Review

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Personalized Medicine

How can we address the uncertainties regarding the potential clinical utility of polygenic score-based tests?

Sowmiya Moorthie*[1,2], Alison Hall[1], Chantal Babb de Villiers[1], Joanna Janus[1], Tanya Brigden[1], Laura Blackburn[1] & Mark Kroese[1]

[1]PHG Foundation, University of Cambridge, 2 Worts Causeway, Cambridge, CB1 8RN, UK

[2]Cambridge Public Health, University of Cambridge School of Clinical Medicine, Forvie Site, Cambridge Biomedical Campus, Cambridge, CB2 0SR, UK

*Author for correspondence: sowmiya.moorthie@phgfoundation.org

As common low penetrance variants associated with diseases are uncovered, attempts continue to be made to harness this knowledge for improving healthcare. Polygenic scores have been developed as the mechanism by which knowledge of common variants can be used to investigate genetic contributions to disease risk. They serve as a biomarker to provide an estimate of the genetic liability for a particular disease. Discussion continues as to whether polygenic scores are a useful biomarker and their readiness for incorporation into clinical and public health practice. In this paper, we investigate the key challenges that need to be addressed, in the description and assessment of the clinical utility of polygenic score-based tests for use in clinical and public health practice.

Plain language summary: The risk of developing many common diseases, such as heart disease is influenced by both genetic and lifestyle factors. Polygenic scores (PGS) are one way of assessing an individual's risk of developing certain diseases. There is still uncertainty as to whether and how to use PGS for individual care. Much of this is because it is unclear as to whether tests that give a PGS can provide useful information for the care of individuals and patients as part of prevention or healthcare pathways. In this paper, we describe some of the challenges that need to be addressed, so that we can move forward and better understand when and how to use these tests for population and individual benefit.

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Polygenic scores (PGS), also referred to as polygenic risk scores or genetic risk scores, are a means by which the impact of multiple low-impact genetic variants can be investigated. In healthcare, they can serve as a biomarker to provide an estimate of the genetic liability (risk) for a particular disease by capturing the aggregated impact of multiple genetic variants associated with particular diseases or traits. Many published studies discuss how this form of genomic analysis could potentially inform clinical and public health management of common diseases [1–3]. These have fueled debate on the use of such analyses and the evidence that is required for implementation within clinical and public health practice. Specifically, evidence of utility or usefulness in terms of 'clinical utility' and 'personal utility', along with differing views of the evidence base in relation to these terms, are a key feature of these discussions. We undertook an analysis of the hypothetical implementation of PGS analysis as a novel biomarker test within the UK NHS [4–6]. This process allowed us to examine the specific issues regarding their use from healthcare evaluation, regulatory and implementation perspectives. These analyses were informed by reviewing academic publications and grey literature, as well as conducting semi-structured interviews with experts in the field of PGS research. In addition, these investigations also led us to identify several challenges that need to be considered and addressed to identify the clinical utility and support the implementation of applications based on PGS analysis.

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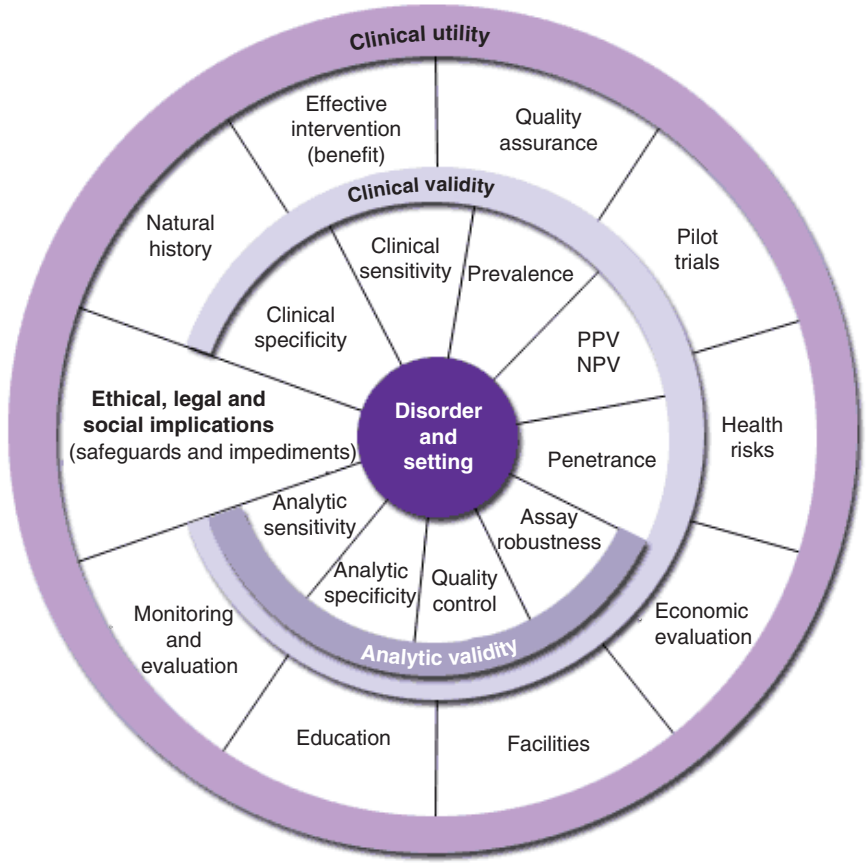

Figure 1. Analytical validity, clinical validity, clinical utility and ethical, legal and social implications model system for collecting, analyzing and disseminating information on genetic tests.
PPV: Positive predictive value; NPV: Negative predictive value.
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In this paper, we describe these challenges and how they impact on considerations of the clinical utility and the implementation of healthcare tests incorporating PGS analysis.

The multidimensional nature of clinical utility

Decision makers, whether they are test users or policy makers, will often want to determine if a test is useful, or in other words has utility [7]. This is often a value judgement based on consideration of different parameters. Within the sphere of healthcare test evaluation, demonstration that test use leads to improvements in health is often referred to as clinical utility [8]. However, the concept of clinical utility can be viewed from different perspectives and encompass different outcomes upon which differing emphasis is placed [7–9]. This means that ultimately, clinical utility is a subjective decision based on the cumulative assessment from a particular perspective of a range of defined variables. This is captured in the analytical validity, clinical validity, clinical utility and ethical, legal and social implications (ACCE) framework for genetic test evaluation, which includes a range of outcomes that can be deliberated when considering clinical utility (Figure 1).

Clinical utility is necessarily a multidimensional concept, because improvements in health through test use can be achieved by a variety of means. This includes direct impacts on patient outcomes, for example, by facilitating a diagnosis or treatment, or through indirect means, such as by improving clinical decision making, reducing costs or enabling efficiencies within the health system. Furthermore, a range of patient outcomes can also be considered, from those limited to direct clinical end points such as mortality and morbidity to those encompassing concepts of net benefit that include emotional and psychological effects [9,11,12]. The latter are frequently attributed to the concept of personal utility, a term that has emerged more recently and is widely used in relation to genetic tests [13,14]. It is often used to denote the value of the information from an individual perspective and considers

outcomes that may be important to the person being tested. The concept of personal utility is sometimes discussed separately to that of clinical utility. However, these are interlinked concepts, not least because decisions on uptake of testing are personal. Additionally, the majority of tests do not have a direct impact on patient outcomes [8,15]. Thus, consideration of the indirect impacts of test use enables a more comprehensive consideration of the worth of a test, although these may sometimes be regarded as more contentious.

Discussions pertaining to definitions of clinical utility are not novel, nor have they been resolved, much of this due to its multidimensional nature [7,12,16]. This was reflected in our analysis of the literature on PGS, alongside interviews with experts in the field. Our intention was to get a deeper understanding of areas of agreement and disagreement with respect to the concept of clinical utility and PGS analysis. This exercise reiterated that the aspects of clinical utility that were being considered varied among commentators. Nevertheless, there was general agreement that clinical utility involves making a positive change to clinical pathways, and that some level of evidence will be needed to demonstrate this impact. However, there were disagreements over both the level of change required, and the amount of evidence required to show this change. In addition, we identified specific areas which were contributing to the differing descriptions of clinical utility for PGS use. These included, that the discussions regarding the clinical utility of PGS often addressed the field as a whole rather than a specific clinical application. This meant that, ongoing discussions on the ability of genomics to contribute to prediction, together with scientific debate on the methods used in constructing PGS models and the validity of the models all influenced different perspectives on the clinical utility of PGS use. There are examples in the literature where clinical utility is discussed in the context of specific applications or use cases [1,3,17]. While these are useful in informing discussions, they do not by themselves provide a definitive answer to the questions of clinical utility. In addition, discussions still need to move toward more clearly describing the context and purpose of PGS applications.

Linking disorder, setting & intended purpose

PGS are normally distributed in a population and are associated with a range of probabilistic risks, similar to other biomarkers such as cholesterol and blood pressure. Risk is not strongly linked with the presence of particular variants and can be modulated by environmental influences [2]. This differentiates genomic information in the form of PGS from rare high penetrance pathogenic variants, which have a greater influence on risk. Consequently, the way in which PGS information is likely to be used will differ substantially for different conditions, depending on the underlying genetic architecture of the disease as well as the degree to which this information can aid clinical and public health practice [1,2]. This means that determining whether PGS analysis will be useful, or have added value, requires an understanding of how they can inform specific clinical and public health pathways. The importance of linking a potential test with the context of use is embedded in evaluation frameworks used for decision making in healthcare settings [18–20]. This is because context of use influences thresholds that are deemed acceptable for test performance as well as the outcomes that can be considered necessary for clinical utility. Thus linking disorder, setting and intended purpose of a test at the outset are important in informing decisions on clinical utility [18].

There are many disorders and settings for which PGS analyses are proposed, including aiding diagnosis, informing selection of therapeutic interventions, improvement of risk prediction, informing disease screening and on a personal level, informing life and lifestyle planning [21]. However, there has been little detailed consideration of the impact of PGS information on clinical and/or public health pathways. Studies have demonstrated that the use of PGS can lead to improvements in risk stratification for diseases such as cancer and cardiovascular disease [22,23]. These studies often do not clearly describe the test on offer, the patient population and the impact on existing care pathway.

Test evaluation frameworks are an important component of health technology assessment and evidence based decision making [24]. The use of these frameworks enables systematic evidence appraisal, which can then inform decision-making with regards to test implementation. The complexity of testing technologies, together with considerations around opportunity cost and financial pressures on healthcare funders, have led to the development of many frameworks to assess the evidence base of particular tests, including specific frameworks for evaluation of genetic tests [25,26]. While there are a range of frameworks that can be utilized, the parameters they appraise are broadly the same and include analytical validity, clinical validity and clinical utility [27]. Given the multidimensional nature of clinical utility, evidence frameworks have been developed that attempt to clarify this concept and outline evidence requirements. These frameworks can be applied to tests based on PGS analysis to enable an assessment of their clinical utility.

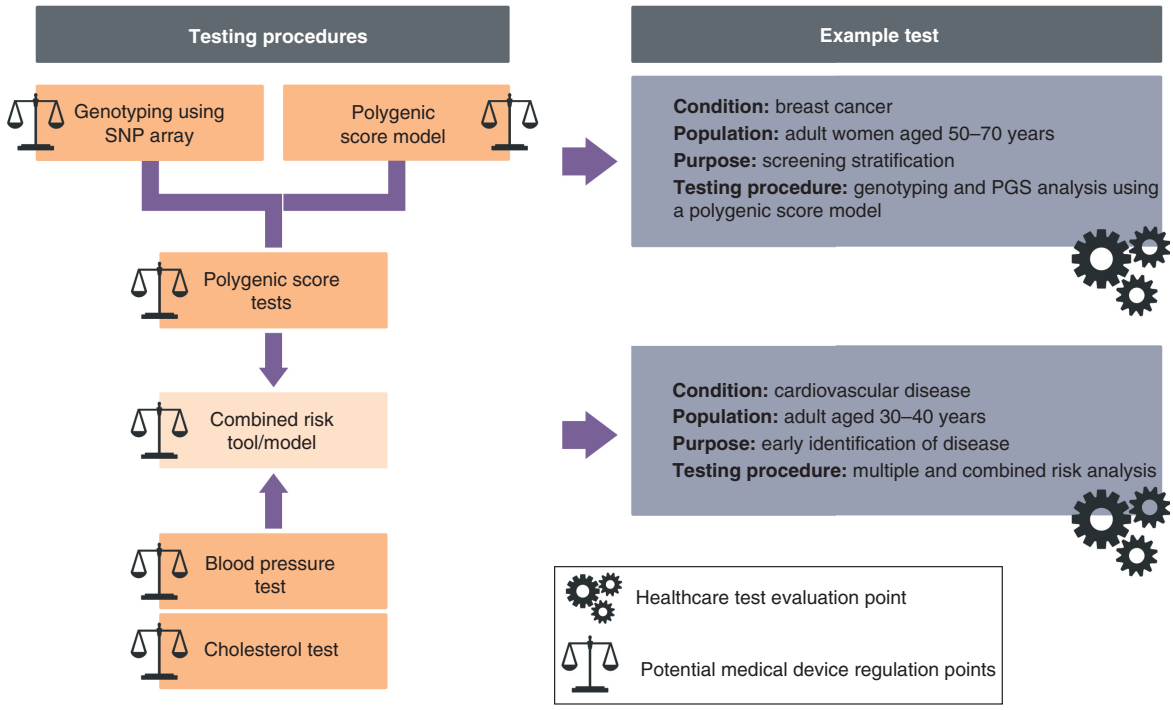

Figure 2. Conceptualising polygenic score tests. This is a simplified illustration of the elements that can contribute to testing procedures and potential tests that may arise from them. Analogous to the different technologies available for genotyping, cholesterol or blood pressure monitoring, there can be diversity in available genetic or combined risk models. These different elements can be combined to provide a range of potential tests serving different purposes. SNP: Single nucleotide polymorphism; PGS: Polygenic Score.

Understanding the nature of the test

There has been much discussion in the literature about the uses of PGS and descriptions of models developed to enable such analysis. However, there has been relatively little discussion around the nature of the test that will be offered and its intended objectives. Healthcare evaluation requires a precise definition of a test which includes the testing procedure, the health condition it is for, the defined population and the specific clinical purpose [28]. The importance of defining tests in such a way has previously been discussed in relation to genetic tests and is particularly helpful when considering testing procedures that can be used for multiple purposes [15,28]. Here distinctions are made between the assay and the test. The term 'assay' is used to denote the method used to analyse a substance, whereas the term 'test' is used to describe the specific use case of the assay. Taking forward this concept and applying it to PGS analysis illustrates that different elements can contribute to the testing procedure and that they can come together to form different tests (Figure 2).

PGS are usually calculated as a weighted sum of a number of risk alleles carried by an individual. The selection and weighting of variants to be included in calculating a PGS is carried out using different statistical methods [29]. We refer to these as PGS models and many have been developed for the calculation of PGS for different diseases [30]. Obtaining a PGS for an individual is reliant; therefore, on standardized processes for obtaining genotype data followed by the application of a PGS model to that data to obtain a score. These scores can then be interpreted by themselves to determine risk of disease. Therefore, PGS models can form the basis of different tests, depending on the population, specific disease and purpose of testing.

For most common health conditions PGS by themselves have limited predictive capabilities but can contribute to disease prediction when considered in combination with other risk factors [1,2]. Analogous to biomarkers such as cholesterol or blood pressure, they may be integrated into a combined risk tool, which collates information on multiple risk factors.

Combined risk tools such as QRISK® [31] or CanRisk [32] bring together information on a range of biomarkers to provide a combined risk estimate for cardiovascular disease and breast and ovarian cancer, respectively. Discrete tests such as cholesterol testing need to be conducted to gather relevant data for a tool such as QRISK. This data

are then analysed collectively. Depending on whether PGS are intended to be used by themselves or as part of a combined risk model, the testing procedure to be evaluated will be either a discrete test or part of a risk tool.

Our review of the field identified that research progress for PGS-based applications across different disease areas is at various stages with respect to the development of a test, whether it is a discrete test or part of a risk tool. The focus of current research efforts has been on development of PGS models or combined risk models and examination of their predictive ability for a particular trait. While model development is a prerequisite for test development, our analysis indicates that the progress being made in this area is often conflated with availability of a validated test. While these are not mutually exclusive processes, evaluation of particular modeling approaches should not be conflated with evaluation of a test.

Achieving appropriate regulatory oversight

Regulatory oversight ensures that tests are safe and effective. While regulation does not make a judgment about clinical utility, it occurs in parallel with some aspects of test evaluation. Therefore, regulatory aspects feed into considerations of clinical utility and implementation from a health service perspective [19]. Regulatory oversight may take account of a number of different elements including the test technology, the assay or procedure that is adopted, the target population and application (the test), the setting in which the test is run, or the expertise of the user offering or administering the test. Depending on the context for offering the test, different elements may come under scrutiny. Different testing procedures (and intended uses) of PGS analysis may not only impact on how their utility is viewed but could also be subject to different types and extents of regulation.

As described above, the use of PGS as a biomarker requires development in many different areas, depending on their intended use. This includes the creation of a model to calculate a PGS, and/or a model that enables combined risk estimation, incorporation within an existing risk tool or development of a novel risk tool and subsequent use for a specific purpose and population. Under current EU medical device regulation, depending on how they are used, the target population and the pathways involved, each of these steps could be viewed as generating a discrete medical device, itself subject to independent regulatory oversight. Alternatively, these components could be regarded as a single device with multiple components which must work interoperably (Figure 2).

As a result of the UK's departure from the EU, in the short term the UK is continuing to rely on EU Directive 93/42/EEC [33] and relating directives relevant to active implantable medical devices and *in vitro* medical devices. However, the UK has signaled its intention to revise its medical devices regulatory landscape through the Medicines and Medical Devices Act [34]. The dynamic nature of the regulatory landscape and the interpretative flexibility about what constitutes a medical device for regulatory purposes makes achieving effective regulatory oversight particularly challenging. One difficulty is identifying the nature, quality and quantity of evidence necessary to ensure sufficient safety and effectiveness for market authorization. Furthermore, how such tests are integrated and delivered as part of healthcare pathways will impact on additional regulatory oversight that is needed.

Effective and appropriate regulation is vital to demonstrate that medical devices, including PGS models and tools, are safe and effective, that they work as intended, with the appropriate degree of specificity and sensitivity, and that they support decisions that are evidence based and fair. These are all important elements in the overall judgement of the clinical utility of a particular test. Only then will they be trusted by their users (health professionals and lay users). The lack of clarity over the aspects required to enable appropriate PGS analysis, testing and implementation is a continuing barrier to their effective regulation. This in turn can impact on evidence required for decision making on clinical utility and implementation.

Conclusion

PGS analysis holds promise for use within healthcare. However, realizing that promise requires additional evidence to be generated and evaluated. This supporting evidence extends beyond demonstrating the performance characteristics of a PGS model to consideration of the test, its intended purpose and context of use. Only then can the impact of the test on healthcare pathways be fully examined and understood. This approach will also help build greater consensus about the scope, quality and nature of the required evidence prior to implementation.

We have shown that PGS analysis can be viewed as a single test system or as part of a broader risk tool. Furthermore, these test systems can be utilized within or inform different scenarios or clinical questions (Figure 2). Each of these use cases need to be appropriately evaluated to reach conclusions about their utility. The evidence gathering process can be helped by viewing PGS analysis as a technology which can give rise to multiple tests. This also has implications for market approval as well as healthcare evaluation (Figure 2).

For assays and tests to be used as intended, and placed on the market, they must comply with regulatory frameworks. As with healthcare evaluation, it is important to understand the product and its intended purpose for it to be appropriately regulated. However currently, it is unclear how PGS models and tools might best be regulated and what regulatory requirements each needs to fulfil prior to implementation. Furthermore, it is important to note that while there are overlaps in the evidence requirements for both healthcare evaluation and medical device regulation, market authorization does not include a full assessment of clinical utility.

Gathering sufficient evidence or data with respect to the impact of a new test on clinical outcomes and clinical decision making can be an arduous process and is often a neglected aspect of test development [8,16]. Contributing to this is the fact that test utility can encompass a range of outcomes and thus be thought of in narrow or broad terms (Figure 1). This means that the scope and type of evidence required will vary for different tests and settings. Analysis of the impact of information from PGS on specific pathways enables consideration of impact on patient outcomes and other factors under the umbrella of clinical utility. These include impact on clinical decision making, workflow and ethical, legal and social implications. Given that personal utility and clinical utility are part of a spectrum, making a distinction between these is unhelpful and can hinder progress.

Current research focuses largely on demonstrating the predictive ability and validation of different PGS models. The plethora of PGS models in development has driven the creation of the PGS Catalog [30]. The PGS Catalog provides comprehensive information on published models, performance metrics and the extent of their validation in different cohorts. This together with the development of reporting standards for PGS models [35], enables better assessment of available models. Such efforts are important in indicating areas of potential utility and identifying models that can be taken forward for implementation. Linking the use cases of PGS models and their performance characteristics will be required, as judgement on the acceptability of test performance characteristics will be influenced by the use case. Furthermore, differing sets of benefits and harms may be associated with different use cases. Thus, as well as validating the variants that are incorporated within the score, and evaluating performance of models, more research is needed into how such models, and tools developed to enable use of these models, might fit with existing infrastructure and personnel. As with other risk prediction models, the availability of a model is not sufficient reason for its implementation.

Much of the current debate over whether the use of PGS can provide clinical utility can be resolved if: the intended use of each PGS-based test is explicitly defined; the requirements for utility are clearly laid out; and evidence for their ability to impact clinical pathways and outcomes demonstrated. From a healthcare evaluation perspective, this requires an accurate description of what constitutes a PGS-based test, in order to examine its implications on healthcare pathways and in turn to undertake the studies to provide the evidence for its impact. It is only through such an approach that there can be a common understanding of the proposed clinical utility of such tests.

Future perspective

The development of PGS-based tests is ongoing, with certain applications holding promise for use within healthcare. Studies are beginning to assess issues related to implementation and use as part of healthcare pathways. It is likely that PGS will be combined with other risk factor information and incorporated within existing risk prediction models in the near future. The use of PGS in isolation to influence prevention efforts has been proposed as a possibility, but the evidence for and possible applications of such an approach remain to be developed.

Executive summary

- The information obtained from polygenic score analysis can be used to inform different healthcare scenarios.
- We need to understand the 'polygenic score test' on offer and its intended purpose to make a judgement on clinical utility.
- This includes a clear understanding of what this information means, the context of its use and how this fits with regulatory requirements.
- We do not yet have a full picture of utility in relation to polygenic score analysis.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

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