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Inquiry on Genomics and Genome Editing: response from PHG Foundation

The PHG Foundation is non-profit health policy think tank. We work to achieve the prompt, effective and responsible application of biomedical and digital technologies within health systems

- Genomics could improve disease prediction, prevention, diagnosis and treatment
- The full potential of genomics to improve health undoubtedly lies some way in the future, but actions now can ensure that UK citizens gain maximal short- and mid-term health benefits from genomics
- Making the most of infectious disease genomics offers clear and rapid health gains
- Ensuring that the 100,000 Genomes Project offers widespread clinical benefits requires evaluation of clinical impact, and attention to issues of NHS data sharing; health professional engagement and education; and funding for genomic testing

Introduction to the PHG Foundation and our response

An independent health policy think-tank, we aim to make science work for health. We have twenty years' experience in issues surrounding the responsible and effective use of genomics within health services. Given the broad scope of this Inquiry, we have addressed only those questions

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where we feel we can add the greatest value. Other recent [consultation responses](#), including our Nuffield Council on Bioethics inquiry on genome editing [submission](#), are freely available from our website along with related [reports](#) and [briefing notes](#). We are happy to comment in greater depth on request, or to provide oral evidence.

The impact of genomics on human health

The introduction of genomics to healthcare has had life-changing effects for some, predominantly selected rare disease patients, but genomic technology remains irrelevant for the health of much of the population. Actions are needed to maximise the impact of genomics for the (relatively) few in the short term, and to broaden its utility to many more in the future.

Diagnosing and managing rare disease

Typically genetic in origin, rare diseases present in most clinical specialties; accurate genomic diagnosis is often the first step towards understanding a patient's disease and improving clinical management. It also provides crucial information for counselling patient and family on risks and reproductive options, and may allow access to repurposed drug treatments or clinical trials.

Barriers to patient benefit

Access to genomic diagnostic testing for many rare disease patients remains poor because:

- Lack of awareness amongst clinicians means that patients often experience long delays and multiple investigations with associated costs, physical and psychosocial harms.
- Insufficient NHS funding for genomic testing and associated clinical services for all the patients for whom they are clinically indicated.

Actions required

These barriers must be dealt with irrespective of the outcomes of the [100,000 Genomes Project](#) in transforming NHS infrastructure and capabilities to deliver genomic medicine. Priority should be given to:

- Increased resource allocation by commissioners for genomic diagnostics
- Effective '[mainstreaming](#)' of knowledge on the availability and utility of genomics amongst front-line clinicians

Managing infectious disease

Our [major strategic review](#) of the role of genomics in infectious disease revealed enormous opportunities for implementation across UK healthcare and public health systems to transform how we manage

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infectious disease and deliver long-term population health benefits. Bacterial and viral genome sequencing is useful for surveillance, detection and investigation of disease outbreaks, and in some cases detection of antimicrobial resistance.

Barriers to patient benefit

The UK is a world leader in translational research in infectious disease genomics, but we have failed to capitalise on this advantage. Woeful underfunding and neglect by policy-makers has unnecessarily delayed by years the implementation of genomics services by Public Health England (PHE), although gastrointestinal surveillance now uses genomics and a TB diagnostic service will be rolled out this year.

Actions required

Modest investment and strategic direction in this area could yield both short and long term improvements in population health (preventing infectious disease in the community, tackling hospital acquired infections, managing AMR and detecting emerging threats) greater than anything likely to arise from any other application of genomics. Achieving global eminence necessitates political and health system leadership and coordination to drive development of a coherent strategy for implementing infectious disease genomics.

Precision medicine – targeting treatments

Precision medicine uses genomic testing to identify susceptibility or resistance to particular therapeutics, notably for cancer, where genetically targeted therapies are proliferating. Genomics can also guide the use of other drugs where there are known associations between common genomic variations and drug metabolism that may render standard dosages ineffective or cause adverse effects.

Barriers to patient benefit

Major barriers to patient benefit from precision medicine include:

- **Cost** – precision cancer therapeutics are extremely expensive, so significantly improved patient outcomes are needed to justify their cost. Genomic diagnostics have an important role to play in achieving this.
- **Access** – too often the genomic test result cannot be made available in time for clinician and patient to make a decision, or are unavailable altogether for cost reasons.
- **Lack of incentive to implement non-commercialisable genomic tests** – the NHS is generally resistant to implementing new tests that could improve patient care, but also introduce additional testing costs and changes in practice into well-established pathways.

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Actions required

In the short to medium-term, the NHS should focus on technologies that can provide point of care genomic tests to enable it to improve the quality and volume of care in a cost-effective manner. This must include supporting the re-engineering of the patient pathways in which they will be embedded and the changes in clinical practice required to deliver them.

Personalised prevention

Genomics contributes to common disease risk in individuals. Used in combination with other information (lifestyle, sociodemographic and environmental factors) genomic data could support personalised targeting of preventative interventions to those in whom they are most likely to be more effective than harmful.

An example is cancer screening, where research has shown inclusion of genomic data with other types of risk information improves the accuracy of [risk prediction for breast or prostate cancer](#). This could permit more accurately targeted screening to those at greatest risk example by including younger people at high risk (not currently screened) and excluding many others currently screened but actually at low risk, who are more likely to be harmed by over diagnosis than to have a true cancer detected.

Barriers to patient benefit

With the exception of cancer screening, there is however currently a lack of evidence for the clinical utility of genomic information as a tool in stratifying risk and subsequent patient access to preventive medicine.

Action required

NHS professionals and policy makers should engage with the idea of a future in which patients dominate the management of their own health, where access to genomic information will become routine, and the use of genomics in provision of personalised preventive interventions may well become a reality.

Are current regulatory frameworks fit for purpose in the genomic era?

Current frameworks

In recent years, EU law relating to clinical trials, data protection and medical devices has undergone radical reform. Within three years, new EU Regulations will be directly enforceable on Member States (including the UK) until Brexit takes effect. Although many proposed reforms have taken some account of genetic and genomic technologies, considerable challenges remain. Some are infrastructural: existing regulatory

frameworks are applied on the basis of whether the entity being regulated is a discrete 'product' or a 'process' with a clear set of endpoints. Moreover, the regulations tend to be application specific (whether a product or process is to be used for clinical care, research or for public health). In genomic medicine, the boundaries between these categories are sometimes difficult to draw, such that some areas of law (such as data protection) are hard to apply where an activity straddles these categories.

The EU In Vitro Diagnostic Devices Regulation

Other areas of law (such as the EU in vitro diagnostic devices Regulation currently being finalised by the EU Parliament) has incorporated genetic and genomic tests within its scope for the first time. The requirement for specific clinical evidence of utility for each test type as part of the licensing process under the EU In Vitro Diagnostic Devices Regulation may be onerous for some types of test, particularly for populations affected by rare diseases, which by definition may struggle to reach statistical significance. Ensuring a proportionate approach to other types of tests, such as platform technologies, may also become an obstacle if one platform can be used for multiple types of test with differing patient populations and outcomes. The requirement for evidence of clinical performance also creates a commensurate need for regulators who are clinically qualified and can understand what is being supplied by test manufacturers and developers. The absence of clinically trained regulators could therefore become a barrier to good governance.

Action required

For these scenarios, (and others involving regenerative medicine technologies for therapeutic applications using gene editing, many of which are already close to clinical application), an urgent challenge is the need to develop scalable approaches that do not pose a disproportionate regulatory burden, yet provide robust safeguards for patient safety and assurances of product effectiveness. An additional set of regulatory challenges are raised by germline gene editing, where the relative ease of using these technologies makes effective regulation challenging and there is a need for greater harmonisation and global approaches to be effective.

What would an ideal system look like?

The current regulatory framework regards genetic and genomic data as exceptional and imposes safeguards on processing these types of data. For medical and public applications, this 'exceptionalist' approach is scientifically inaccurate and inconsistent with the approach taken to other types of data which are equally predictive of future ill-health (data generated from routine medical and lifestyle tests; in the future, data from other 'omic' technologies).

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Furthermore, existing data protection regulation is predicated on data categories which are in many instances no longer meaningful or appropriate.

Important features of an ideal system include that:

- **The protections and safeguards imposed would be proportionate to the foreseeable harms** resulting from use of those data, including misuse or data breach
- **These should be context specific**, allowing a more nuanced regulatory approach. For example, the Global Alliance for Genomics and Health has promoted different tiers of data access depending on the application to which data will be put
- **The distinction between clinical and research uses is becoming increasingly challenging to apply in practice**
- **There should be increasing use of codes of conduct to drive proportionate, harmonised practice.** For example, the EU General Data Protection Regulation includes provision for increased harmonisation of Member States' policies by utilising codes of conduct (pursuant to Article 40). Pressing topics for development include effective anonymisation and pseudonymisation; what constitutes 'the public interest', data security and information provided to data subjects and the public.

The 100,000 Genomes Project

Data management

The informatics architecture of the 100,000 Genomes Project (100KGP) comprises a secure data centre; computing infrastructure for data processing and analysis; and a resource for accruing insight gained from the clinical and genomic datasets e.g. links between genes and diseases.

The use of this informatics architecture beyond the Project (other than for ongoing research) has not been clearly articulated - specifically, whether and how it will serve NHS services. This is concerning, since the NHS currently lacks the robust, advanced informatics infrastructure vital for delivering genomic medicine.

Genomic data sharing

Genomic data sharing is essential for clinical service delivery, but there is no dedicated NHS database for aggregating and sharing relevant genomic data and findings, which compromises service quality, patient care and safety. It is therefore frustrating that while the 100KGP expends significant resources on enriching datasets for research, **there is no clear strategy for using the infrastructure it has built to support the collation and sharing of genomic data between NHS genetic services, which would yield immediate patient benefit.**

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Consent and the research vs clinical care conundrum

The current regulatory framework distinguishes between clinical care and other secondary uses of clinical (and genomic) data, including research. However, clinical genomics practice increasingly relies on utilising research activities (and in the absence of an NHS database, research resources) to directly inform clinical care, since information on one patient's genomic variation and symptoms can be crucial to diagnosing and caring for another. **Maintaining a clear distinction between direct care and research with respect to genomic information is therefore increasingly problematic.** In the longer term, a learning healthcare system approach needs to be taken to foster robust, evidence based practice.

Realising the benefits for rare disease patients

Whilst the 100KGP will benefit research, it is not clear how far it will directly benefit services for more than a handful of patients with rare disease (those who will receive a molecular diagnosis who would not otherwise have done so) unless it is fully embedded in initiatives that tackle the underlying problems faced by this patient group. Unless the increased potential for genomic testing is built into a major initiative to improve rare disease services such as that envisaged in the UK Rare Disease Strategy, the Project will have limited impact.

Transforming the NHS – creating a legacy

We are concerned that an integrated evaluation plan has not been included in the 100KGP. Knowledge about the impact of the results on clinical decision making and patient outcomes is vital to inform the implementation of these new testing methods into routine clinical practice.

Investment in NHS infrastructure and skills to take forward genome medicine

Workforce training

The potential for genomic medicine to improve patient care will only be realised if it is fully embedded in clinical care. Currently, most expertise in using genetic tests rests with the small specialty of clinical genetics, but ultimately other [mainstream specialties](#) (cardiology, ophthalmology, neurology etc.) need to take the lead role in care of patients with inherited disorders within their specialty . However, it is clear from [formal national audits](#) that the [provision of specialist inherited disease services](#) is extremely deficient and patchy across the UK. Competence in genomics also falls far below what will be required. Only cardiology has developed the necessary formal curriculum to ensure all those in specialist training have some exposure to genomics, and this is the first specialty to have developed a programme (still being piloted) for subspecialty training.

Professional organisations formally charged with the responsibility for medical education at different levels should be asked to review their curriculum in genomics and develop an action plan for improving competency amongst clinicians

Limitation of the Health Education England genomics programme

Programmes such as the [HEE Master's in Genomic Medicine](#) may interest some clinicians, but they are largely research oriented and available at insufficient volume to have much impact on overall clinical provision. Without training being properly embedded in the various levels of the curriculum across all specialties, including those in specialist training, the necessary breadth and depth of genomic skills to ensure equitable provision of genomic medicine throughout the NHS cannot be achieved. Although HEE has been given the formal lead (and budget) for developing genomics education, there has been insufficient focus on medical professionals.

Action required

We believe that the professional organisations formally charged with the responsibility for medical education at different levels should be asked to review their curriculum in genomics and develop an action plan for improving competency amongst clinicians. This will include the GMC (undergraduate), royal colleges and faculties (specialty training) and local education and training boards under HEE.

NHS data and IT infrastructure

Genomics is a data-intensive discipline. Without the adequate computational infrastructure and approach to data management, the successful delivery of genomic medicine in the NHS cannot practically be achieved.

Essential requirements

Critical to the clinical application of genomics is:

- **Access to computational capacity** to support the collection, analysis, interpretation and storage of high volume genomic data
- **The ability to collate and integrate genomic data with a patient's clinical records**
- **The ability to aggregate and share genomic data across NHS providers**

Limitations of current infrastructure

In its current form NHS IT cannot support these essential requirements, because:

- The computing resources are inadequate to meet the demands of genomic analysis
- The slow pace or absence of digitisation of medical records in many hospitals and NHS Trusts impedes the transfer and collation of patient clinical data

Policy supporting the genomics in healthcare should therefore be considered in the context of simultaneous scientific and societal developments, not least a changing role for individual citizens

- There is no designated NHS database (or system) for genetic services to share relevant genomic data for the purposes of ensuring safe and high-quality care for patients, and informing and improving services

Actions required

In addition to addressing the above challenges, NHS genomic medicine will require commitment to support the maintenance of necessary infrastructure that is also responsive to evolving computational technology supporting the demands of genomic analysis.

Concluding comments

Making the most of genomics for health and wealth

This is a critical era for genomic medicine; major research initiatives such as the 100,000 Genomes Project are laying the groundwork for a future where a comprehensive understanding of genomics in health and disease will underpin better disease prediction, prevention, diagnosis and management. However, our preparations and actions now will also make a major difference to the short and medium term medical benefits for UK citizens offered by genomics.

The economic importance of genomics as one of the foundations of the UK's life sciences sector has been recognised, and the Industrial Strategy should seek to maintain and expand national genomics research excellence and commercial innovation should be highlighted in the Industrial Strategy. Simultaneously maximising the benefits for the health of UK citizens requires careful coordination between different health system stakeholders.

Towards personalised healthcare

Progress towards increasingly personalised healthcare will undoubtedly be reliant on genomics, as well as a range of other biomedical and digital insights and innovations. Policy supporting the genomics in healthcare should therefore be considered in the context of simultaneous scientific and societal developments, not least a changing role for individual citizens in maintaining their own health. This means taking into account issues such as the future need to integrate complex genomic data alongside other 'big data', derived both from within the NHS and from external sources, in informing and directing healthcare.

For more information about the PHG Foundation visit
www.phgfoundation.org