PROPHET TOOLBOX
FACTSHEET#7

JULY 2026

Polygenic Risk Scores (PRS) in Chronic Disease Prevention

PROPHET
a PeRsOnalized Prevention roadmap
for the future HEalThcare

What is Polygenic Risk Score?

A **Polygenic Risk Score (PRS)** is a numerical estimate of an individual's genetic susceptibility to a particular disease. It reflects the cumulative effect of multiple common genetic variants, known as single-nucleotide polymorphisms (SNPs). These variants are identified through genome-wide association studies (GWAS), and the score is calculated by summing the risk alleles carried by an individual, weighted according to their estimated effect on disease risk. Each SNP individually has only a minimal impact on risk; however, when aggregated into a single score, they can identify those with elevated or reduced risk.

A PRS is calculated from DNA obtained through a blood or saliva sample, typically genotyped using a SNP array, followed by bioinformatics processing to combine the effect of relevant genetic variants into an individual risk score. At the population level, PRS values follow a normal distribution, allowing clinicians to assess how a patient’s genetic risk compares to the population average.

It is critical to distinguish PRS from high-penetrance variants (e.g., BRCA1/2 for breast cancer, LDLR for familial hypercholesterolemia). High-penetrance variants are rare and confer a substantial, sometimes near-deterministic, increase in individual risk, although they account for only a limited proportion of the genetic contribution to most common diseases. PRS, by contrast, provides a probabilistic estimate of risk, capturing the polygenic background upon which environmental factors act.

These two categories are not independent, as an individual’s polygenic background can substantially influence the penetrance of high-penetrance variants. Among monogenic variant carriers, estimated disease risk by age 75 can vary according to PRS, ranging from 17% to 78% for coronary artery disease (CAD), 13% to 76% for breast cancer, and 11% to 80% for colon cancer, suggesting potential clinical implications.

The American College of Medical Genetics and Genomics (ACMG) emphasizes that PRS provides relative rather than absolute risk and should be used as an adjunct tool, not a replacement for monogenic testing. The National Comprehensive Cancer Network (NCCN) guidelines state that PRS should not be used for clinical management at this time outside of clinical trials.

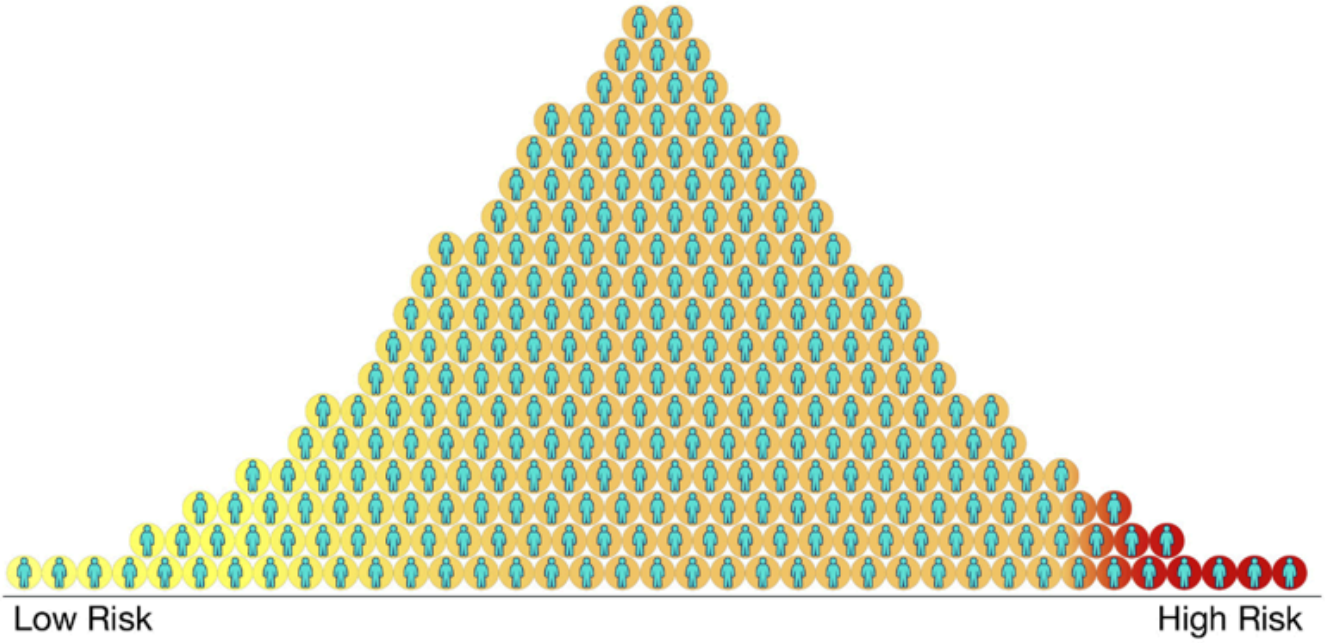

Fig 1. The graphic illustrates the distribution of PRS across a population, with most individuals falling around average risk and fewer individuals at the low- and high-risk tails. (From: National Human Genome Research Institute (NHGRI), Polygenic Risk Scores, https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores)

Why PRS may be relevant for Chronic Disease prevention

PRS allows the identification of individuals at elevated genetic risk before the onset of disease, when preventive strategies are likely to be most effective. Unlike traditional risk scores, based on clinical risk factors that typically emerge in adulthood or middle age, PRS is a static, lifelong biomarker that can be assessed from a single sample at any age. It provides predictive information, complementary to conventional risk factors such as age, sex, blood pressure, cholesterol, and smoking status.

Earlier screening:
a key advantage of PRS is its potential to enable targeted screening for high-PRS individuals. A recent modeling study across seven diseases with established screening programs (abdominal aortic aneurysm, breast cancer, colorectal cancer, CAD, hypertension, prostate cancer, and type 2 diabetes) found that very high-PRS individuals can reach the conventional screening threshold 10.8 years earlier on average, and PRS-guided screening was estimated to reduce premature mortality in high-risk individuals by 23.3%.

Risk is modifiable:
the effects of high polygenic risk can be substantially attenuated by healthy lifestyle and pharmacotherapy. Healthy behaviors (no smoking, regular physical activity, healthy diet) are associated with similar relative reductions in disease incidence across PRS categories, but the absolute risk reduction is greatest in those with the highest score thus reaching a population level potential impact.

Applications and integrated risk prediction tools

PRS are currently being explored or piloted across several chronic disease areas, with the most clinically advanced applications in cardiovascular disease (CVD), breast cancer, and type 2 diabetes. In the GENVASC study, adding a CVD-PRS to QRISK2 improved the identification of individuals who subsequently experienced major cardiovascular events, increasing detection from 61.5% to 68.7%, with a particularly marked improvement among adults aged 40-54 years.

In breast cancer, PRS313, a PRS based on 313 SNPs, explains over 30% of heritability, and women in the highest PRS percentiles have approximately 2.5-fold population-average risk, comparable to carriers of moderate-penetrance variants in ATM and CHEK2.

PRS can also be integrated into multifactorial prediction tools such as CanRisk/BOADICEA v6, which combines family history, germline variants in breast cancer susceptibility genes, mammographic density, lifestyle and hormonal factors, allowing more refined risk stratification.
For type 2 diabetes, an Indian-specific PRS demonstrated an AUC of 0.80, with the top 25% PRS group showing 5.8-fold increased risk. On the other hand, a recent UK Biobank study highlighted the current limitations of PRS for clinical use in psychiatry. Risk classification varied substantially across different PRS, with many individuals assigned to different risk categories depending on the score used. In addition, the scores showed variable sensitivity and low specificity for detecting the diagnosis of interest.

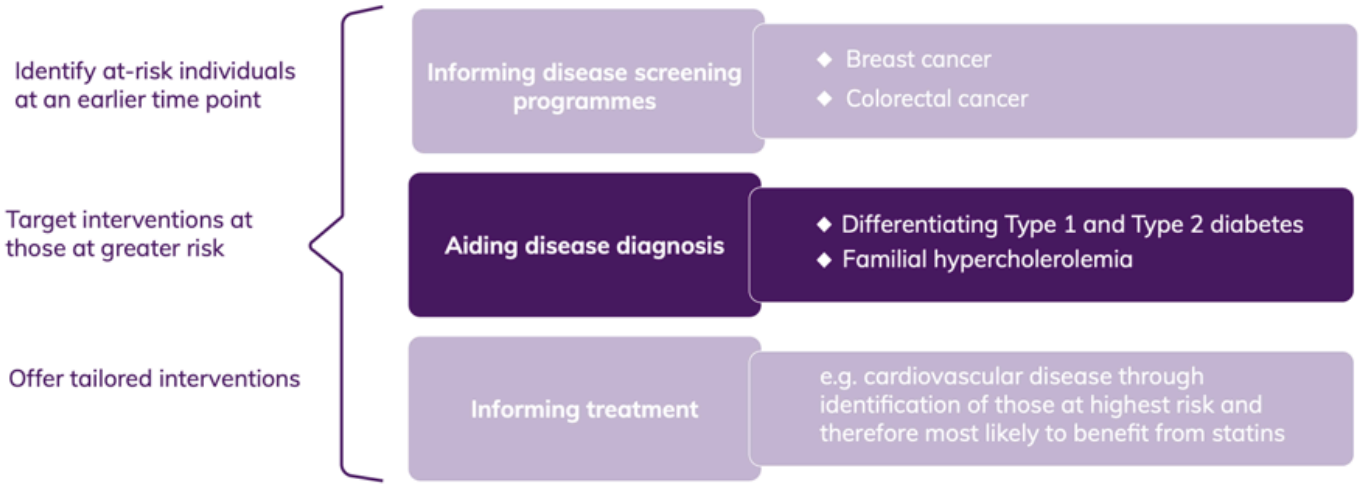

Fig 2. Applications of polygenic score information. (From Moorthie S. Application of polygenic scores in healthcare. PHG Foundation; 2023.)

The NCCN Breast Cancer Risk Reduction Guidelines note that routine use of PRS in risk assessment is currently discouraged outside of research settings. The European Society of Cardiology (ESC) consensus statement acknowledges PRS value but does not advocate routine clinical use.

Limitations and challenges

Limited predictive accuracy:
the predictive ability of PRS for complex diseases remains limited, as they capture only part of the genetic contribution to risk and do not fully account for rare variants, or gene-gene interactions and gene-environment interactions. Their discriminatory performance is often modest, with high scores not necessarily implying disease and low scores not excluding it.

Poor transferability across ancestry:
since most GWAS have been conducted in populations of European ancestry, PRS perform less accurately in non-European populations, with the potential of exacerbating health inequities. Emerging computational approaches, including PRS-CSx, PolyPred, TL-PRS, and multi-ancestry GWAS are improving cross-population prediction but have not yet closed the gap.

Lack of standardization:
for the same trait, different scores may be developed using different methods, variants, and populations; in addition, clinically relevant risk thresholds are not consistently defined, and reporting practices may vary substantially across laboratories.

Limited prospective evidence:
despite strong observational and retrospective evidence, direct evidence that PRS-guided management improves clinical outcomes remains scarce.

Ethical/legal concerns:
PRS may be misinterpreted as deterministic, raising concerns about fatalism; there's a risk of potential genetic discrimination, particularly for life or long-term disability insurance, as well as data privacy, secure storage and secondary use of genomic information; moreover, the need for ancestry-specific calibration may reinforce biological concepts of race and increase the risk of discriminatory misuse.

Implementation barriers:
clinical adoption is hindered by limited knowledge among healthcare professionals, absence of established workflows for generating PRS and integrating them into electronic health records, clinical decision support systems, or referral patterns, and insufficient genetic counselling capacity for large scale implementation. In addition, the lack of guidelines for routine PRS use creates uncertainty about their appropriate role in clinical practice.

Uncertain cost-effectiveness:
Current evidence suggests that PRS may be cost-effective in selected clinical areas, particularly cardiovascular disease and some cancers (e.g. prostate). However, most estimates are based on economic models and cost-utility analyses rather than real-world studies. In oncology, PRS have primarily been used to optimize screening strategies, while in other fields they are more commonly used to guide preventive treatment decisions. Further evidence is needed regarding implementation costs, delivery models, population representativeness, and long-term health and non-health outcomes.

Interpreting and communicating PRS results to patients

PRS results provide a statistical prediction of genetic susceptibility and are interpreted using three key measures:

percentile rank: the individual's position within the population distribution of PRS values;

relative risk: the increase or decrease in risk compared with population average;

absolute risk: the estimated probability of developing the disease over a defined time horizon.

The ACMG emphasizes that PRS does not directly provide absolute risk for disease development; the National Society of Genetic Counselors (NSGC) recommends communicating absolute rather than relative risks wherever possible, as these are more understood by patients. A person can be in a high-risk percentile, but still have low absolute risk.

1. **Pre-test counseling:** Explain that PRS is not diagnostic and differs from monogenic testing. Clarify that results cannot predict family members' risk, that scores may change as GWAS improve, and that ancestry match affects confidence. Adapt communication to the individual's literacy level and values.

2. **Results reporting:** Use absolute risk wherever possible. Employ visual aids: bell curves (population distribution), icon arrays (100-dot diagrams), and color-coded gradients using neutral colors (avoid red/green). Use word-based descriptors ("average," "above average," "high") alongside percentiles, rather than odds ratios, which are poorly understood and should be avoided in patient-facing reports.

③ **Framing the result:** use PRS results as an opportunity to discuss modifiable risk factors, emphasizing that genetic risk is not deterministic; clarify that PRS captures only part of genetic risk, which itself represents only one component of overall disease risk.

④ **Psychological impact:**
RCTs and systematic reviews suggest that PRS disclosure is not associated with substantial psychosocial harm. However, PRS results may increase perceived risk and worry in high-PRS individuals, particularly when delivered without professional counseling, or to individuals with limited understanding of PRS. These findings underline the importance of adequate pre-test education, clear communication, and personalized return of high-risk results. Low-risk PRS results do not appear to be associated with maladaptive behaviors.

Although PRS information is expected to empower individuals by providing personalized genetic risk estimates, a systematic review of RCTs reports effects close to null for most lifestyle, clinical, and psychological outcomes, including physical activity, diet, alcohol consumption, BMI, weight, blood pressure, cholesterol levels, and screening attendance.

Some studies have reported modest improvements, such as increased statin use among high-risk individuals, better adherence to dietary recommendations, or improved sun-protection behaviors, but these findings remain inconsistent. To influence preventive care, PRS should be embedded within structured prevention pathways, supported by healthcare professionals, and combined with evidence-based behavioral interventions.

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