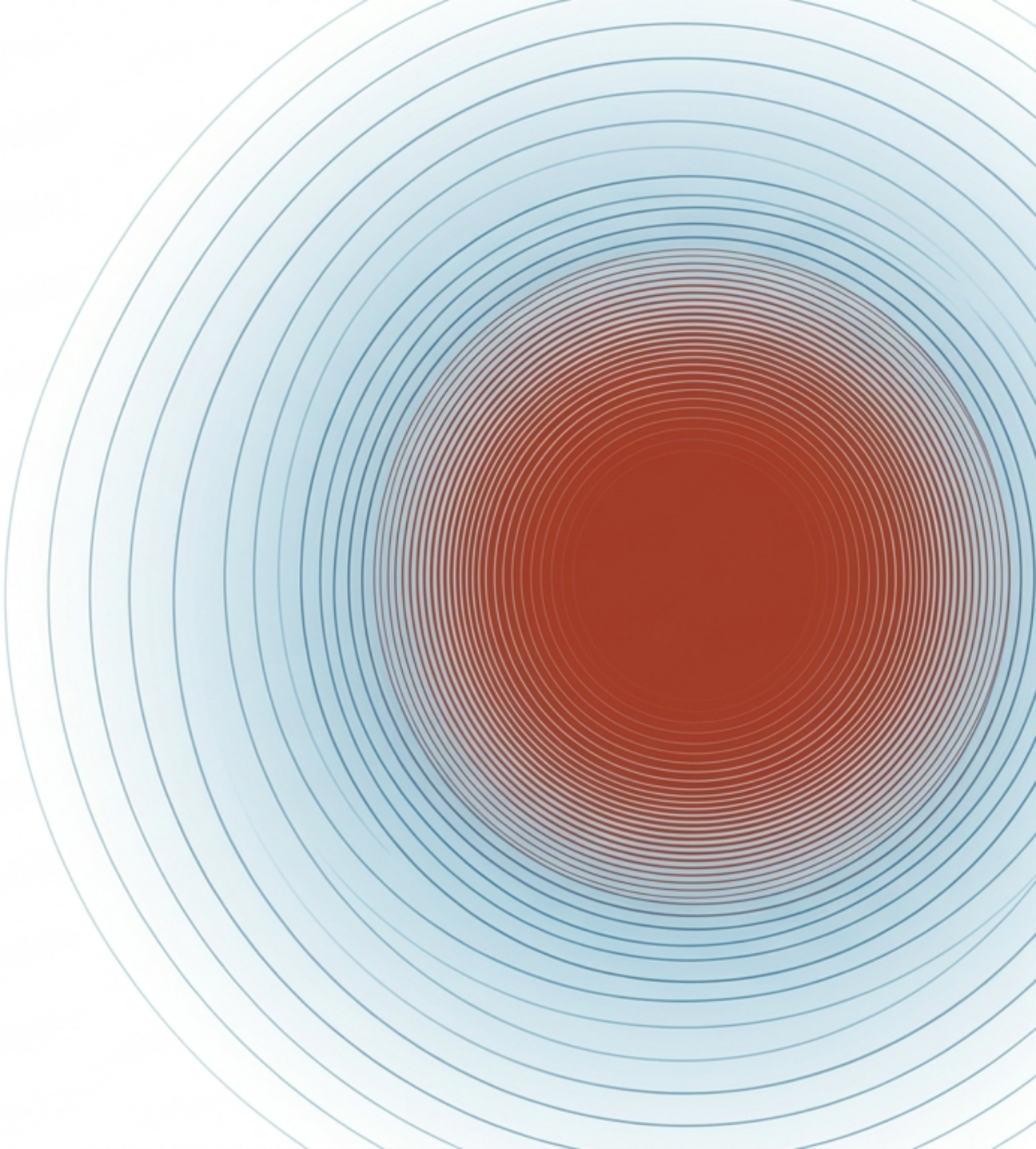
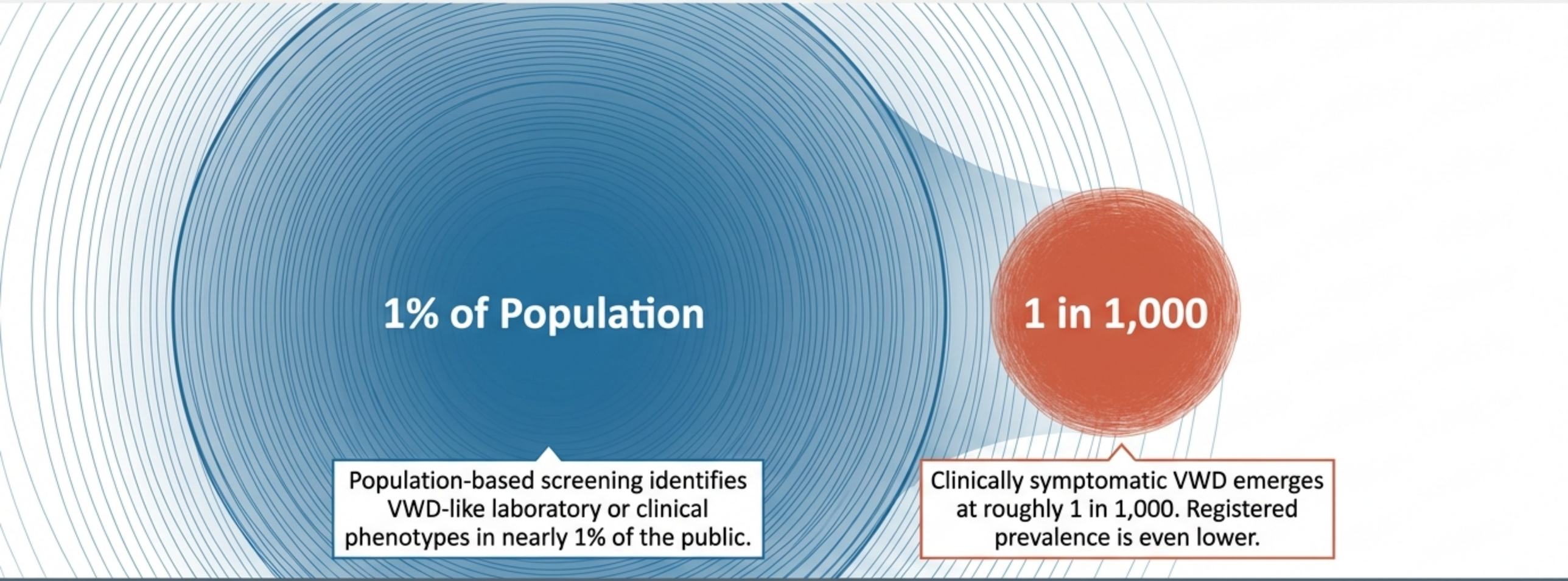
The Hidden Denominator

Rethinking Epidemiology and Visibility in von Willebrand Disease



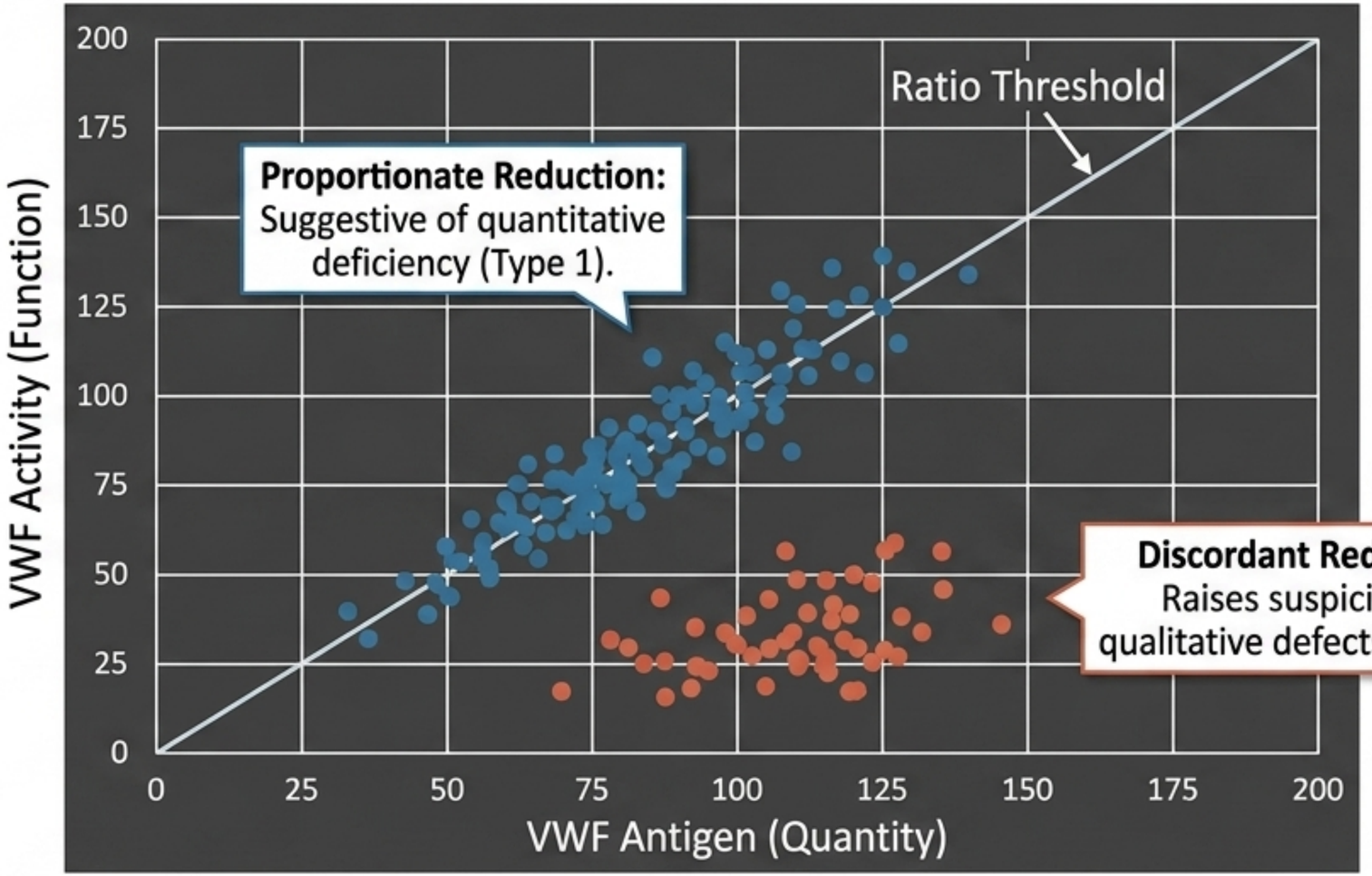
The 1% Paradox

Clinicians often hear that VWD is the most common inherited bleeding disorder. This is true, but incomplete.



The gap between laboratory prevalence and symptomatic disease fundamentally changes clinical reasoning. Commonness does not imply triviality, and rarity does not imply severity.

Interpreting the First-Line VWF Panel

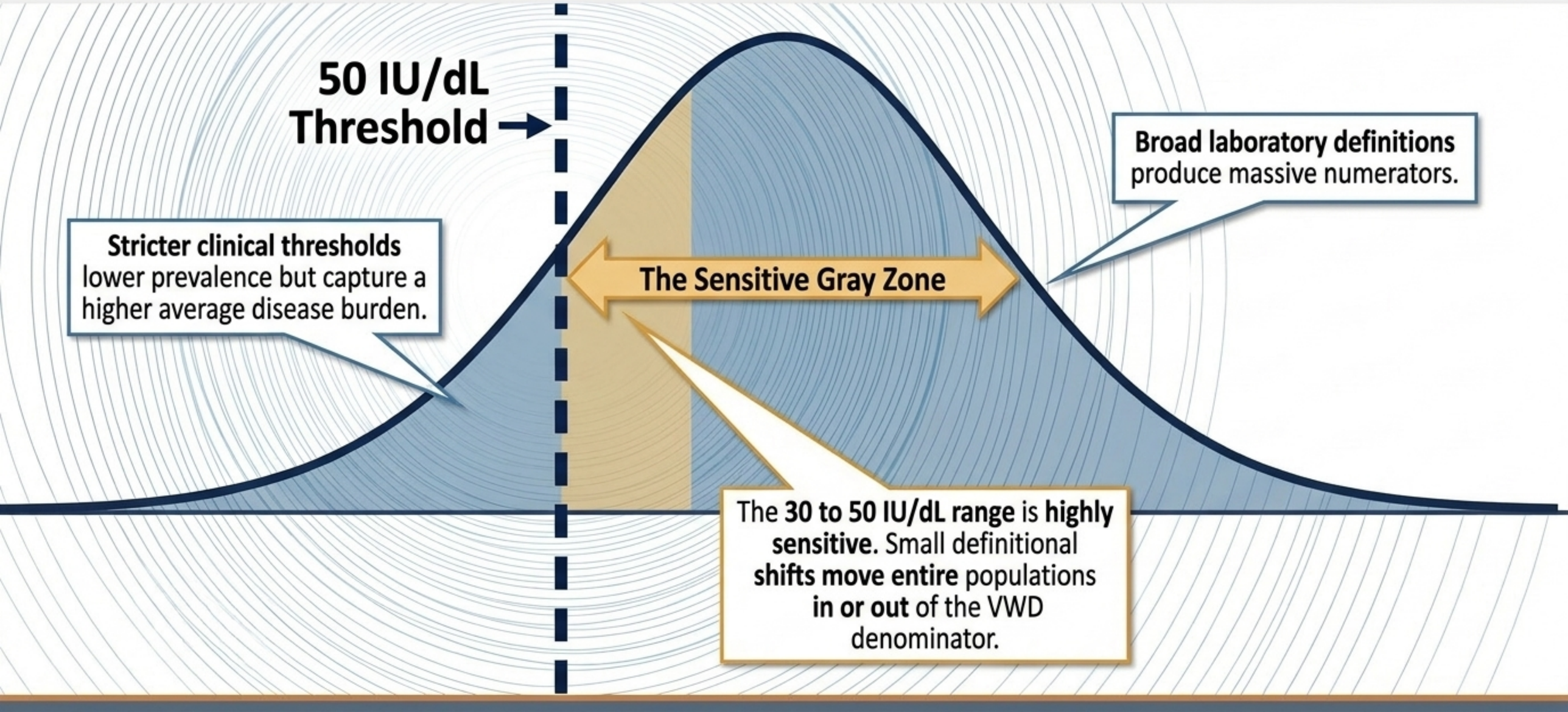


Third Variable: FVIII Activity reflects VWF's carrier function.

Insight: Normal first-line results lower the likelihood of VWD but never completely exclude the diagnosis if the bleeding history is compelling. The ratio is a practical guide, not an absolute boundary.

The Numerator Problem: Boundaries on a Continuous Curve

VWF levels are continuous. There is no natural biological cliff separating normal from disease.
Prevalence depends entirely on the case definition.



Guideline Divergence in the Gray Zone

ASH/ISTH/NHF/WFH 2021

Stance: Classifies patients with abnormal bleeding and VWF levels below 50 IU/dL as Type 1 VWD.

Motivation: Prioritizes avoiding missed diagnoses and improving access to care and treatment for symptomatic patients.

BSH 2024

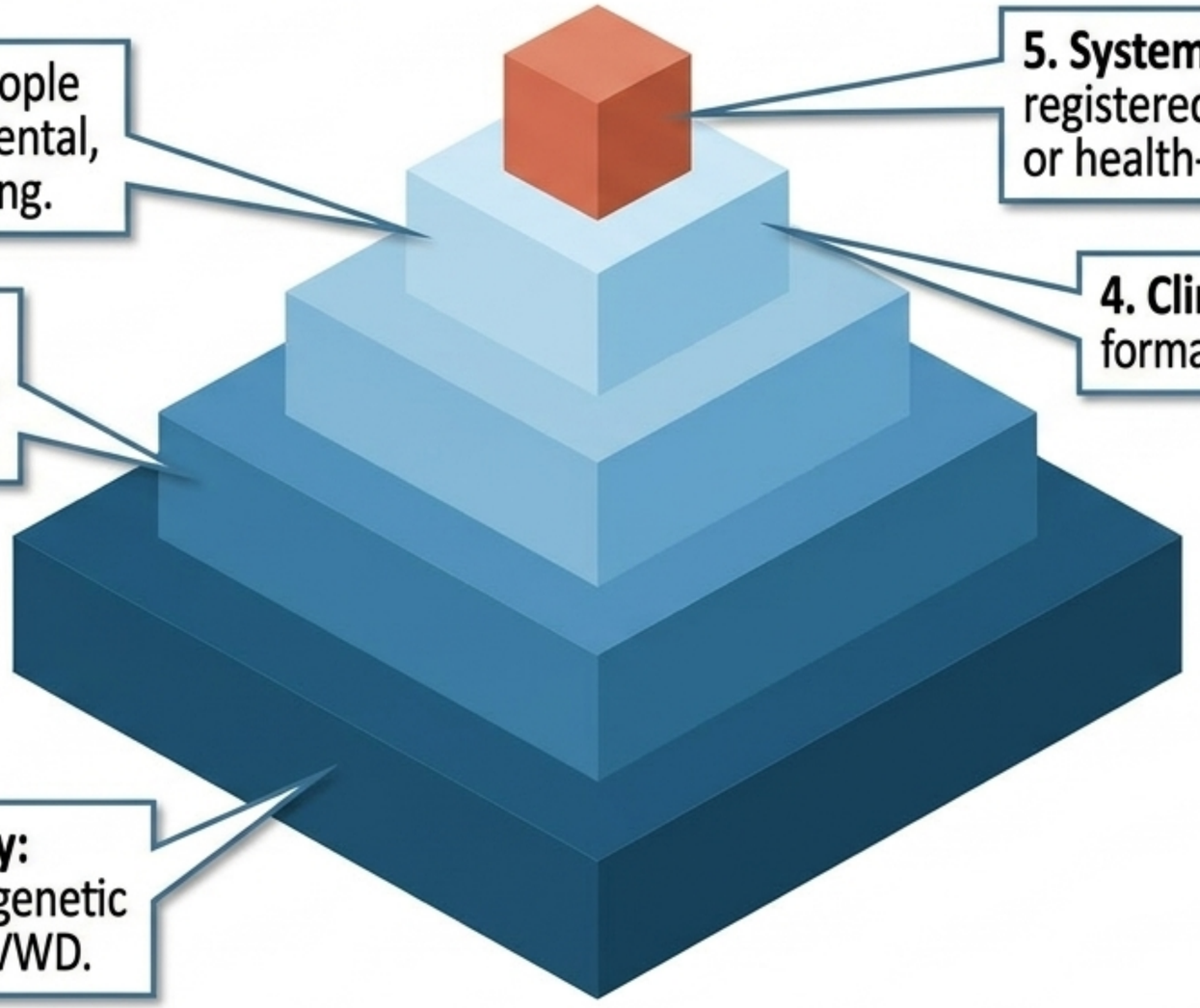
Stance: Preserves diagnostic caution around the 30–50 IU/dL range.

Motivation: Emphasizes that associations among VWF levels, bleeding, and variants are weaker here, warning against labeling common overlapping symptoms as inherited disease.

Guidelines provide structure, not certainty.
The number is not the disease.

The Nested Sieve: Defining the Unstable Denominator

The hidden denominator is the massive population that exists biologically, but is filtered out before they are ever counted.



5. System Retention: People registered in a tertiary center or health-system database.

4. Clinical Label: People who formally receive a VWD diagnosis.

3. Triggered Evaluation: People whose bleeding (surgery, dental, reproductive) leads to testing.

2. Expressed Disease: People with actual bleeding symptoms and low VWF.

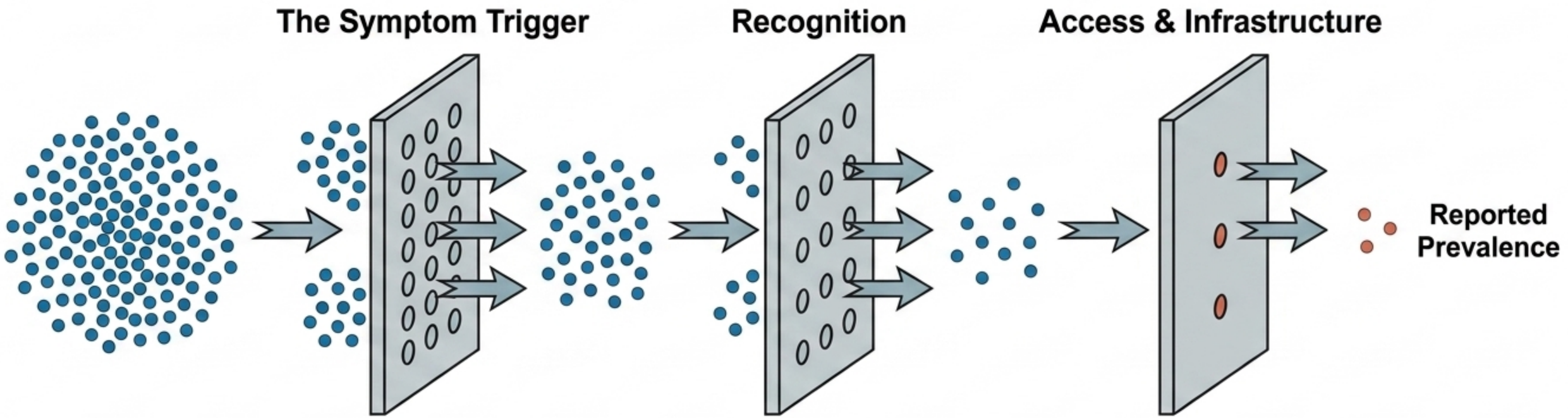
1. Biological Possibility: People with VWF levels or genetic variants associated with VWD.

The Four Lenses of Prevalence

EVIDENCE STREAM	WHAT IT MEASURES	ESTIMATED RATE	THE HIDDEN DENOMINATOR
Population Screening	Broad laboratory/phenotypic denominator	Near 1%	Misses clinically significant bleeding context.
Primary Care	Clinically expressed symptomatic disease	~1 in 1,000	Misses those who normalize symptoms or lack access.
Registries	Diagnosed, reported, and retained cases	Highly variable	Misses regions with limited health-system infrastructure.
Molecular / Genetics	Biological possibility	Often exceeds clinical rate	Misses variable expressivity; low VWF is not equivalent to disease.

These are not competing estimates.
Each perfectly describes a different layer of visibility.

How the Denominator Becomes Hidden



Many are never tested because they lack a hemostatic challenge (e.g., children without surgery).

Symptoms like easy bruising or heavy menses are highly common, normalized, or attributed to non-hemostatic causes.

Specialized coagulation testing is inaccessible in many settings. People are only tested because someone asks a question.

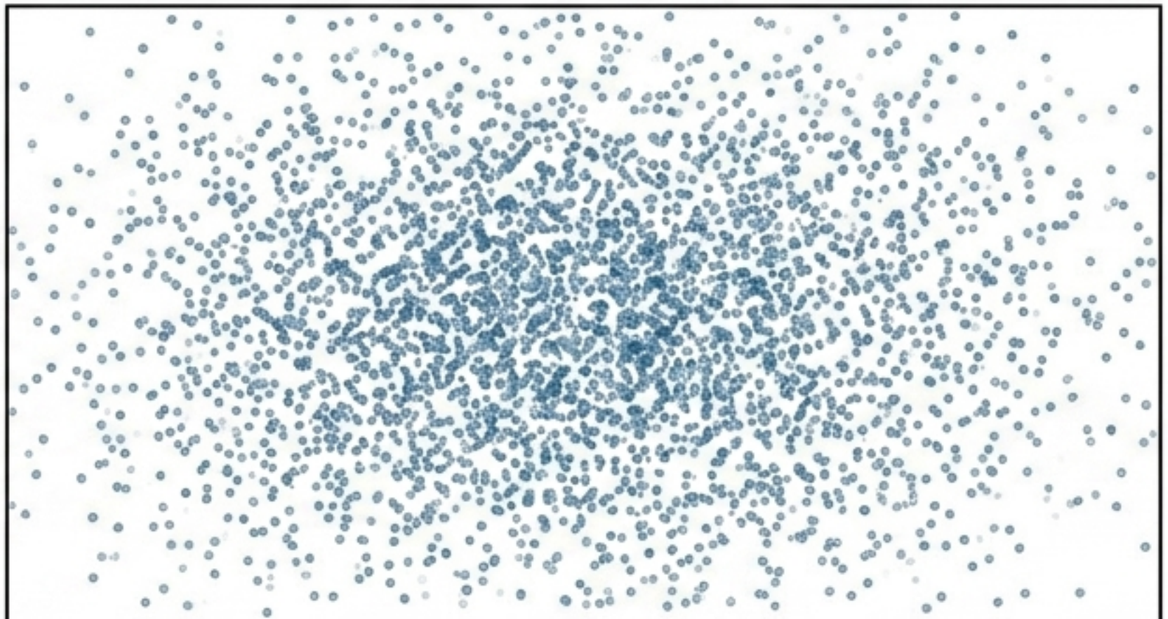
True clinical disease lies at the intersection of bleeding phenotype, VWF biology, inheritance, and context.

The Visibility Paradox

Severe Disease (Type 3)

- Biologically Rare (~1 per million).
- Clinically Loud (severe phenotype).
- Epidemiologically Visible (reliably reaches specialty care).

Mild Disease (Type 1)

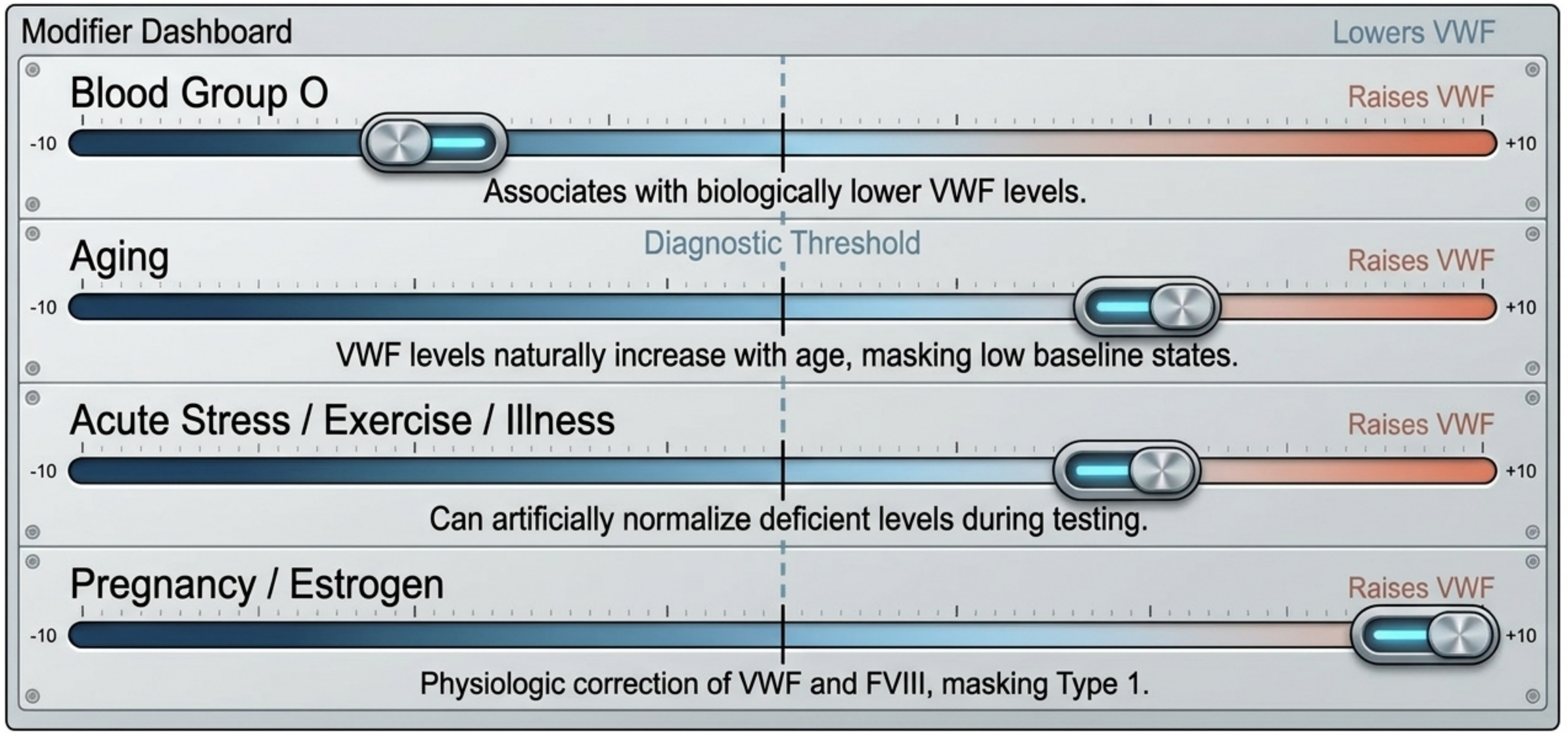


- Biologically Common.
- Clinically Quiet (requires specific triggers).
- Epidemiologically Hidden (drives the vast variability in global registration).

In lower-income settings, Type 3 accounts for a disproportionate majority of registered cases. Mild VWD is not biologically absent there—it is epidemiologically **quiet**.

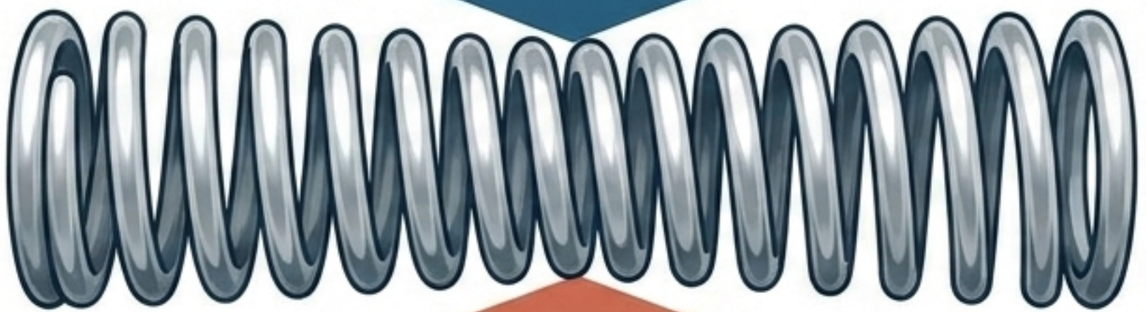
Dynamic Biology: A Moving Target

VWD epidemiology is difficult because the measured variable is not fixed.
Prevalence becomes conditional on when we test.



The Sex-Specific Tension Spring

Forces Driving Invisibility:
Reproductive bleeding is culturally normalized, minimized, stigmatized, or attributed strictly to gynecologic causes without hemostatic evaluation.

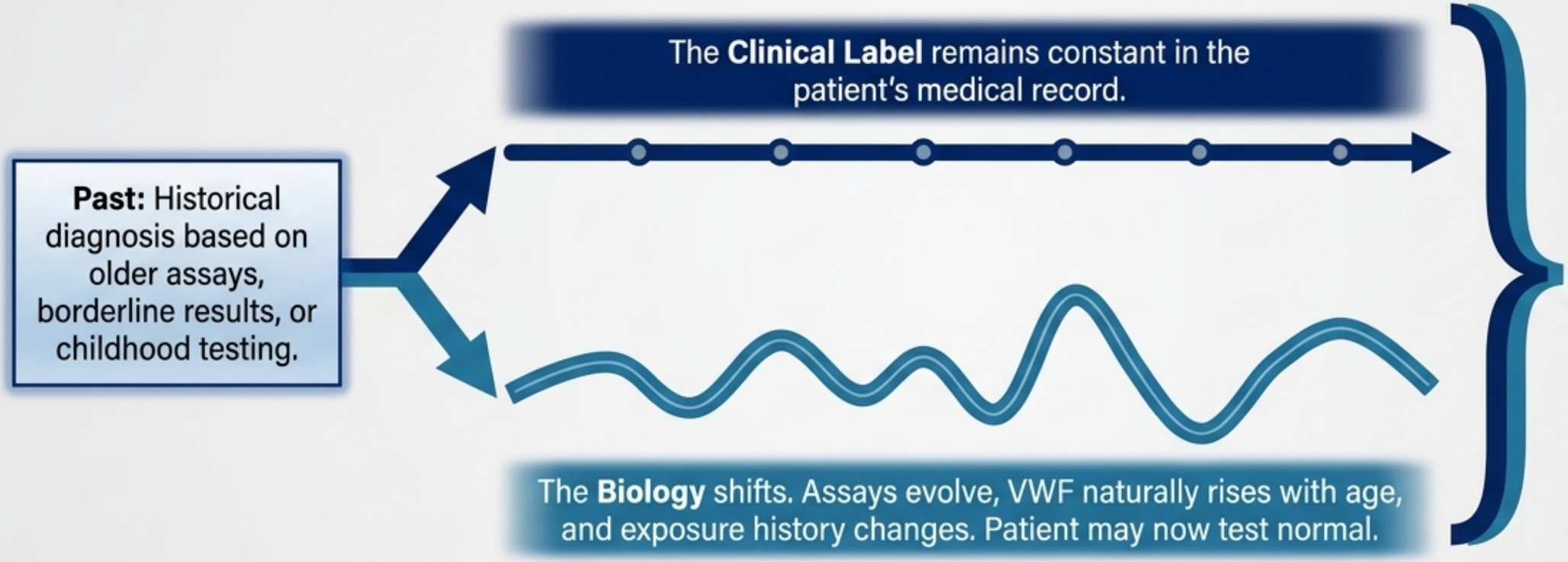


Forces Driving Visibility:
Heavy menstrual bleeding, postpartum hemorrhage, recurrent iron deficiency, and gynecologic procedures act as major bleeding triggers, pushing women toward testing.

Global Evidence: Females represent the majority of registered VWD globally.
Yet in low-income countries, males often predominate in registries—reflecting the severe under-recognition of gynecologic bleeding.

The Dual Threat: Underdiagnosis and Overdiagnosis

Epidemiology is not just about missed disease; it is also about labels that persist after the evidence changes.

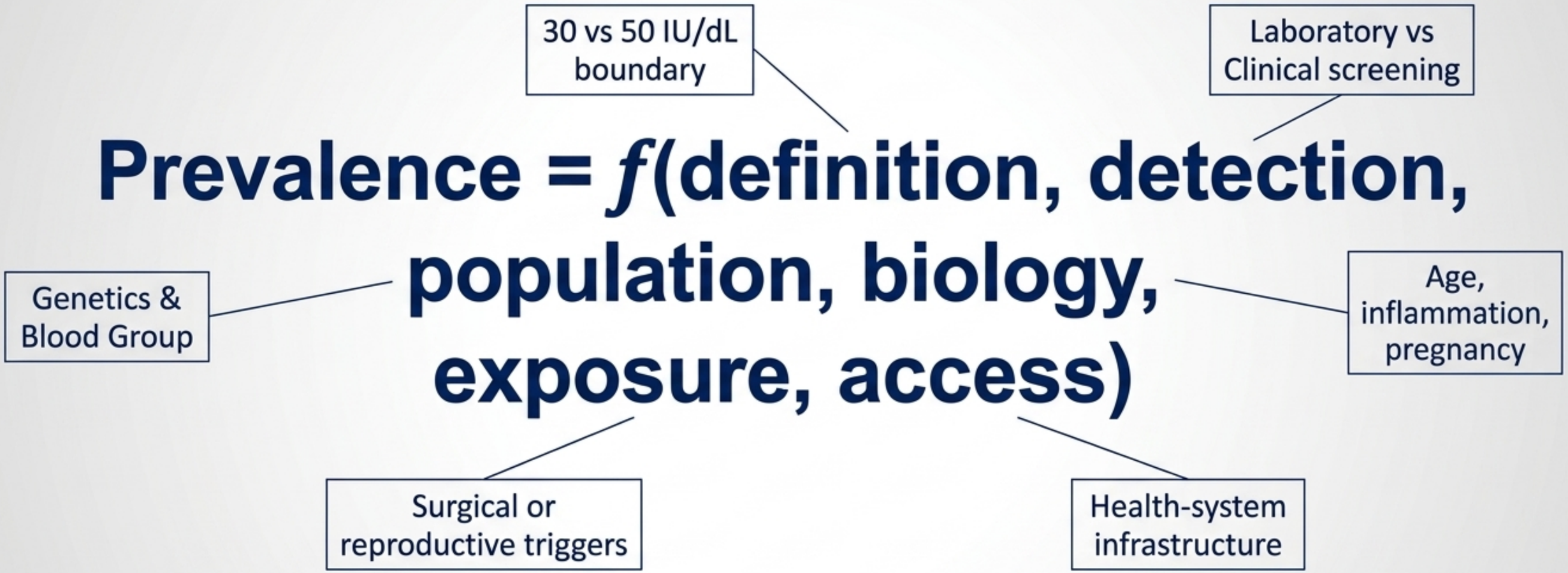


The Clinical Dilemma

The original diagnosis may not have been incorrect, and bleeding risk may persist. But maintaining the label artificially skews epidemiology.

A label can be protective and access-enabling, or burdensome and anxiety-producing. Good epidemiology accounts for both.

Epidemiology as a Function, Not a Number



Asking 'What is the prevalence of VWD?' is the wrong question.
The right question is: 'Under what conditions does VWD become visible?'

Clinical Application: Context, Not Verdict

Patient Profile

- 24-year-old female.
- VWF activity: 42 IU/dL.
- History: Heavy menses, recurrent iron deficiency, prolonged bleeding post-dental extraction.
- Never previously evaluated.

The Population Context: Is she part of the 1% biological prevalence, or the 1 in 1,000 symptomatic prevalence?

The Biological Context: Was she tested during estrogen exposure, inflammation, or acute illness?

The System Context: How many similar women remain hidden in the denominator, normalizing their iron deficiency?

Labeling her 'Type 1 VWD' changes her systemic visibility and access to care, but the label does not change her bleeding biology.

The Final Lens

Six Questions for Evaluating Prevalence Claims:

1. What definition was used?
2. Who was actually tested?
3. What triggered the testing?
4. Were bleeding symptoms required?
5. Under what physiologic conditions were measurements obtained?
6. **Who was never tested at all?** (The Hidden Denominator)

In VWD, epidemiology does not give the answer. It tells you which question you are asking. Treat prevalence as context, not a verdict.