

**THE HOUSE OF LORDS SCIENCE & TECHNOLOGY SELECT COMMITTEE
SUBCOMMITTEE II GENOMIC MEDICINE**

MEMORANDUM by ASTRAZENECA RESEARCH & DEVELOPMENT

About AstraZeneca

AstraZeneca is one of the world's leading ethical pharmaceutical companies, providing innovative and effective products to fight disease in important areas of medical need. AstraZeneca is an international company with its corporate headquarters in London and several Research and Development (R&D) centres across the UK. Globally, the Company also has R&D centres in Sweden, North America and Asia-Pacific, manufacturing operations in 19 countries, and sales operations in over 100 countries. AstraZeneca employs over 67,000 people world-wide, with approx. 13,000 employed in R&D. The world-wide expenditure on R&D in 2007 was more than £ 5 billion.

AstraZeneca employs well over 100 specialist genetics and genomics staff. In addition, many of its skilled bioscientists carrying out research in disease areas routinely use genetics/genomics as one of their research tools. The AstraZeneca facilities are considered to be state-of-the-art in DNA banking and genotyping.

Research and development in the pharmaceutical industry makes an immense contribution to human health and well-being, and most areas of our work are regulated by law, and governed by strict ethical considerations. With regard to genetic research, as with other kinds of clinical research, AstraZeneca upholds high ethical standards, in accordance with the demands placed upon us. The protection of patient confidentiality is paramount and AstraZeneca does not seek to acquire any personal data relating to human subjects which is not strictly necessary for the purposes of analysing and reporting studies.

Policy Framework

Who is in charge of setting and reviewing policy in this area?

Policy for genomic medicine should be a shared process in consultation with the interested parties of which, within the UK, DoH, RCUK and the pharmaceutical industry would be key stakeholders. Policies should recognise the widespread implications of genomic medicine across the whole healthcare system.

Who provides scientific advice on policy development? Who monitors and anticipates potential scientific developments and their relevance to future policy? How effective are these mechanisms?

The UK is fortunate to have a solid base of world-class scientists in academia, industry and the healthcare system. These scientists provide input into surveys and policy reports such as "Our inheritance, our future: realising the potential of genetics in the NHS" by the DoH (2003) and "Personalised medicines: hopes and realities" by the Royal Society (2005). Such mechanisms are effective; however, due to their nature, they must be continually updated in order to keep pace with scientific developments.

Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies? Are there any regulatory gaps?

Currently the regulatory guidelines for drug-diagnostic co-development are different between the US and EU, with the requirements for in vitro diagnostics (IVDs) being more flexible in the EU compared with the US. The US also has many different guidelines that

apply to genomic medicine including “Pharmacogenetic Tests and Genetic Tests for Heritable Markers” and “Drug Metabolizing Enzyme Genotyping System” and “In Vitro Diagnostic Multivariate Index Assays” These variations in regulation can create confusion for UK companies trying to implement personalised healthcare globally and may not be optimal of the development and translation of genomic medicine.

In what way is science and clinical policy decision-making informed by social, ethical and legal considerations?

Genetics, in a broad sense, is an area of great current sensitivity and there is much debate about the ethical, legal and social implications for genetic research. AstraZeneca are keen to contribute to that debate and to promote full understanding of how industry is involved. We actively gather information on guidelines, laws, policies and attitudes around the world on a continuous basis, to enable us to understand and comply with international standards of best practice in this field. It is recognised that there are many ethical issues around genetic investigations but it is also clear that ethical viewpoints vary from country to country and change with time. Whilst the debate continues, it is difficult to define detailed company policies and procedures, but we have developed some high-level policies for our involvement in this field. In common with other pharmaceutical companies, AstraZeneca is currently striving to define ‘best practice’ for the performance of genetic studies.

How does the framework compare internationally?

The UK contributes to the harmonisation of frameworks around clinical practice, clinical study conduct under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) which brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

Research and Scientific Development

What is the state of the science? What new developments are there? What is the rate of change?

We define Genomic Medicine as the use of genetic information to inform clinical decisions regarding a patient’s risk of developing disease, to assist with diagnosis and prognosis and/or to predict a patient’s likely response to therapy. The definition may be more broadly interpreted to include the use of other types of information such as gene expression analysis at RNA and protein level, which provides transient measurements and is more subject to experimental variation, but we will not focus on these aspects in our evidence.

The completion of the draft sequence of the human genome in 2001 raised hopes that genetics would make a substantial contribution to medical practice. However in reality the only significant impact to date has been upon the elucidation of the genetic basis for single gene disorders which are mainly rare and do not affect the majority of the general population. The common conditions which affect large numbers of individuals have proved more difficult to analyse in the same way. This is because they are probably due to a combination of genetic and environmental factors which interact to give rise to the disease. Many studies have tried, with varying degrees of success, to identify the major genetic factors predisposing to disease but to date the information has seldom had any effect on clinical decisions. However, there is a growing aspiration among the academic community to learn from previous failures and undertake bigger and better studies to identify more and more genetic factors associated with disease and so this area is likely to be more fruitful within the next decade or so in determining a comprehensive atlas of genetic factors and their role in disease.

AstraZeneca, in common with the majority of large pharmaceutical companies has been collecting DNA samples from patients participating in Company-sponsored clinical trials world-wide for several years. The donation of DNA by patients unless as a pre-defined entry criterion does not affect a patient's enrolment in the study. AstraZeneca policy in complying with legislation does not permit the collection and export of DNA samples from all countries and compliance with local ethics committees in some countries may also result in failure to collect some intended samples for a clinical trial. For these reasons, AstraZeneca's DNA collection is not a comprehensive representation of all clinical studies. However, AstraZeneca has accumulated samples representing approximately seventy thousand individuals suffering from diseases such as asthma, cardiovascular disease and inflammatory diseases, all of which are held in secure, GLP-standard automated or manual archives.

AstraZeneca has conducted a number of genetic investigations over the last few years on the samples we have collected. The main interest of the Company is to identify genetic factors contributing to patients' response to our medicines and all our investigations have had this objective. However, wherever possible, we have also requested permission within the informed consent to use the samples to identify potential genetic risks associated with the disease being treated.

Who is taking the lead in the consideration and co-ordination of research and the development of new technologies?

Research and development is not well co-ordinated at present, and this needs to change because translation into medical practice will require changes in the UK healthcare system and integrated efforts across the various stakeholder groups. However, individual initiatives arising from DoH, Wellcome Trust and MRC as well as a substantial amount of work within the pharmaceutical industry is being undertaken.

How effective is the policy and investment framework in supporting research in this area?

Progress in genomic medicine and translation to clinical practice will require an integrated approach between stakeholders; including scientists to discover and develop biomarkers, diagnostic companies to develop enabling technology to test the biomarkers, pharmaceutical companies to conduct clinical trials demonstrating the clinical utility of the diagnostics and the healthcare system to translate the linked drugs and diagnostics to clinical practice. At present there are many obstacles to this integrated approach both in the policy and investment framework. For example, investment in personalised healthcare is not linked to value-based reimbursement to either the diagnostic or pharmaceutical industry. In addition, regulatory policies for drug-diagnostic co-development are different in the EU and US, making it difficult for UK-based companies to achieve global reach for their personalised healthcare products.

How does research in the UK compare internationally? How much collaboration is there?

There are two main requirements for undertaking successful genetic research in either disease genetics or pharmacogenetics. These are large, well defined population-based samples and the capability to undertake large scale genotyping. Several UK initiatives have the potential to give the UK an advantage in this area. The UK biobank initiative has the potential to provide a useful DNA collection, the DoH "Connecting Patients for Health" should enable better use to be made of clinical information held throughout the DoH and the investment of the Wellcome Trust and Research Councils in supporting genotyping and sequencing centres of excellence within the UK are all positive factors.

What are the current research priorities?

From the patient's perspective, research towards understanding adverse events and side effects of drugs is a priority and this is being addressed by various groups. The FDA have sponsored a Serious Adverse Events Consortium. A further priority for industry is to understand why some medicines are effective only in some individuals. A major Public Private Partnership, the Innovative Medicines Initiative (IMI) has recently been set up with funding from the EU and European pharmaceutical companies to address some of the issues which hinder the development of truly differentiated, effective and safe drugs. The FDA'S Critical Path Initiative seeks to answer similar questions in the USA.

What is the role of industry? How much cross-sector collaboration takes place?

AstraZeneca, like other pharmaceutical companies, has conducted human genetic research into common diseases as described above (known as disease genetics), but has become increasingly interested in the related area of research known as Pharmacogenetics. Pharmacogenetics involves the analysis of genetic variability in populations of patients receiving a given drug and its association with variability in response to that drug. These genetic investigations take place in conjunction with normal drug trials. The ability to understand the genetic basis of variability in response to drug treatments will allow us to use this information predictively and optimise treatment to individual patients. The goal is to be able to use simple diagnostic tests to identify which patients will respond best to which treatment, and to avoid giving an inappropriate drug to a patient at risk of experiencing side effects.

AstraZeneca has used pharmacogenetics analysis successfully in a number of cases to provide data to regulatory authorities. The US Food and Drug Administration have been very proactive in encouraging the submission of such data under a voluntary scheme which takes account of the fact that much of the science is at the exploratory stage at present. Their activities, supported by the US Government, have placed the USA at the forefront in progressing research towards translation into medical practice. Europe and the UK are currently taking a following position in the area.

The pharmaceutical and biotech industries in the UK have a good deal of potentially useful experience and resources which could be exploited more effectively in collaboration with academic and clinical research groups to the benefit of the UK. Public-Private Partnerships would be an excellent way of determining how this might be undertaken. AstraZeneca, along with many other pharmaceutical industry companies, is a founding member of the EU-based EFPIA Pharmacogenetics (PGx) group and the US-based Pharmacogenetics Working Group (PWG), both of which operate at the pre-competitive level to share best practice in pharmacogenetics and provide a point of contact with regulatory authorities. Both of these groups have co-authored several publications on the translation of genomic medicine,

Data Use and Interpretation***Is genomic information published, annotated and presented in a useful way? Should there be a common, public database? If so, who should fund, and have responsibility for, such an initiative?***

Genetic information relating to sequence and variation is published and held in a variety of databases which are easily accessible. The digital nature of DNA sequence data enables the information to be presented in a consistent way and be readily utilised. In contrast, information derived from other genomic analyses, such as gene expression analysis, is much less compatible and is susceptible to experimental design.

Who should provide the framework for optimal evaluation of data and translational

opportunities? What policy and funding mechanisms are in place for recognising and utilising potential opportunities?

Is other medical information recorded in a suitable format to allow optimal interpretation of genomic data? How should genomic data be brought together with other health information?

Medical information is increasingly being held electronically and the UK could have a substantial advantage here in its aims of generating databases of electronic records across the NHS through the “Connecting for Patient Health” programme of work. If funded and managed appropriately this will provide a tremendously valuable resource for analysing UK patient health and healthcare.

What are the implications of the generation and storage of genome data on personal data security and privacy, and on its potential use or abuse in employment and insurance? How should these be addressed?

In AstraZeneca, all genetic data deriving from an individual are stored in secure computer-operated systems, with restricted access, with all personal identifiers (names, addresses, dates of birth, etc.) replaced by code numbers. Code keys are generally held externally, e.g. by clinical investigators. They may sometimes be deliberately destroyed, so that the data and samples are permanently ‘anonymised’. The processes used to protect confidentiality vary, dependent on the type of study, and the demands of external regulatory agencies and ethical committees.

The generation and storage of genome data for research and medical practice will require systems to be established to ensure personal data security and privacy are maintained. It is understood that the ongoing Research Capability Programme within the NHS Connecting Patients for Health initiative will address this, and the UK Biobank should also have systems in place. The potential use or abuse of information in both employment and insurance are issues which should be addressed via both public consultation and by discussion with relevant professional or trade associations.

A very large proportion of the genetic data collected during investigations can be considered to be non-sensitive, having little or no obvious implications for the present or future health of the subject or their family. For example, the revelation that an asthma patient carries a gene believed to underlie susceptibility to asthma, does not change the situation for that individual at all: they already knew they had the disease. Similarly, investigations that demonstrate that most members of a population carry versions of genes that allow them to metabolise a given drug normally, such that they exhibit no unusual side-effects, generate volumes of genetic data that are of great importance to the company developing that drug, but which are not considered sensitive for any of the individuals studied. Even when individuals are found to carry variations in genes that cause them to be relatively deficient in metabolising a drug, the implication may be no more than that they would be best advised to avoid using that drug. Participating in a genetic research study should not be classified (e.g. for insurance purposes) as having had a ‘genetic test’ performed. Since the ethical, social and legal risks of collecting such genetic data appear to be extremely low, and the potential benefit, in terms of developing better treatments, is high, there is a very strong argument in favour of continuing, and expanding, the use of genetic analyses in pharmaceutical research.

It is recognised that, as with all areas of research, there is an element of uncertainty, and that what appears to be of no importance now may be revealed to be of greater import in the future. The processes that AstraZeneca uses to protect patient confidentiality, are designed to take into consideration that element of uncertainty, and to treat all genetic data as if it was very sensitive.

Translation

What opportunities are there for diagnostics, therapeutics and prognostics - now and in the future?

AstraZeneca sees substantial opportunities for diagnostic tests linked to therapeutics, both now and in the future. Personalised Healthcare products (defined as diagnostic tests linked to drugs) have the potential to deliver benefits to many areas of the healthcare system by delivering superior outcomes to patients and increasing the ability to predict which patients will respond to which drugs.

In Disease Genetics, the objective is to identify variations in genes that cause or contribute to susceptibility to disease. Such an insight into the mechanisms of disease may be used in two ways. In the community healthcare setting, it may allow the doctor or health worker to advise patients as to the risks and potential preventative measures. In the industry, the information may allow us to identify new targets for drug therapy, and thus the development of new, effective treatments.

In Pharmacogenetics, the objective is to identify patients who are more likely to benefit from medicines. This information will lead to predictive testing prior to treatment, known as Personalised Medicine.

Both of the situations above will require a substantial change in medical practice in that diagnostic or prognostic tests will need to be undertaken. The challenge of genomic medicine will be to ensure that these tests are available, cost-effective and integrated into the current healthcare system.

Who is responsible for translation to clinical practice?

The healthcare system, supported by opportunities emerging from genomic science and healthcare industry, will decide on the rate of translation of Personalised Healthcare to clinical practice. There are already several examples of drugs linked to diagnostics providing genomic information in clinical practice and bringing clinical benefit to patients.

Given the pace of technological advance, how 'future-proof' is healthcare investment in this area?

Technologies and science are advancing rapidly in this area, so healthcare investment should support the application of genomic information to benefit the healthcare system, rather than being tied to a particular technology.

How does the UK compare to other countries and what lessons can be learnt?

The UK compares favourably with many other countries in the understanding and application of genomic information in the healthcare system. Some countries in the EU have introduced increased oversight of genetic research in clinical trials, although this frequently introduces delays and there is little evidence that it is beneficial to clinical trial subjects.

In the US, there have been many initiatives from the FDA to encourage the application of genomic information in the healthcare system and the development of personalised healthcare. However, the regulatory system for the registration of diagnostics linked to therapy is more flexible in the EU compared with the US. As a result, many diagnostics are registered as in vitro diagnostics (IVDs) in the EU in advance of their filing in the US.

How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?

Putative genetic associations emerging from genome-wide association studies should be replicated in an independent collection. This is even more essential if the results are

intended for use in clinical practice, whether in the form of improved medical advice or a predictive test given before treatment. It is also important that the replicated associations be biologically evaluated. Before pharmacogenetic associations can be used in the clinic, they should be studied in adequately powered clinical trials to assess to what extent the associated genetic variants can improve the clinical benefit: risk ratio of the drug.

The transition of genetic data derived from research projects into validated tests for specific predictive use has been accomplished but is not a simple task. The clinical utility of the test needs to be clear and this requires testing in adequately powered clinical trials in the normal way.

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?

Genome-wide association (GWA) studies and other genetic analyses can be used to identify genetic biomarkers for selecting patients for treatment (in the case of drug efficacy or serious adverse events), drug dosing, or disease definition. Although most of the success in GWA studies to date has been in the field of complex diseases there have been a number of successes in drug response. In the case of identifying biomarkers for drug response, the case–control design is commonly used.

Frequencies of alleles at genetic markers (typically single nucleotide polymorphisms or SNPs) are contrasted between cases and controls. If the phenotype is qualitative (e.g. objective response in terms of tumour shrinkage, or a specified hypersensitivity reaction), the appropriate controls will be subjects with matched disease and treatment, but without the phenotype in question. Where the phenotype is quantitative (such as plasma concentration of the drug or change in forced expiratory volume [FEV1] of the lungs), all the subjects can be used in a quantitative trait analysis. Alternatively, cases and controls can be selected from the extremes of the trait distribution.

GWA and subsequent analyses will lead to biomarkers of a particular disease subset. In addition to these, biomarkers may arise from gene expression analysis using RNA, proteomic analysis, metabolite analysis or clinical image analysis. It is likely that in the future a combination of biomarkers may be used for predictive medicine.

What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?

The integration of genotyping data and epidemiological data held in the UK Biobank and other biobanks will provide a powerful resource for the future expansion of knowledge of health and disease, provided that sufficient high quality samples and data are stored and access is well managed.

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?

In the future more diseases will be classified on the basis of molecular information. One example is GIST (Gastrointestinal Stromal Tumors) which is now classified by the presence of a biomarker, cKIT+. This biomarker is specified in the drug label of Gleevec (Novartis), which is indicated for treatment of GIST, and the linked diagnostic for cKIT expression (Ventana). In the future it may be possible to have drugs indicated for any disease characterised by a genomic biomarker, rather than on the basis of symptoms.

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?

In certain cases genomic information is already provided as part of individualised medical advice. For example, prescription of drugs like Herceptin, Erbitux, Gleevec, Maraviroc and Tykerb all depend on genomic information. There is no evidence that individuals find the information provided to them in these cases any more burdensome than other medical information, so long as their physicians are able to explain this to them.

Genomic information may also be provided to individuals via tests to diagnose genetic disease (such as BRCA testing for hereditary breast cancer). In these cases genetic counseling is provided to help individuals manage the information, uncertainty, risk and treatment options. This is particularly necessary as the genomic information provided has implications not only for the individual tested but also their family. The perception of genetic exceptionalism should be avoided wherever possible.

Should there be a regulatory code (mandatory or voluntary) covering the provision of this advice?

AstraZeneca fully supports the provision of genetic counseling to individuals receiving genomic information with familial implications. However, regulatory codes may not be the best way to achieve this.

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?

There is evidence that physicians in the UK may find interpretation of genomic information in diagnostic tests difficult, and that this may present a barrier to the uptake of personalised healthcare. It is a priority that the education of physicians and others in the healthcare sector should be updated to include interpretation of genomic information.
