

**House of Lords Science and Technology Committee:
Genomic Medicine Inquiry**

**Memorandum of Evidence on behalf of the
Human Genetics Commission**

Summary

The Human Genetics Commission (HGC) welcomes the appointment of a sub-committee of the House of Lords Science and Technology Committee, chaired by Lord Patel, to provide an assessment of genome technologies and their actual and potential impact on clinical practice.

There are robust frameworks governing the conduct of genomic research in the UK and the HGC would not wish the administrative burden on researchers to increase. Nevertheless, as well as its undoubted benefits, genomics research has the potential to give rise to significant consequences for individuals, groups and society, including the potential to give rise to unfair discrimination. Engagement with the public on these issues is therefore important.

Genomics research can deliver substantial benefits in understanding drug sensitivity and adverse reactions. Appropriate frameworks exist to govern clinical practice and clinical trials. Care must be taken, however, in deciding which knowledge and products generated by research will be useful in clinical practice, and when and how they should be introduced. There are greater opportunities to involve clinicians and patients in research leading to the development of clinical interventions; there are also opportunities for greater collaboration between the public and private sectors. Some examples of good practice are, however, emerging.

There should be a presumption that individual genetic information should be under the control of the person to whom it relates; genetic solidarity and altruism implies a common interest in successful genetics-based research. The accumulation and sharing of data that supports this research is desirable, but there should be robust governance arrangements for databases that contain genetic information (examples of good practice exist) combined with appropriate sanctions for improper use of genetic information.

More research is required to establish the utility of tests for susceptibility to disease as part of a clinical service. The HGC continues to have concerns that there are real risks associated with tests marketed and sold directly to the public, and this field is insufficiently regulated at present. The implications of genetic test results that are intended to identify susceptibility to disease are, in general, poorly understood, and more information and education at all levels, and in particular an increase in capacity of genetic counselling services, are required.

The Human Genetics Commission

1. The Human Genetics Commission is the UK Government's advisory body on developments in human genetics and their ethical, legal, social and economic implications. The Commission is sponsored by the Department of Health, the Department for Innovation, Universities and Skills and the devolved administrations of Scotland, Wales and Northern Ireland. The HGC's terms of reference are annexed to this submission.

Policy Framework

2. We expect the Government's response to provide a descriptive account of the framework for informing, setting and reviewing policy in relation to genomic medicine. We therefore offer no comment on this except to highlight the HGC's own role and relationships.
3. The regulatory and advisory framework for biotechnology was comprehensively reviewed by Government in 1999. As a consequence of that review three advisory committees on human genetics – the Advisory Committee on Genetic Testing, the Advisory Group on Scientific Advances in Genetics and the Human Genetics Advisory Commission – were wound-up and the HGC established to take on their responsibilities. There have undoubtedly been substantial developments in human genetics – in science, technology, their application to healthcare and the institutions that support them – since the HGC was established. During the latter half of 2007, the HGC underwent an independent review, the findings of which are currently with Ministers and expected to be published during the present Inquiry. The review addressed the HGC's effectiveness, necessarily in the context of the broader advisory framework of which the HGC is a part. We expect the findings of this review to be highly pertinent to the present inquiry and would urge the Committee to take account of them when they are published.

4. The HGC works within the context of devolution settlements for Scotland, Wales and Northern Ireland. Government policy on human genetics is reserved to Westminster, but responsibility for National Health Service (NHS) genetics services is the responsibility of each devolved administration. Although there are differences in commissioning arrangements, the general pattern of service delivery is the same throughout the UK. Issues, such as relations with the EU, which are more effectively dealt with on a single UK basis, are reserved to Westminster and ethical and legal matters relating to human genetics are also generally reserved, along with policy and regulation relating to medical devices (including genetic tests) and the control of medicines.
5. It is important to distinguish the ethical conduct of research from the ethical consequences of the research. The conduct of research in the UK is governed by strict frameworks requiring the informed consent of participants, research ethics committee approval and adherence to relevant guidelines and legislation (such the Clinical Trials Directive, the Human Tissue Act 2004 and the Human Tissue (Scotland) Act 2006, and the Data Protection Act 1998). We would wish to minimise the burden of this framework on researchers as far as possible, consistently with protecting the interests of the public and the individuals involved. While the current governance frameworks are robust, it remains important to continue to monitor their effectiveness, particularly in relation to genetic databases, where issues around consent for future use of data remain problematic. The ethical consequences of the use of data generated by some genomics research, on the other hand, are less well anticipated and may affect our understanding of certain categories that are influential in the popular understanding of our relationships, such as ‘normality’, ‘individuality’, ‘responsibility’ and ‘humanness’. Relatedly, the blurring of boundaries, for example between research and clinical practice or between health and enhancement, and issues relating to data sharing, will continue to trouble current conceptualisations and practices.
6. We observe that kinds of ethical questioning of new developments in genomics are not bound to national jurisdictions, although there is often a close association between particular political, historical, religious, legal and philosophical traditions and political territories; different jurisdictions consequently struggle to resolve ethical debates in their own particular ways. Conversely, it is equally important to recognise the pluralism of modern British society, which owes much to its hospitality to co-existing religious, cultural and philosophical traditions. These observations lead to two exigencies: on the one hand, to seek solutions, where possible, at a supra-national level as the

counterpart to increasing international collaboration in scientific research¹; on the other, to engage with a plurality of perspectives in the formulation of domestic policy in a way that manages diverse values and any tension between collective and individual interests.

7. Alongside the policy framework there has emerged, over perhaps the last couple of decades, an ethical framework that underlies policy development and a more-or-less established procedure for ethical reflection that informs it. The framework has become substantially aligned with an interpretation of the rights enshrined in documents such as the European Convention for the Protection of Human Rights and Fundamental Freedoms (ECHR), and is typically mediated through a calculus of relevant and likely harms and benefits, informed by evidence gathered from broad – usually public – consultation. This approach has proved effective in identifying workable solutions to potential conflicts between interests and values in the context of the UK as a mature liberal democracy, underwritten by economic stability, and in which political secularism (or tolerance for a plurality of value systems) prevails. We are supportive of the very specific attempts to include public consultation in new areas of genomics research, for example regarding the UK Biobank and Generation Scotland and continue to encourage public engagement and consultation in line with our own remit. In this way, regulatory changes and be informed by, and indeed sometimes reflect, wider interests and concerns.
8. However, notwithstanding the relevance of the ECHR, this ethical framework does not formally constrain the development of policy, and the UK has not implemented measures adopted in other countries and achieved through, for example, adoption of the Council of Europe Convention on Human Rights and Biomedicine and its protocols.² At a purely domestic level, the HGC has also identified a need for genetic discrimination to be recognised explicitly in anti-discrimination legislation, in particular the Government’s proposed Single Equality Bill, prospectively to ensure fairness in access to insurance, employment, healthcare and other public services.

¹ In this connection we note the development of ICH guidelines on Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data And Sample Coding Categories

² Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. (‘Oviedo Convention’). In *Inside Information* (at paragraph 2.7 – see note 4, below, for full citation) the HGC recommended that the UK Government take steps towards signing this Convention (although we acknowledge that reservations would need to be entered in specific areas already covered by domestic legislation).

Research and Scientific Development

9. Undoubtedly, scientific advance in genomics is exciting and potentially has a significant impact on clinical medicine and human welfare. We recognise the advances in pharmacogenetics leading to improvements in prescribing practice through the identification of validated genomic biomarkers for a range of conditions such as HIV, cancer, psychiatric illness and cardiovascular disease. Frameworks related to Good Clinical Practice and clinical trials apply globally. The United States Food and Drug Administration, the European Medicines Agency (EMA – which includes the Medicines and Healthcare products Regulatory Agency) and the Japanese Pharmaceutical and Medical Devices Agency (PDMA) have all developed guidelines and procedures to evaluate the use of pharmacogenetic information during the development and prescribing of medicinal products. These three regions have also collectively produced ICH guidelines³ on pharmacogenetic terminology in order to facilitate research by adoption of a common set of definitions and terms.
10. Some genetic knowledge may lead us to re-evaluate our current models for research, drug development and clinical practice. The greater part, however, will need to fit in to the current framework for healthcare delivery. We will only reap the benefits of these developments if we think very carefully about which tests to introduce into clinical practice, and when and how this should be done. We are concerned that enthusiasm generated by the ability to sequence the genome has the potential to obscure the challenges that exist in understanding the data being generated, assessing its validity and utility, and deciding whether and how it should be introduced into clinical practice. There is a danger of not recognising the contribution that clinicians must make in order to realise the potential of genomic research to develop effective interventions in clinical practice. Other than in basic research, where the case is somewhat different, we would therefore encourage the inclusion of patients and, where appropriate, their families, and healthcare providers in evaluating research proposals to address the translation of research into clinical practice.
11. The HGC believes there are important opportunities for greater integration of research activities between the academic and clinical communities and the private sector to make best use of resources, including use of research subjects. We note that in the US and Asia, for

³ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data And Sample Coding Categories – see www.ich.org/LOB/media/MEDIA3383.pdf

example, governments have promoted and supported large-scale collaborative enterprises involving both public and private sectors. However, oversight is essential to ensure that the interests of those, for example, with rare conditions are answered alongside the more common conditions and those areas of research most attractive to the commercial sector. In addition, it would ensure that the capacity of the pharmaceutical sector to process and analyse genomic information, and the drug regulators to apply to pharmaceutical development, may be married with the expertise of, for example, physicians in carrying out clinical trials, of clinical geneticists in relation to understanding disease-gene relationships and with epidemiologists, statisticians and others in academic institutions.

12. The HGC is aware that certain conditions – such as the cost of postdoctoral funding in the UK and level of incentive for academics to collaborate with industry on research projects under the proposed Research Excellence Framework – are not currently optimised for collaboration between the pharmaceutical industry and academia. We are encouraged, however, by the example of the Genetics Research Network being developed in Scotland to bring together genetic clinicians, researchers and the biotech industry and provide a forum for discussion that, it is hoped, will facilitate translation activities. A Public Engagement network will run alongside this. Other examples are the Scottish Stem Cell Network and the recently established UK Stem Cell Network. Finally, the newly emerging Academic Health Science Centres (AHSCs) may also have a valuable role to play in translational research in the future.

Data Use and Interpretation

13. In its report *Inside Information, balancing interests in the use of personal genetic data*, the HGC set out a number of principles for balancing the interests of the individual and the community.⁴ Two key concepts described were genetic solidarity and altruism, and respect for persons. In considering the balance of interests, the HGC firmly expected that individual genetic information should be under the control of the person to whom it relates. However, the concept of genetic solidarity implies that we all have an interest in successful genetics-based research. A number of recommendations in this document are pertinent to the present inquiry, including that the governance of large,

⁴ *Inside Information, balancing interests in the use of personal genetic data* (HGC, 2002). More recently the HGC made a number of comments relevant to this strand of the present inquiry in response to the recent Ministry of Justice consultation on the use and sharing of personal information (see: www.hgc.gov.uk/Client/document.asp?DocId=142&CAtegorYId=4).

population-based genetic research and DNA collections should allow for oversight by an independent body that is separate from the owners and users of the database. This recommendation has been met in the establishment of the independent Ethics and Governance Council of the UK Biobank, and the independent Generation Scotland Advisory Board, both examples of good practice in this area. Biobanks provide the opportunity to understand the basis of health status in a given population and if managed to a high research standard (both data and samples) will provide a unique resource for epidemiological exploration. There is a case to be made for some standardisation of governance practices, including methods and content of data collection, regarding genetic databases, particularly as they are currently developing access policies regarding use of these research resources.

14. Whilst many research genetic databases contain sequence data that is anonymised, the nature of such data is so individual that, in principle, it is possible to identify individuals by recognising common factors or markers in different databases. This will create new challenges from the point of view of data protection. The HGC is aware of the valuable work of the European Bioinformatics Institute – which exists to ensure that information from molecular biology and genome research is placed in the public domain and accessible freely to all within the scientific community in ways that promote scientific progress – and of the concerns that they have about this issue; and it is one that the Commission proposes to investigate further during its current work cycle.
15. The Commission does not believe that it is feasible for separate arrangements to be made for the storage of genetic information within the health service. The proposed integration of NHS records for clinical and research purposes under the National Programme for Information Technology (NPfIT) promises an opportunity to create a research and clinical resource of enormous importance, for example, in improving patient safety through the active monitoring of safety and efficacy of new and existing medicines, the identification of disease patterns for allocation of resources, facilitating research on health outcomes following intervention, and assisting the identification and design of clinical research programmes.
16. The generation and retention of genetic data have some unique implications, for example, some information may be generated that is potentially of importance to other relatives, non-paternity may be revealed or results may provide information about disease risk that may manifest in the future, but which do not affect the patient at the time of testing. Ensuring that this information is provided to the patient

(and, if appropriate, their family) in a manner that is easily understood and will be remembered is a complex process, requiring specific skills on the part of the clinician involved. Increasingly these skills will need to be acquired by staff working outside the Regional Genetics Centres as more testing is carried out by other healthcare professionals or even initiated by the patients themselves ('over the counter' testing).

17. Genetic information pertinent to individuals needs to be available within their own hospital or GP medical records while Regional Genetics Centres will continue to hold family records and, where necessary, take responsibility for the identification of relatives who may benefit from genetic counselling and possible testing once a specific mutation of clinical significance has been identified in a family. We believe that the requirements of medical confidentiality and the specific considerations that relate to genetic data should be clearly understood by all those with access to genetic information. At present, the potential for misuse (and misinterpretation) is high whilst the general level of understanding remains low. While confidentiality pertains to all personal medical information, additional concerns pertain to genetic information owing to its relevance beyond the individual: there may, for example, be tensions between an individual who wishes to keep their results private, and the potential benefits to relatives if they knew that there was a specific mutation within the family for which they could be tested. We believe that renewed consideration should be given to the most appropriate way of ensuring effective sanctions, not excluding new legislative provisions, to support current requirements for confidentiality.

Translation

18. The challenge for the future is translating the evidence derived from research into useful diagnostic tests, prognostic information and therapeutic interventions. The Cooksey report identified two gaps in translation research: one between the laboratory and the development of new ideas and products, the second in translating new products and ideas into clinical practice. The greater part of translational research funding has, to date, tried to address the first gap with much less attention being paid to the second. Observation of an association between a genetic variation and susceptibility to disease at a population level, even if it is replicated in large studies, does not necessarily imply any clinical utility for an individual.
19. We believe that more research is needed to generate evidence of performance in use so that this can ensure that the data are

appropriately analysed and evaluated, and that there is public access to the evidence. The HGC applauds the work done by the UK Genetic Testing Network (UK GTN) in establishing standards for determining the appropriateness of offering tests within the National Health Services in the UK and similar arrangements for prioritising new developments in the Scottish molecular genetics service.

Complementing this, in its reports *Genes Direct*⁵ and *More Genes Direct*⁶ the HGC makes recommendations relating to the evidence that should be required before a test is brought to the private market and the necessity for that evidence, or lack of it, to be in the public domain. Whilst many requirements are already in place under the auspices of drug regulatory authorities such as the MHRA and NICE, these do not always extend to suppliers marketing tests directly to the public.

20. There is reason to believe that, notwithstanding advances in personalised medicine, such as Herceptin and the HER2 receptor in breast cancer, the major impact of advances in understanding of genomics on healthcare will be stepwise, given the timeframes associated with drug development and validation. For this reason we believe it is important that sustained, ‘future proof’ programmes of investment should be established and that, within these, attention should continue to be given to rare diseases in the light of the concerns expressed above.⁷
21. For the benefit of pharmacogenetics to be translated into improved therapeutic outcomes, the assessment of medicines which employ pharmacogenetic information during prescribing by relevant bodies such as NICE must take place in a timely and appropriate manner.

Biomarkers and Epidemiology

22. The HGC recognises that genome-wide association studies contribute to basic scientific knowledge that may lead to elucidation of novel biological pathways and development of novel biomarkers for disease susceptibility or drug response. However, these still require evaluation in use and, as stated above,⁸ there is a gap to be bridged between research and clinical practice.
23. In view of concerns about direct-to-consumer testing, the HGC is concerned that there is a potential for providers of such services to

⁵ *Genes Direct, ensuring the effective oversight of genetic tests supplied directly to the public* (HGC, 2003)

⁶ *More Genes Direct, a report on developments in the availability, marketing and regulation of genetic tests supplied directly to the public* (HGC, 2007)

⁷ See paragraph 11 above.

⁸ See paragraph 18 above.

undermine the credibility of genomic medicine, by making inflated or misleading claims in marketing their products. The HGC currently has a programme of work in place to encourage and assist the sector to develop guidelines of good practice and ethical conduct, and to encourage the provision of appropriate information to the public.

Use of genomic information in a healthcare setting

24. It is accepted that it is unethical to give advice without an adequate evidence base and information should only form part of individualised advice if it is meaningful. To establish this there is a need to assess clinical validity and utility in specific clinical pathways, as a recent PHG Foundation/Royal College of Pathologists report has recommended.⁹ However, proper evaluation of clinical utility takes time and may require large-scale studies; the provision of government funding for this sort of work would help to ensure that the benefits that could derive from further development of some types of genetic testing might be realised.
25. The accumulation of evidence to support some pharmacogenetic advice in prescribing across a range of conditions is currently encouraging. However, sufficient evidence does not yet exist for most tests currently available for genetic susceptibility to be used in a clinical setting. We have identified concern that there is a ‘technologically driven’ wish to introduce more genetic testing into clinical practice as the result of a misapprehension that such tests can generate information that will be useful in clinical practice. This is undoubtedly aggravated by the fact that some tests are already offered directly to the public, sometimes via the Internet, by private companies.¹⁰
26. The fact that evidence of an association at a population level is not equivalent to evidence of clinical utility for the individual appears to us to be poorly understood at present, which allows some commercial test providers to offer over-the-counter genetic tests on the basis of evidence of an association alone, giving information that is open to misinterpretation. This can have serious consequences if patients make inappropriate lifestyle modifications (e.g. continue to smoke because they believe that their genetic predisposition to lung cancer is reduced and therefore they are immune or if ‘adverse’ test results create unnecessary anxiety). Likewise, the difference between relative risk, absolute risk and population attributable risk is also not clearly

⁹ Furness *et al.*, *The evaluation of diagnostic laboratory tests and complex biomarkers* (PHG Foundation/RCPATH, March 2008), available from www.phgfoundation.org/pages/projectlist.htm.

¹⁰ See, for example, Lenzer, J., and Brownlee, S., “Direct to Consumer Genetic Testing: Knowing me, knowing you” (BMJ 2008;336:858-860)

understood by health professionals let alone their patients. This is one reason for the HGC's recommendations in *More Genes Direct* that specific tests should only be offered through specific outlets or by specific healthcare professionals¹¹ and that there should be regulatory mechanisms to cover all genetic tests, including so-called 'lifestyle' tests.¹² These would include clear provisions relating to whether and how a company would enable clients to get updated interpretations of their risk profile, as the ability to interpret the same set of DNA results is bound to improve over time.

27. The huge amount of information coming from genomics presents a significant challenge to professionals who offer genetic counselling or use information from genetic tests. Equivalent challenges exist in terms of educating people outside the clinical genetics community so that they know how and when to make appropriate use of these tests and this will include education both of other healthcare professionals and, also, of the general public.
28. While it is likely that Regional Genetics Centres will always concentrate on highly predictive genetic tests for single gene disorders, more and more tests will no doubt be developed that identify predisposition but that are not, in themselves, specifically diagnostic. As the relevance of genetic information moves beyond specialist genetic services both within the NHS and through direct-to-public testing, substantial efforts will need to be made to incorporate this meaningfully into practice, on the one hand, and to absorb a new area of demand for health advice on the other. Examples of early initiatives in this direction are the National Screening Committee's Pegasus initiative (training for delivery of perinatal genetic screening programmes), the work of the Birmingham Genetics Education and Development Centre and ScotGen (the Scottish Genetics Education Network), which works collaboratively with the Birmingham centre. We welcome the commitment of Scottish and Welsh financial support to the Birmingham centre in recognition that training and education is a UK-wide issue. However, a significant amount of this requirement is likely to fall on genetic counsellors to support families in which new disease-predisposing genetic variations are identified and for which tests are developed, and we recognise the need to support additional posts to meet this demand.

¹¹ *More Genes Direct*, paragraph 3.14.

¹² *ibid.*, paragraphs 3.9 – 3.14.

Conclusion

29. We trust that the comments above are helpful to the Committee in pursuing their inquiry. If the Committee requires any additional information or clarification we will be happy to provide it. We also welcome any future conclusions and comments from the Committee that we may take into account in our future discussions in this important area. To comply with the HGC's open working style a copy of this response will be placed on the HGC's website.

Human Genetics Commission
April 2008

Annex – Human Genetics Commission Terms of Reference and Contact information

Terms of Reference

- To analyse current and potential developments in human genetics and advise Ministers on:
 - their likely impact on human health and healthcare;
 - their social, ethical, legal and economic implications.
- To advise on strategic priorities in the delivery of genetic services by the NHS.
- To advise on strategic priorities for research.
- To develop and implement a strategy to involve and consult the public and other stakeholders and encourage debate on the development and use of human genetic technologies and advise on ways of increasing public knowledge and understanding.
- To co-ordinate and exchange information with relevant bodies in order to:
 - identify and advise on the effectiveness of existing guidance and of the regulatory and advisory framework as a whole, taking account of European and global dimensions;
 - look at the lessons learnt from individual cases requiring regulatory decision to build up a wider picture.
- To consider specific issues related to human genetics and related technologies as requested by Ministers.
- To operate in accordance with best practice for public bodies with regard to openness, transparency, accessibility, timeliness and exchange of information.