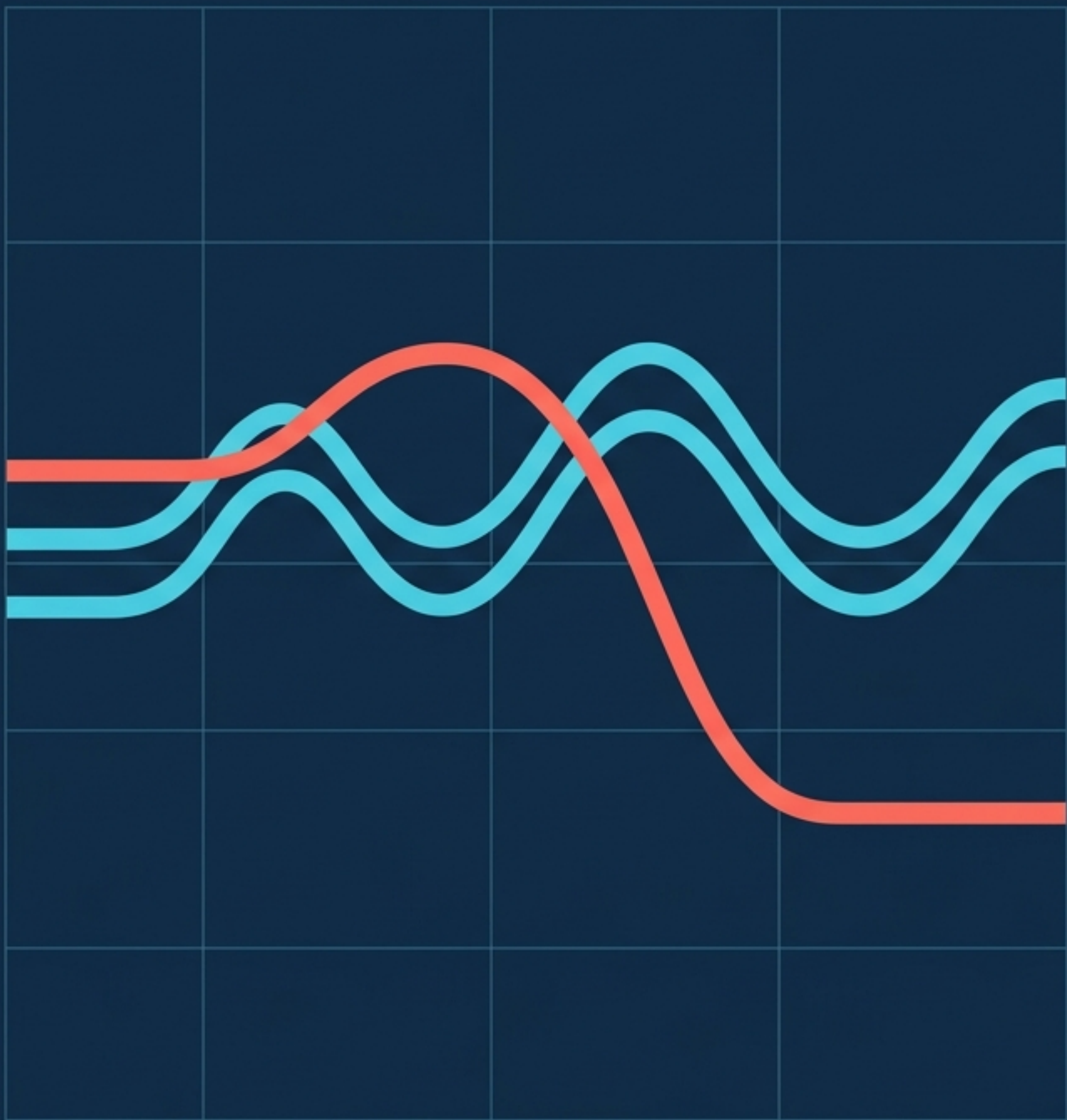




# Patterns Over Numbers

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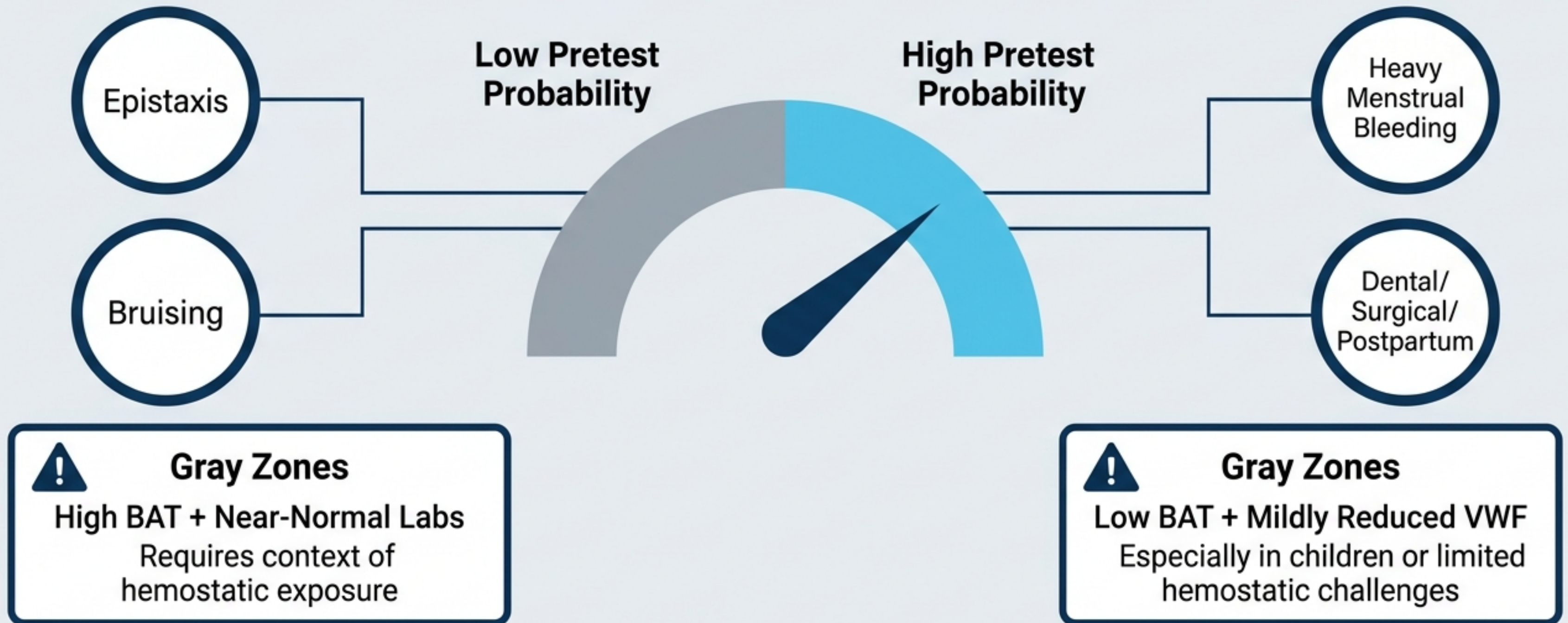
The Relational Interpretation  
of von Willebrand Disease

Why diagnosis isn't reading  
numbers—it's recognizing mechanisms.



# The Foundation: Phenotype Anchors the Lab Signal

Bleeding Assessment Tools (BATs) organize symptoms into a structured score to shift diagnostic probability. They do not diagnose VWD alone.

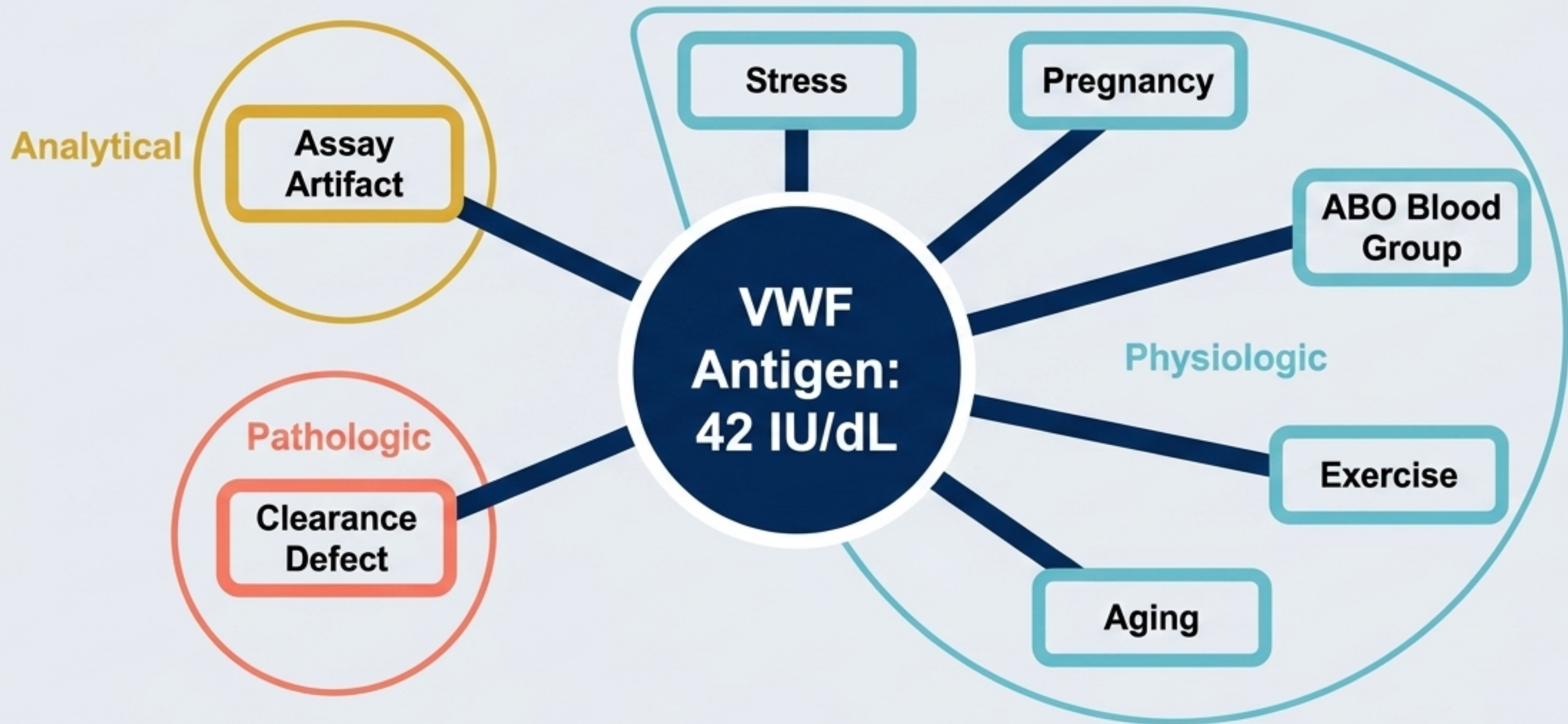


**Bottom Line:** Phenotype must fit the reproducible laboratory findings.



# The Trap of the Isolated Number

A single value of 42 IU/dL contains inherent ambiguity. It cannot differentiate between true clearance defects and normal physiologic variation.



That ambiguity is built into VWF biology. The number alone cannot tell you the truth; only a pattern can.

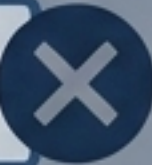


# The Relational Paradigm

When reviewing VWF results, ask one question first:  
**Do these values move together or apart?**

Each value as an answer.

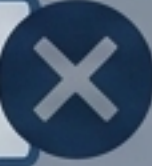
VWF:Ag



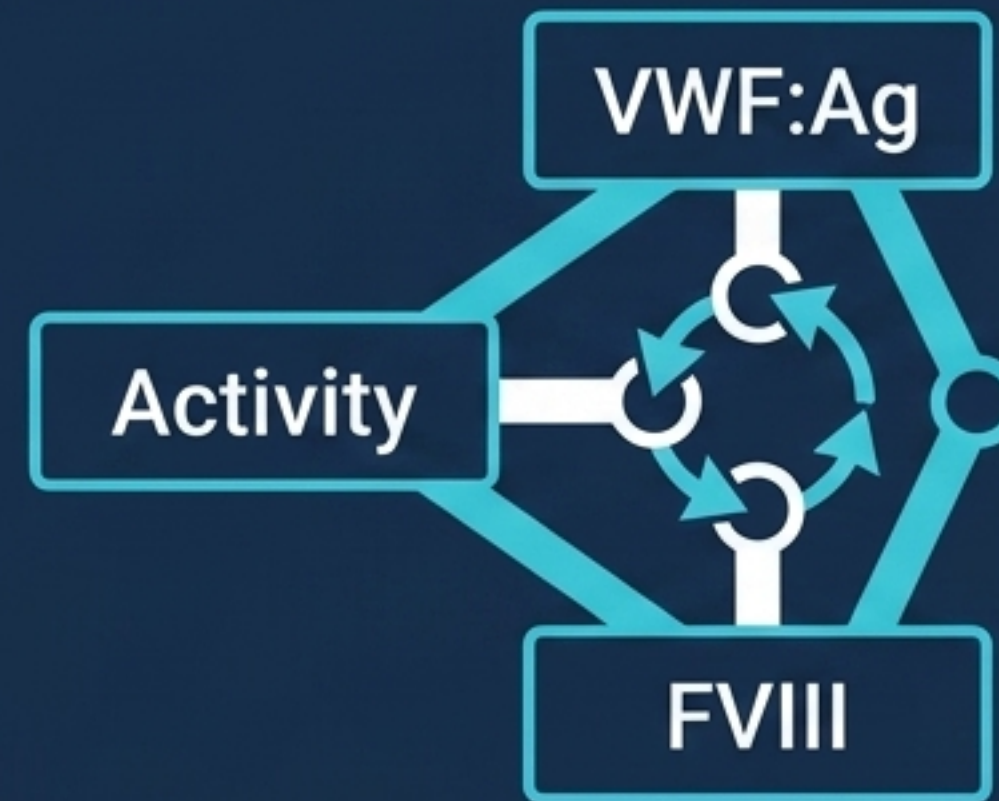
Activity



FVIII



**A system of comparisons.**

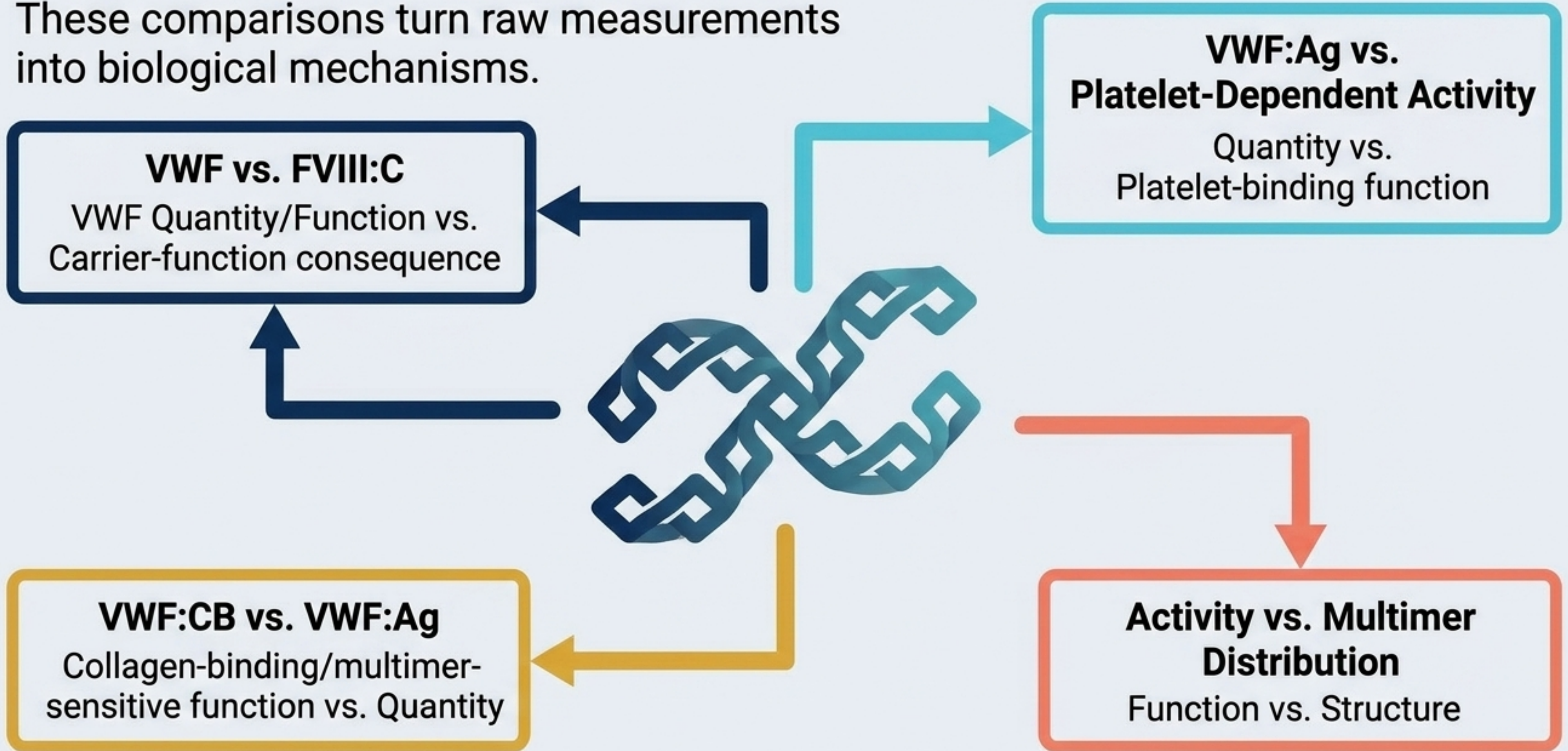


No single assay can reliably classify VWD.  
Meaning emerges from relationships.



# Mapping the VWF Dimensions

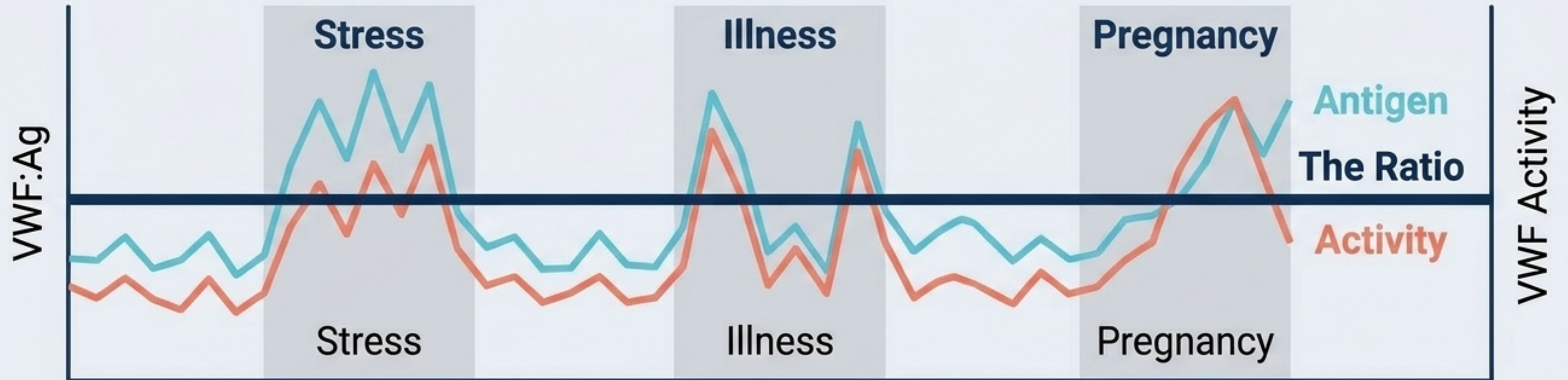
These comparisons turn raw measurements into biological mechanisms.





# Ratios Preserve Signal Across Biological Noise

Absolute VWF values move with physiology. **Ratios preserve proportional relationships** across these changing conditions.



## The Reality of Ratios

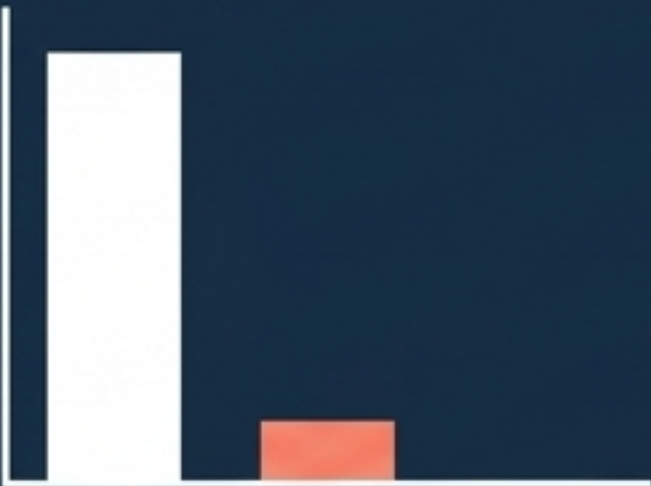
They localize mechanism.

They are assay-dependent.

They do not eliminate ambiguity, but provide a reliable compass.

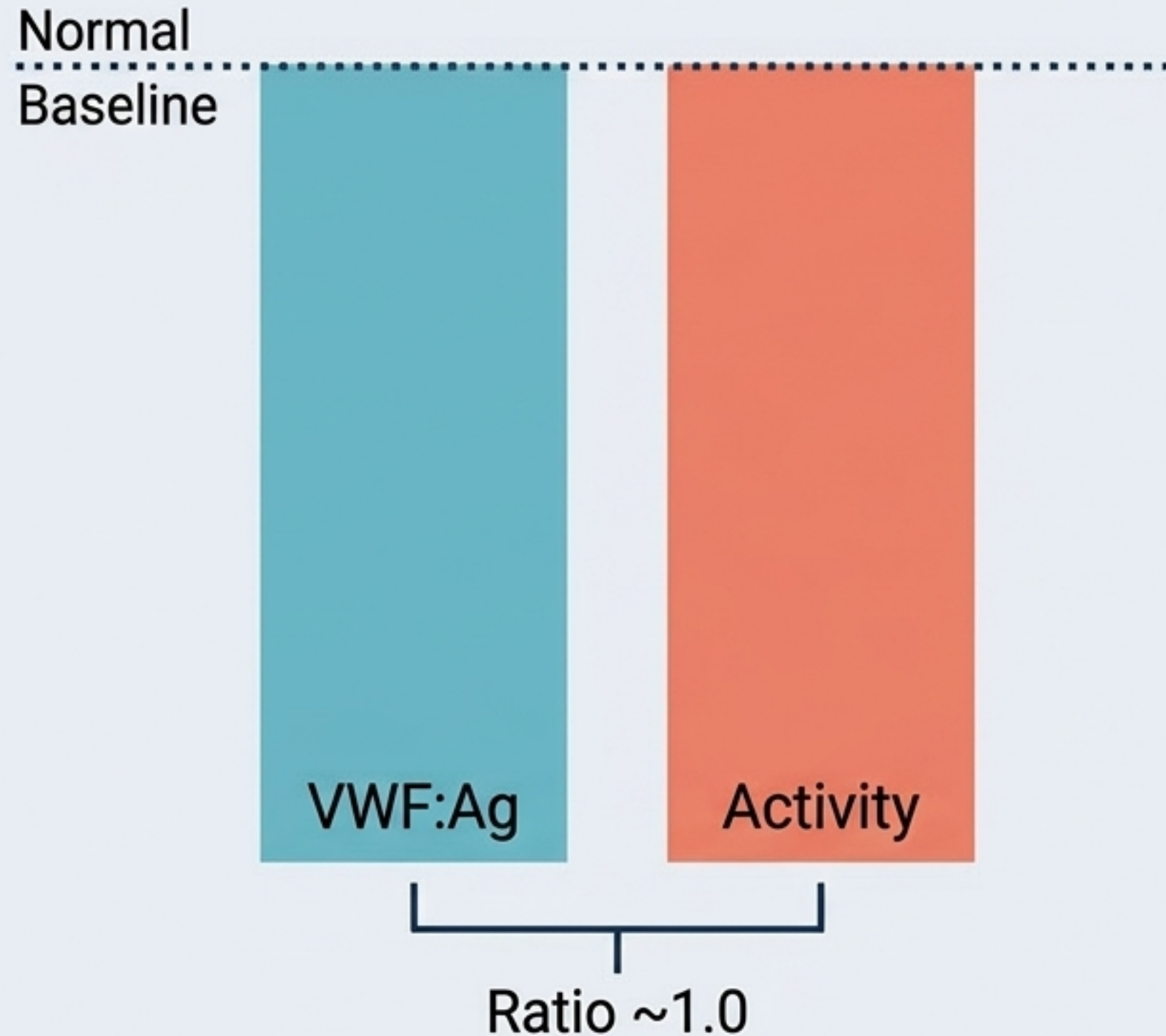


# The VWD Diagnostic Matrix: Three Core Patterns

| Pattern 1: Parallel Reductions                                                                             | Pattern 2: Disproportionate Reduction                                                                        | Pattern 3: FVIII Discordance                                                                                 |
|------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
|  <p>Ag Activity FVIII</p> |  <p>Ag Activity FVIII</p> |  <p>Ag Activity FVIII</p> |
| <b>Visual Signal:</b> Ag and Activity drop equally. FVIII tracks closely.                                  | <b>Visual Signal:</b> Ag near baseline, Activity drops severely.                                             | <b>Visual Signal:</b> Ag/Activity normal-ish, FVIII plummets.                                                |
| <b>Inference:</b> Quantitative. Protein works, but there is less of it.                                    | <b>Inference:</b> Qualitative. Molecule exists but doesn't behave normally.                                  | <b>Inference:</b> Carrier/Binding. Problem lies in VWF's binding role, or FVIII itself.                      |



# Pattern 1: Parallel Reductions (Quantitative)



## The Laboratory Signal

Antigen and platelet-dependent activity fall together. The activity ratio is roughly preserved.

**Mechanism:** VWF quantity is reduced; function per molecule is relatively preserved.

## Clinical Phenotypes

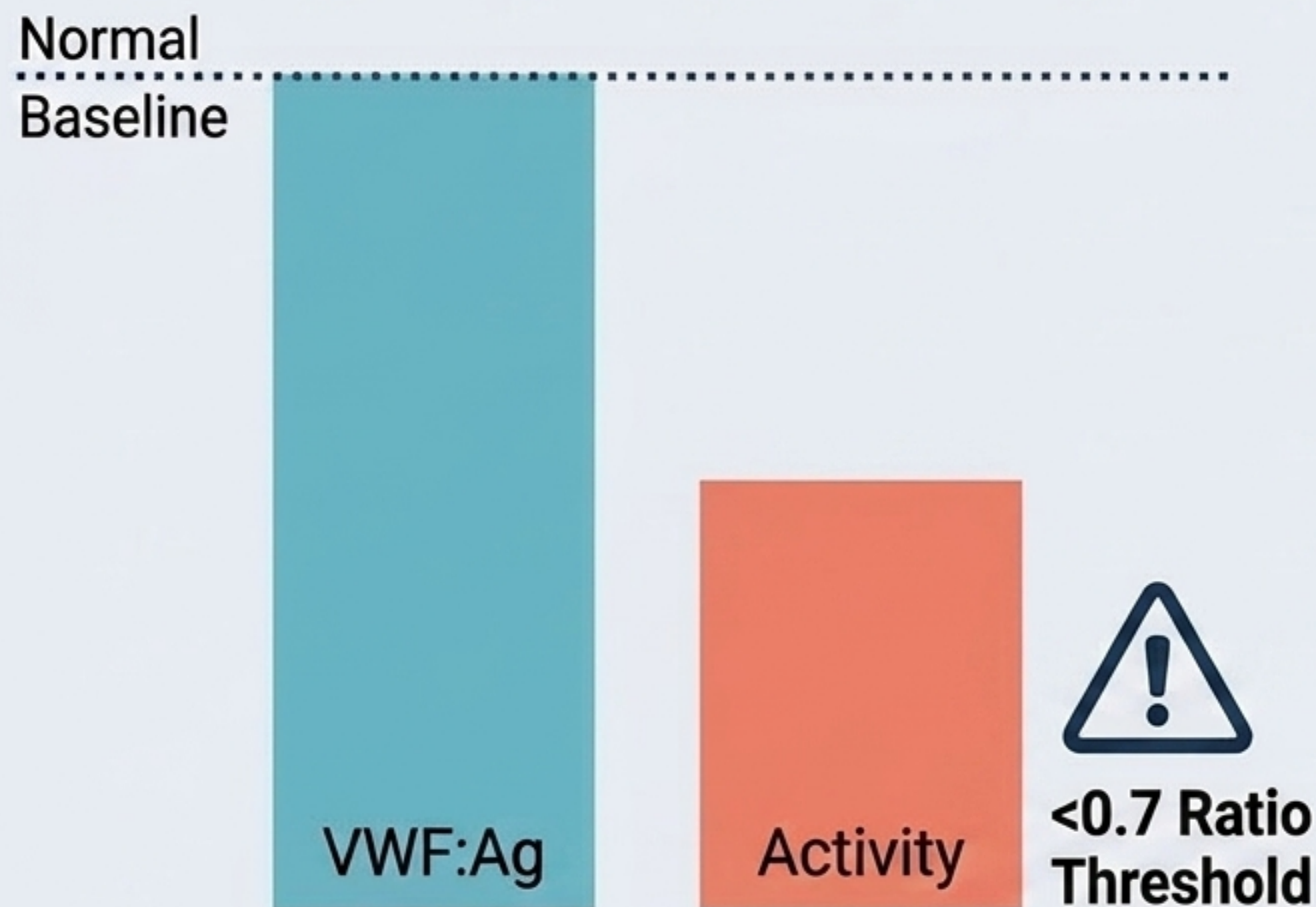
- Type 1 VWD patterns
- Type 3 VWD (absent/nearly absent)
- Physiologic low-VWF states

## Therapeutic Implication

Therapies releasing endogenous VWF (desmopressin) are conceptually logical since the released protein is functionally intact.



## Pattern 2: Disproportionate Activity (Qualitative)



### The Laboratory Signal

Platelet-dependent activity is significantly lower than antigen.

**Mechanism:** VWF quantity is present, but function is impaired.

### The Trigger Point

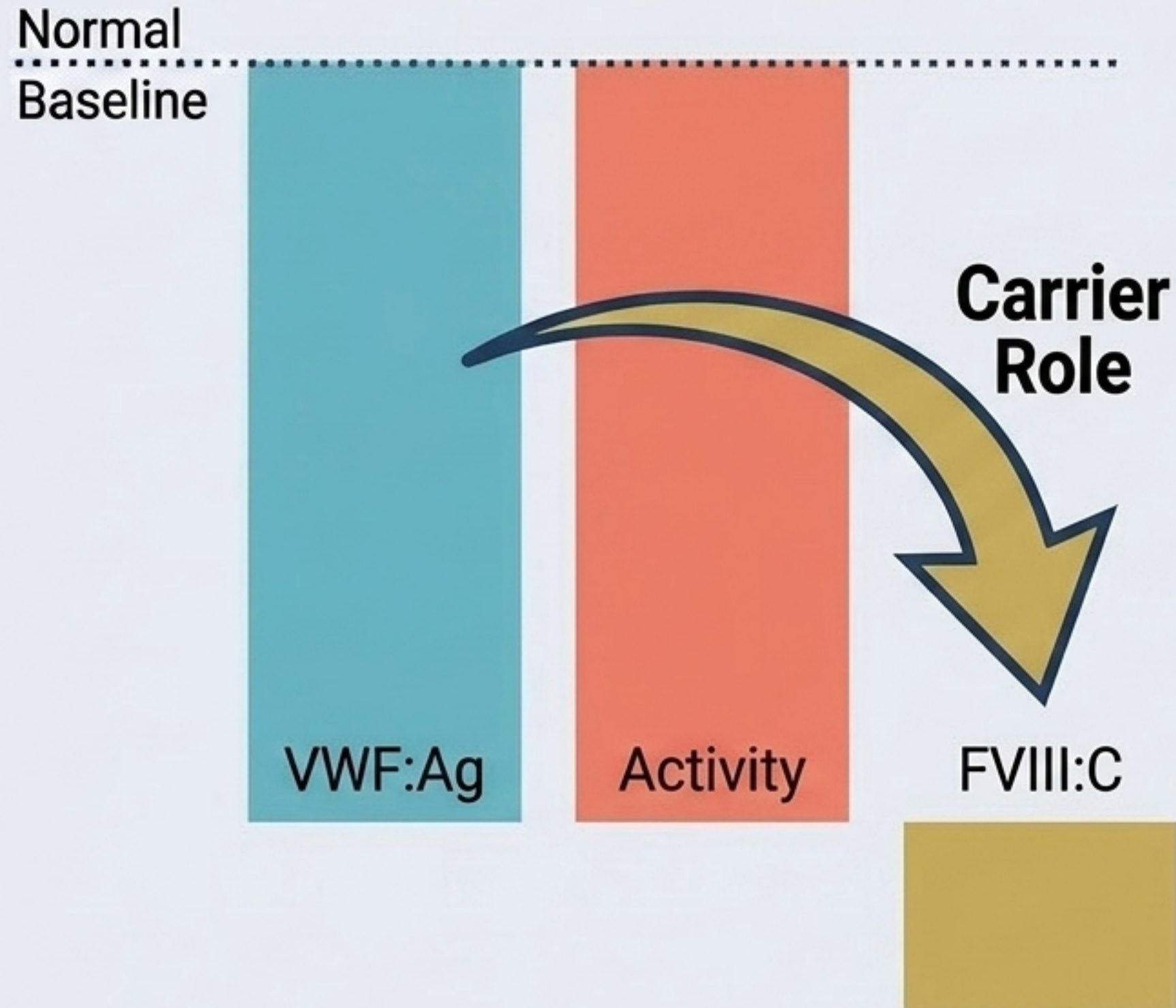
An activity ratio of  $<0.7$  should prompt consideration of type 2-like mechanisms.

### Next Steps

Drives the question of whether the loss is explained by abnormal multimer architecture, altered platelet binding, altered collagen binding, or assay artifacts.



# Pattern 3: FVIII Discordance (Carrier Function)



## The Laboratory Signal

FVIII is disproportionately low compared with VWF.

**Mechanism:** FVIII is a downstream reporter of VWF's carrier role. This pattern indicates an impaired VWF-FVIII interaction.

## Diagnostic Forks

- Impaired VWF-FVIII interaction (Type 2N mechanism)
- An FVIII-centered disorder (mild hemophilia A)

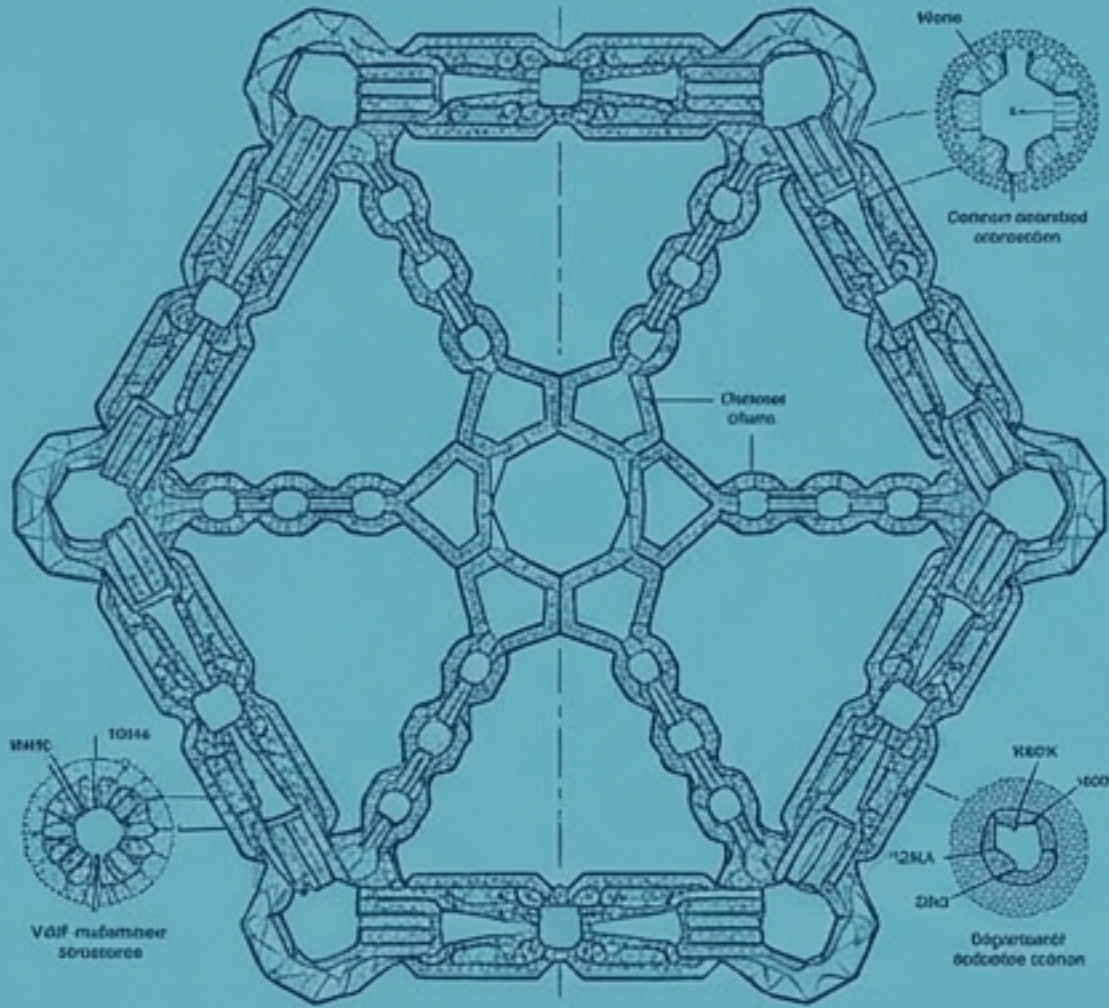
## Action

Confirmatory approaches require the VWF:FVIII:B assay and/or genetic testing.



# The Structural Dimension: Architecture Dictates Function

Many qualitative patterns are structure-function stories in disguise.



## VWF:CB (Collagen Binding)

Serves as a highly practical surrogate for multimer-sensitive function. Loss signals Type 2A or 2B patterns.

## Architecture

Multimers reflect architecture. High-molecular-weight multimers are the most hemostatically effective forms.



## Function

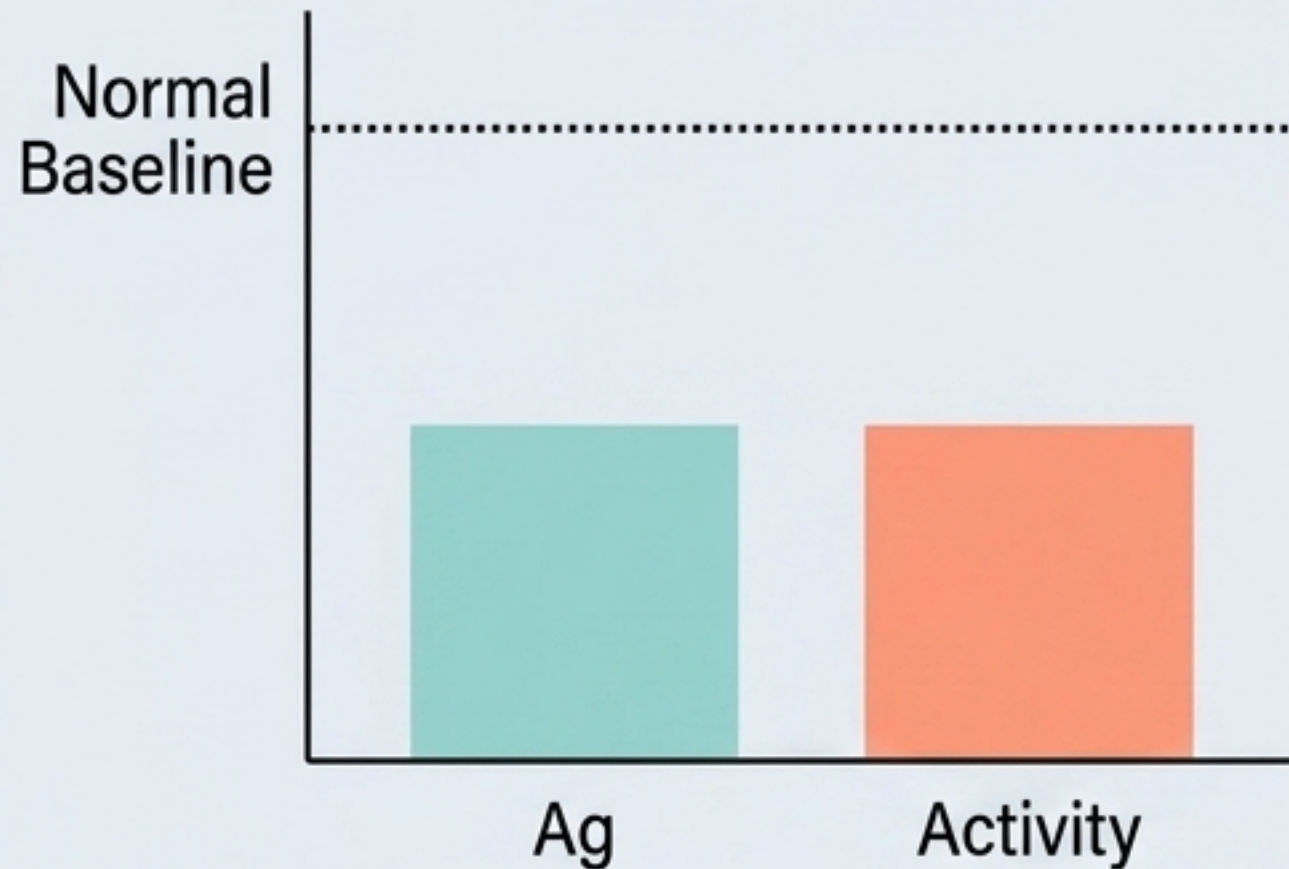
Activity reflects function.



# Unmasking Hidden Clearance Patterns

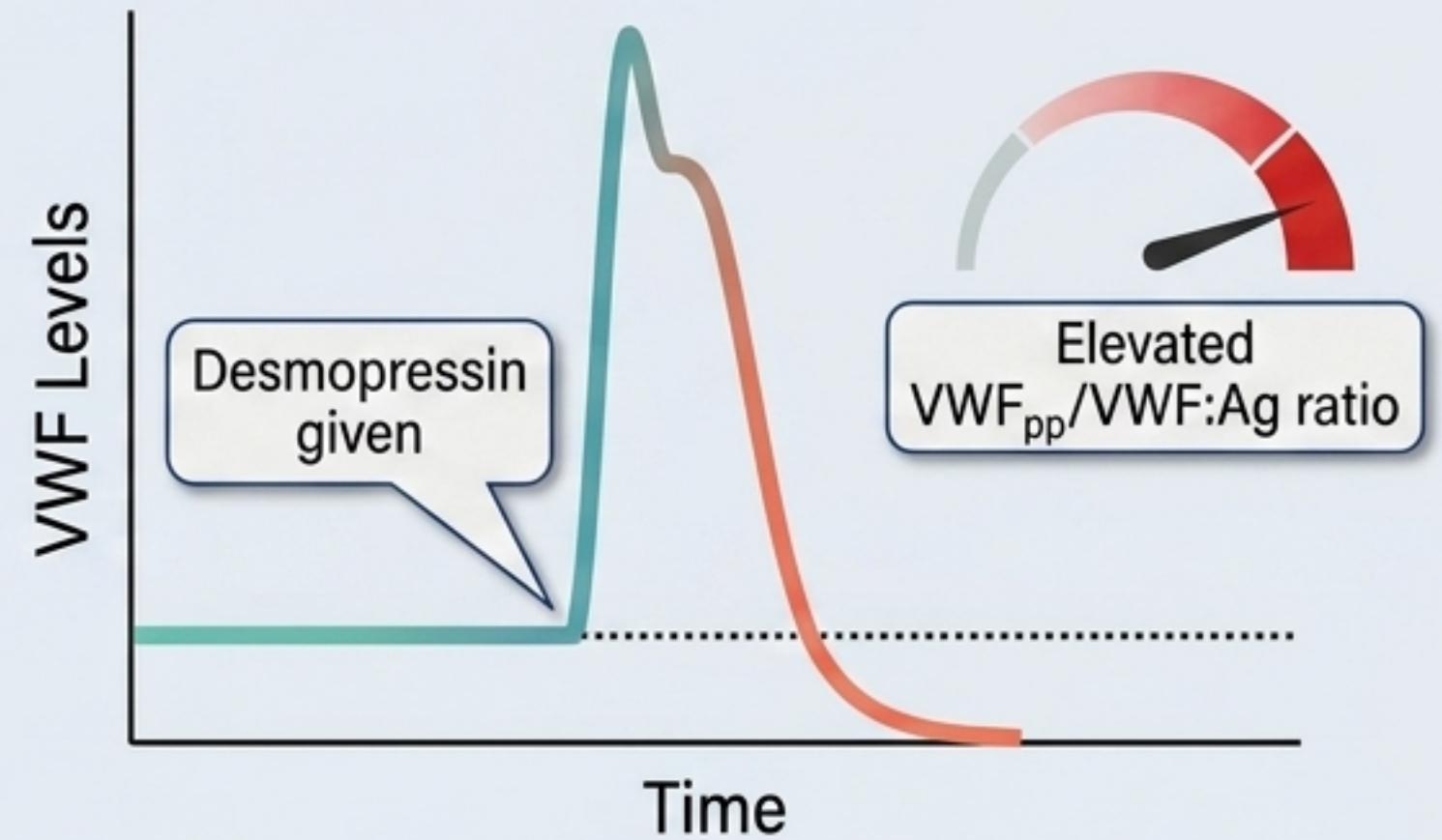
Some patients appear quantitative at baseline, but the mechanism is rapid clearance, not low production.

## The Trap



**Apparent quantitative baseline**

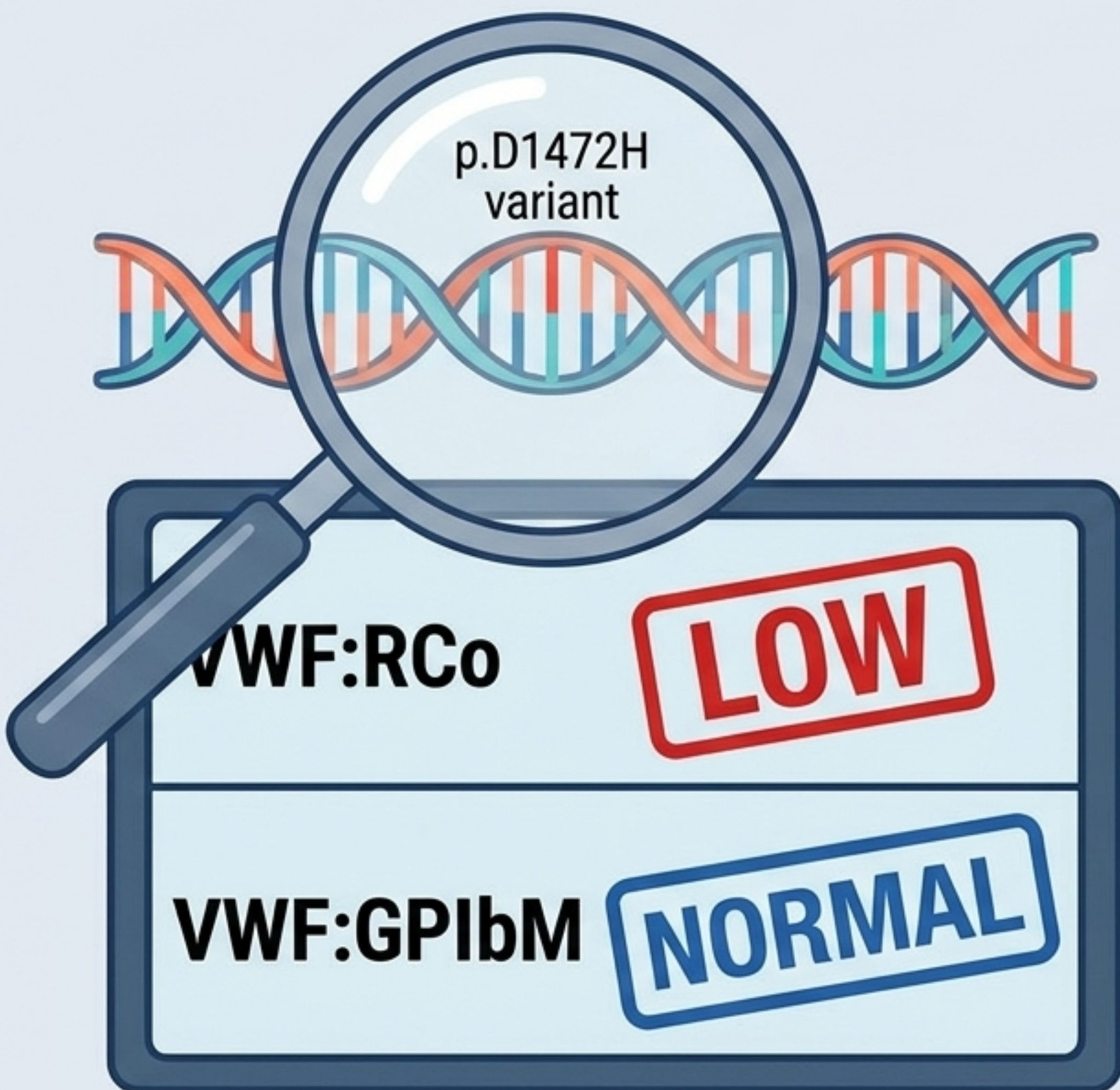
## The Reality



- **Mechanistic Clue:** Elevated  $VWF_{pp}/VWF:Ag$  ratio points to enhanced clearance.
- **Clinical Probe:** Desmopressin response shows VWF rising but falling more rapidly than expected.



# When Numbers Mislead: The Assay Artifact



## The Problem

Some sequence variants alter ristocetin-dependent interaction in *vitro* without causing true in-vivo hemostatic dysfunction, creating a false qualitative pattern on paper.

## The Solution

Emphasize modern GPIb-based methods (VWF:GPIbM, VWF:GPIbR).

## The Persistence Rule

Pattern-based interpretation demands asking:

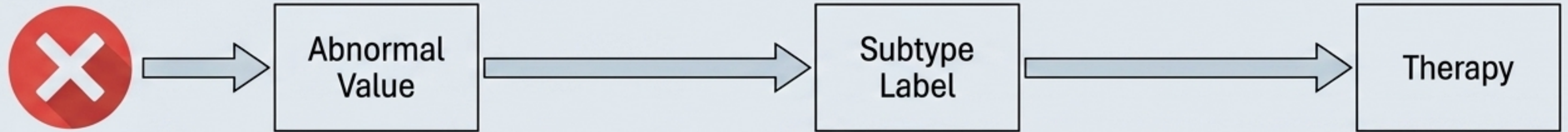
- Is the discrepancy consistent across assays?
- Does it persist on repeat testing?
- Does it fit the bleeding phenotype?



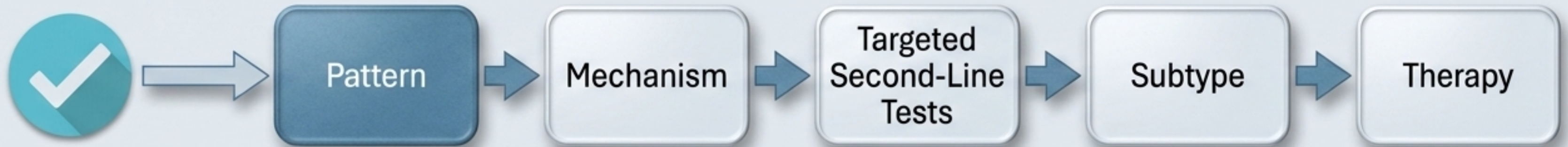
# The Subtype Mistake: Reordering the Workflow

Subtype is a conclusion, not a starting point. Advanced tests exist to explain an observed pattern, not simply to confirm a number.

## The Flawed Path



## The Optimized Path



**Impact:** Relational thinking prevents premature labeling, reduces overdiagnosis, and guarantees therapy aligns with mechanism.



# Reflect & Apply: Clinical Synthesis

**VWF:Ag: 78 IU/dL**

**Activity: 32 IU/dL**

**FVIII: 85 IU/dL**

**Calculated Ratio ~0.4**

## **Step 1: Identify the Pattern**

Activity is disproportionately reduced.  
This is a Qualitative Defect Pattern.

## **Step 2: Rule Out**

FVIII is normal. Not a Carrier/Binding defect.

## **Step 3: Apply the Workflow**

Do not immediately label as Type 2 VWD.  
Order targeted second-line tests  
(Multimers, VWF:CB) to explain the  
activity-antigen mismatch.

The pattern points toward mechanism. The mechanism guides the next test.