POLYGENIC RISK SCORES (PRS) IN CARDIOVASCULAR DISEASE PREDICTION

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I THE CONCEPTUAL RATIONALE: MONOGENIC VS. POLYGENIC ARCHITECTURE

- **The Monogenic Limitation:** Rare, high-penetrance monogenic mutations—such as pathogenic variants in ***LDLR, APOB,* or *PCSK9*** causing **Familial Hypercholesterolemia (FH)** (prevalence ~1 in 250 to 310)—confer a 3- to 4-fold increased risk of premature Coronary Artery Disease (CAD), but are identified in **less than 2 to 5 percent** of patients presenting with early-onset myocardial infarction.
- **The Polygenic Reality (Khera et al., *Nature Genetics* 2018):** In the vast majority of individuals, inherited susceptibility to CAD (as well as Atrial Fibrillation, Hypertension, and Type 2 Diabetes) is driven by the **additive cumulative burden of thousands to millions of common Single Nucleotide Polymorphisms (SNPs)** distributed across the genome. While any single common SNP exerts a tiny effect size (odds ratio 1.02 to 1.15), their aggregated genome-wide sum produces a wide Gaussian distribution of lifetime genetic risk.
- **Mathematical Construction of a Genome-Wide Polygenic Risk Score (GPS / PRS):** Calculated as the **weighted sum of risk-associated alleles** carried by an individual across *M* genetic variants (**PRS = Sum of [Beta_i x Dosage_i]**), where *Beta_i* is the log-odds effect weight derived from large discovery **Genome-Wide Association Studies (GWAS)** (e.g., CARDIoGRAMplusC4D, Million Veteran Program, UK Biobank) using linkage-disequilibrium clumping or Bayesian shrinkage algorithms (**LDpred, PRS-CS**).

II CLINICAL APPLICATION: THE "LIFETIME RISK-ENHANCING" PARADIGM

- **Capture at Birth (Primordial and Early Primary Prevention):** Because germline DNA does not change over a lifetime, a **Polygenic Risk Score can be calculated from birth or young adulthood (age 20 to 40 years)**—decades before age-dependent clinical calculators (such as the 10-year Pooled Cohort Equations, SCORE2, or PREVENT) cross treatment thresholds.
- **The "Polygenic FH Equivalent" (Khera et al., *Nature Genetics* 2018):** In the UK Biobank (n = 288,978), individuals in the **top 8 percent (and especially the top 5 percent)** of the genome-wide CAD Polygenic Risk Score distribution carry a **3-fold or greater increased risk of CAD**—a risk magnitude **identical to carrying a monogenic Familial Hypercholesterolemia mutation**, yet **15 to 20 times more prevalent** in the general population (80 per 1,000 vs. 4 per 1,000 for monogenic FH). Crucially, unlike monogenic FH (which is flagged by LDL-C >190 mg/dL), individuals with a high polygenic CAD score often have **normal or borderline lipid and blood pressure levels**, rendering them invisible to standard clinical screening.
- **Interaction with Monogenic Mutations:** Even among patients who carry a pathogenic monogenic **FH (*LDLR*)** or **HCM/Brugada/LQTS** variant, the background **Polygenic Risk Score acts as a potent genetic modifier** that explains incomplete penetrance and variable expressivity (e.g., why one family member with an *LDLR* mutation suffers an MI at age 35 while a sibling with the same mutation remains event-free at age 65).

III LANDMARK CLINICAL EVIDENCE MATRIX

Clinical Utility Domain	Landmark Study / Trial Substudy	Key Quantitative Finding & Clinical Implication
Polygenic "FH Equivalent" Identification	**Khera et al. (*Nature Genetics* 2018; UK Biobank)**	Top **8% of CAD PRS** confers **>=3-fold CAD risk** (same as monogenic FH, but **20x more common** and not identifiable by LDL-C alone)
Lifestyle Offsets Genetic Risk	**Khera et al. (*NEJM* 2016 — "Genetics vs. Lifestyle")**	Among patients in the **highest genetic risk quintile**, adherence to a favorable lifestyle (no smoking, BMI <30, physical activity, healthy diet) **reduced 10-year incident CAD events by 46%** ("Genetics load the gun, lifestyle pulls the trigger")
Superior Benefit from Statins & PCSK9 Inhibitors	**WOSCOPS / JUPITER / ASCOT** (Statins) & **FOURIER / ODYSSEY OUTCOMES** (*Circulation* 2020 — Evolocumab / Alirocumab)	Patients in the **highest PRS tier** derive a **markedly greater relative and absolute risk reduction** from Statins (nearly double the relative risk reduction of lower-risk tiers) and **PCSK9 inhibitors** (37% RRR in high PRS without clinical risk factors; **NNT halved**)
Integration with Coronary Artery Calcium (CAC)	**MESA & Rotterdam Study Cohorts (*JAMA* 2023)**	**CAC remains superior** to PRS in older adults (>55 yr), whereas **PRS adds strongest reclassification in younger adults (<45–50 yr)** before macroscopic calcification develops

IV CURRENT GUIDELINE STATUS (ESC 2021 PREVENTION / ESC 2023 CARDIOMYOPATHY / AHA SCIENTIFIC STATEMENT 2022)

- **General Population Screening (Class III — Not Recommended):** The **2021 ESC Guidelines on Cardiovascular Disease Prevention** do **not** recommend routine genetic or polygenic risk scoring in the general population (Class III, Level B) due to modest incremental C-statistic improvement (+0.01 to +0.03) when added to SCORE2 in middle-aged/older cohorts and lack of dedicated randomized clinical trial outcome data.
- **Targeted Clinical Scenarios (AHA 2022 Scientific Statement on PRS / Selective Risk Enhancer):**
  - **Borderline or Intermediate 10-Year ASCVD Risk (5% to 20%):** A high CAD PRS (**>=80th to 95th percentile**) acts as a **risk-enhancing factor** that reclassifies 10 to 15 percent of intermediate-risk adults upward to favor **early statin initiation**.
  - **Young Adults (<40 to 45 Years) with Premature Family History:** Identifies lifetime genetic vulnerability before CAC becomes positive (>0), guiding early intensive LDL-C/ApoB lowering.
  - **Secondary Prevention Intensification:** Identifies post-ACS patients in the top PRS decile who derive the greatest absolute MACE reduction from **PCSK9 inhibition** (**FOURIER / ODYSSEY OUTCOMES** genetic substudies).

V LIMITATIONS AND THE "EUROCENTRIC DIVERSITY TRAP"

- **Ancestral Transferability Bias:** Historically, **75 to 85 percent of GWAS discovery cohorts were of European ancestry**. Because **allele frequencies, linkage disequilibrium (LD) block structures, and causal effect sizes** differ across ancestral groups, European-derived PRSs show significantly degraded predictive accuracy (by 30 to 70 percent in African ancestry and 15 to 30 percent in South Asian ancestry) unless calibrated using multi-ancestry models.
- **Non-Genetic Determinants:** A PRS captures only common germline additive variance (heritability of CAD is ~40 to 50 percent); it does not capture somatic clonal hematopoiesis (**CHIP — *TET2, DNMT3A, ASXL1, JAK2***), epigenetic modifications, or acute environmental triggers.

VI PRACTICAL APPLICATION IN THE INDIAN CLINICAL CONTEXT

- **South Asian Multi-Ancestry PRS Development (Wang & Khera et al., *JACC* 2020; Patel et al., *Nature Medicine* 2023; GenomeIndia Project):** Dedicated **South Asian-calibrated Genome-Wide Polygenic Scores** (validated in Indian case-control cohorts, PROMIS, and UK Biobank South Asians) demonstrate an odds ratio of **1.6 to 1.7 per standard deviation** and identify the **top 5 percent of Indians who carry a >3- to 4-fold risk of premature Myocardial Infarction**.
- **Highest Clinical Yield in India:** In Indian preventive cardiology clinics, combining a **South Asian-calibrated PRS** with **Lipoprotein(a)** and **Apolipoprotein B** in **young adults (aged 20 to 45 years) with a family history of premature CAD** identifies high-risk individuals during the "CAC-zero window" (when non-calcified lipid-rich soft plaque is forming), justifying early lifestyle intervention and statin therapy.

KEY REFERENCES

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- **O'Sullivan JW, Raghavan S, Marquez-Luna C, et al.:** Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association, *Circulation*, 2022.
- **Marston NA, Kamanu FK, Nordio F, et al. (FOURIER Investigators):** Predicting Benefit From Evolocumab Therapy in Patients With Atherosclerotic Disease Using a Genetic Risk Score, *Circulation*, 2020.