

Joint Committee on Medical Genetics

The Royal College of Physicians

The British Society for Human Genetics

The Royal College of Pathologists

Remit, membership and summaries of meetings: http://www.bshg.org.uk/joint_committee/joint_committe.htm

18th April 2008

Response to the Call for Evidence on Genomic Medicine from the House of Lords Science and Technology Sub-Committee

Submission of evidence from the Joint Committee on Medical Genetics (JCMG)

Background.

The JCMG was established in 1999 with principal representation from the Royal College of Pathologists (RCPATH), Royal College of Physicians (RCP) and the British Society for Human Genetics (BSHG) to provide a unified forum “to promote and maintain the highest standards of practice and education in both clinical and laboratory applications of genetics in health”. The Chairmanship and administration rotates on a three yearly basis; initially it resided with the RCP, then rotated to the BSHG and since 2006 has been chaired by RCPATH. The Committee advises Government and other bodies on policy and services issues relating to genetics in medicine; reports and receives information from the parent bodies including representative from the Royal College of Paediatrics and Child Health, the Scottish RCP, Faculty of Public Health, Royal College of General Practitioners, Royal College of Obstetrics and Gynaecology, and observers from the Department of Health, National Screening Committee, the Foundation for Genomics and Population Health, MetBioNet and the Genetics Interest Group. In 2006, the JCMG welcomed an observer from the National Genetics Education and Development Centre. The JCMG seeks to co-ordinate advice on workforce planning and initiates working groups on specific topics of particular importance. Members of the JCMG were asked to submit responses based on the six headings provided by the House of Lords Science and Technology Committee. A summary of these responses is detailed below.

Key points.

- The U.K. is a world leader in basic human genome research and in the development and research application of many of the technological spin-offs associated with the Human Genome Mapping Project (HGMP).
- NHS Genetics Service delivery in the U.K. to date has been facilitated by the close collaboration between clinical geneticists, genetic laboratory scientists and technologists, University Human and Medical Genetics Departments all based around 23 Regional Genetics Centres providing centres of excellence and critical mass populations for efficient and effective service delivery. This infrastructure must be maintained although centralisation of some novel technologies, e.g. bioinformatics, might be appropriate.
- The government recognised that expansion in the workforce and infrastructure investment would be required to take advantage of the HGMP output and has

invested significantly in England via the 2003 White Paper “Our Inheritance Our Future”. The recently published (April 2008) review of the White Paper’s achievements to date confirms that the Government is “committed to bringing new genetic advances to bear wherever they can be used to benefit patients”. Matching these aspirations with a long term commitment to infrastructure, funding and support, remains one of the greatest challenges facing the delivery of genomic medicine and technology via the NHS.

- The pace of technological advances arising directly and indirectly from the HGMP is making translation from research into clinical service increasingly difficult to plan and implement.
- There is a significant funding gap in the final stage of translational research i.e. those stages which bridge the gap between assessment, evaluation and implementation. This is particularly problematical and acute in technologies providing high resolution whole genome analyses. The exclusion of research proposals including novel laboratory testing from the current funding calls of the NHS National Institute of Health Research (NIHR) is significantly exacerbating this problem.
- The NHS commissioning process is not structured or resourced to react to rapid change such as those currently being seen in all aspects of genetics service delivery i.e. in both constitutional (germ line) and acquired (e.g. cancer) genetics. The NHS public health advice to these processes is extremely limited in capacity (almost non-existent).
- NHS IT infrastructure, especially internet bandwidth capacity and download speed, needs significant improvement especially for the rapid dissemination of increasingly large genomic datasets between Regional Clinical Genetic, Genetic Laboratories and appropriate analytical bioinformatic centres.
- Training for the interpretation and clinical utility of data from novel genomic technologies is required both for genetics professionals as well as for pathology, medical and surgical specialities increasingly utilising genome technologies.
- The NHS is currently reviewing training for all clinical scientists and is proposing a modular inter-disciplinary approach to pre-registration (i.e. first 3-4 years) training. The impact of this model needs careful scrutiny in the context of the need for greater flexibility in recruitment of scientific staff with appropriate genomic and bioinformatic backgrounds.
- The planning, provision, implementation and funding of present and future Biochemical Genetics and associated Screening programmes requires ongoing and strategic investment.

Specific JCMG committee members’ responses are inserted under the relevant headings.

Policy Framework

- There are professional groups, (laboratory, pharmaceutical, public health, clinical and social) that are well aware of the opportunities and difficulties that can arise from the development of genomic technologies. There is however no clear mechanism to provide this information to institutions responsible for health and other policies and particularly those who can implement these technologies. Much of the implementation is still done on an *ad hoc* basis with local commissioners who only have a limited understanding of the subject and many conflicting priorities. Furthermore many of the benefits may be many years into the future and in areas away from the clinical specialities making the initial financial investment. “Invest to save” is a laudable aim but rarely implemented on a significant scale. This opens the market to private providers who most likely will have short term commercial financial gain as the priority rather than clinical benefit and long term health gain for the population. There remains scant regulation on the implementation of molecular technologies.

- The existing policy framework involving the NHS Genetics Team (England), UKGTN, and GENCAG needs strengthening and recognition that genomic technologies transcend geographical boundaries so that consistent implementation might be achieved throughout the U.K.
- The JCMG endorses the responses in this area from the Foundation for Genomics and Population Health (PHG Foundation), and the Histopathology Specialist Advisory Committee of the Royal College of Pathologists.

Research and Scientific Development

- Research and collaboration in the UK is strong and remains one of the world leaders, despite the difficulties in translating this new knowledge into the clinical field. Much of current research in clinically applicable areas is obviously driven by interested parties. To a significant degree this is justified as the largest gains may well be in areas such as cancer genetics, cardiac genetics and common chronic adult diseases. The identification of novel molecular markers and development of new therapies has great potential. However to gain the greatest benefit from these we also need to achieve the simpler things e.g. the engagement of the public and wider medical profession so that it is possible to identify patients who will benefit from these interventions. It remains difficult to succeed in getting this recognised as a clinical priority.
- There are good funding opportunities in the U.K. mainly from the Wellcome Trust and the MRC for basic research into many aspects of genomic structure and studies utilising novel genome technologies. The NHS Research and Development funding has recently been re-organised and is co-ordinated by the National Institute of Health Research (NIHR). The NIHR has clear research priorities linked to specific proposals such as “research for patient benefit”. Unfortunately, the NIHR currently excludes all proposals linked to laboratory based research which effectively blocks NHS applications for translational research involving many novel genomic technologies. Other sources for NHS translational and technological funding e.g. the Health Technology Assessment programme are not currently filling this funding gap.

Data Use and Interpretation

- We need investment in IT in clinical genetics as well as in the laboratories – most of our systems do not “speak to” hospital PAS systems, other genetic centres and even our laboratory systems. This is essential if we are to be able to pool large numbers of patients into clinical trials and new therapies.
- A nationwide system for family records is needed to cascade genetic information related to disease risk to other family members who might benefit and to maximise efficiency of gene testing within families.
- Data storage remains a concern but storage of clinical data in general should not be seen as a lesser priority than genetic and molecular data. Confidentiality of both should be a high priority. Genomic data should be protected against abuses in the employment and insurance sector but this is a different issue and would very likely benefit from legislation. Sharing of a common public database would speed up the accrual and interpretation of genomic knowledge but anonymisation would seem to be the only acceptable way forward at the current time.
- Mechanisms are required to independently assure the quality and validity of data submitted and that the data is regularly updated.

Translation

- There are already substantial benefits from diagnostic, prognostic and now early therapeutic interventions which will continue to grow. Careful evaluation of the clinical effectiveness and cost benefit in clinical practice will be complex as many of the gains will be many years into the future, which again returns to the invest to save principle. This does not fit well with the current poor understanding of genomic medicine in the wider healthcare system or current commissioning mechanisms being delegated to PCT level.
- **Strengthening specialised services** – money was placed into the NHS to increase the numbers of trained genetic counsellors and trainers for lab staff. There was major investment in lab equipment and laboratory IT systems. This was all welcome BUT:
 - There is a need to continue to train more genetic counsellors as it remains difficult to fill posts and the demand is increasing year on year and will continue to increase as more disorders become amenable to genetic testing.
 - There has to be a continued commitment to update lab equipment as technology changes – soon the White Paper capital equipment will be superseded.
- Whilst there is a thrust to see genomics impact on common disease, clinical geneticists remain advocates for families and patients with rare diseases, of which there are several thousand. There are many of these that cannot be tested for or where tests have to be sent overseas. The UKGTN assesses tests that labs wish to develop but a national audit on the numbers of tests being sent out of the UK and for which disorders would determine if there are significant “holes” in our local provision. The UKGTN LMA has shown that there is no clear central process for identifying and ensuring services are set up. At present it is an *ad hoc* arrangement that means some of the larger/complex services are less likely to be set up or at least not without considerable delay. This should lead to commissioning and funding of labs to set currently exported tests up locally.
- **Building genetics into mainstream medicine:** The developments in cancer genetics have been very significant and assisted by NICE guidelines for breast cancer. Similar guidelines in other common cancers would further develop the service. With regard to breast cancer, women could soon have their risks stratified by testing a few genetic markers rather than simply by their family history. This may impact on screening capacity by mammography and MRI and treatments. Similarly in affected patients, pharmacogenetic and tumour expression array tests may help indicate which women may respond to certain therapies.
- Cancer genetics is ahead of the field – the White Paper sought to improve the detection of single gene forms of heart disease (hypercholesterolaemia, *LDLR*, ApoB, *PCSK9*, *HCM*, *MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*) and diabetes (*MODY*) but there is a long way to go in the genetic stratification of the population for the non-Mendelian forms of these diseases. It is also not clear what interventions would be recommended if we could adequately stratify the population into high, medium and low risk on genetic information. Major developments have however occurred in the identification of some Mendelian forms of heart disease, notably the cardiomyopathies (some with complex inheritance patterns) and rhythm disorders and in Marfan syndrome where the findings may have therapeutic implications for aneurysms in general. Such conditions will need to be recognised, diagnosed and managed primarily within the mainstream discipline by clinicians with special interest and knowledge in genetics who are supported by specialist genetic departments.
- Finding “susceptibility” genes may in the first instance lead to new insights into pathogenesis and hence into novel therapies rather than genetic screening. An area not mentioned in the White Paper but of huge public health importance is mental illness and hopefully increasing genetic understanding of psychoses, dementia etc. will lead to novel therapies or interventions.
- The White Paper sought to increase antenatal and neonatal screening for some common genetic conditions and this is on-going. However, with respect to new neonatal screening for metabolic disease (*MCADD*), there is at present limited capacity to provide expert care for babies so identified.

- The development of primary care genetics was championed in the White Paper – all GPs will need some genetic skills and putting funding into training genetic counsellors to work alongside practices may be a better investment.
- When seeking to translate genomic information into practice we should not forget the need for counselling families when all these test results are produced. In Poland for example they have screened their population for 3 BRCA1 mutations and have 3930 carriers – a lot of counselling required. If similar screening for genetic risks occurs in the UK we need a lot of trained counsellors to cope. The implications for life insurance also need to be considered.
- In view of the complexity of genetic tests and their interpretation there is a need for clear criteria for testing and evidence-based guidelines for their use in clinical practice.
- The transition from conventional karyotyping to array-cgh based analytical platforms in some referral categories will have implications for the recruitment, training and retention of Clinical Cytogeneticists. These technologies also have significant impact on the clinical genetics services with interpretation and genetic counselling. Similar developments in high throughput genomic sequencing technologies will have similar implications for the re-configuration of the laboratory molecular genetics workforce.
- Training of current staff in new skills is required to match the new technologies.
- The JCMG endorses the responses in this area from the Foundation for Genomics and Population Health (PGH Foundation), and the Histopathology Specialist Advisory Committee of the Royal College of Pathologists.
- **Biochemical Genetics and Newborn Screening:** Enzymic and metabolite assays provide direct genetic information leading to genetic counselling and pre-natal diagnosis in many patients. Indeed, newborn screening for conditions such as phenylketonuria and sickle cell disease depend exclusively on these techniques while disorders such as medium chain acyl CoA dehydrogenase deficiency and cystic fibrosis are primarily identified and often confirmed by these approaches. This means that these diagnostic approaches are overwhelmingly the predominant means of genetic testing in the UK at present with in excess of 3.0 m tests performed annually. The importance of this means of providing genetic information is reflected in the inclusion of metabolic testing for inherited disorders and newborn screening within Specialist Medical Definition set 20 but investment is severely lacking.
- It is important for the patient that these varying approaches are integrated and co-ordinated to provide a seamless service and set of standards for the user. This is not the case at the moment, as an example differing turnaround times requirements apply and are addressed under differing initiatives eg “the six week diagnostic wait” does not apply for some forms of genetic testing.
- Training initiatives and funding for technological development are primarily aimed at molecular, cytogenetic and clinical genetics while workforce planning and training for screening remains unfunded within these initiatives. Some limited but valuable funds are available for biochemical genetics.
- Direct support for the exploitation of new technologies such as Tandem Mass Spectrometry and their implementation into practice could significantly extend the range of conditions accessible to newborn screening. This approach is mandated in the USA and has been adopted by many countries in Western Europe, the UK now lags significantly behind developed and developing countries in this regard.
- High though put whole population screening demands carefully designed IT support and an integrated IT system linking Child Health Records Departments, Maternity Units and Screening Laboratories. This is long overdue. The lack of investment of IT in this area affects both the safety and efficiency of these services.
- Many vulnerable services such as specialist diagnostic service dependent on enzyme assay are poorly resourced and there is little resilience in the system with the real risk that new developments are unavailable in the UK and some existing services may be under threat. There is a real opportunity to develop these services both to serve the

NHS and to pioneer healthcare technological innovation as a means of income generation from overseas.

Biomarkers and Epidemiology

- The impact of Recent Genome Wide Association studies on risk factors in, for example colorectal cancer, already makes it possible to combine data from 10 Single Nucleotide Polymorphisms (SNPs) to observe a 10-fold range of lifetime risk (i.e. risks that are not related to the known high penetrance genes) with potential clinical utility. Similar risk profiles will undoubtedly soon be available for other cancers and multifactorial disorders.
- We are already at the \$100,000 genome and this will start to impact on demands and expectations by users and on capacity and deliverables of genetics services. For example a 100-fold reduction in sequencing costs may change thresholds at which certain tests become cost-effective. At the same time, they will place increasing demands on informatics capacity and support that the NHS is not currently well-placed to meet. It may perhaps be timely for the genetics community to develop desirable performance specifications for next generation sequences such that they will meet the needs of the diagnostic community which in turn could inform a dialogue with potential suppliers.
- The scale and costs of new technologies are pushing in the direction of greater integration of pathology beyond the traditional genetics/pathology boundaries. This in turn means that the genetics and wider pathology disciplines need to begin serious and structured dialogue to facilitate the most efficient and cost effective ways of facilitating this integration (see also the Histopathology SAC response from the Royal College of Pathologists).

Use of genomic information in a healthcare setting

- What impact will genomic information have on the classification of disease? How will it affect disease aetiology and diagnostic labels? **JCMG: We are already seeing significant changes in our understanding, diagnoses and prognoses for rare single gene diseases. Genomic information will impact just as greatly in multifactorial conditions. Genomic information will expand and increase understanding necessitating a re-thinking on disease classification; e.g. common conditions will be broken down into genomically-defined sub-groups, which show differential response to therapies and/or different prognosis.**
- How useful will genomic information be as part of individualised medical advice? What provisions are there for ensuring that the individual will be able to understand and manage genomic information, uncertainty and risk?.. **JCMG: Genomic information will become extremely useful as part of individualised medicine, but this presupposes that all due support in terms of pre-test counselling, within laboratory interpretation, and post-test advice is provided, and this all necessitates adequate education and training of healthcare professionals throughout the NHS. For the individual patient, both their inherited genome and any subsequent changes that have occurred in neoplastic disease (i.e. acquired somatic mutations) will be relevant.**
- Should there be a regulatory code (mandatory or voluntary) covering the provision of this advice? **JCMG: NHS patients obtain pre-test advice by registered specialist professionals, analysis and interpretation from accredited laboratories staffed by registered clinical scientists, and have the results conveyed by registered professionals. The NHS has a duty of care to ensure all staff have the necessary training as genomic medicine spreads to all groups. This level of training and statutory protection via registration should apply equally to the private sector.**

- What are the implications of developments in genomic technologies for the training of medical specialists and other health professionals? Are there any gaps that need addressing? What is the assessment and planning for future needs in capacity? **JCMG: *Dissemination & training needs associated with genomic medicine will be widespread throughout disciplines. The assessment and planning for future requirements in capacity needs inter-disciplinary input especially between genetics and pathology in which disciplines “genomic” implementation and assessment is already impacting significantly and will continue to do so.***