Application of polygenic scores in healthcare

Summary

◆ A polygenic score provides a single measure of the cumulative effect of multiple individually low-impact genetic variants

◆ Polygenic scores provide data that can potentially contribute to decision making in a variety of healthcare contexts

◆ Potential applications of polygenic score analysis in healthcare include identification at an earlier time point of at-risk individuals, refining diagnosis or offering tailored interventions

◆ Research and development is continuing across all these areas, with trials ongoing for some specific use cases
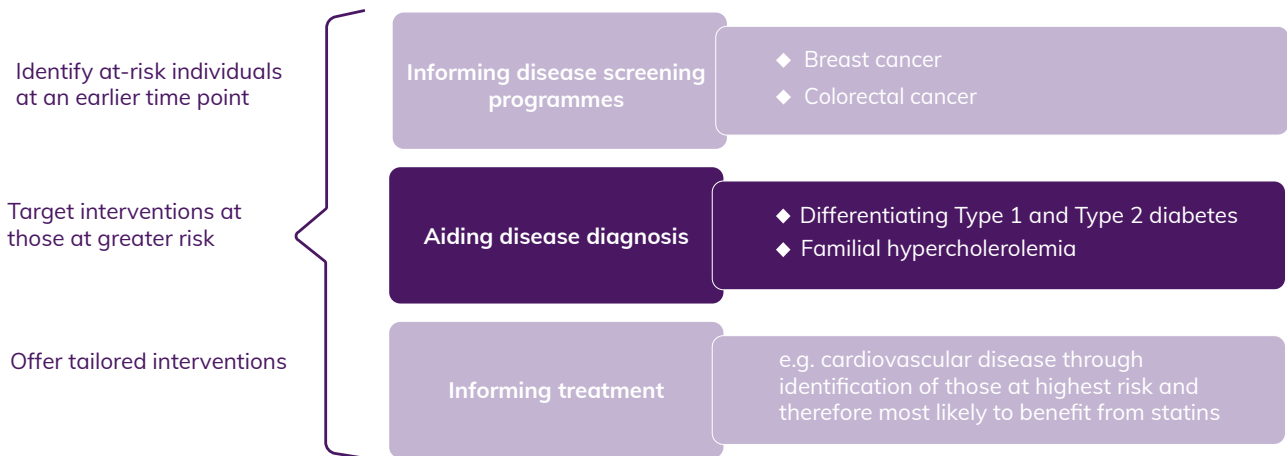
A polygenic score is a measure of risk for a specific disease taking into consideration the cumulative effect of multiple low-impact genetic changes. Risk information from polygenic scores can be used in a variety of ways as part of healthcare pathways. In this briefing we discuss some of the proposed uses. For a reminder as to what a polygenic score is, see 'Unpacking polygenic scores'.

Risk prediction and stratification

Risk prediction is a method by which to estimate the likelihood of a particular outcome (e.g. developing or having a disease). Risk prediction is used across healthcare, to inform decisions about what actions to take. However, the mechanisms through which risk is determined can vary. Risk tools that collate data on a variety of factors (e.g. age, sex symptoms) already exist and are widely used, especially in identifying desirable medical interventions.

The term **stratified prevention** refers to a process whereby populations are divided into groups according to their level of risk. Interventions may be proposed or offered to some of these groups depending on their level of risk. Risk prediction and stratification can be applied to asymptomatic individuals as well as to those who are already suspected of having a particular disease.

Applications of polygenic score information

Identify at-risk individuals at an earlier time point	**Informing disease screening programmes**	◆ Breast cancer ◆ Colorectal cancer
Target interventions at those at greater risk	**Aiding disease diagnosis**	◆ Differentiating Type 1 and Type 2 diabetes ◆ Familial hypercholerolemia
Offer tailored interventions	**Informing treatment**	e.g. cardiovascular disease through identification of those at highest risk and therefore most likely to benefit from statins

Polygenic scores provide a mechanism to obtain information on genetic risk and are an additional data point that can contribute to risk prediction and stratification. Incorporation of polygenic score information as part of risk prediction and stratification has the potential to inform prevention, early detection, management and treatment of different diseases. Below are three examples of how information from polygenic scores can contribute to risk prediction and stratification.

Informing disease screening programmes

The use of polygenic scores to identify the eligibility of asymptomatic sub-populations for particular preventative interventions has been proposed in several disease areas. This is through their incorporation into existing risk prediction tools, or by creating new risk prediction tools that allow integrated risk assessment.

Examples include incorporating a polygenic score for coronary artery disease into the existing QRisk® tool for cardiovascular disease[1], or for certain cancers as part of cancer risk prediction tools.[2]

Such tools can be developed for the general population or for specific groups who are already classified as at higher risk to refine risk prediction. For example, there are individuals with a strong family history for a cancer but for whom a pathogenic genetic variant has not been identified. In these situations polygenic scores can refine the risk prediction processes already undertaken to aid decision making with regard to available management options for these individuals.

Aiding disease diagnosis

Polygenic scores are proposed to help refine a diagnosis (i.e. in individuals with symptoms of a condition) within a defined clinical pathway, for which the utility has already been demonstrated.

For example, when diagnosing a person suspected to have diabetes, a polygenic score may help differentiate Type 1 from Type 2 diabetes. This is useful as recommended treatment options for these conditions differ.

In the context of familial hypercholesterolemia (FH), testing for the presence of pathogenic variants in a subset of genes that cause FH is established practice for individuals who are suspected of having this condition. However, an underlying causal variant is not identified in everyone. In such cases a polygenic score can help in further assessing whether the condition is present and therefore the appropriate intervention.[3,4]

The value of information from polygenic scores in these contexts is not in identifying the underlying genetic cause, but in improving the accuracy and/or diagnostic yield. It also informs further management of individuals and their families.

Risk stratified screening

Risk stratified screening programmes aim to screen those at higher risk sooner and/or more frequently, whilst those at lower risk would be screened later and/or less frequently. This risk-based approach to screening has been mostly discussed in the context of cancer, where it is anticipated by some to potentially lead to improved benefits and a more efficient programme.

These anticipated benefits would arise through more accurately targeting a screening test to those with a higher probability of developing disease, which could lead to increased identification of cases and reductions in overdiagnosis. The role of polygenic scores in this application is likely to be most effective/appropriate in combination with other risk factors to classify people into different risk categories.

Informing treatment

Pharmacogenomics aims to determine how genetic variants affect an individual's response to drug treatment. Much of the research that is currently underway on the role of polygenic scores in this area is in relation to mental health disorders, specifically to improve antipsychotic and antidepressant treatment outcomes. There are several challenges in conducting pharmacogenomics research including recruiting large enough cohorts of uniformly treated patients with enough data to assess clearly defined outcomes.[5,6]

Another approach being investigated is using polygenic score information on overall disease risk to inform treatment response. For example, it is well established that treatment response to statins is better in those at highest risk of cardiovascular disease. As polygenic scores can contribute to identifying those at highest risk, they can be useful in identifying those who may benefit from treatment.

Are implementation-ready applications available?

Several research groups and companies have developed automated computational modules or algorithms that enable conversion of genetic data into a risk score (either standalone polygenic score or integrated risk score). These are mainly in the areas of cardiovascular disease and cancer. Some of these are being tested as part of clinical trials.

There are still challenges that need to be overcome prior to considering implementation including determining the level of evidence required in support of different applications. It is unlikely that **all** polygenic score applications will be useful, and we need to consider each case separately. Important considerations include:

◆ Where risk prediction and stratification are an established part of clinical practice e.g. the use of QRisk®, it will need to be shown that polygenic scores can add value to current clinical practice

◆ Where risk prediction and stratification are not an established part of clinical practice, the first question becomes whether risk prediction is useful in this context - e.g. how can it improve clinical practice and outcomes, and what is the best mechanism to achieve this

Polygenic scores do not provide information on the genetic cause of disease, although they can be used in some contexts to aid the process of achieving a diagnosis.

There are many proposed applications of polygenic score analysis that could be considered to be relevant to healthcare. Nevertheless, clear descriptions of products or test pipelines that can be implemented and the evidence supporting their use are still lacking.

References

1. Moorthie S, Babb de Villiers C, Brigden T, et al. Polygenic scores, risk and cardiovascular disease. PHG Foundation. 2019

2. Yang X, Kar S, Antoniou AC et al. Polygenic scores in cancer. Nat Rev Cancer (2023). https://doi.org/10.1038/s41568-023-00599-x

3. Tandirerung FJ. The Clinical Importance of Differentiating Monogenic Familial Hypercholesterolemia from Polygenic Hypercholesterolemia. Curr Cardiol Rep. 2022

4. Yanes T, Young MA, Meiser B, et al. Clinical applications of polygenic breast cancer risk: a critical review and perspectives of an emerging field. Breast Cancer Res. 2020. 22(1): p. 21

5. Allardyce J, Leonenko G, Hamshere M, et al. Association Between Schizophrenia-Related Polygenic Liability and the Occurrence and Level of Mood-Incongruent Psychotic Symptoms in Bipolar Disorder. JAMA Psychiatry. 2018 75(1): pp. 28-35

6. Johnson D, Wilke MAP, Lyle SM, et al. A Systematic Review and Analysis of the Use of Polygenic Scores in Pharmacogenomics. Clin Pharmacol Ther. 2022. 111(4): pp. 919-930

For more quick guides to polygenic scores and their implementation, go to phgfoundation.org

Author: **Dr Sowmiya Moorthie** Published: **October 2023**

UNIVERSITY OF CAMBRIDGE