The Academy of Medical Sciences

April 2008

Submission to House of Lords Science and Technology Committee Inquiry into Genomic Medicine

1. The Academy of Medical Sciences welcomes the opportunity to respond to the House of Lords Science and Technology Committee Inquiry into Genomic Medicine. The Academy's core objectives are to promote advances in medical science and to ensure these are converted as quickly as possible into healthcare benefits for society. 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. Genomic medicine holds the promise to revolutionise care and prevention of common diseases. While genetics is the study of single genes and their effects, genomics is the study of the functions and interactions of all the genes in the genome. The science of genomics applies to common conditions such as cancer, diabetes, cardiovascular disease and mental illness – all conditions that are due to the interactions of multiple genes and environmental factors. Genomic techniques allow the identification of predisposing or protective genetic factors for these diseases – for the first time in history, health and disease can be defined by 'molecular fingerprints'. Using genomic information it is possible to: design more effective drugs; screen and diagnose disorders more effectively; prescribe the best treatment for each patient; identify and monitor individuals at high risk from a disease; and avoid adverse drug reactions. Although the promise of genomic medicine has yet to be fully realised, new genetic discoveries bring the reality of this promise ever closer.

3. The most exciting advances relevant to genomic medicine come from the recent explosion in Genome Wide Association (GWA) studies. These studies involve rapidly scanning polymorphic markers across the complete genomes of large numbers of individuals to find genetic variations associated with a particular disease. These typically involve 300,000-500,000 or more single nucleotide polymorphisms (SNPs). GWA studies have only become possible in recent years due to advances in DNA sequencing and genotyping. These new methodologies have accelerated the rate at which genomic data can be generated, whilst at the same time reducing the cost. For example, new sequencers from Roche, Illumina or ABI can sequence many thousands of base pairs of DNA in a single run lasting 1-5 days. As a result, the number of identified genetic disease markers has risen from only a handful in 2002 to over 100 in 2007, including robust information on genetic markers for diabetes, heart disease, Crohn's disease and several cancers.[1]

[1] Feero *et al.* (2008). *The genome gets personal – almost.* JAMA **299**, 1351-1352.

4. In addition to the association between SNPs and human disease, copy number variation (i.e. individual differences in the number of copies of a particular gene or genomic region) is also likely to influence predisposition to some common diseases. Very high frequencies of copy number variations have been documented at many different sites in the human genome.[2] It is estimated that up to 8% of live births have congenital malformations, of which at least 50% have underlying genetic causes, including those described as copy number variants, as well as duplications and deletions. The societal costs of congenital malformations is high, and there are strong arguments to use array CGH (comparative genomic hybridisation), MLPA (multiplex ligation-dependent probe amplification) and other genome sequencing technologies to test affected babies. It is only by identifying the mutated genes and genomic regions responsible that we can understand the biological pathways involved and so develop new treatment modalities.

5. Consideration of genomics must also include the role of epigenetic changes in disease, particularly later onset diseases and cancer. Epigenetic changes do not alter the underlying genomic sequence, but instead, stably modify the DNA and chromatin proteins associated with the sequence, thus affecting gene expression. Such changes can be increasingly readily assessed using methylation status and chromatin structure studies. Understanding the potential role of epigenetic changes in mediating gene-environment interactions is a key research question that is being actively pursued. In the future, it is possible to envisage chromatin-modying drugs that could repair/induce epigenetic changes.

6. Importantly, the ability to interpret genomic data accurately, and to use this information to develop interventions to prevent or treat disease, still requires a great deal of research effort. Furthermore, it is far from evident that the UK environment for translating advances in genomic medicine into healthcare practice is optimal. The Office for the Strategic Co-ordination of Health Research (OSCHR) will be a key structure in underpinning the necessary new era of collaboration between academia, industry and the NHS. Investing in this area could reap dividends if a solid large-scale infrastructure for genomic medicine is developed in the UK that could then be marketed to other countries.

7. In this submission we focus on the translation of genomics into healthcare in the following areas:
    - Risk factor prediction and prevention of disease.
    - Diagnostics, pharmacogenetics and stratified medicines.
    - Pathogen genomics.
    - Genetic privacy and education.

[2] Pinto et al. (2007). *Copy-number variation in control population cohorts.* Human Molecular **Genetics 16**, R168-R173

Risk factor prediction and prevention of disease

8. While the GWA approach is a potentially powerful way of identifying genetic factors associated with disease, it can be problematic for a number of reasons. For virtually all of the genetic loci identified through GWA studies, the effect sizes are modest in some cases (i.e. a relative risk of ~1.3-1.5) and small in most cases (relative risk of ~1.1-1.3).[3] These effect sizes support the view that many different genes play a role in genetic susceptibility to common diseases, but it means that very large sample sizes are needed for GWA studies. Further problems include the potential to over-estimate true effect sizes (i.e. to generate false positives) through the sheer number of statistical tests performed, or to under-estimate effect sizes because the causative variant is not directly measured. Many of the associations identified by GWA studies to date have not involved genes previously suspected of being related to the disease under study, and some have been in genomic locations harbouring no known genes. This lack of information on gene function, together with poor data on how genetic risk factors combine with environmental risk factors, insensitivity to rare genetic variants and possible biases due to case and control selection, are further important limitations of GWA studies.

9. In bringing this knowledge into the clinic, doctors and scientists need to understand the limitations described above to be able to interpret GWA results accurately for themselves and for their patients. There are also important issues around how predictive risk information can be most effectively utilised over an individual's lifetime. At a more fundamental level, harnessing the power of genomic medicine will require a shift in the UK health care delivery system and incentive structures, which are currently focused on 'sick care' rather than disease prevention.

10. The use of GWA findings to design 'gene tests' for individual disease risk – already being marketed commercially – can be problematic. There is still relatively little information on how the prevalence and risk contribution of genetic loci vary amongst individuals, or how the inheritance of multiple markers affects an individual's risk for various diseases. Using a gene test to predict disease risk will also require evidence that the test adds to information on known risk factors (e.g. age, obesity, family history), that effective interventions are available, that improved outcomes justify the costs, and that there are no adverse consequences for patients and their families.

11. Rather than predicting *individual* disease risk, the primary use for GWA studies in the near future is likely to be in predicting disease risk in *population groups*. Preliminary data generated by groups at the Wellcome Trust Centre for Human Genetics in Oxford have shown significant levels of relative risk in 'high-risk' population groups.[4] For example, from these data, the top 5% of the population at risk from Crohn's disease have a relative risk of 5-8; the top

[3] See for example, Wellcome Trust Case Control Consortium (2007). *Genome-wide association study of 14,000 case of seven common disease and 3,000 shared controls*. Nature **447**, 661-678.
[4] See http://www.wtccc.org.uk

1% have a relative risk of 9-15 and the top 0.1% have a relative risk of 17-29.[5]

12. Making the simplifying assumption of independence across diseases, then simple probability calculations show that across 50 diseases:
    - ~95% of people will be in the top 5% of genetic risk for at least one disease.
    - ~40% of people will be in top 1% of genetic risk for at least one disease.
    - ~5% of people will be in the top 0.1% of genetic risk for at least one disease.

    Therefore, while the predictive power of genomic tests for any one disease might be limited, for most people, across 50 diseases, there will be a few diseases for which the individual is at particularly high risk. Personal genomic screening might therefore be more usefully viewed as a way to identify the 2 or 3 diseases for which an individual has the highest risk.

13. Identifying at risk population groups also has important implications for disease screening, particularly in cancer. GWA findings can be used to guide cancer risk profiling strategies, for instance to determine the size of the population that should be screened to identify a given proportion of cancer cases. This is important where screening is expensive; screening mechanisms that are currently too costly, such as MRI for breast cancer, might be made more attractive if they are applied to only a proportion of the population.

14. Overall, harnessing the opportunities of genomic medicine in risk factor identification and disease prevention will require the development of novel statistical approaches to integrate complex data sets, construct detailed molecular 'signatures' of disease and develop predictive models of risk and outcomes. This, in turn, will require researchers' access to high quality data from prospective studies and disease registries, which raises complex questions around data privacy and confidentiality (see paragraph 26). Selective screening procedures will also requires more education of patients and the general public on risk and benefit.

Diagnostics, pharmacogenetics and stratified medicines

15. There is a strong case for innovation in the application of genetics and genomics to diagnostics – to create a new era of 'molecular' diagnosis that can facilitate stratification of patient populations, generate more precise identification of disease states, and lead to more efficient use of drugs. It is possible to envisage a molecular pathology laboratory of the future, which is at the hub of clinical genetics, cytology, haematology and pathology services.

16. But there are several obstacles to the optimal translation of genetics and genomics in the NHS. For instance, there is the problem of current hospital

[5] Professor Peter Donnelly FRS FMedSci (personal communication).

structures, where clinical genetics, pathology, cytology and haematology are served by discrete operations. Multiple different decisions on commissioning new diagnostic tests, taken by multiple different Trusts and PCTs around the country, can also stifle innovation.

17. Traditionally, diagnostic tests have simply been required to measure their target variable accurately and reliably. However, the new breed of molecular diagnostics will need to demonstrate clinical utility, i.e. that knowing the outcome of the diagnostic test allows better clinical practice. This will require a review of current paradigms for developing, testing and regulating new diagnostics. The current regulatory system lacks a clear pathway for molecular diagnostics and several questions remain to be resolved:
    - Who should regulate the development of these tests?
    - How will the regulatory framework cope with tests for many different genetic biomarkers that have varying degrees of utility?
    - How will the regulatory framework adapt to allow for iterative changes during product development?
    - Will molecular diagnostic tests be carried out by NHS clinical laboratories or private companies?
    - Will trials for clinical utility of new molecular diagnostics be undertaken by diagnostic companies or the health service?
    - How will the extra costs of testing for clinical utility be borne and reflected in pricing?

    Furthermore, thought must be given to intellectual property issues in the development of molecular diagnostics - a key factor in ensuring that companies are incentivised to innovate in this field.

18. The promise of pharmacogenetics and stratified (or personalised) medicines - to optimize efficacy of drug treatment through identifying responders and non-responders and to reduce adverse drug reactions - has received much attention in recent years. This field has been explored in a recent publication from the Academy's FORUM with industry, 'Stratified medicines'. This report concluded that stratification is desirable for patients and healthcare systems, but cited considerable challenges associated with tackling the regulatory, investment and structural obstacles:
    - There is often a barrier in defining stratification prior to drug registration because of the difficulty in developing a therapeutic and diagnostic simultaneously.
    - There may be relatively little incentive for diagnostic companies because of problems with protecting intellectual property and the cost of demonstrating clinical utility (see above).
    - There may be relatively little incentive for pharmaceutical companies in 'post-approval' stratification because their current commercial environment lacks pricing flexibility.
    - The research structure with which to assess clinical utility does not always exist (see above).

19. With regard to improving the regulatory and investment framework, it is important to devise new incentives for companies to develop therapeutics (pricing flexibility linked to demonstrable value) and diagnostics (new approaches to patent protection and support for clinical development programmes). The Cooksey Review proposal on conditional approval – allowing new drugs in NHS priority areas to be made available to patients following preliminary safety studies and proof of efficacy – may provide one means to become more flexible in assessing the value of stratification and, thereby, advance genomic medicine.[6]

20. Alongside the need for regulatory reform, there are significant new opportunities for public-private partnership to establish clinical utility in genomic medicine. These opportunities include:
    - Greater academic involvement in generating fundamental knowledge in exploratory drug development (for example, identifying biomarker signals).
    - The use of public infrastructure for clinical trial sample collection to inform the conditional approval process, assist pharmacovigilence and develop a better framework for diagnostic evaluation.

21. There is an additional strategic issue for off-patent drugs. While it is clear that the public sector has a major interest in supporting research, if there is to be public-private partnership to generate pharmacogenetic data for off-patent drugs, then it is necessary to be unambiguous about the nature and quality of the evidence required and who pays to collect it.

22. Pharmacogenetics has already been translated into clinical practice in some instances, for example the US Food and Drug Administration (FDA) recently altered the labels of both warfarin and carbamazepine to encourage healthcare professionals to consider pharmacogenetic testing prior to prescribing these drugs in certain situations. DNA microarray technology provides a powerful tool for molecular classification of disease states and personalised disease management. Such technology can be used to classify tumours according to their gene expression 'signature' and thus guide treatment – this is already under way in breast cancer patients. A range of other genetic factors have also been identified that could be used to define responsive populations for drug treatment, for example Bcr-abl and Gleevec; Her-2 and herceptin; B-adrenoreceptor and B-agonists; FcRa IIIa and CD20 antibody; and EGF receptor and Iressa.

23. Genomic medicine is rapidly advancing our ability to identify novel drug targets for efficacy. But some of the technology platforms underpinning the development of genomic medicine (transcriptomics, proteomics, metabolomics) are also proving increasingly useful in both pre-clinical and clinical studies in the safety assessment of new drugs, as discussed previously in the context of stratified medicines. The broader scientific opportunities and the implications for regulatory authorities and policy-makers are discussed in the Academy's Forum report 'Safer Medicines' (2005). Advances in this area

[6] http://www.hm-treasury.gov.uk/media/4/A/pbr06_cooksey_final_report_636.pdf

promise to aid the detection of safety signals or characteristic molecular fingerprints that define potential risks by improving the speed, sensitivity and specificity of analysis. Such advances may make it possible to achieve some reduction in the number and duration of exposure of animals used in safety tests and, in addition to their ability to contribute directly to patient safety, may help to diminish the currently high rate of attrition in new the development of new medicines.

24. Extensive collaboration is required between pharmaceutical companies, academia and the regulatory authorities to validate new technologies. This will require companies to share safety data and to engage in new pre-competitive joint research in the UK and internationally. Other implications for building international networks and large databases are described further in the 'Safer Medicines' report. Overall, the incorporation of pharmacogenetic methods into clinical trial methodologies (in both the public and private sector) could do much to improve safety and efficacy outcomes.

Pathogen genomics

25. The contribution of genomic medicine to improving public health should not be seen as limited to research on the human genome. Advances in our understanding of pathogen genomics are creating many new opportunities (in diagnostics, therapeutics and vaccines) to tackle infectious diseases where there are unmet medical needs and major threats to public health, e.g. the growing problem of antimicrobial resistance and the prospect of pandemic influenza. A recent joint Academy of Medical Sciences/Royal Society meeting[7], building on the previous joint report 'Pandemic influenza: science to policy',[8] highlighted several unresolved issues for influenza pathogen genomics research and innovation policy that are generalisable and highly relevant to the questions posed in this inquiry. For example:
    - There is need for international effort to improve the sharing of human pandemic influenza virus genetic sequences and to encourage collaborative research.
    - It is important to ensure that sequence data are used optimally for novel diagnostic and vaccine development – this raises issues for incentivising companies, protecting intellectual property and sharing benefits.
    - Concomitantly, there is need to facilitate the regulatory framework with clear standard setting to expedite the development of novel products.
    - Greater integration of clinical databases by researchers and research funders would help to improve assessment of the determinants of therapeutic responsiveness.

[7] For a report of the symposium see: http://www.acmedsci.ac.uk/p101puid122.html
[8] To download the original report see: http://www.acmedsci.ac.uk/p99puid89.html

Genetic privacy and education

26. The promise of genomic medicine is accompanied by the challenge of protecting the privacy of genetic data and the threat of genetic discrimination. The use of personal information in medical research has been discussed in the Academy's 2006 report 'Personal data for public good: using health information in medical research'. That report argued that protecting individual privacy should not be at the expense of the important public benefits that are derived from research.

27. Further consideration must also be given to how genetic information impacts on insurance and employment etc. Research institutions in the US continue to advocate for federal legislation to prevent genetic discrimination by employers and health insurance providers; discussions at the UK and European level will also be needed on this issue.

28. The realisation of genomic medicine will ultimately depend on educating both healthcare professionals and the general population. A recent US study by the RAND Corporation concluded that the primary care workforce, who will be required to be on the front lines of the integration of genomics into clinical practice, feels 'woefully under-prepared to do so'. The RAND study also revealed a lack of basic knowledge about genetics amongst health professionals and therefore a lack of confidence in interpreting genomic data. As well as raising general levels of knowledge in the healthcare sector, a significant investment will need to be made in training more specialist genetic counselors. Ultimately, there is a need to: integrate genetics and genomics professionals into the health care workflow; develop genomic decision-support tools for health care professionals; and incorporate complex diagnostics into evidence-based clinical guidelines as appropriate.

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The Academy of Medical Sciences

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The Academy seeks to play a pivotal role in determining the future of medical science in the UK, and the benefits that society will enjoy in years to come. We champion the UK's strengths in medical science, promote careers and capacity building, encourage the implementation of new ideas and solutions – often through novel partnerships – and help to remove barriers to progress.

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