Considerable progress has been made in uncovering common single nucleotide variants and developing mechanisms for genomic profiling. Using this knowledge routinely as part of clinical and public health practice is an ongoing aspiration. While products that enable conversion of genomic data into genome-based risk scores such as polygenic scores (PGS) are available, they are not widely used. Key barriers are uncertainty and a lack of evidence regarding the value of polygenic score information and how to approach evidence gathering and appraisal.

In this report, we discuss and present our analysis of the application of the principles of medical test evaluation to PGS based products. Medical test evaluation frameworks such as the ACCE framework can be used in evidence assessment and contribute to more informed and transparent decision making. Central to this process is consideration of context of use and application of an iterative process to examine evidence across domains of scientific, analytical, and clinical validity and utility. Evaluation of any PGS application will require evidence for and consideration of these different domains.

We demonstrate how specific factors drive these uncertainties about products that provide or incorporate a PGS. These include:

- Conflation of terminology relating to polygenic scores, models and algorithms.
- Inadequate description of specific applications, in relation to intended population, role and purpose as part of specific healthcare pathways.
- Failure to define and evaluate all the key elements of PGS applications.
- Lack of real-world evidence (RWE) for PGS applications.

Failure to adequately address these factors lead to a challenge for decision makers because, the existing evidence base (a) fails to show what information polygenic scores are providing (b) does not define with adequate precision how the product is to be used in health care or its intended purpose or objective or (c) how such use can be beneficial to the individual patient or to the health system as a whole. The consequence is that we are left with a body of evidence that is inadequate for the determination of the clinical validity or utility of a product in relation to its intended purpose. We have shown that it is possible to resolve these issues and address the needs of decision-makers through a more systematic approach to evidence generation.

Chapters 2-4 provide background information that may be useful and informative for those in different fields. This is to enable readers to develop a shared understanding of relevant topics. In the latter half of the report (Chapters 5-7) we present the results of our analysis which begins by providing clarity to the disparate uses of the term ‘polygenic score’ and examines how polygenic scores can be conceptualised as a biomarker. We also describe processes that either calculate a PGS or an integrated
score including PGS and how they can be considered a test. We then demonstrate how existing evaluation frameworks can be applied to such products.

Polygenic scores are one way of assessing an individual’s genetic risk to developing certain outcomes, including diseases. They are a proxy biomarker, calculated on the basis of an individual’s genotype. Polygenic scores differ from traditional germline genetic markers in a variety of ways. Importantly, calculation of a score requires the use of algorithms which are developed from polygenic score models. Different models and algorithms must be created to predict different diseases and traits. In addition, different approaches may be taken to develop them, suited to each disease and or population of interest. This means that there is a variety of models and algorithms used to calculate a score. There are also differences in the way this information can be used and contribute to clinical practice. It is likely that in some contexts PGS will provide valuable clinical information and it is important to identify where this may be the case.

Currently there is ambiguity regarding how to apply regulations and carry out evaluation in support of products that provide a PGS. This is because there are different components that form the test pathway, namely, molecular testing to obtain genetic data; other clinical data; prediction algorithm(s) for analysis of this data; and digital tool(s) to enable data collation and feedback. This creates uncertainty in the nature, quality and quantity of evidence required for decision making across these components and in relation to a specific test strategy.

We have shown that existing frameworks can be applied to a specific product and application but require consideration of all the component parts. We propose considering these components as part of a test pipeline to allow the application of concepts and techniques from molecular test evaluation, prediction modelling and digital technology evaluation to each separate component of the pipeline. We demonstrate how analytical, scientific and clinical validity parameters can be assessed and some of the issues in determining these. Examination of these parameters across a PGS analysis pipeline can provide evidence of the performance of a PGS-based test. These can then inform the assessment on whether they meet the test’s intended role and purpose.

As stated in our previous reports, clarity regarding the proposed PGS application for implementation helps to determine the evidence requirements, as well as the assessment of wider factors that may impact on its use and uptake. In this report we outline how better definition and descriptions of products can help achieve this and where issues in evidence generation currently lie.

Going forward, it will be important to achieve consensus amongst researchers, developers, health system decision makers and users as to which of the gaps which we
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have identified are critical and how they can be addressed. Progress on establishing both the evidence required for the different components of the PGS test pipeline as well as the acceptable levels of evidence will be necessary for the successful clinical implementation and wider uptake and use of any PGS-based applications.

In conclusion, polygenic scores are likely to be useful under certain circumstances. Identifying these and creating optimal systems for their use requires a more focussed approach to evidence generation and appraisal which is currently lacking.