

Submission to House of Lords Science and Technology Committee Inquiry into Genomic Medicine by Generation Scotland.

1. Generation Scotland welcomes the opportunity to respond to the House of Lords Science and Technology Committee Inquiry into Genomic Medicine. We would be pleased to expand on any of the points outlined in this submission and to assist the Committee further in its Inquiry.

Background

2. Genome wide analysis of sequence and copy number variation is now both technically feasible and affordable. The success of the original Wellcome Trust Case Control Consortium study of 14,000 cases/controls of seven common diseases is being followed by a second round of such studies on existing cohorts and this general approach has now been widely adopted. These early studies have not only highlighted the potential value of this research, but also the critical need for replication and validation at the population level, in cohorts with high quality phenotypic data. Such cohorts are essential for translating genomic discovery into health gain. Generation Scotland is poised and positioned to serve that need.

Overview of Generation Scotland

3. Established in 2001, Generation Scotland (www.generationscotland.org) anticipated the ever advancing technological revolution in genomics. Generation Scotland is funded by the Scottish Government and the Scottish Funding Council. The founding principle of Generation Scotland is that a co-ordinated effort of an inter-disciplinary team of clinicians, scientists, social scientists and lawyers at the Universities of Aberdeen, Dundee, Edinburgh and Glasgow, in close collaboration with the National Health Service in Scotland, would be necessary to create a sustainable genomics research programme of international standing.
4. Generation Scotland comprises several large biobank collections: (1) the Scottish Family Health Study is a high fidelity phenotyped family based cohort (comprising ~6,000 and projected to ~50,000 recruits). (2) An ancestry cohort with associated lymphoblastoid cell lines (currently ~1000 recruits, projected to ~2,500); (3) a blood donor DNA database (5,000 recruits); (4) a proteomics biomarker project; and (5) an extensive public consultation exercise and ethics/social/legal programme generating theoretical and practical concepts, such as benefit sharing. Generation Scotland also has a programme of capacity building in genomics, mathematical biology, health informatics and related research.

5. Fieldwork

The Scottish Family Health Study is explicitly designed to serve as a platform for gene discovery, for replication and for validation across a wide spectrum of health domains. Moreover, the family based structure not only offers substantial advantages of statistical power over population based cohorts for genetic studies, but also provides, in the longer term, the exciting opportunity of transgenerational studies. Demographic, lifestyle and clinical information, plus

blood samples are collected from participants, along with intensive phenotyping for a number of quantitative traits that relate to major disease areas, including cardiovascular disease, obesity, mental health and musculoskeletal disease. Particularly worthy of mention are the unique mental health and cognitive function phenotype. Our Phase 1 data suggest 26% of participants require formal SCID interviews for major mood disorders. "Probands" are individuals aged between 35 and 65 years, who are recruited with at least one full sibling and typically more, along with other first degree relatives. Larger families (particularly groups of aunts/uncles) are targeted for recruitment, to maximise the power of the study.

6. **Governance** has been a key focus. An Advisory Board Chaired by Lord Sutherland and reporting to the Scottish Government's Chief Scientist Office, is enshrined in a memorandum of understanding between the four Scottish Medical Schools and the NHS in Scotland; an Access Policy is modelled on Wellcome Trust guidelines and existing funded biobanks; and a dedicated web site provides information for researchers and the lay public (www.generationscotland.org). Unique features of the Scottish Family Health Study include its family base, the associated phenotype information gathered at the time of recruitment and the capacity to add further high quality, lifetime phenotypic information by secure and confidential linkage to the NHS Scotland electronic health record.
7. An extensive programme of **public consultation** has been undertaken through exit questionnaires, public survey, consultation with Public Partnership Groups and interviews with participating families. Study documents, procedures, SOPs and staff training were refined following an initial pilot phase, taking account of the public consultation, plus advice from the GS Advisory Board; and international evidence emerging from the wider ethical, social and legal issues of biobanking. We are also generating theoretical and practical concepts, such as benefit sharing, relevant to Generation Scotland and other biobanking proposals;
8. Generation Scotland sees knowledge transfer of genetics into the clinical community as key for the future adoption of genomic science. The **Scottish Genetics Education Network** (ScotGEN) is an extant group of healthcare professionals, university academic staff and computer scientists involved in genetics education for nurses, midwives, doctors and other health professionals in Scotland. Funding in Phase 1 was used to co-ordinate the development of computer delivered education in genetics for healthcare professionals in Scotland. Two components were delivered: (i) the mapping of existing materials to core competencies and specification of work required; and (ii) design of four teaching modules delivered in an e-learning format.
9. A secure **informatics** environment developed as a service-oriented architecture including re-usable services and client applications, linking with required NHS systems through mediating client applications sitting on NHSnet; including electronic research data capture on phenotypic data and quality management applications. Written informed consent allows prospective and retrospective linkage to routine NHS records.

10. **Laboratory Integration** has been implemented across the four Scottish academic centres. Key laboratory technologies have been procured, installed and implemented, including ultra-high throughput genotyping platforms, capable of supporting genome wide association studies and an integrated Laboratory Information Management system, networked across all sites, to manage, govern and track all biological materials associated with Generation Scotland projects; a secure database system and Linux analysis cluster established for genetic analyses.

11. **Statistical Genetics**

Detailed simulations based upon known Scottish family demographics and recruited family structures have been conducted. These confirm the theoretical added power of family based studies to test quantitative trait hypotheses. They also provide a clear protocol for optimizing resource allocation in recruitment of family structures.

We would like to make the following general comments in response to the questions and issues raised by the committee.

12. **Policy Framework**

For researchers, the policy framework is complex, with a large number of bodies, both European and UK, involved in setting and reviewing policy relevant to issues that impact upon genomic medicine. This is a congested and rapidly moving area. The Health Departments and statutory bodies such as the Human Fertilisation and Embryology Authority play a lead role. They are supported by numerous Government advisory bodies such as the Human Genetics Commission. The MRC, post-Alderhey and increasingly, the Wellcome Trust have taken a lead in policy development around biomedical research, particularly in the area of access and governance of bio resources. Other charitable bodies such as and Nuffield Council on Bioethics have made key contributions as well as professional bodies including the Academy of Medical Sciences. Internationally, P3G and HUGO play a major role.

For researchers, translation of policy into “best practice” that is clearly in the public good is a key priority. Generation Scotland has therefore been fortunate to benefit from the Generation Scotland Advisory Board (GSAB). This is an independent body, accountable to the Scottish Government, which advises the Generation Scotland Scientific Committee on policymaking so that Generation Scotland practices and resources are used to the best advantage of participants and the wider community. GSAB is chaired by Lord Sutherland of Houndwood.

The five GSAB members were appointed by the Health Minister on the basis of open competition and following Nolan procedures on public appointments. Between them they have an impressive breadth and depth of experience in law, ethics and genetics.

13. **Research and Scientific Development**

- **What is the state of the science? What new developments are there? What is the rate of change?** Genomic science is rapidly evolving, with ever lowering costs, increasing sensitivity and specificity. Whereas assembling the consensus human genome sequence required international effort over a decade and at a cost of around \$1 per base, or \$3billion total, the next generation genomic technologies promise whole genome resequencing at around \$1,000 total.
- **Who is taking the lead in the consideration and co-ordination of research and the development of new technologies?** National funding agencies, such as the NIH, MRC and Wellcome Trust play a key role, not least in coordinating major research infrastructure initiatives, such as the HapMap (an average genetic profile of major ethnic groups that can make population genetic studies more efficient and cost effective), the 1,000 genome project, which aims to resequence in full the genomes of 1,000 representative individuals, and the EUCOM and KOMP projects, which will genetically engineer a mutant mouse for every gene in the mammalian genome. New technologies are generally borne in academia, but then rapidly commercialized. Marker leadership is only assured by innovation. There is a close relationship between the major genome centres and industry as they serve as the alpha and beta testing centers for next generation genomics tools.
- **How effective is the policy and investment framework in supporting research in this area?** Investment in biobanks is costly and requires long term investment and is thus not entered into lightly. The idea however of a 'one size fits all' study, is unrealistic and misses the point and indeed the scale of the opportunity. The need for multiple themes and rounds of investment is being recognized, for example by the Wellcome Trust in funding a second phase of genome wide case-control studies. Whilst supportive in principle, it is not clear the MRC budget provides the flexibility and head room to be proactive beyond the UK Biobank and other established commitments.
- **How does research in the UK compare internationally? How much collaboration is there?** The UK was a lead player, technically, scientifically and financially in the Human Genome Project. The UK has arguably taken the lead internationally with the UK Biobank and the Wellcome Trust Case Control Consortium. There is a high level of international collaboration, through EU Frameworks 5, 6 and now 7. There have been high level collaborations between the UK (in particular the Wellcome Trust) and the US (NIH). International organizations such as HUGO and P3G play their part, but as non-funding agencies, they have a limited agenda-setting role.
- **What are the current research priorities?** To identify genetic variants that modify disease risk across all relevant medical domains of unmet need, including mental health; to do so at the individual, family and population level; to translate such genetic information into understand of the biological underpinning of disease; to use that understanding as a platform for preventative medicine and rational therapy.
- **What is the role of industry? How much cross-sector collaboration takes place?** Industry as a technology provider is essential, as is a competitive market for the introduction and application of innovative technologies. The traditional role of industry in drug target discovery and development has never been under more pressure than currently as blockbuster drugs inexorably move off patent. The flow of new molecules to the market place has slowed despite increasing R&D investment. The 'merge-to-survive' philosophy of recent years has been a sticking plaster on the problem. Pharma have largely ignored the genomics

driven concept of personalized medicine. Biologics, largely the product of academia and biotech spin outs, herald a new era, but will depend upon core pharma 'know how' and financial muscle to solve production and formulation issues and work their way through ever increasing and costly regulatory hoops. Partnership with healthcare providers who can provide access to well phenotyped and genetically stratified patient groups to improve clinical trial efficacy and reduce Phase 2 attrition will be invaluable.

14. **Data Use and Interpretation**

We propose that the accurate, reproducible characterization of phenotypic data and environmental exposures are of equal important to DNA sequence data if genomic medical research is to reach its full potential. The availability of longitudinal datasets that allow genotypic/phenotypic linkage are key. Scotland has a longstanding, international reputation in using record linkage of medical records for epidemiological, genetic and clinical trial research. Compared with the rest of the UK, data quality is high, the centralisation of data in NHS Scotland is efficient, and the comprehensive computerisation of routine clinical data, alongside the mandated use of a unique patient identifier (the Community Health Index, CHI) for all health episodes, means that access to data for research is becoming easier and costs are falling. Building on these strengths, Generation Scotland has been the catalyst for an informatics work stream on the quality, quantity and governance of research using electronic patient records. Developing existing strengths in Scotland and extending them via the NHS CfH Research Capability Programme will enable research to achieve its full potential as a "core" activity for healthcare. This is essential if the United Kingdom is to keep pace with or even surpass similar research programmes elsewhere, particularly in Scandinavian countries. Generation Scotland has therefore brought together leading Scottish groups in record linkage; epidemiology; social science; legal and ethical issues; health informatics and clinical trials design and execution. This has allowed linkage of genomic data to routine clinical data for studies of pharmacogenetics as well as GWA studies of common phenotypic traits.

15. **Translation**

- **What opportunities are there for diagnostics, therapeutics and prognostics - now and in the future?** The promise in this area is very high. Indeed, it would be an unimaginably wasted opportunity if genomic diagnostics, therapeutics and prognostics did not become available widely and quickly. We are already seeing the first offerings in the field, with biologics matched to genetic tests. Increasingly these tests will become indirect – a 'genomic' version of a blood glucose 'dip stick' test, if you like - where the test is a measure of a gene product rather than of the genetic material itself..
- **Who is responsible for translation to clinical practice?** Unless there is a radical societal change leading to Government commissioned (or philanthropic sponsorship of) health product development, this will remain a complex and uncertain negotiation between invention and IP protection; clinical need; willingness to pay; and the need to offer shareholder value.
- **Given the pace of technological advance, how 'future-proof' is healthcare investment in this area?** As suggested above, by the very nature of the field,

- which is currently in R&D and 'discovery' mode, there is no 'one size-fits-all' investment. There is however no obvious challenger to genomic medicine.
- **How does the UK compare to other countries and what lessons can be learnt?** As suggested above, the UK compares favorably, but there is no room for complacency. Indeed, as with many previous examples of UK technology leads, there is a very real danger that the commercial benefits will fall to others. The level of inward investment in academic lead R&D is low compared to North America and to the national level of investment being made by, for example, Singapore, South Korea and China.
 - **How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?** As discussed above, genetic tests for common complex disorders, where risk is shared between multiple genetic risk factors, will be of a different class and utility from those that are definitive for rare, single gene, 'all or none' inherited conditions. In the internet era, genetic 'testing' is all but impossible to regulate. That does not mean that there should not be tight regulation of UK providers, where the emphasis must be on the underlying evidence base, QA, QC and how the results should be interpreted.

16. **Biomarkers and Epidemiology**

- **In what way do genome-wide association studies contribute to the identification of biomarkers? How is the study of genetic factors and biomarkers integrated for translational purposes?** This has been broadly addressed in the foregoing.
- **What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?** We have summarized this above for Generation Scotland.

17. **Use of genomic information in a healthcare setting**

- Although this research is at a relatively early stage, it is likely that many diseases (such as asthma, diabetes and schizophrenia) will be re-classified based on molecular factors that affect prognosis and response to treatment.
- With few exceptions, genetic testing for individualized medical advice is unlikely to be routinely available for many years. Any gene that is found to be associated with a clinical condition (or a response to treatment) needs first to be replicated in other population-based studies, quantified for its contribution to the condition in question (alongside other genes and environmental factors), validated in a clinical setting, and commercialized. As well as education of the public in the meaning and interpretation of genetic findings, there must be extensive education of health professionals. These can proceed in parallel, but are both in their infancy.
- Because of the need for replication, quantification and validation, there should be regulation of the marketing and use of genetic testing arising from new research. Without this, there is considerable risk of producing misleading results and causing anxiety and mis-treatment.
- The results emerging from genetic research will introduce new concepts of disease and illness, and, eventually, the possibility of genetic testing and decision-making based on the results of these. This will be very new to most

health professionals. It will be of a different class to that which currently operates for highly heritable and disabling disorders for which future reproductive planning is an important part of the genetic testing. For the common complex diseases researched through biobanks, genetic testing will be more about modifying risk of developing symptoms and of optimizing treatment choice as and when symptoms manifest. There is little research on the prospective needs for training and education of health professionals in this area. Such research as there is suggests a perceived major gap in knowledge and the ability handle the resultant uncertainty. More research in this area is needed, urgently.