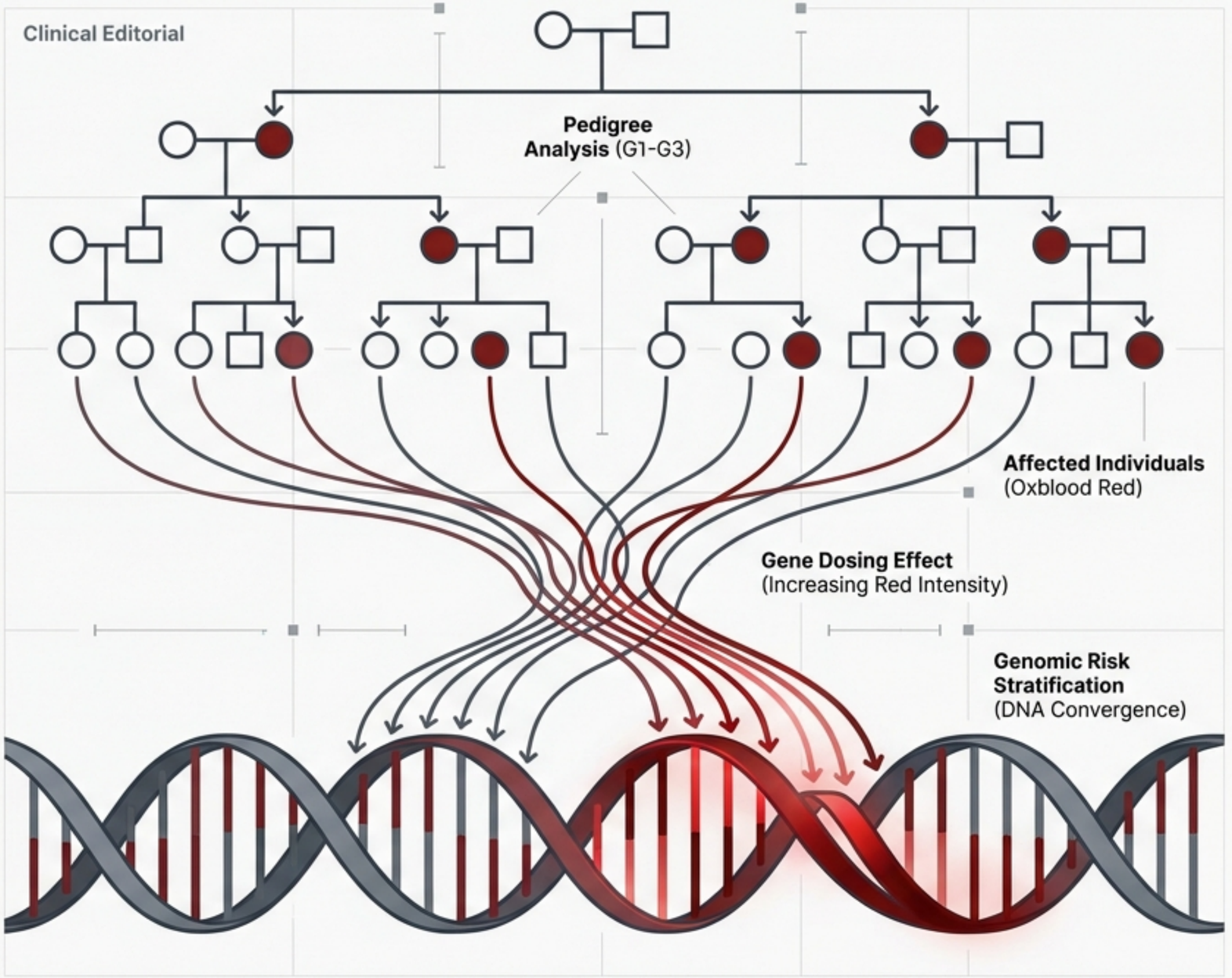
The Inherited Hazard

Gene Dosing and Pedigree-Based Diagnostics



Moving beyond population probability to granular risk stratification in the genomic era (2024–2026). Based on "Pathophysiological Stratification and Risk Modeling of Premature Cardiovascular Events."

The Failure of Population Probability

Age is a surrogate for exposure. For the gene-dosed, exposure begins at conception.

The Illusion

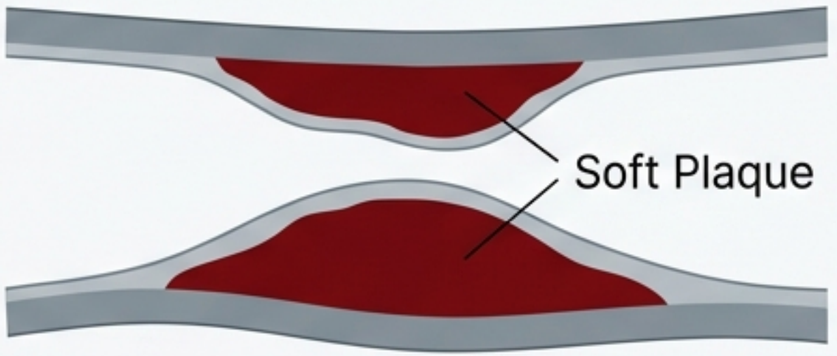
Patient Profile:
20-Year-Old Male

Framingham Risk Score

<1%

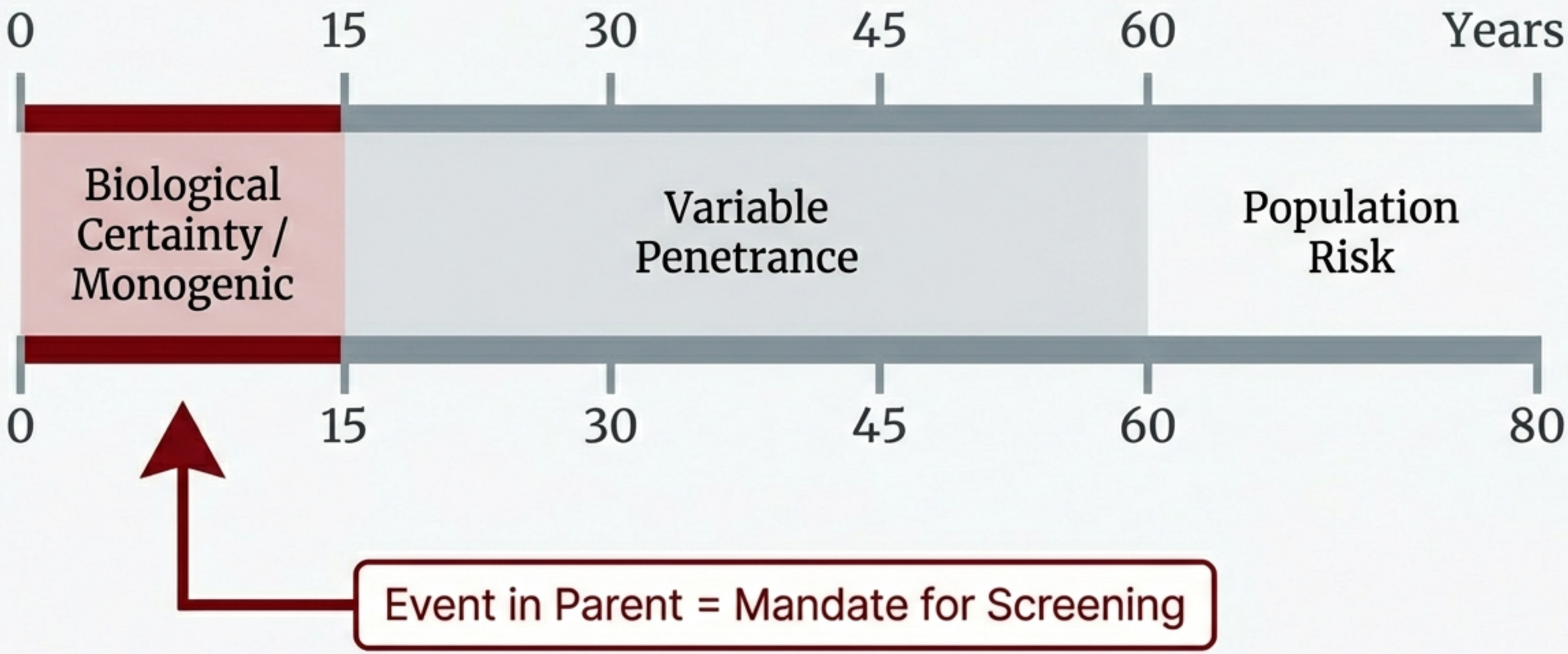
The Reality

Coronary Artery Cross-Section:
20-Year-Old Male



Standard models yield a <1% risk score due to youth, masking the catastrophic biological reality of early-onset disease.

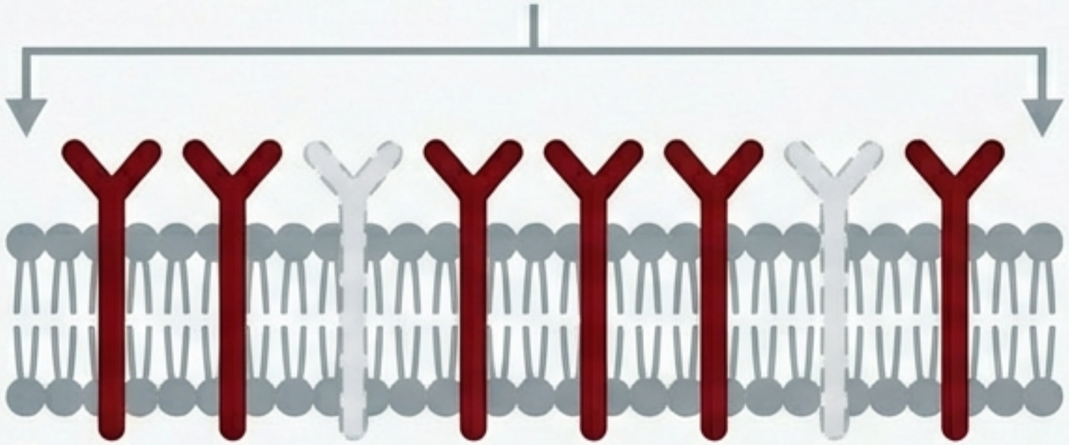
The “Under 15” Red Flag



Defining the Gene Dose

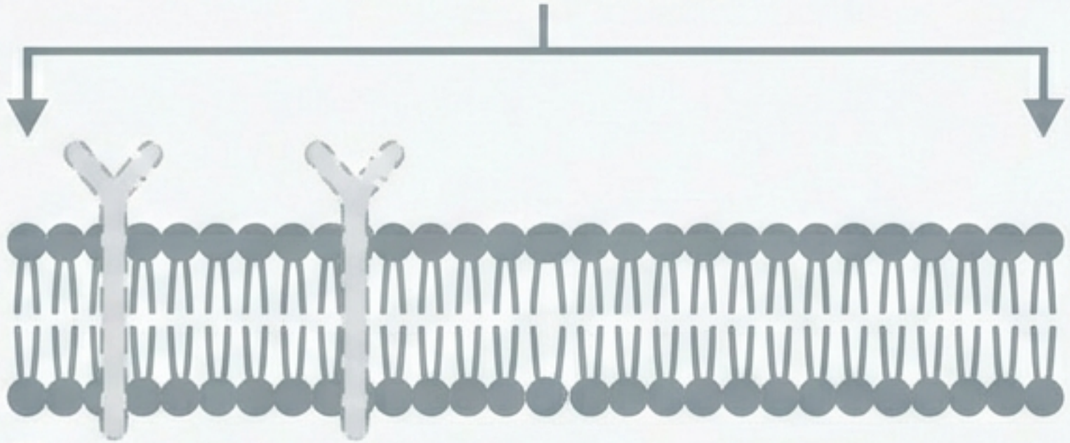
The accumulation of pathogenic alleles correlates with phenotype severity.

1 Vial - Heterozygous



50% Function. Event Age: 30–55.

2 Vials - Homozygous



<2% Function. Event Age: <15.

Prototype: **Familial Hypercholesterolemia (LDLR Function).**

Beyond Lipids: The Dominant Negative Effect

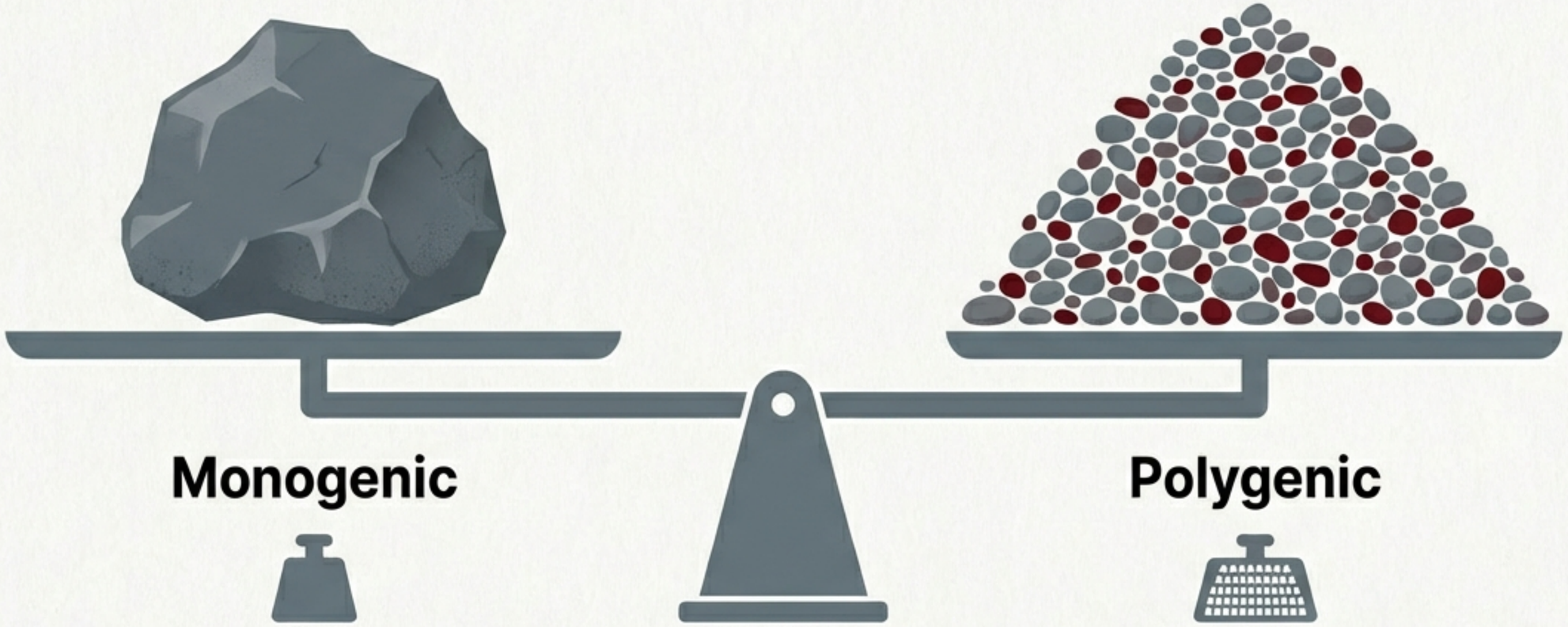
Long QT Syndrome (LQTS) and functional impairment.

In Hereditary Arrhythmia, a single mutation can mimic a "double dose" by ruining the structural integrity of the entire channel.

Risk of cardiac event by age 15: 74% (Males).

The Polygenic Burden

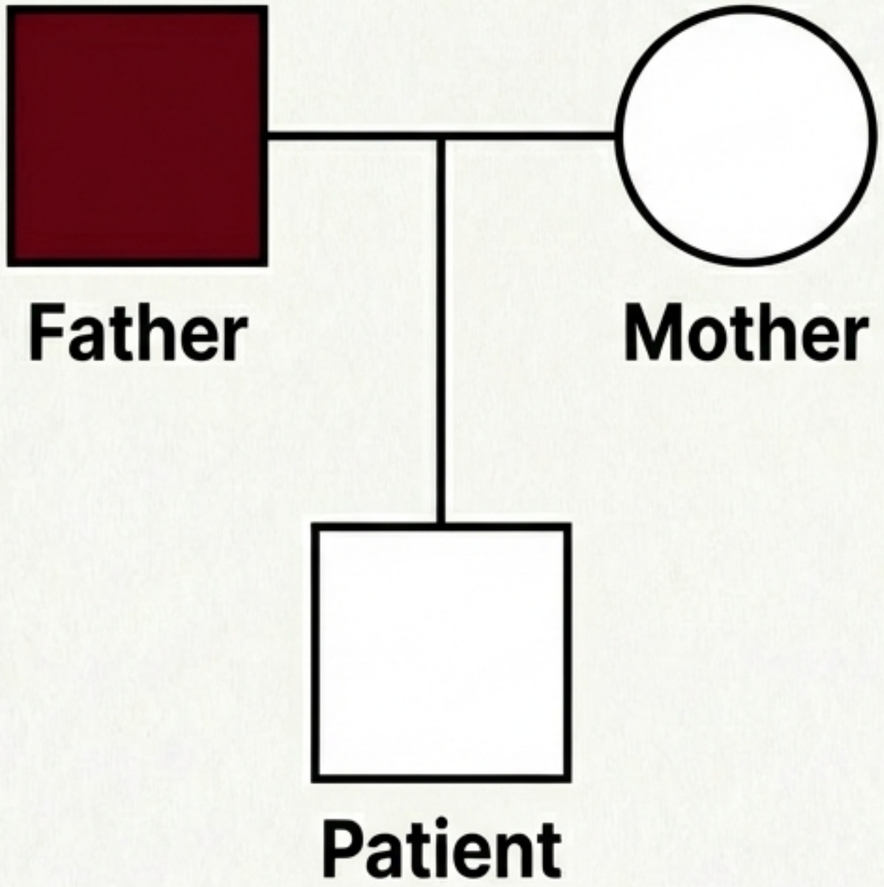
A synthetic gene dose created by thousands of small variants.



Cumulative common variants can push LDL to **160–220 mg/dL**.

Cohort 1: The Single Parent Hazard

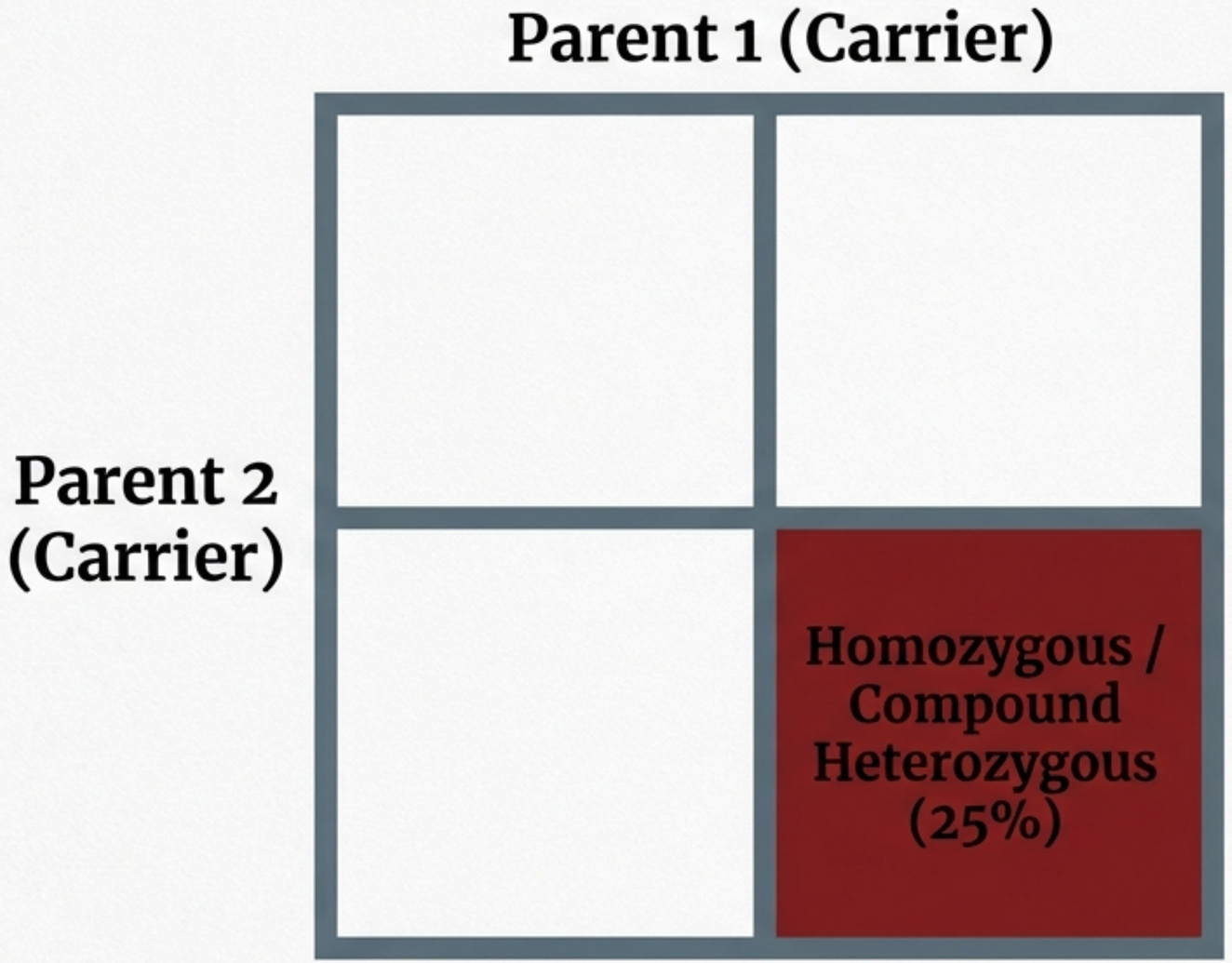
One parent with an event <55 (men) or <65 (women).



RR = 1.74

Definition: One parent with an event <55 (men) or <65 (women). This is a ‘Risk Enhancer” necessitating statin consideration.

Cohort 2: The Double Dose



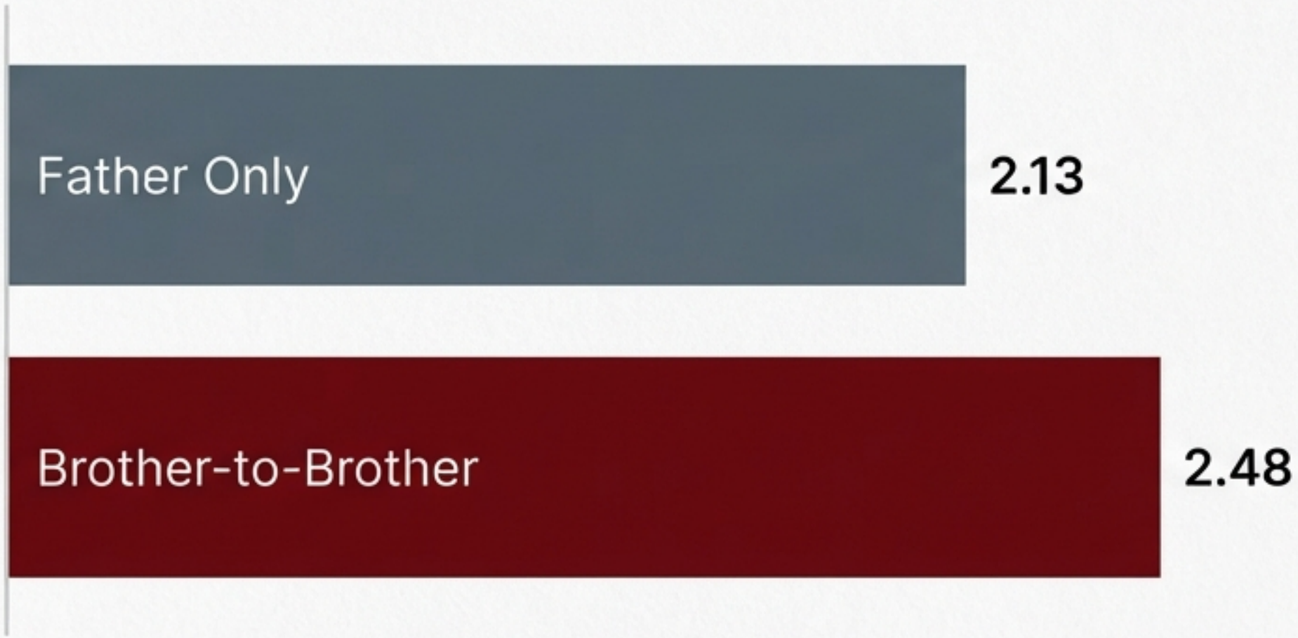
Relative Risk

> 2.26

Risk of fatal event <15 years increases ~100-fold.

Cohort 3: The Sibling Signal

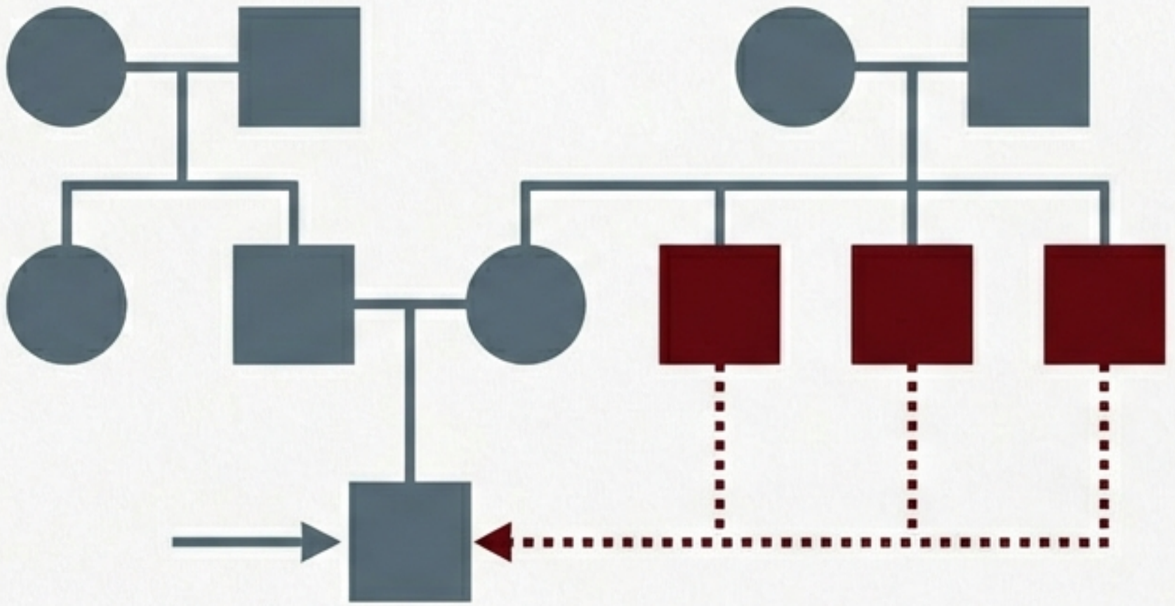
Why a brother is more dangerous than a father.



Siblings share DNA plus the same **early-life environment** and **polygenic background.** This makes **sibling history the strongest predictor for subclinical atherosclerosis.**

Lateral Clustering

Uncles, Aunts, and the ‘Silent’ Signal.



Multiple affected second-degree relatives confirm a genetic signal even if parents are silent carriers or died of non-cardiac causes.

The Pedigree Is the Test

Detailed Pedigree + Physical Signs (Xanthomas) = Definite Diagnosis (98% PPV)

- **LDL-C > 135 mg/dL in child** of affected parent = 98% Positive Predictive Value for FH.
- **Sudden Infant Death** in Uncles = Phenotypic marker for LQTS.

The Inherited Hazard Coefficient

$$H = \sum \left(N \times R \times \left(\frac{1}{A} \right) \times W \right)$$

- N = Number of affected relatives
- R = Coefficient of relatedness (0.5 for sibling/parent)
- A = Age of onset (inverse relationship)
- W = Severity Weight (Death <15 > Heart Attack)

The Imaging Trap: CAC vs. CCTA

Why a Zero Calcium Score is a false negative in young cohorts.

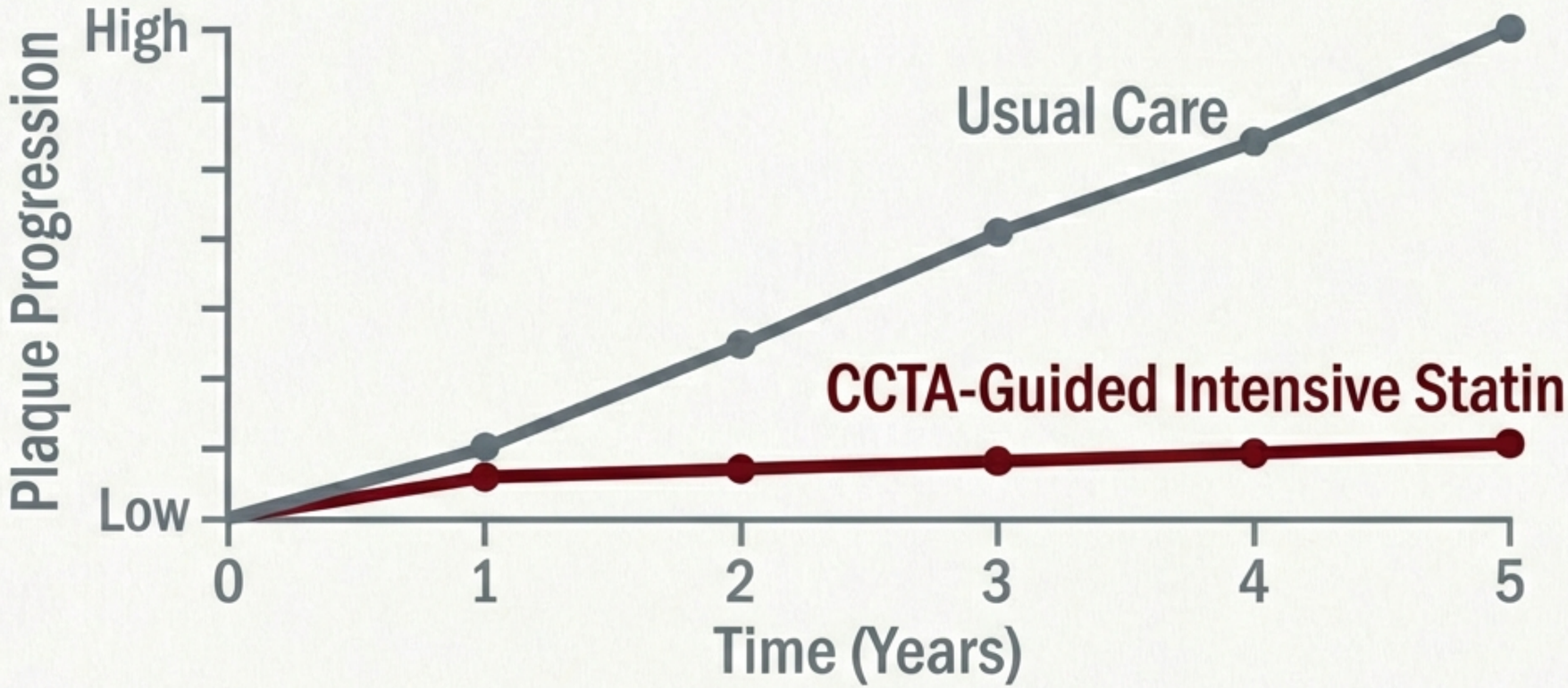
A. Calcified Plaque (CAC Detectable).

B. Soft Vulnerable Plaque (CAC Invisible).

- In **young, gene-dosed patients,** soft plaque predominates. Family history overrides a zero calcium score.

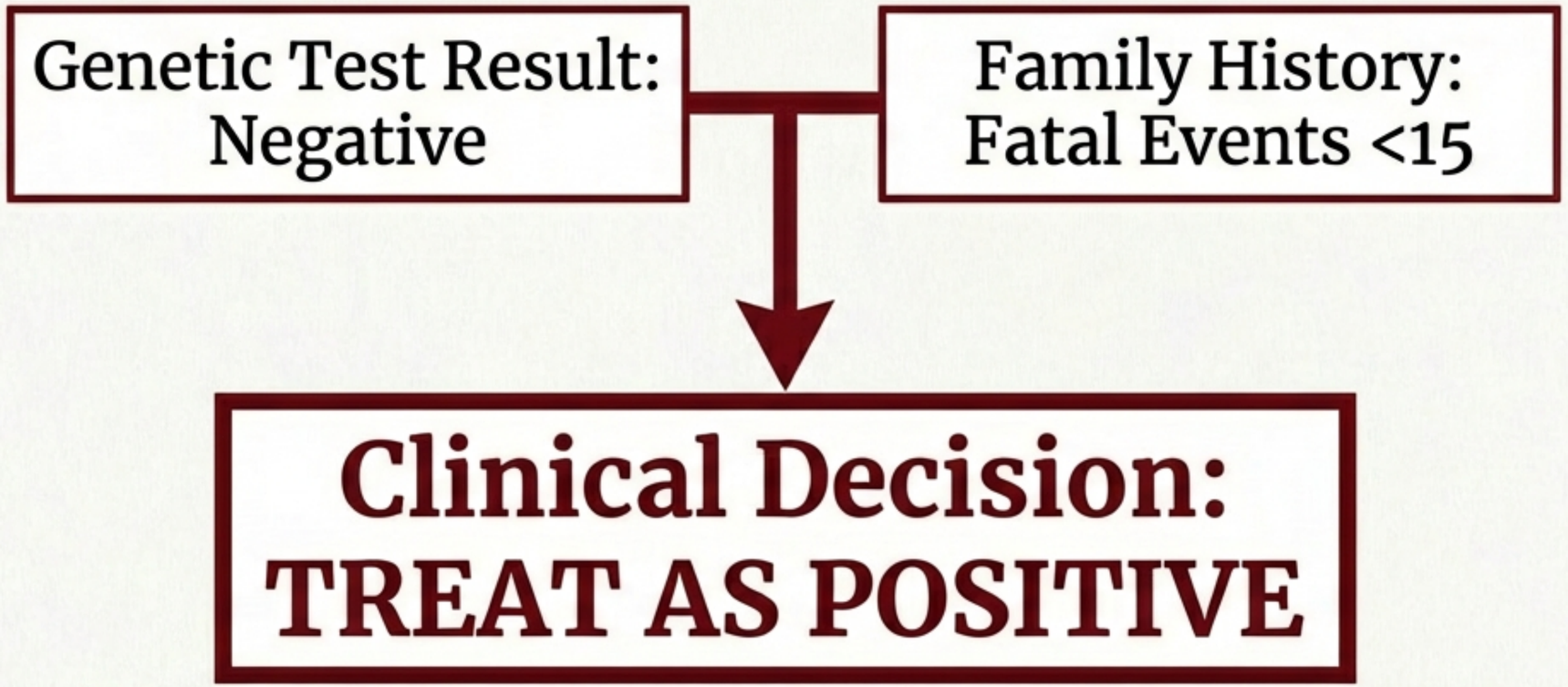
CCTA: The Gold Standard

Evidence from the CAUGHT-CAD Trial (JAMA 2025).



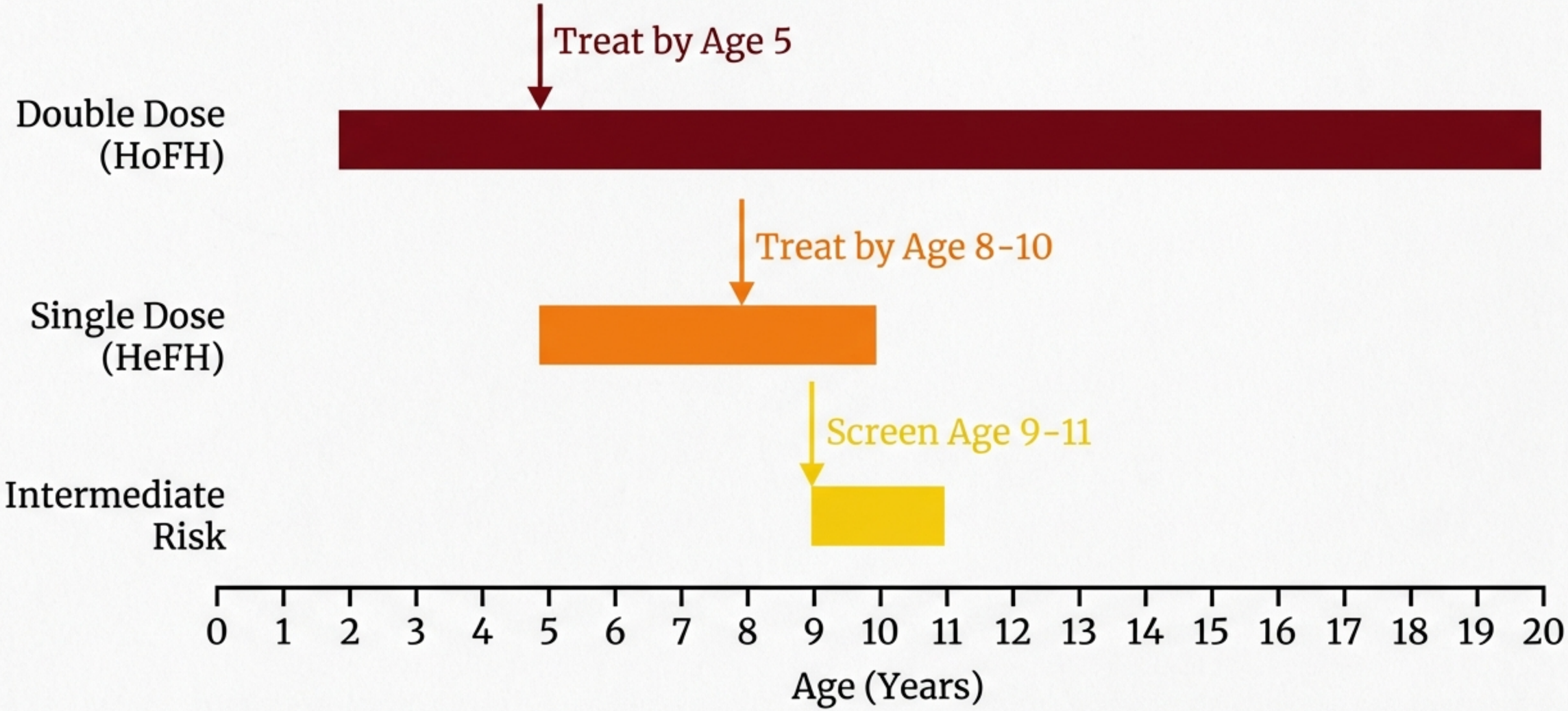
- For patients with a brother/uncle dead <15, CCTA is the preferred modality to identify non-calcified plaque.

The Actionability Paradox



"For the clinician, the phenotype is the genotype.
The body count in the pedigree is the ultimate truth."

Timeline of Intervention

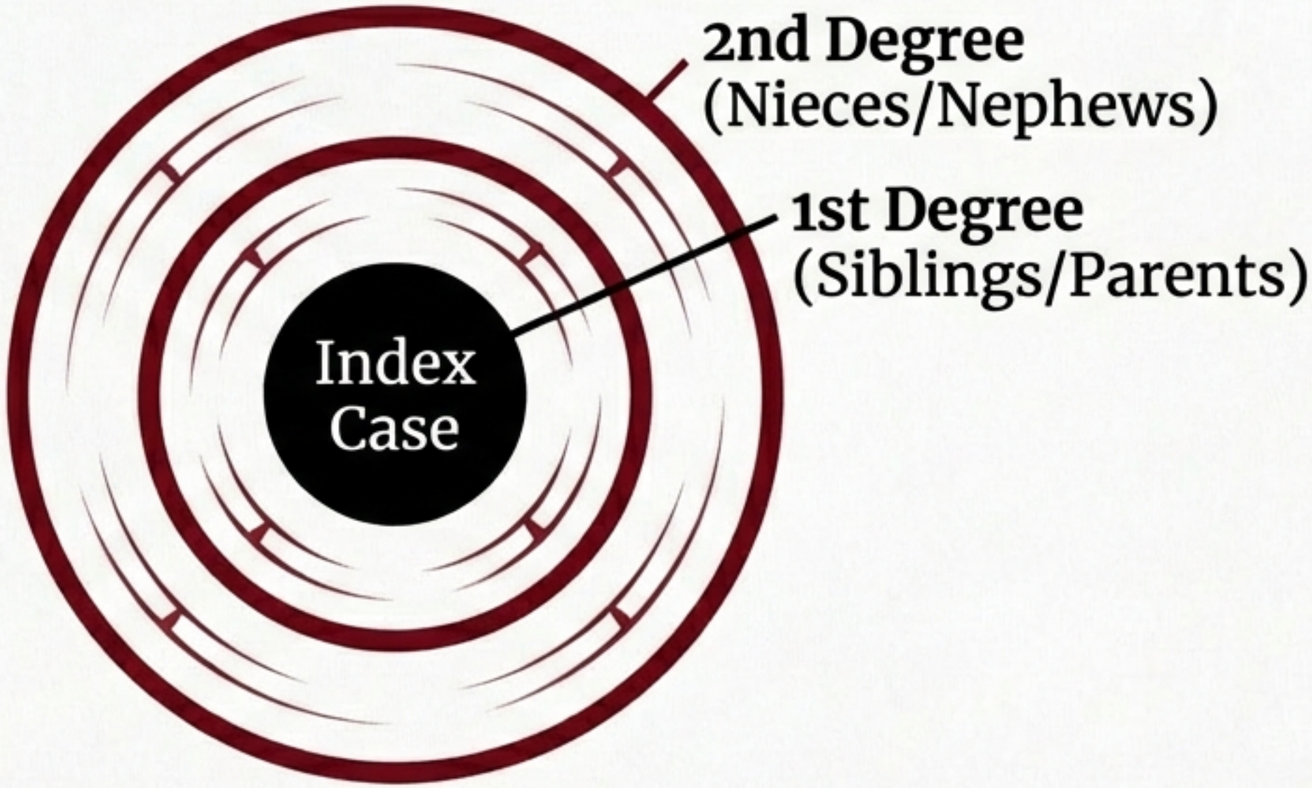


Survivorship Bias

The anomaly of the healthy old relative.

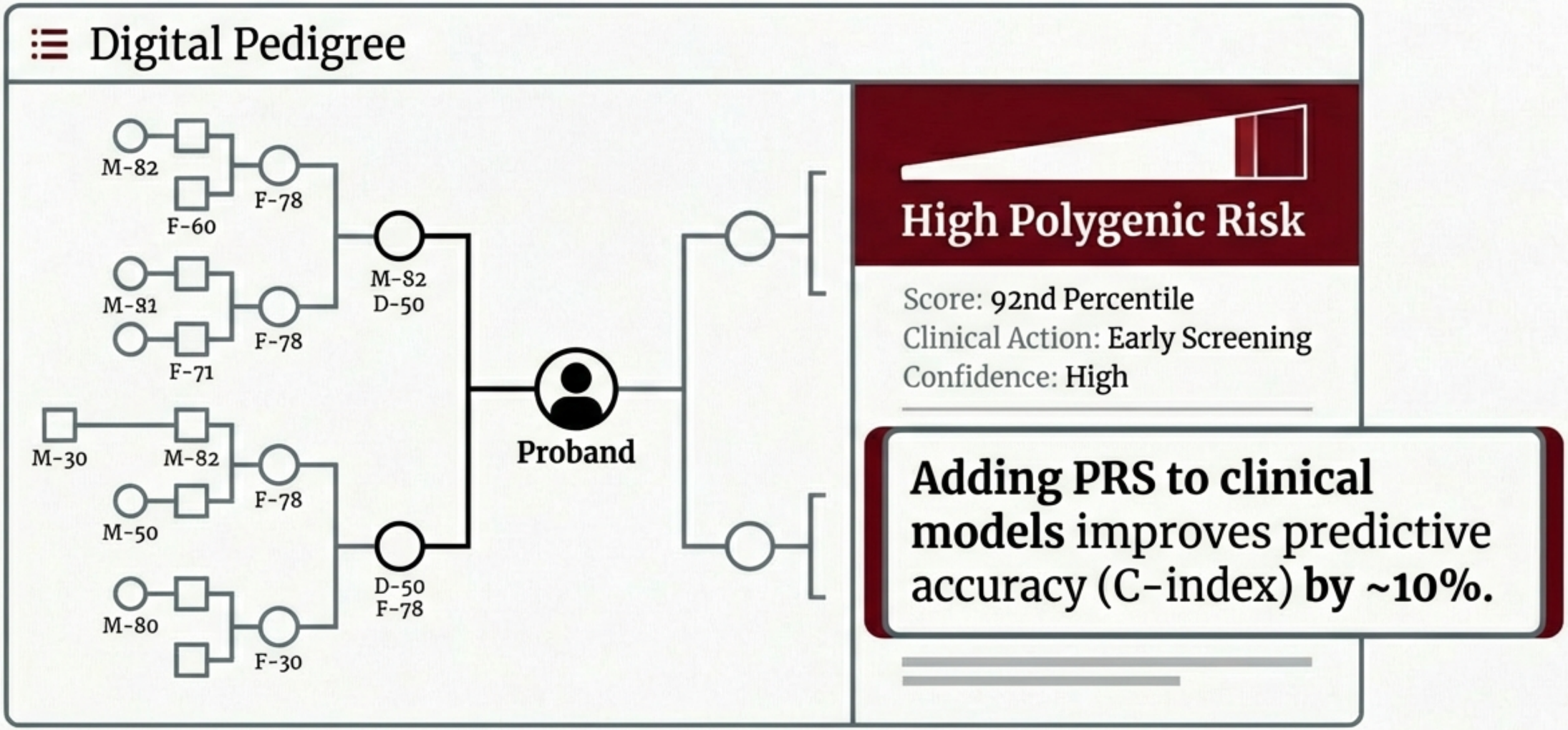
- **Protective Variants:** Loss-of-function mutations (e.g., ANGPTL3) that neutralize deleterious genes.
- **Biologic Robustness:** Endothelial resilience factors.

Cascade Screening



Screening second-degree relatives is highly effective if initiated before age 15, before lifestyle factors cloud the genetic signal.

The Future: Polygenic Risk Scores (PRS)



Clinical Directive: Stratifying the Inherited Hazard

Cohort	Hazard Level	Imaging	Action
Double Dose / Under 15	Extreme	CCTA Required	Treat by Age 5
Sibling / Brother	High (OR 2.48)	CCTA Preferred	Treat by Age 10
Single Parent	Intermediate (RR 1.74)	Lipid Panel / CAC	Treat if LDL Elevated

Utilize the data encoded in family history to intervene before the first event.