

House of Lords Science and Technology Committee

Genomic Medicine

Evidence from the Foundation for Genomics and Population Health (the “PHG Foundation”)

Key points

- The current pluralistic approach to policy development for genomic medicine should be retained. There is a need for increased representation of public health expertise in policy development.
- ‘Genetic exceptionalism’ should be avoided in policy development: DNA is one amongst several different types of biomarker that may be used in the diagnosis of disease or estimation of disease risk.
- Genomic science is in a robust state but progress is dramatically slower in evaluating the clinical and public health relevance of these scientific advances and in developing systems for effective translation of validated tests and interventions into clinical practice.
- Insufficient attention has been paid to the final stage of translation, which bridges the gap between assessment/evaluation and implementation. This is not a research activity but a process of change management that includes knowledge integration and synthesis, knowledge brokering, stakeholder dialogue and consensus-building, clinical and public policy development, service review and reorganisation, education and training.
- A framework has been developed for evaluation of DNA tests. Statutory regulation of biomarker tests should be confined to ensuring their safety, and that evidence relating to test performance is transparent and publicly available. Funders of health services, and clinicians, should be discouraged from using tests that are not backed by appropriate clinical evidence.
- In the context of common disease, advances in genomics are unlikely to enable a person to be given a precise, individually tailored diagnosis or disease risk. Genomics will improve our ability to place him or her within a band or segment of the population characterised by a particular array of diagnostic features or a particular *average* disease risk. In turn, this will enable better targeting of interventions.
- As genomics is increasingly applied in mainstream medicine, new service models are needed in which appropriately trained health professionals from other clinical specialties take responsibility for routine genetic aspects of care, with access to specialist genetics referral where necessary.

1. Introduction

- 1.1 The PHG Foundation is the successor body to the Public Health Genetics Unit, established in 1997. Our response focuses on our particular area of expertise: the effort to develop an appropriate public and clinical policy framework for the evaluation of genome-based technologies and interventions and their implementation to benefit population health.

2. Policy Framework

- 2.1 At Government level, the public health mandate of the Department of Health includes policy and guidance on genomic research and the implementation of genome-based knowledge and technologies in public health and health services. Many different non-governmental groups and organisations, representing a variety of views and expertise, contribute to policy-making and policy review. We believe that the present pluralistic approach has significant strengths and that it should be retained.
- 2.2 In general, scientific knowledge is represented effectively in policy advice but there is insufficient representation from organisations and professionals with expertise in public health.
- 2.3 Some aspects of the current regulatory environment for research and development are problematic for the development and translation of genomic medicine. In particular, the research process in the UK is hindered by the complex legal environment controlling the definition and use of personal data, and the storage and use of human tissue. There is a tendency to interpret legislation in an overly cautious manner in order to avoid any risk of litigation.
- 2.4 The ethical, legal and social implications of genomic medicine receive considerable attention. There is a formal mechanism for considering these issues, through the advisory role of the Human Genetics Commission (HGC). A weakness of having a formal body dedicated to the ethical aspects of genetics is that it encourages genetic exceptionalism: that is, the belief that genetic/genomic information is uniquely powerful and therefore requires uniquely draconian regulatory and policy measures. Genetic exceptionalism is problematic for two reasons: firstly, that it leads to unrealistic expectations (both positive and negative) from genomic medicine; and secondly that it sets up an artificial distinction between tests and characteristics that are deemed to be 'genetic' and those that are not. In fact, genetic factors contribute to all biological characteristics and therefore all tests for such characteristics are to some degree 'genetic tests'. A more productive approach is to consider DNA as one amongst several different types of biomarker that may be used in the diagnosis of disease or estimation of disease risk. It may be appropriate to replace the HGC by a new advisory body with a wider remit more in keeping with a modern understanding of biology.
- 2.5 More generally, there has been a tendency for policy decision-making to be driven by a political response to high-profile events. An example is the complex regime for regulating the removal, storage and use of human tissue (the Human Tissue Act), which arose out of the scandal of organ retention at the Bristol Royal Infirmary and Alder Hey Hospital but reaches far beyond the legislative measures needed to prevent such gross misconduct. The measured, consultative approach that should apply in the development of such legislation was conspicuously lacking in the initial drafting of the Human Tissue Bill. Although open, public debate on ethical, legal and social issues arising from genomic medicine is important and to be encouraged, the views of scientists and clinicians and their representative organisations must also be given due weight in policy development.

3. Research and Scientific Development

- 3.1 Genomic science is in a robust state and will be commented on at length in submissions from other organisations. Progress is dramatically slower in evaluating the clinical and public health relevance of these scientific advances and in developing

systems for effective translation of validated tests and interventions into clinical practice. We shall return to this point below. Cross-sector collaboration involving government, academic research groups and industry is vital for realising the full potential of genomic medicine and should be actively encouraged.

4. Data Use and Interpretation

- 4.1 Data on gene-disease associations are published in the scientific literature and are available in research-level databases. However, these data do not in themselves constitute an evidence base for genomic medicine. The HuGENet initiative is an international collaboration devoted to systematic review and appraisal of claimed gene-disease associations. This information is assembled in a web-based knowledge base for use by healthcare providers, researchers, industry, government and the public in making decisions involving the use of genomic information for disease prevention and health promotion. Initiatives such as HuGENet, which has a coordinating centre in the UK (www.hugenet.org.uk) must be adequately funded.
- 4.2 All sensitive personal information, biological or otherwise, should be appropriately protected. Policy for data use and protection should not make a special case of DNA information but should deal more broadly with any data – genomic, proteomic, metabolomic, transcriptomic – that emerge from the new biology. The over-arching principle should be the need to achieve an optimal balance between individual autonomy and the wider public good. An over-emphasis on individual privacy and security can negate the potential benefits from research and put unnecessary obstacles in the way of people who wish to volunteer to participate in this research for altruistic reasons.
- 4.3 In the clinical sphere, genomic information (in its widest sense) will increasingly become part of an individual's medical record, raising both technical issues and questions of privacy and security. A question of particular relevance to clinical services is how familial information should be dealt with. For some highly penetrant single-gene diseases, such as familial hypercholesterolaemia, cascade testing within extended families can be used to identify affected individuals who may benefit from treatment or prophylaxis. Effective cascade testing requires an electronic record system that covers a wide geographical area (possibly even the whole country) and is linked to the individual medical records of family members. A single generic system would be preferable to separate systems for individual conditions. The issue of how such a system could be established without jeopardising patient confidentiality has not been resolved.
- 4.4 We believe that calls for 'genetic discrimination' to be outlawed as part of the proposed single equality bill are misguided because it will not be possible to arrive at a consistent legal definition of the term, and because such legislation would unfairly privilege DNA-based information over other types of information that may be equally or more predictive. A preferable approach would be to require all third-party users of predictive test information to make the evidence base for their practice publicly available and to justify their use of such tests.

5. Translation

- 5.1 'Translation' is not a single process. It comprises the 'bench to bedside' phase (including clinical trials), followed by phases of evaluation, assessment, appraisal and implementation into clinical practice and healthcare systems. The initial phase of

translation is part of clinical research and development, with actors in both the public and private research sectors.

- 5.2 Evaluation and assessment fall within the publicly funded Health Technology Assessment (HTA) and Health Services Research programmes. There is currently a lack of attention to the systematic work on the clinical validity and utility of genomics-based technologies (in particular, diagnostic tests) that is needed to inform the evaluation process. A new approach is needed, akin to the way pharmaceutical companies run Phase III clinical trials. It is likely that this system will need to be established as a public-private partnership.
- 5.3 Optimal translation of new technologies into clinical practice requires both assessment and appraisal of the technology. In the UK (in contrast to some other countries, such as Canada) these processes are separate, with the HTA programme stopping at assessment, and NICE responsible for appraisal (i.e. developing policy and guidance). We believe this approach reduces the value of the HTA programme and that assessment should always be followed up by policy and guidance.
- 5.4 Insufficient attention has also been paid to the final stage of translation, which bridges the gap between assessment/evaluation and implementation. This is the area within which public health genomics operates and which forms the core of the work of the PHG Foundation (www.phgfoundation.org). It is not in general a research activity but a process of change management that includes knowledge integration and synthesis, knowledge brokering, stakeholder dialogue and consensus-building, clinical and public policy development, service review and reorganisation, education and training. Given the pace of technological advance, it is essential that this final phase of the translation process is explicitly recognised and adequately resourced.
- 5.5 Like any other type of clinical test, a test based on genome variation data may be 'meaningful' – in the sense of providing clinically useful information – or not. The important thing is to have a process to distinguish which tests (genomic or otherwise) fall into which category. A framework for evaluation of DNA tests has been developed. This framework has already been implemented by the UK Genetic Testing Network for tests that are currently used by clinical genetics services. Its major components are assessment of the analytical validity, clinical validity and clinical utility of the test, and a consideration of any ethical, legal or social issues arising from its use.
- 5.6 The existing statutory regime for market authorisation of diagnostic tests (of which the major component is the EU In Vitro Diagnostic Devices Directive) is in general restricted to an examination of safety and analytical validity. Statutory regulation does not extend to requiring evidence of a test's clinical utility; that is, evidence that the use of the test leads to an improved health outcome. This issue is controversial. Our view is that the current regulatory regime would be sufficient provided there were a requirement for any information about the clinical validity and utility of the test to be placed in the public domain. At present EU legislation allows any such data to be retained in private by the company selling the test.
- 5.7 Particular concern has been expressed by some commentators about the regulation of genomic 'lifestyle' tests available direct to consumers via the internet. Companies selling these tests give dietary and lifestyle advice purportedly based on analysis of an individual's genomic profile. We do not support the HGC's view that genomic 'lifestyle' tests should be subject to a specific regulatory regime. We believe the role of statutory regulators should be confined to ensuring the safety of all biomarker tests, and that evidence relating to test performance (or lack of it) is transparent and publicly

available. Funders of health services, and clinicians, should be discouraged from using tests that are not backed by appropriate clinical evidence.

6. Biomarkers and Epidemiology

- 6.1 We question the implied distinction between DNA variants and biomarkers: genomic factors are simply one type of biomarker. We have previously outlined our argument that all biomarkers should be formally evaluated as part of the translational process, and that this phase of translation must be afforded more recognition.

7. Use of Genomic Information in a Healthcare Setting

- 7.1 Genomic information is expected to have a major impact on the classification of disease. Evidence for this is already available, for example in the field of oncology, where genomic approaches such as microarray technology are beginning to define sub-categories of disease related to differences in prognosis and disease management.
- 7.2 Currently, the major clinical impact of genomics is in the context of single-gene and chromosomal disorders. The molecular-genetic basis of thousands of single-gene disorders is now known. Although these conditions are individually rare, they are collectively numerous, representing a substantial burden of morbidity and mortality in the population. There is increased and/or earlier diagnosis of several conditions through neonatal screening programmes (e.g. sickle cell and thalassaemia, MCADD, cystic fibrosis), family cascade testing (e.g. current pilots for familial hypercholesterolaemia) and good clinical practice (e.g. the National Service Framework guidelines for investigating possible genetic causes of sudden cardiac death). Some individuals identified through these routes may never have had recognised symptoms of disease but are nevertheless at risk of life-threatening events and therefore in need of services. All health professionals need a basic understanding of genetics, to enable more effective recognition of highly penetrant genetic conditions, some of which are rare subsets of more common diseases.
- 7.3 In some single-gene disorders, knowledge of the disease-causing mutation is already leading to more individualised treatments. For example, in some inherited retinal dystrophies the use of specific gene therapy is being trialled and molecular analysis is leading to fine-tuning of more general treatments.
- 7.4 Our experience in service development for genetics in mainstream medicine indicates that the current paradigm of joint clinics involving clinical genetics departments and other specialist departments (cardiology, oncology, ophthalmology etc) is likely to become untenable as the number of available tests for single-gene diseases increases and their cost drops. This means that patients will largely be looked after in the relevant specialty by health professionals knowledgeable in aspects of genetics relevant to that specialty and with access to expert genetics referral for more complex issues such as interpretation of complicated test results.
- 7.5 This model for integration of genetics into mainstream services requires a substantial investment in education and training. Genetics must be included in all aspects of specialty training (eg medical, nursing and other associated specialities), and opportunities provided for sub-specialty training, for example through provision of fellowships.

- 7.6 Investment is also needed to ensure that these new services are properly set up and that family-based record systems are established as set out in 4.3.
- 7.7 In the context of common disease, the term 'individualised medicine' may be misleading. Advances in genomics are unlikely to enable a person to be given a precise, individually tailored diagnosis or disease risk. Rather, genomics will improve our ability to place him or her within a band or segment of the population characterised by a particular array of diagnostic features or a particular *average* disease risk. In turn, this will enable better targeting of interventions. This process does not differ in principle from stratification by, for example, cholesterol levels or blood pressure. Genomics will enable us to refine such categories by using a richer array of information to define them.
- 7.8 The ethical issues raised by these developments are those raised more generally by population stratification, prediction and prevention – these are not issues that are basically genomic. If there is to be advice or codes of practice it should not be directed at the technology but used more generally to inform the management of disease risk or the appropriateness of treatments.
- 7.9 There is a need for more research on how people perceive risk and how they behave in response to information about their risk. Although we discourage genetic exceptionalism, we recognise a widespread lay belief that genomic information is 'special'. It is important to understand how existing beliefs affect people's response to genomic information and whether including such information in risk profiling will motivate the behavioural changes that are necessary to improve disease prevention and public health.
- 7.10 As genomic tests and information are incorporated into strategies for the routine diagnosis and management of common disease and the estimation of disease risk, many – if not most – health professionals will need to understand how to interpret test results and risk information and to be able to explain the implications to patients. They will also need to be able to make informed judgements about which tests are appropriate for different patients and clinical situations. General practitioners are likely to find themselves in the 'front line' of these developments and will need appropriate training.
- 7.11 Commissioners and managers will need to be able to assess the population need for genome-based tests, technologies and interventions, and to understand the evidence base supporting their use.
- 7.12 The education of public health professionals will need to move away from an exclusive emphasis on social and environmental causes of disease, towards a more sophisticated understanding of the interplay between genomic and environmental factors in disease causation. This more modern understanding of health and disease may enable the development of more successful strategies for disease prevention targeted at population subgroups in whom the underlying aetiology of the disease is more clearly defined.

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