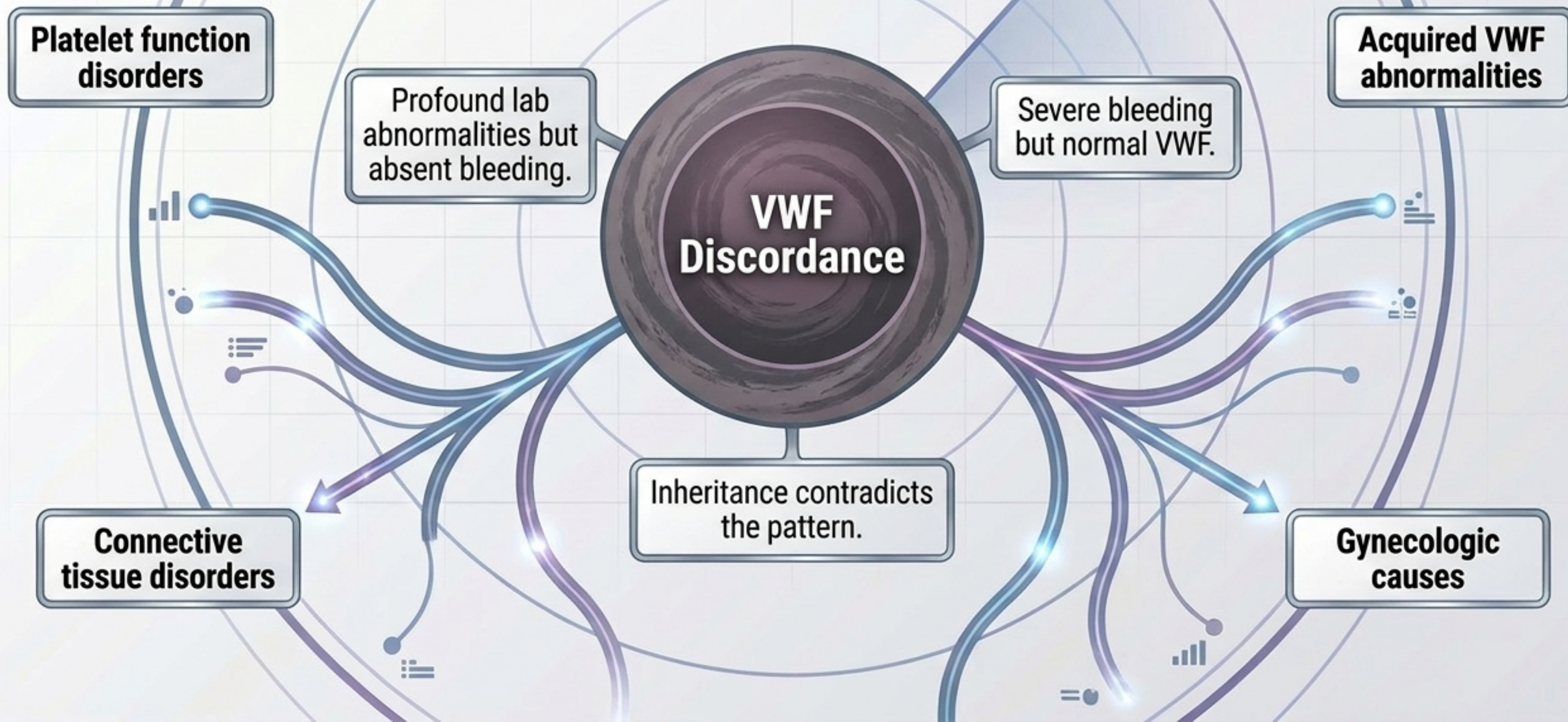
Longitudinal Discordance: The “Normalized Over Time” Problem

A patient diagnosed with Type 1 VWD later tests >50 IU/dL. Does the disease disappear?
Normalization of the number does not necessarily normalize the bleeding phenotype.



Red Flags: When to Widen the Differential

When the central signal is muddy, clinicians must scan the perimeter for answers.



Guideline Guardrails: Navigating the Uncertainty

Guidelines do not eliminate uncertainty; they teach clinicians how to manage it.

What Guidelines Support

- ✓ • Using Bleeding Assessment Tools (BATs) to structure history.
- ✓ • Initial testing triad (VWF antigen, platelet-dependent activity, FVIII:C).
- ✓ • Repeat testing for borderline/discordant results.
- ✓ • Reconsidering, rather than automatically removing, diagnoses when levels normalize.

What Guidelines Do Not Support

- ✗ • Diagnosing from symptoms alone.
- ✗ • Dismissing serious bleeding because VWF is near normal.
- ✗ • Treating a single borderline value as a lifelong label.

Resolution: Mismatch is the Process, Not a Flaw

The task is not to choose the number or the story. It is to let probability, not preference, lead.

Patient A (VWF:Ag 28, No bleeding)

tempered by low
clinical severity.

Patient B (VWF:Ag 62, Severe bleeding)

demands a wider differential
(e.g., platelet disorder).

Laboratory

Phenotype

Inheritance

Diagnostic confidence emerges
from convergence over time.