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Polygenic risk scores in cardiovascular disease: are they ready for clinical use?

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Take Home Messages

- Cardiovascular disease risk tools remain imprecise. It remains unclear how to integrate polygenic risk scores with these tools.
- Integrated risk tools have been evaluated in primary care combining genetic risk with other clinical data.
- Polygenic risk scores can enhance cardiovascular disease risk stratification with the potential to impact on preventive therapy.
- Further prospective studies of polygenic risk scores and the impact on preventive medications and risk reduction are required.

Background

Cardiovascular disease (CVD) including coronary artery disease and stroke remain the leading cause of death worldwide, driven by lifestyle, clinical and sociodemographic risk factors, in addition to genetic predisposition. Polygenic risk scores (PRS) show promise for identifying individuals with a higher genetic risk of CAD, though data for non-CAD diseases remains limited (1). They have been integrated into existing risk prediction tools in the clinical setting with encouraging results (2,3). PRS offers the potential for personalised prevention and treatment strategies when used alongside clinical and lifestyle risk factors (**Figure 1**). Prevention of heart disease features in the 2019 NHS Long Term Plan and is likely to continue to be a focus of subsequent health care policies (4). This editorial explores the potential use of PRS in CVD and challenges.

What is polygenic risk?

PRS are derived from genome-wide association studies (GWAS), which identify common genetic variants, known as single nucleotide polymorphisms (SNPs), associated with increased risk of disease. Each SNP may confer only a small amount of risk, but when

combined, these variants can collectively offer significant insights into an individual's genetic predisposition to disease.

What are the barriers to widespread clinical use of PRS?

Despite its promise, there are several challenges to the widespread clinical use of PRS in cardiology (**Table 1**).

Multi-ancestry performance

Most GWAS and PRS studies have been conducted in populations of European ancestry. PRS may not be as predictive in other populations, and underperforms particularly in those of African ancestry (5). This may be due to higher genetic diversity, different population structures and challenges with calibration for African ancestries with ongoing efforts to address this (**Table 1**).

Clinical Utility

The addition of PRS to existing risk prediction tools may have incremental value, but there are several areas that remain under evaluation. HEART was a device performance evaluation designed to evaluate the feasibility of a cardiovascular disease integrated risk tool (IRT) which enrolled participants eligible for a CVD risk assessment, as part of the NHS health check (2). An IRT incorporating PRS and the QRISK2 was feasible and well accepted by participants and health care professionals with the results associated with planned changes in primary prevention strategies (2). In those without CVD undergoing an NHS health check, the addition of a CVD PRS alongside QRISK2 resulted in a 47.7% relative increase in identification of individuals in the 40-54 years age group who went on to have a major cardiovascular event (3). Genome-wide arrays cost less than many routinely requested blood tests and the addition of PRS into CVD risk assessment could lead to clinical benefit. However, integration into routine clinical

practice will require robust health economic analysis, mechanisms to update the PRS calculation as new genetic information emerges, and further implementation studies. Our Future Health aims to be the UK's largest ever research programme with disease prevention as its primary objective (6). PRS will be collected for all volunteers and integrated with family history, environmental and lifestyle risk factors, to learn how PRS can be effectively used for each disease. Future clinical trials could even leverage PRS as an inclusion criterion to identify high-risk individuals, potentially increasing power and reducing sample size to demonstrate the efficacy of novel drug therapies for CAD beyond the existing standard of care.

Society guidelines are yet to incorporate CVD PRS despite evidence which parallels existing risk factors such as LDL cholesterol. However, using PRS in an IRT is in keeping with the goals of existing NICE guidance which advocates a systematic strategy for primary prevention of CVD and prioritising those at highest risk (7).

Ethical Considerations

The increasing use of genetic information raises ethical concerns around privacy particularly with regards to General Data Protection Regulation (GDPR) compliance, genetic discrimination, and informed consent. Healthcare professionals, patients and public bodies must navigate these issues carefully to ensure that patients' genetic data is used responsibly and equitably. Standardised reporting is essential as direct-to-consumer genetic testing companies grow, to enable appropriate use of data.

Conclusions

Using genetic data in PRS offers a new frontier in the prevention of CVD. IRT can enhance risk stratification, and targeted intervention to higher risk individuals. Challenges around ancestral diversity, cost effectiveness and clinical efficacy must be addressed before PRS becomes routinely utilised in clinical practice. Additionally, risk model profile only includes common variants not rare ones which may nonetheless be

clinically relevant. PRS can improve the prevention of CVD if it can be integrated effectively into screening tools delivering measurable benefits that surpass existing risk prediction tools.

Disclosures

None to report.

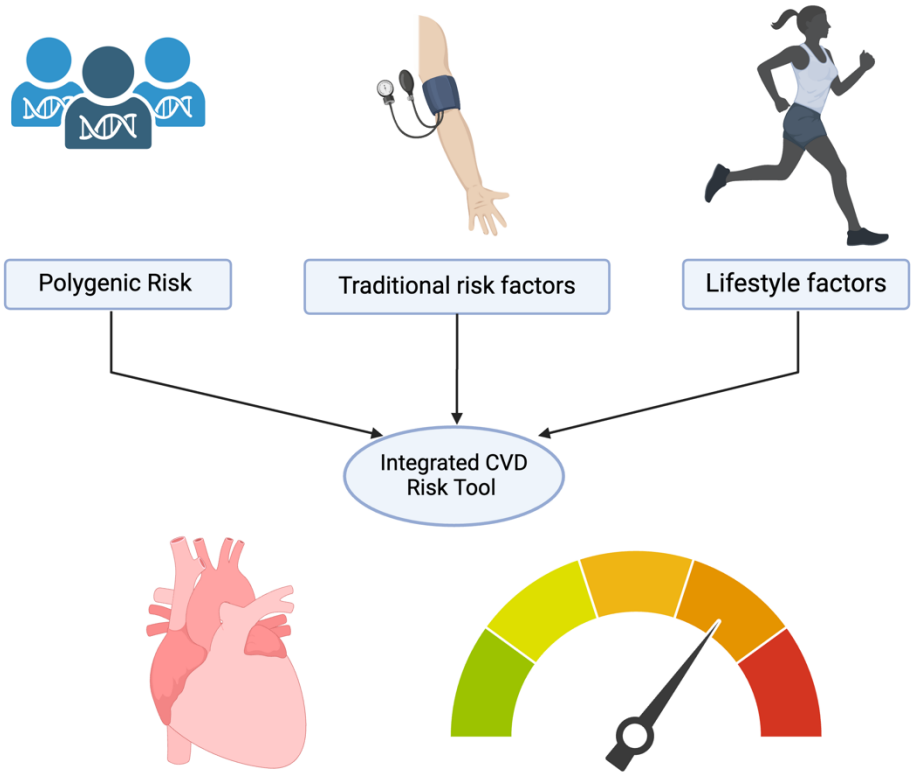

Figure 1 Genetic, lifestyle and traditional risk factors combined in an integrated risk tool for cardiovascular disease. The bottom right part of this figure illustrates the output of an integrated CVD risk tool with colours from green to red corresponding to increasing CVD risk. This is an original figure created with Biorender.com. CVD, cardiovascular disease

Table 1 Challenges with polygenic risk scores for cardiovascular disease and efforts to address these

Challenge	Ongoing efforts
Reduced cross-ancestry performance	Increased diversity of large genomic studies Improved computational methods
Standardisation of reporting	Hospital system implementation Direct-to-consumer genetic testing companies
Scalable implementation frameworks	Our Future Health (6), eMERGE (8)
Guideline adoption	AHA Scientific Statement (9) Increasing advocacy and awareness
Insufficient prospective studies	GenoVA (10), PROACT (11,12)

eMERGE, Electronic Medical Records and Genomics; AHA, American Heart Association; GenoVA,Genomic Medicine at Veterans Affairs Study; PROACT, a randomised clinical trial titled Polygenic Risk-based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health

References

1. Patel AP, Wang M, Ruan Y, Koyama S, Clarke SL, Yang X, et al. A multi-ancestry polygenic risk score improves risk prediction for coronary artery disease. Nat Med. 2023;29(7):1793–803.

2. Fuat A, Adlen E, Monane M, Coll R, Groves S, Little E, et al. A polygenic risk score added to a QRISK®2 cardiovascular disease risk calculator demonstrated robust clinical acceptance and clinical utility in the primary care setting. Eur J Prev Cardiol. 2024 Jan 19;zwae004.

3. Samani NJ, Beeston E, Greengrass C, Riveros-McKay F, Debiec R, Lawday D, et al. Polygenic risk score adds to a clinical risk score in the prediction of cardiovascular disease in a clinical setting. Eur Heart J. 2024 Jun 7;ehae342.

4. NHS Long Term Plan » The NHS Long Term Plan [Internet]. [cited 2024 Sep 12]. Available from: https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

5. Fahed AC, Aragam KG, Hindy G, Chen YDI, Chaudhary K, Dobbyn A, et al. Transethnic Transferability of a Genome-Wide Polygenic Score for Coronary Artery Disease. Circ Genomic Precis Med. 2021 Feb;14(1):e003092.

6. Our Future Health [Internet]. [cited 2024 Sep 12]. Our Future Health. Available from: https://ourfuturehealth.org.uk/

7. Recommendations | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE [Internet]. NICE; 2023 [cited 2024 Aug 28]. Available from: https://www.nice.org.uk/guidance/ng238/chapter/Recommendations

8. eMERGE Genomics Risk Assessment and Management Network [Internet]. [cited 2024 Sep 12]. Available from: https://www.genome.gov/Funded-Programs-Projects/eMERGE-Genomics-Risk-Assessment-and-Management-Network

9. O'Sullivan JW, Raghavan S, Marquez-Luna C, Luzum JA, Damrauer SM, Ashley EA, et al. Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2022 Aug 23;146(8):e93–118.

10. Hao L, Kraft P, Berriz GF, Hynes ED, Koch C, Korategere V Kumar P, et al. Development of a clinical polygenic risk score assay and reporting workflow. Nat Med. 2022 May;28(5):1006–13.

11. Study Details | Polygenic Risk-based Detection of Subclinical Coronary Atherosclerosis and Intervention With Statin and Colchicine | ClinicalTrials.gov [Internet]. [cited 2024 Sep 12]. Available from: https://clinicaltrials.gov/study/NCT05850091

12. Study Details | Polygenic Risk-based Detection of Subclinical Coronary Atherosclerosis and Change in Cardiovascular Health | ClinicalTrials.gov [Internet]. [cited 2024 Sep 12]. Available from: https://clinicaltrials.gov/study/NCT05819814