THE ROYAL SOCIETY

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Genetics White Paper: three year review

1 Summary

- The area of genetics has developed significantly since the publication of the 2003 White Paper *Our inheritance, our future – realising the potential of genetics in the NHS* and is an important part of the future of medical research and practice. The hype surrounding the potential of genetics to affect clinical practice has subsided since 2003 and researchers and clinicians are now more realistic in their perspective of the impact of genetics on healthcare. New diagnostics, treatments and new disease classifications will emerge with increasing frequency but will not change the basics of clinical care overnight.
- Genetic tests are currently the most important contribution genetics offers to healthcare, predominantly to screen for inherited monogenic diseases. The situation is different for multifactorial disease although a limited number of predictive screening tests may emerge over the next twenty years.
- Pharmacogenetics offers the potential to develop a new generation of medicines, to help maximise their efficacy and enhance their safety, which could have implications for healthcare. Over the next ten to twenty years we expect to see further pharmacogenetic products enter mainstream healthcare, particularly in the field of cancer, although advances will be on a case-by-case basis. The major determinant of the rate of progress will be the clinical use and cost effectiveness of the new treatment regimes rather than development of the technology.
- Current regulations on the licensing of pharmacogenetic drugs and associated tests are confusing and there is no requirement for the manufacturer of a test to show that the test has any clinical applicability.
- This may lead to a situation where the use of an important new medicine is predicated by a test of poor calibre and whose clinical validity was in doubt.
- Education in genetics has trailed behind the enormous scientific and technical advances in this field and the Royal Society strongly believes that the teaching of genetics to doctors, pharmacists and nurses at undergraduate, postgraduate and continuing medical education levels must be increased as a matter of urgency.
- The Department of Health must take into consideration the public concerns and expectations of the applications of genetic technology, including issues of consent, confidentiality and reliability.

2 The current and future potential for genetics in healthcare

The Royal Society welcomes the opportunity to contribute to the three year review of the genetics White Paper. Genetics and genomics are key to increasing our understanding of biological pathways and have revolutionised basic biological research in the last fifty years. Genetics is already providing diagnostics for conditions in which the genetic component is very substantial and the test is therefore strongly predictive. Furthermore the increased understanding of biological pathways is expected to eventually lead to new treatments of disease. To date, genetic tests are the most important contribution genetics offers to healthcare and genetic testing is routinely used, predominantly to screen for inherited diseases controlled by a single pair of genes (monogenic disease), in the following ways:

- to confirm disease diagnosis, for example for Duchenne muscular dystrophy or fragile X syndrome;
- to predict increased risk of developing disease, for example mutations in the BRCA1 and BRCA2 genes increase the risk of developing breast cancer;
- to inform an individual if they are a carrier of an inherited disorder that they might pass on to their children, such as cystic fibrosis or Tay-Sachs disease;
- in prenatal testing to examine an unborn child whose parents are at risk for having children with a chromosomal abnormality or an inherited genetic condition, such as Down syndrome or spina bifida;

- in neonatal screening, the most widespread type of genetic testing, which examines infant blood samples for abnormal or missing gene products, such as phenylketonuria (PKU), cystic fibrosis or haemoglobinopathies;
- for pre-implantation genetic diagnosis of embryos in in vitro fertilisation. Only those embryos free of the genetic mutation screened for are implanted into the uterus.

Whilst we believe that increased knowledge of genetics and genomics in the long term will impact substantially on the way in which we understand and treat disease, the impact on healthcare is just beginning and will not be dramatic over a short timescale. Instead, new diagnostics, treatments and new disease classifications will emerge with increasing frequency but will not change the basics of clinical care overnight. An area of particular promise is the cancer field, where genetic analysis of the tumour can be used to specify the likelihood of a patient responding to a genetically based medicine, resulting in more precise specification of cancer therapy. It is vital that research into diagnostics and potential therapeutics is well funded in this area.

3 The future impact of genetics

3.1 Multifactorial disease

Common multifactorial diseases such as coronary heart disease, diabetes and asthma are caused by a combination of genetic and environmental factors. Although our knowledge of how genes contribute to complex multifactorial diseases is increasing, genetics is not likely to impact on clinical practice in the near future. We believe that over the next twenty years there may be a few examples of clinically useful predictive screening tests for genuinely multifactorial disease, but these will be limited in clinical practice.

The most important factor in understanding the genetic component of multifactorial disease is the requirement for accurate disease phenotyping. In addition to collecting genetic information, gene banks, such as UK Biobank, must also be supported by further clinical research to dissect common diseases and provide accurate clinical data to correlate genotype and disease phenotype. This research should be supported by the Department of Health.

3.2 Pharmacogenetics

In 2005 the Royal Society published the report of a policy study entitled *Personalised medicines: hopes and realities*[1] and we refer the Department to the report's conclusions and recommendations (see annex). The Royal Society believes that pharmacogenetics offers the potential to develop a new generation of medicines, to help maximise their efficacy and enhance their safety, which could have implications for healthcare, both in the developed and developing world. The advances in, and potential for, the application of pharmacogenetics are closely related to rapid advances in the underpinning genetic testing technologies which are increasingly becoming possible on a large scale and at a reasonable cost.

Currently, pharmacogenetics has very little impact on clinical practice and it is unlikely to revolutionise or personalise medical practice in the immediate future. However, there are now a few products on the market, predominately in the field of cancer, for which there is good evidence for the benefit of pharmacogenetic testing. As related research identifies sub-groups of common diseases based on different genetic or environmental causes, and knowledge of pharmacogenetics advances, it should become possible to introduce genetic testing to predict people's response to at least some drugs. Over the next ten to twenty years we expect to see further pharmacogenetic products enter mainstream healthcare, again particularly in the field of cancer, although advances will be on a case-by-case basis. The major determinant of the rate of progress will be the clinical use and cost effectiveness of the new treatment regimes rather than development of the technology.

[1] Royal Society (2005). *Personalised medicines: hopes and realities*. The Royal Society: London

Pharmacogenetics is likely to become increasingly important in drug discovery and development as knowledge of the relative importance of genetic factors helps to identify optimal populations for a particular medicine. However, pharmacogenetics potentially limits the target number of recipients and this may prove too expensive for pharmaceutical companies to pursue without financial incentives. Therefore industry will continue to favour drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next ten to twenty years. It will be necessary to validate the clinical use of both the diagnostic test and the drug by large, controlled, clinical trials, performed on a case-by-case basis, to enable new products to enter the clinic.

Information is also needed about the potential application of pharmacogenetic screening to existing medicines, including off-patent generic medicines, which constitute the bulk of those used in the NHS. In our 2005 report we recommended that public–private partnerships be established between the NHS, the Medical Research Council, research charities and the pharmaceutical and diagnostic industries to fund trials on existing medicines.

As the field of pharmacogenetics evolves it will be necessary for regulation to follow the scientific developments and their applications closely. Regulatory authorities will have to establish standards of validity for the use of genetic tests if pharmacogenetic data are to be incorporated into licensing procedures. In Europe, a pharmacogenetic-based drug is approved by the European Medicines Agency as a medicine, but the diagnostic test which accompanies it is regulated at a national level as a medical device under a different regulatory regimen. This has the potential to lead to regulatory delay, conflict and disagreement. Furthermore, there is no requirement for the manufacturer of the test to show that the test has any clinical applicability. We are concerned that this may lead to a situation where the use of an important new medicine is predicated by a test of poor calibre and whose clinical validity was in doubt.

The development of pharmacogenetics raises important social and ethical questions and as part of our study the Royal Society's Science in Society programme facilitated a public dialogue on potential developments in personalised medicines[2]. This involved three workshops with 76 members of the public and specialists. Most of the participants thought the technology would yield benefits, including helping doctors and patients to make informed choices. But worries existed over issues of consent, confidentiality and reliability of test results. Some thought GPs would find it hard to keep up with the emerging technology and would struggle to offer up to date patient advice. The majority thought that pharmacogenetic tests should be administered by doctors and not be sold over the counter or via the internet. The Department of Health must take into consideration the public concerns and expectations of the applications of genetic technology, both in relation to pharmacogenetics, and more widely.

3.3 Other areas where genetics is likely to have an impact on healthcare

- *Gene therapy* – We believe that definitive gene therapy is still some way from clinical use and it will take at least another ten years before the first gene therapies become widely available, probably for either monogenic conditions or cancer therapy.

- *RNA interference (RNAi)* is a technique for selectively and precisely switching off gene expression. It is a very powerful technique experimentally for examining disease pathways. It is being explored therapeutically and we believe that it has the potential to have a significant effect on healthcare in the future, although its true potential will not be known for some time.

[2] Royal Society (2005b). *Pharmacogenetics dialogue*. The Royal Society: London

- *Pre-implantation genetic diagnosis (PGD)* is used to diagnose a severe genetic or chromosomal condition in an embryo to avoid commencing an affected pregnancy. We believe that we are likely to see a substantial rise in demand for PGD for both early and late onset monogenic diseases of moderate severity.

- *Infectogenomics* - Genetic variation of both the pathogen and the host may play a role in determining severity and outcome of many infectious diseases. Infectogenomics examines how host genetic variation plays a role in determining the outcome of infection and increasingly, infectogenomics will be used to identify infectious states, understand host response, predict disease outcomes, monitor responses to therapies and to indicate new types of treatment.

4 Future priorities for Government to enable appropriate uptake of genetic knowledge and technology in healthcare

4.1 Education and training

In the future doctors, pharmacists and nurses will require a much stronger basic training in the fundamentals of human genetics. Education in genetics has trailed behind the enormous scientific and technical advances in this field and the Royal Society strongly believes that the teaching of genetics at undergraduate, postgraduate and continuing medical education levels must be increased as a matter of urgency. We recommend that the current and future training and education needs of these healthcare professionals should be reviewed by the appropriate professional bodies and funding made available to address these needs.

4.2 Translational medicine

We believe that there is a growing imbalance between efforts to define the molecular basis of genetic disease and efforts to translate the molecular understanding into therapies, as opposed to diagnosis. Over the last two decades considerable resources have been used to define the molecular basis of most major monogenic diseases, based on the premise that this might lead to new therapies. In the large majority of cases this has not happened yet and there could be many reasons for this, not least that the initial timescales were unrealistic. However, we believe that there is also a strategic problem in that though many of these diseases are quite common, they are not common enough to attract major interest from the large pharmaceutical companies who have the best resources to develop therapeutics. So there is a growing imbalance between new genetic knowledge of the molecular bases of diseases such as polycystic kidney disease, cystic fibrosis, major neurodegenerative diseases and inherited cardiomyopathies and the development of therapeutics for their treatment. This is an area which should be considered by Government as part of its new focus on translational medicine.

4.3 Facilitating research

The Department of Health should also concentrate on facilitating and enabling appropriate research by providing a research friendly environment; minimising bureaucracy while maintaining appropriate safety and ethical standards; and putting some money into high quality research (although we recognise that the Department's own current research budget does not allow it to become a major player in this field of genetics). It is important to link genetic research and practice with epidemiology and this should be considered in developing the clinical centres of excellence. The Department should also consider undertaking a long-term review of both genetic services and research. Not only has the area developed significantly since the 2003 White Paper, but the hype surrounding the potential of genetics to affect clinical practice has subsided and researchers and clinicians are now more realistic in their perspective.

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Annex

Summary of the Royal Society report *Personalised medicines: hopes and realities*

One of the most important approaches towards more personalised medical care is the study of pharmacogenetics. This emerging science seeks to determine how people's genetic make-up affects their response to medicines. It offers the potential to develop a new generation of medicines, to help maximise their efficacy and enhance their safety, which could have implications for healthcare, both in the developed and developing world. The field of pharmacogenetics has been widely discussed by scientists and policy makers, and the pharmaceutical and diagnostic industry has been investing in exploring it for developing genetic technologies to enhance drug discovery and development. The advances in, and potential for, the application of pharmacogenetics are closely related to rapid advances in the underpinning genetic technologies. Hence it is now possible to foresee genetic testing on a very large scale and at a reasonable cost.

Currently, pharmacogenetics has very little impact on clinical practice. However, there are now a few products on the market, predominately in the field of cancer, for which there is good evidence for the benefit of pharmacogenetic testing.

Pharmacogenetics is unlikely to revolutionise or personalise medical practice in the immediate future. Rather, as related research identifies sub-groups of common diseases based on different genetic or environmental causes, and knowledge of pharmacogenetics advances, it should become possible to introduce genetic testing to predict people's response to at least some drugs. Appropriate trials and cost analyses will first have to be performed on a case-by-case basis.

Pharmacogenetics is likely to become increasingly important in drug discovery and development as knowledge of the relative importance of genetic factors helps to identify optimal populations for a particular medicine. Industry will continue to favour drug candidates that avoid the effect of genetic variation, but where that is not possible, the development of drugs with an associated diagnostic test is expected to become routine in the next ten to twenty years. It will be necessary to validate the clinical use of both the diagnostic test and the drug by large, controlled, clinical trials to enable new products to enter the clinic.

For new drugs, the clinical trials will be conducted by industry. However, information is also needed about the use of pharmacogenetic screening of existing medicines, including off-patent generic medicines, which constitute the bulk of those used in the National Health Service (NHS). Under the current arrangements industry has no obvious motive to investigate the pharmacogenetics of most of these products on its own. We recommend that public–private partnerships are established between the NHS, the Medical Research Council, research charities and the pharmaceutical and diagnostic industries to fund trials on existing medicines. All pharmacogenetic clinical trials should have the input of health economists to assess their clinical cost–effectiveness.

The future impact of pharmacogenetics will be linked to the continuing development of diagnostic tests that can deliver reliable and rapid diagnostic data to healthcare professionals. As this field evolves it will be necessary for regulation to follow the scientific developments and their applications closely. Regulatory authorities will have to establish standards of validity for the use of genetic tests if pharmacogenetic data are to be incorporated into licensing procedures. We recommend that regulators should incorporate some form of post-market monitoring, beyond phase III clinical trials, which links data on genetic variability to clinical outcomes in the healthcare system.

Education in genetics at undergraduate, postgraduate and continuing medical education levels has trailed behind the enormous scientific and technical advances in this field. In the future doctors, nurses and pharmacists will require a much stronger basic training in the fundamentals of human genetics. We recommend that training and education needs of these healthcare professionals are reviewed by the appropriate professional bodies.

Studies of pharmacogenetic variability will require the analysis of large repositories of clinical data during and after a clinical trial. Industrial and academic researchers undertaking such studies will require an ethical framework that provides guidance on how to collect and store information and samples with proper consent, while protecting the rights and confidentiality of the individual. This needs specific consideration by Government, the NHS, and the newly established Human Tissues Authority.

Public attitudes will play a crucial role in realising the potential of scientific and technological advances. Most participants engaged in the public dialogue commissioned as part of this study saw the potential development of pharmacogenetic testing as beneficial for helping people make informed choices. However, there were major concerns, including issues of consent and confidentiality in the handling of biological samples, and whether the Government and the healthcare system could successfully deliver genetic technology in the future. We recommend that the public should be regularly consulted about the applications of pharmacogenetics.

We endorse the recommendation of the World Health Organization that the introduction of simple DNA diagnostics for common genetic and infectious diseases in developing countries is vital. We recommend that the Medical Research Council and research charities commission more research into the cost effectiveness of the use of pharmacogenetics in developing countries, particularly for drugs for malaria, tuberculosis and HIV and for assessing drug resistance in common parasites.

Over the next ten to twenty years we expect to see several pharmacogenetic products enter mainstream healthcare, particularly in the field of oncology, although advances will be on a case-by-case basis. The major determinant of the rate of progress will be the clinical use and cost effectiveness of the new treatment regimes rather than development of the technology**.**