

Genetic Testing for Common Disorders: Proposed Recommendations of the European Society of Human Genetics

Response from the PHG Foundation

Introduction

The Foundation for Genomics and Population Health (PHG Foundation) is the successor body to the Public Health Genetics Unit. Its overarching purpose is to foster and enable the application of biomedical science, particularly genome-based technologies for the benefit of human health. Among its specific objectives is the promotion of a social and regulatory environment that is receptive to innovation, without imposing an undue or inequitable public burden. The Foundation has a particular interest in the way that new technologies are translated within health services, and in genetic research and its impact upon clinical and public health services.

General Comments

The PHG Foundation is generally supportive of new technologies if their use can improve health care. Elsewhere we have argued that, in the context of laboratory diagnostic tests, the findings of any test should be robust (i.e. that there should be evidence of scientific and clinical validity), and claims made about the significance of a test should be supported by evidence¹. We have also called for structural changes such that new tests are subjected to a more responsive and proportionate assessment as part of the pre-market review process, and that information about test performance is placed in the public domain.

Some of these principles are relevant to this consultation, and we have laid out our comments below under each of the headings used in the consultation document itself.

Specific Comments

Definition of susceptibility testing and screening

Whilst we support the separation of testing and screening, we feel that the definition of the latter used in the document is actually that of a 'genetic susceptibility screening programme', not *screening* itself which is a rather wider concept. Unlike a screening test, a screening programme is a public health service in which a test is offered to an asymptomatic population (or sub-population) in a systematic and explicit manner; it provides a joined-up pathway to secondary prevention, from identification of a particular subpopulation for screening, through to follow-up diagnostic testing for screen-positive individuals, and ultimately treatment for those who need it.

Moreover, the term 'screening' is used perhaps inadvertently in the later recommendation regarding '*Counselling in relation to susceptibility screening*', which appears to relate simply to testing rather than a proactive offer to screen a certain sub-population in an organised manner.

Evidence

We broadly agree with the evidence presented in this section, and wish to emphasise the importance of validating genetic susceptibility loci and risk models within the target population; for example, the effect of a particular susceptibility allele identified in one

¹ PHG Foundation. The evaluation of diagnostic laboratory tests and complex biomarkers. (2008)

study group may differ significantly with ethnicity. This prospective validation of test performance forms a key part of clinical validity.

Translation of research findings

We agree that the relative risks conferred by individual common susceptibility variants are generally low, and that future successful translation is therefore likely to involve a combination of multiple genes and environmental factors. It should be noted, however, that this may not be the case for rare variants underlying common disease, which may have substantially larger associated risks.

Assessment

We support the use of a model based on the ACCE framework for the evaluation of genetic tests for common diseases, and wish to make the following two points:

- 1) Clinical validity is comprised of two components, which we term scientific validity and test performance. The former refers to the strength of evidence that the gene-disease association is true, which is necessary but not sufficient for a valid clinical test; the latter refers to a prospective clinical trial of the test (or model) in the target population, in order to establish its sensitivity, specificity and predictive ability. Care is needed when independent gene-disease associations from separate studies of different populations are combined to purportedly offer a multigenic risk model applicable to all these or additional populations. This dichotomy should be referred to explicitly in the accompanying background paper.
- 2) With respect to the statement '*in the absence of insufficient information on clinical validity and clinical utility, introduction of susceptibility tests is often premature*', we take the view that evidence of clinical validity and clinical utility is often limited when a test is launched. If regulators were to insist upon evidence of clinical validity and clinical utility as a prerequisite to commercial use, this would have a stultifying impact on the sector. However, we believe that evidence supporting the gene-disease association should be a requirement for all tests, and where evidence of clinical utility is lacking, there should be careful monitoring of claims made by manufacturers through regulation and consumer protection systems. Before a test is used within a state funded health system, there should be a mechanism for assessing clinical utility and any deficiencies addressed, such as the gene dossier system developed by the UK Genetic Testing Network.

Priorities

With regards to the statement that '*in some cases, applications are feasible*', it is important to point out that, in addition to being feasible, for a test to be used in clinical practice it must also have demonstrated clinical utility such that using the test brings about an improvement in patient care. For example, if a test were developed to determine genetic risk factors for cardiovascular disease, if it would not affect patient management or public health advice (since the preventative advice to have a healthy diet and take regular exercise would remain essentially unchanged), so such a test would be clinically irrelevant even if it were feasible.

Direct-to-consumer tests

We have recently produced a set of five key recommendations for the regulation of direct-to-consumer (DTC) genetics tests, which we believe are simple enough to be practicable and would adequately protect the consumer from fraudulent products and incompetent services. Although several of these points are already covered in this recommendation, we have reproduced all five below in the interests of clarity and thoroughness:

- 1) Provision of a proportionate set of informed consent procedures, such that the citizen is unambiguously informed about the nature of what he will receive by way of information and its possible implications.
- 2) A requirement that all laboratories undergo accreditation procedures and subject themselves to stringent QA requirements, the details of which are publically available, such that citizens themselves can have confidence in the assay results that are generated.
- 3) Statutory regulations should be put in place to ensure that the scientific validity of the clinical claim is established, i.e. the link between the disorder and the genetic variant is established as a true and real relationship, and thus the claimed association is valid.
- 4) All providers should ensure that they have access to appropriately qualified professionals with the necessary competence to interpret the results of the test and provide advice and support to consumers regarding the interpretation of the test result to consumer.
- 5) Guidelines and consumer protection regulations should be strengthened to prevent misleading claims for the product or service, including unsubstantiated and overhyped assertions concerning clinical utility.

Regulation

Our view is that all technologies that purport to make predictions about future health or disease should be regulated in a consistent manner: hence we oppose regulation that seeks to treat genetic or genomic tests as exceptional. Our position on the requirements for the regulation of DTC genetic tests is stated above, and is based upon a consideration of the potential harms caused by testing, which can be dichotomised into direct harm caused by the test itself, and indirect harm caused by knowledge of the result of the test. The potential for direct harm caused by genetic tests is minimal (as they use *in vitro* samples obtained from saliva, buccal swabs, a finger prick, etc.), whilst indirect harms may include false reassurance, anxiety and undertaking detrimental lifestyle changes or interventions. However, the evidence for these indirect harms with respect to genetic testing for susceptibility to common complex diseases is limited, and we posit that these arguments are equally or even more valid for numerous other biological measurements - including weight, height, cholesterol level and blood pressure - for which tests are already available DTC. Nevertheless, we recognise that the liberal regulatory approach outlined above may need to be supplemented by a more stringent assessment process in the context of a state funded health service, to ensure that funds are spent wisely. Finally, it is important to note that it is extremely difficult - and, we would argue, unnecessary - to demonstrate and ensure clinical utility for DTC tests, as any claimed utility will ultimately depend upon the autonomous actions of the consumer (e.g. making a particular lifestyle choice) and hence is not under the control of the company, a physician or the health care system.

Harmonisation

Whilst harmonization within the European Union may be intellectually appealing and practically useful, we believe that it is likely to be extremely difficult, if not impossible. Different countries are already taking extremely contrasting approaches; Germany has recently passed a law banning genetic tests except those performed by a qualified medical doctor, whilst the Human Genetic Commission in the UK is developing a Common Framework of Principles to which companies can chose to adhere. We therefore question the merits of calling for EU harmonization, particularly given the global nature of the market, with the possible exception of agreeing a set of minimum requirements (such as those outlined above).

Commercial valorisation and responsible entrepreneurship

No comment.

Solidarity in the wake of personalised medicine

We do not support the recommendation that a system of *'collective insurance is needed to realise the potential of individualised medicine'*. There are numerous different ways in which individuals can be distinguished based on biological and non-biological differences, and genetics is just one of these. In the UK, health insurance is based on the principle of actuarial fairness, in which individuals are categorised into populations with differing levels of risk, and their premium calculated appropriately; for example, women are generally charged lower insurance rates than men. We suggest that a much deeper examination of the issues around solidarity, fairness and discrimination is needed before a system of collective insurance can be contemplated.

Legal aspects

We note the recommendation that *'governments proceed with additional non-discrimination legislation'* so that *'unfair discrimination on the basis of one's genome should be avoided.'* Whilst we are not formally against a position on this issue, we wish to highlight several issues:

- 1) What is exactly is meant *'unfair discrimination'*? As we have seen, discriminating between individuals underpins the principle of actuarial fairness widely used in the insurance industry in the UK. In choosing potential employees, an employers' use of genetic information may be highly relevant. For example, it is considered fair to discriminate between two candidates for a job based on their past education, which will be determined in part by their genetics.
- 2) What is meant by the term *'based on one's genome'*? Does this include visible traits (such as sex or height), family history, any biomedical test that genetic information, or only tests which use DNA as the analyte? The science of human genetics has advanced significantly in the past decade, such that it is no longer possible to define diseases or traits as either genetic or non-genetic; in reality, most human traits have a genetic component, and therefore any discrimination (fair or unfair) will relate in part to an individual's genome.

Although discrimination by insurers and employers based on genetics may be highly problematic in certain specific cases i.e. highly penetrant single gene disorders such as Huntington's disease, we do not believe it to be so for genetic information, particularly in the context of common diseases. Therefore, the remit of any anti-discrimination legislation which is specifically intended to prohibit the misuse of genetic information must be extremely clearly defined, and avoid using the term 'genetics' entirely where possible. For example, legislation to prevent 'genetic' discrimination already exists in most countries in the form of equality bills that outlaw discrimination based on sex, which itself is a strongly genetic trait. It is also noteworthy that in the UK, the Government has specifically rejected the possibility of legislation that outlaws genetic discrimination on the grounds that there is insufficient evidence that it is a problem². Other mechanisms, such as a moratorium against use of genetic test information by third parties including insurers and employers, may be as effective as legal remedies and more practical.

Ethical and social aspects

We agree that empirical evidence concerning the impact of genetic susceptibility testing remains scanty and more work is urgently required in this area so that proportionate regulatory frameworks can be put in place.

² UK House of Commons Library: Research Paper on the Equality Bill 09/42 at page 139. Available at <http://www.parliament.uk/commons/lib/research/rp2009/rp09-042.pdf>

Role for clinical geneticists in health care

We broadly agree with the point made here, and wish to emphasise the increasing need for training, service development and collaboration in order to support the mainstreaming of genetics into the rest of medicine.

Counselling in relation to susceptibility screening

It is currently unclear what risks are considered '*high*' or how genetic tests that are currently available for one disease may be linked with a high risk of another in the future. Moreover, once full genome sequencing is available, rare highly penetrant diseases that were previously unsuspected may be uncovered in some individuals. We therefore suggest that access to a trained genetic counsellor should be made available, though not mandated, by DTC genetic testing companies and in relation to susceptibility testing.

Training

No comment.

The public

No comment.

Developing Countries

Whilst it may be true that environmental factors (such as sanitation, nutrition and exposure to infections and parasites) play an important role in the prevention and control of common complex diseases in developing countries, diseases such as sickle cell disease and the thalassaemias would suggest that the interaction between genotype and phenotype is both a crucial determinant of ill health, but also provides a means of improving population health³. Moreover, many developing countries are currently going through an epidemiological transition; a growing proportion of childhood morbidity and mortality will therefore be due to congenital birth defects, and genetic services will play an increasing role in alleviating childhood diseases.

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³ World Health Organisation (2002) Genomics and World Health available at <http://whqlibdoc.who.int/hq/2002/a74580.pdf>