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The path to using polygenic scores in healthcare

Summary

- Automated computational algorithms allow genetic data to be converted into a polygenic score. This score may be interpreted by itself or with other risk factors to provide an integrated risk score
- Risk scores that include polygenic score information are not widely used in healthcare. Challenges to implementation fall into three broad areas: imprecise decriptions around what they are and what they can do; lack of evidence for the predictive value of polygenic information; concerns they may exacerbate health inequalities
- Ensuring "polygenic score tests" are safe, effective and equitably implemented requires an iterative, multidisciplinary process centred around specific healthcare pathways

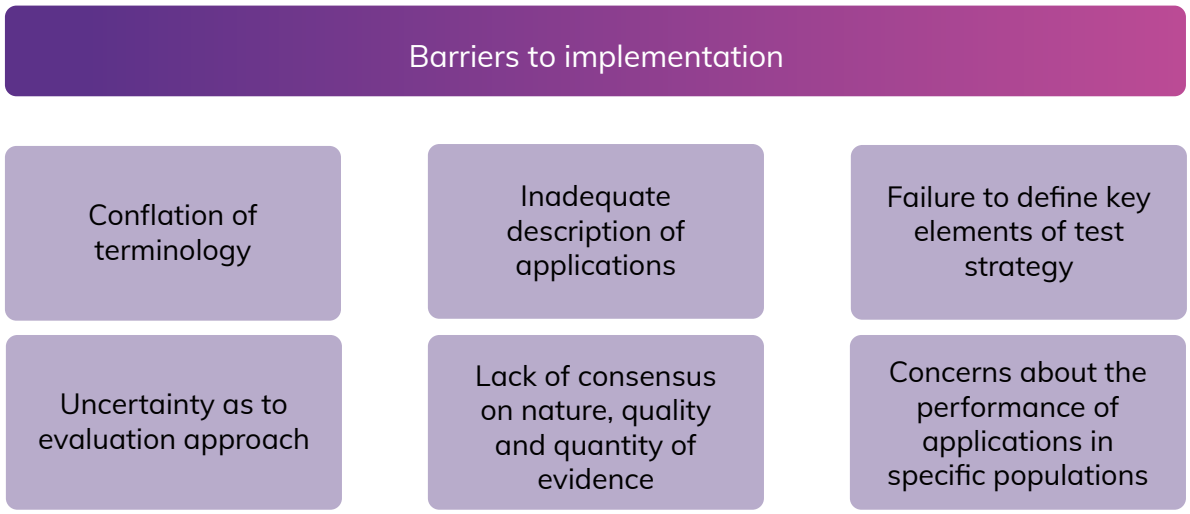
Considerable progress has been made in the discovery of common single nucleotide variants and developing mechanisms for genomic profiling. There is aspiration to use this knowledge as part of clinical and public health practice. While products allowing the conversion of genomic data into genome-based risk scores are available, they are not widely used. In this briefing we outline some issues and how addressing them might help move the products towards appropriate implementation in healthcare.

Standardising terminology

The term polygenic score is often used to describe:

- the result produced by a polygenic score model
- the underlying model that generates this score
- the test pipeline employed in the analysis

This conflation of terminology for polygenic scores often leads to confusion in discussions related to validity and utility of specific polygenic score applications. It also contributes to the challenges of evidence generation, evaluation and appraisal of these applications.



Our examination of the field of polygenic score research and discussions around clinical utility found that polygenic scores tend to be discussed as if they are a single entity equally applicable to all clinical scenarios.

However, polygenic scores have varied uses across diseases and health care pathways. Polygenic score models can be developed for different diseases and can be interpreted by themselves or incorporated into multifactorial risk prediction. Information from polygenic scores or multifactorial risk prediction can also be applied at different points in a healthcare pathway. Furthermore, as described in other briefings, products that calculate or incorporate a polygenic score can be configured in different ways.

Given this diversity, improving terminology and being specific when describing a polygenic score application - including where and how best to use the information it provides - is critical.

Context-specific evaluation

As with any other biomarker or test, defining the intended purpose, role and population is essential in evaluation.[1] This means being specific about the disease, the population the test will apply to, and how it is to be used as part of a specific pathway. Such contextualisation is important in developing the evidence base for demonstrating clinical validity and utility. This is because characteristics of the population and thus the prevalence of disease and case mix varies in different contexts. These factors impact on test performance characteristics. Contextualisation is also important to understanding the benefits and harms of a new test by enabling comparison with current practice.

Clarity as to the specific application of a score will also help in understanding how best to deliver it in a test pathway. This includes developing workflows, infrastructure and resources to support its use, such as training for healthcare professionals and public and patient communication material.

Example of the different evaluation contexts

- **Condition:** Breast cancer
- **Population:** Women aged 50-70 years
- **Purpose:** Identifying women eligible for screening test

- **Condition:** Breast cancer
- **Population:** Women with a family history of breast cancer
- **Purpose:** Providing information on risk to decide subsequent interventions e.g. mastectomy or frequency of screening

Clarity on all the elements of test pipeline

Products that calculate or incorporate a polygenic score require bringing together molecular testing, prediction algorithms and potentially digital tools. The evaluation of all of these components is complex. This has created challenges for developers and decision makers in determining the studies that need to be undertaken to generate the necessary level of evidence.

Medical test evaluation principles can be applied to polygenic scores and applications that incorporate this information.[2] However, much of the effort in this field has been in evaluating the performance of polygenic score models. Evaluation is now needed for tests or test pipelines developed from such models as well as research into how they might function as part of specific care pathways.

Establishing evidence requirements for decision making

Confusion around terminology, context of use and elements of a test pipeline all contribute to a lack of consensus on whether current evidence is sufficient to support the implementation of specific polygenic score applications. The type of evidence and amount necessary is likely to vary for the different uses of polygenic scores. Furthermore, among stakeholders - researchers, developers, health system decision-makers and users - there is a lack of agreement as to where current gaps in evidence lie, which ones are critical, and how they can be addressed.

There are two areas in which evidence for evaluation and decision making is lacking:

1. Evidence in relation to each of the components of a test
2. Evidence in relation to how the test performs in a given healthcare pathway

Establishing evidence requirements across both these areas is necessary for the successful clinical implementation and wider uptake and use of any PGS-based applications.

A better understanding of impact on health inequalities

As with other areas of human genomics, there are concerns that inherent biases in genomic datasets that are used to create polygenic score models can increase health inequalities.[3] However, the impact on health inequalities in real world settings is yet to be assessed and other factors may either enhance or mitigate against biases in genomic datasets. These include the design and development of related technologies such as genotyping and digital tools; processes and populations used in validation of tests; and the way in which products are implemented and used.

A better understanding of polygenic score products combined with a healthcare pathway perspective is needed for clearer assessment of their potential to exacerbate or contribute to health inequalities. In addition, this contextualisation is needed to identify mechanisms to mitigate against any inequalities that may potentially arise, many of which may be in relation to wider systems and processes that are beyond a particular test or product.[4]

Conclusion

Polygenic scores are likely to be useful under certain circumstances. Decision-makers (public, patients, clinicians, policy makers) need a better understanding of these circumstances, the existing evidence and the gaps that need to be considered. Addressing the issues outlined can help ensure tests are safe, effective, and successfully and equitably implemented.

References

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