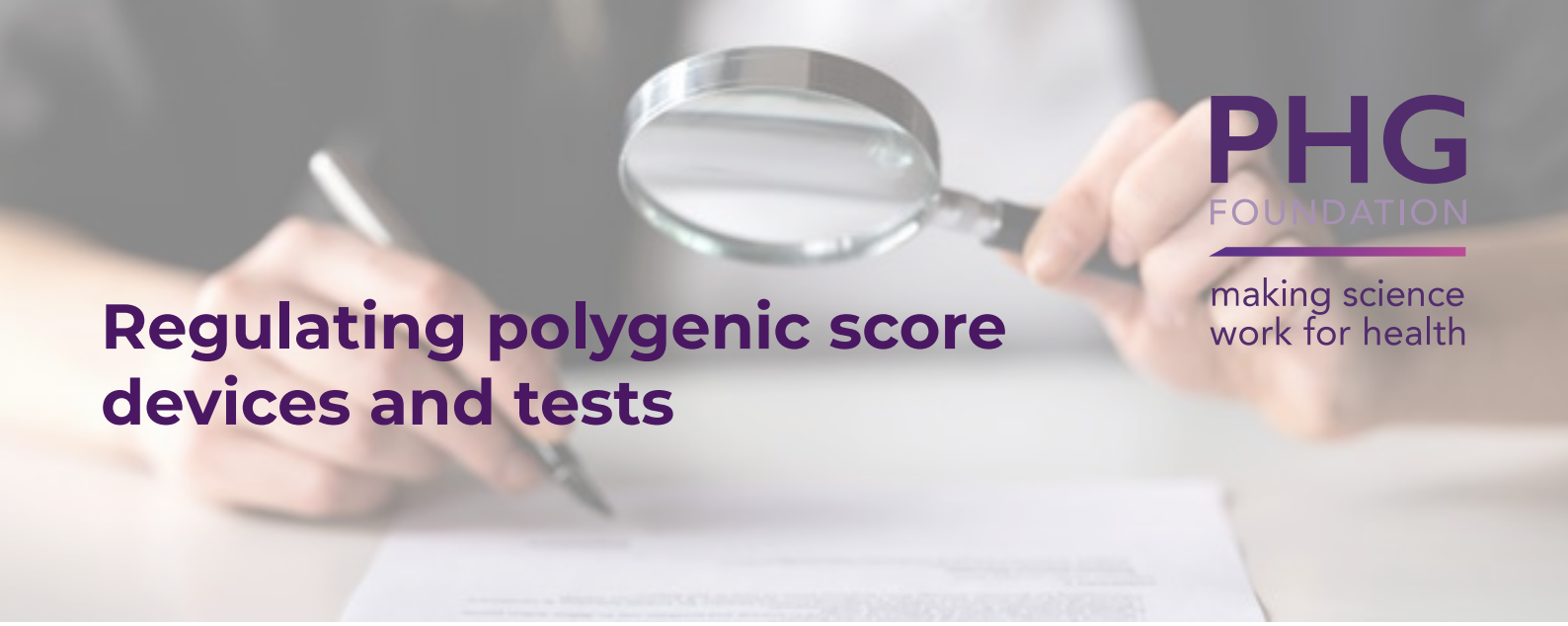

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Regulating polygenic score devices and tests

Summary

- Pipelines to calculate or utilise polygenic score information can be configured in different ways, each having different regulatory implications
- Complexity is added by the status of algorithms or software within these pipelines, whether users are medical practitioners or non-professionals, and the intended use stated by the manufacturer
- This results in ambiguity as to how medical device regulation should be applied to software that provide a polygenic score
- Developing guidance and recommendations which both developers and those scrutinising new devices can follow may aid the regulatory process

A polygenic score provides a single measure of the cumulative effect of multiple individually low-impact genetic changes. Pipelines to calculate or utilise polygenic score information can be configured in different ways, each having different regulatory implications. Assays and tests may be subject to different types of regulation and degrees of scrutiny depending on, for example: the technical features of the test, the purpose of its intended use, the circumstances in which it is used and who is administering it.

Regulations can apply to the test or to the assay itself, the environment in which the test is developed, as well as the competency of the professional offering or administering the test. The European Union's and United Kingdom's medical device regulations are the key regulations governing the development and deployment of assays and tests. This briefing discusses the challenges in the regulation of products that provide or incorporate a polygenic score.

What is medical device regulation?

When a product is placed on the market in the EU, it must have CE marking. This indicates that it has met appropriate standards of safety, performance and quality assurance, and is fit for its intended purpose. Due to United Kingdom's departure from the European Union, the UK regulatory system has been re-evaluated and a UK-specific Conformity Assessed mark system (UKCA marking) has been introduced.

Across the EU's and UK's respective regulations, the principal criterion by which a product may qualify as a medical device is that it is intended for medical purposes. This is a rather broad definition, and most tests carried out within health systems will qualify either as a medical device or an *in vitro* diagnostic (IVD) device.

A medical device is an item (including software) which is intended by the manufacturer to be used for a medical purpose. It includes a wide range of products from plasters to X-ray machines, and includes healthcare assays and tests.

Medical devices that are intended to be used for the analysis of biological samples (blood, urine, tissue etc.) are classified as *in vitro* diagnostic medical devices (IVDs).

The classification of a device as an IVD device is further dependent on the extent to which it is 'driven' by data obtained *in vitro* by the examination of samples like blood, taken from the body.

Clinical evaluation as part of regulatory frameworks

A clinical evaluation report is typically produced as part of the evidence appraisal required for regulatory approval of a medical device. The clinical evaluation of medical devices includes assessing evidence of:

- **Scientific validity** – the association of an analyte (the substance measured by the device) with a clinical condition or physiological state
- **Analytical performance** – the ability of a medical device to correctly detect and measure a particular analyte
- **Clinical performance** – the ability of the medical device to yield results relevant to its intended use, when used by the intended user, in the target population

The evidence that is gathered for regulatory approval of a medical device is similar to that required for the evaluation of a medical test, especially when the intended purpose and target population of a device are the same as that of a test. Overall, the regulations require:

- A target patient group and intended purpose to be clearly specified
- Scientific validity, analytical performance and clinical performance to be demonstrated for the specification
- Weighing the risks against potential benefits to the patient
- Surveillance to capture any unanticipated adverse events following use and uptake

Challenges exist for evidence generation in a regulatory context that are similar to those of test evaluation and many issues faced for polygenic score devices and tests are similar to other medical devices. Particular challenges arise in demonstrating clinical performance, due to the nature of polygenic score analysis as a device. Factors to be taken into account include the multiple components of polygenic score analysis, the status of algorithms or software within the device, the potential users, and the overarching intended use and purpose.

Challenges for regulation of polygenic score products

Application of medical device regulation to polygenic score analysis imports and compounds the challenges facing the regulation of its component parts. Software, for example, may be regulated as part of a device or as a separate device on its own. Regulatory approaches to algorithms and associated digital tools, especially those developed using machine learning are also evolving.

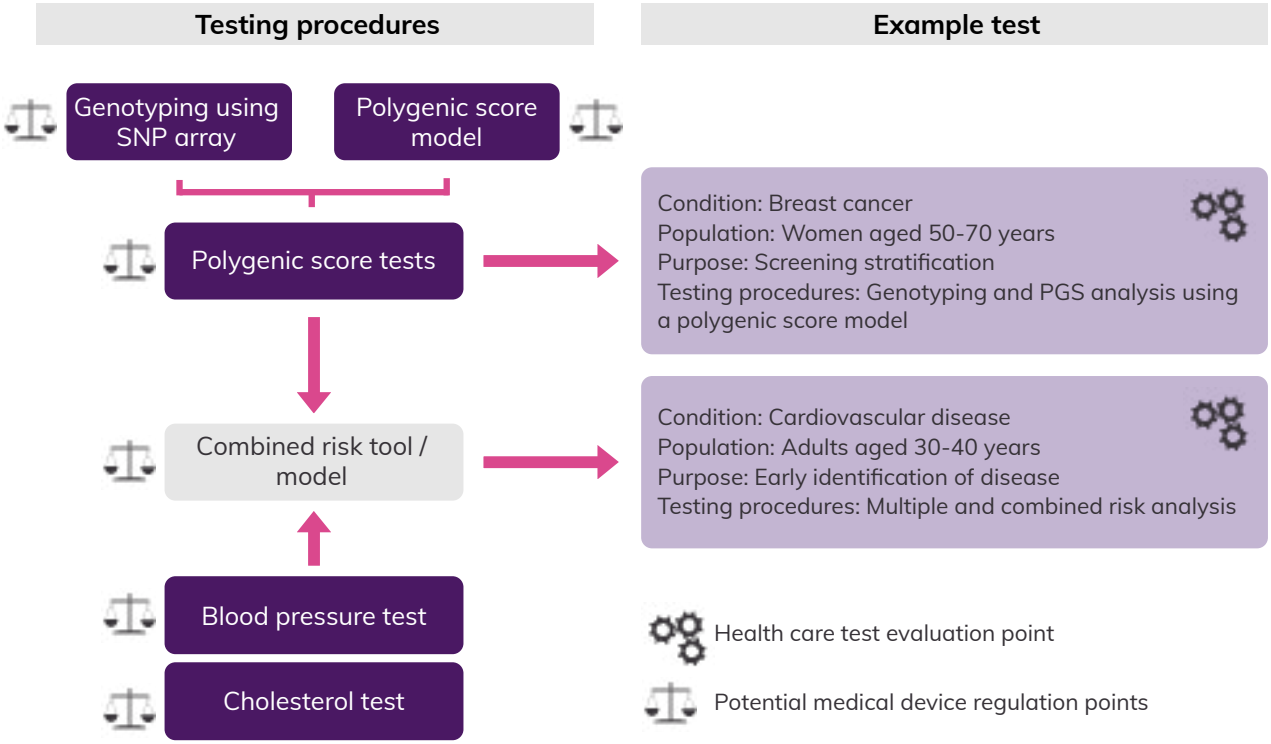
One device or multiple devices?

Under current EU and UK medical device regulations, depending on how they are used, the target population, and the healthcare pathways involved, each of the steps in polygenic score analysis pipelines could be viewed as generating a discrete medical device (or IVD), itself subject to independent regulatory oversight. Alternatively, these components could be regarded as a single device with multiple components which must be reliable and safe when operated together.

It is also unclear whether, or in what circumstances, polygenic score analysis software may qualify as an *in vitro* diagnostic device. The latest guidance from the MHRA suggests this may be the case if the software is 'substantially driven' by IVD results, unless those are the results of 'historical' investigations that are 'unrelated to the software'.[1]

What is not certain is how proximate to the analysis of a biological sample, or how heavily driven by that analysis, software and algorithms are required to be for them to qualify as IVD medical devices. This may affect the nature of evidence required to demonstrate the safety and efficacy of the device(s).

Potential regulatory points in the development and use of polygenic scores



How should these devices be classified?

There are four classes of medical devices, classified according to the risks arising from the intended purpose. Evidence requirements vary in relation to risk classification. Apps and software will generally fall into Class I or II and are regarded as low or medium risk. Under the EU rules, all IVD devices that are intended for 'human genetic testing' will automatically fall into a higher risk category. This means there is a likelihood that products providing a polygenic score may fall into a higher risk category. Determining the classification of a medical device or IVD is crucial for identifying the nature and level of evidence that will be sufficient to demonstrate safety and efficacy.

Addressing challenges in regulation

Expected reforms to medical device regulation in the UK, updating the framework and bringing it into line with international best practice, should enable a proportionate approach to regulating polygenic score devices in relation to their intended purpose.

The challenges lie in further specifying when and in what form evidence is required for these devices, and ensuring consistent interpretation of the rules by manufacturers, notified bodies and the regulator across the sector. This may be achieved through guidance and recommendations, which both developers and those scrutinising new devices can follow, rather than amendments to law and regulation.

References

1. MHRA Guidance: Medical device stand-alone software including apps (including IVDMDs) p20:

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

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