



**ABPI Submission to the House of Lords' Science &
Technology Committee Inquiry on "Genomic Medicine":
*the right medicine, the right patient, the right time***

KEY POINTS

1. Pharmaceutical companies have been investing in genomics and genetics over the last two decades to help aid the discovery and development of new medicines, with the objective of getting ***the right medicine, to the right patient, at the right time.***
2. Companies are investing in two areas:
 - first, in genomics – that is the characterisation of DNA and RNA¹ – to understand the underlying causes of disease to identify potential new targets against which drugs can be developed;
 - second, through understanding genetic variation¹ of patient populations it is possible to: identify susceptibilities to disease; identify those likely to respond to a specific medicine by knowledge of the underlying cause; and understand how particular patients metabolise medicines in order to identify the appropriate dose to improve both safety and efficacy.
3. Genomic markers are one type of biomarker used in drug discovery and development and, indeed, in targeting of medicines to patients. Others include proteomics – the study of the proteins produced by an organism – and metabonomics – the study of metabolic response of cells to disease and subsequent impact following treatment – also provide biochemical markers, and alongside physiological (physical) markers, such as blood pressure, are routinely used in clinical application.
4. If patients are to see the benefit of “genomic medicine”, then six interacting areas need to be connected:
 - emerging science and technology;
 - effective business models for the development and (especially) validation of new genomic markers;
 - the regulatory environment, covering medicines (MHRA and EMEA) and health technology assessment (NICE), should encompass other technologies including diagnostics and clinical imaging;
 - clinical application, including available technologies and appropriate training;
 - e-Health (including incorporation of diagnostic alongside therapeutic information; utilisation of patient electronic records to help inform R&D priorities); and
 - health economics to ensure evaluation, payment and incentive structures support use.
5. There is a significant amount of relevant investment across Government, the pharmaceutical industry and key stakeholders: in the UK, the ABPI works closely with OSCHR², the Translational Medicine Board and relevant Research Councils; in Europe the industry has established a joint undertaking with the Commission called Innovative Medicines Initiative³; and in the USA many companies are engaged with the Critical Path Initiative⁴, led by the FDA. Genomic medicine is one component of these initiatives, which seek to address all the bottlenecks and scientific hurdles in drug discovery, development and targeting.

¹ Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories ICH E15 (Step 5 Implementation), 1 November 2007, <http://www.ich.org/cache/compo/276-254-1.html>

² The Office for the Strategic Coordination of Healthcare Research

³ <http://www.imi-europe.org/>

⁴ <http://www.fda.gov/oc/initiatives/criticalpath/>

INTRODUCTION

6. The Association of the British Pharmaceutical Industry (ABPI) is the trade association for more than 100 companies in the UK that research, develop, manufacture and/or supply more than 80 per cent of the medicines prescribed through the National Health Service (NHS).
7. The ABPI is an active partner with Government to secure the provision of safe and effective medicines for patients, to maintain and strengthen the UK pharmaceuticals industry within Europe and globally, and to advance healthcare innovation within the NHS.

Genomics, genetics, pharmacogenomics and pharmacogenetics

8. The terms genetics and genomics are often used inter-changeably, even amongst academics and regulators. Useful definitions can be found under ICH¹. Wikipedia has more detailed explanations of the underlying science.
 - **Genetics** is the science of heredity and variation in living organisms⁵.
 - **Genomics** is the study of an organism's entire genome⁶ (both DNA and RNA).
 - **Pharmacogenetics**¹ is usually considered to be the study of variations in DNA sequence as related to drug response; this includes clinical research into genetic variation that underlies differing responses by patients to medicines⁷.
 - **Pharmacogenomics**¹ is the broader application of genomic technologies (encompassing both DNA and RNA) to drug response⁸.
9. Pharmaceutical companies are actively involved in pharmacogenetics and pharmacogenomics in the identification of drug targets, as well as drawing upon the underlying sciences of genetics and genomics.
10. For the purposes of this inquiry, we understand that **genomic medicine** encompasses both pharmacogenetics and pharmacogenomics, from discovery to clinical research and application.

Stratified or “Personalised” Medicines: the right patient, the right medicine, the right time

11. Every pharmaceutical company wants to develop medicines that treat disease effectively with minimal side effects. Genetic and genomic markers are part of the array of tools that can be used to achieve this goal. If the ABPI vision of the right patient, the right medicine, the right time is to be realised, then we need to bring together the emerging science, high-level skills and enabling technologies, coupled with developing the appropriate clinical and regulatory environments for delivery.
12. The ABPI is working with other stakeholders on a strategy for UK bioscience, and most importantly patients, to benefit from stratified medicines. The elements of this strategy are highlighted in Figure 1.
13. The ABPI believes that through the auspices of OSCHR, its supporting groups and the Technology Strategy Board, and through its participation in the IMI, the UK has an exceptional opportunity to realise the benefit of stratified medicines. We recommend that this could be pursued through several routes, including the creation of an Innovation Platform⁹ by the Technology Strategy Board, co-sponsored by the Department of Health and DIUS, something we have begun to discuss with the TSB.

⁵ <http://en.wikipedia.org/wiki/Genetics>

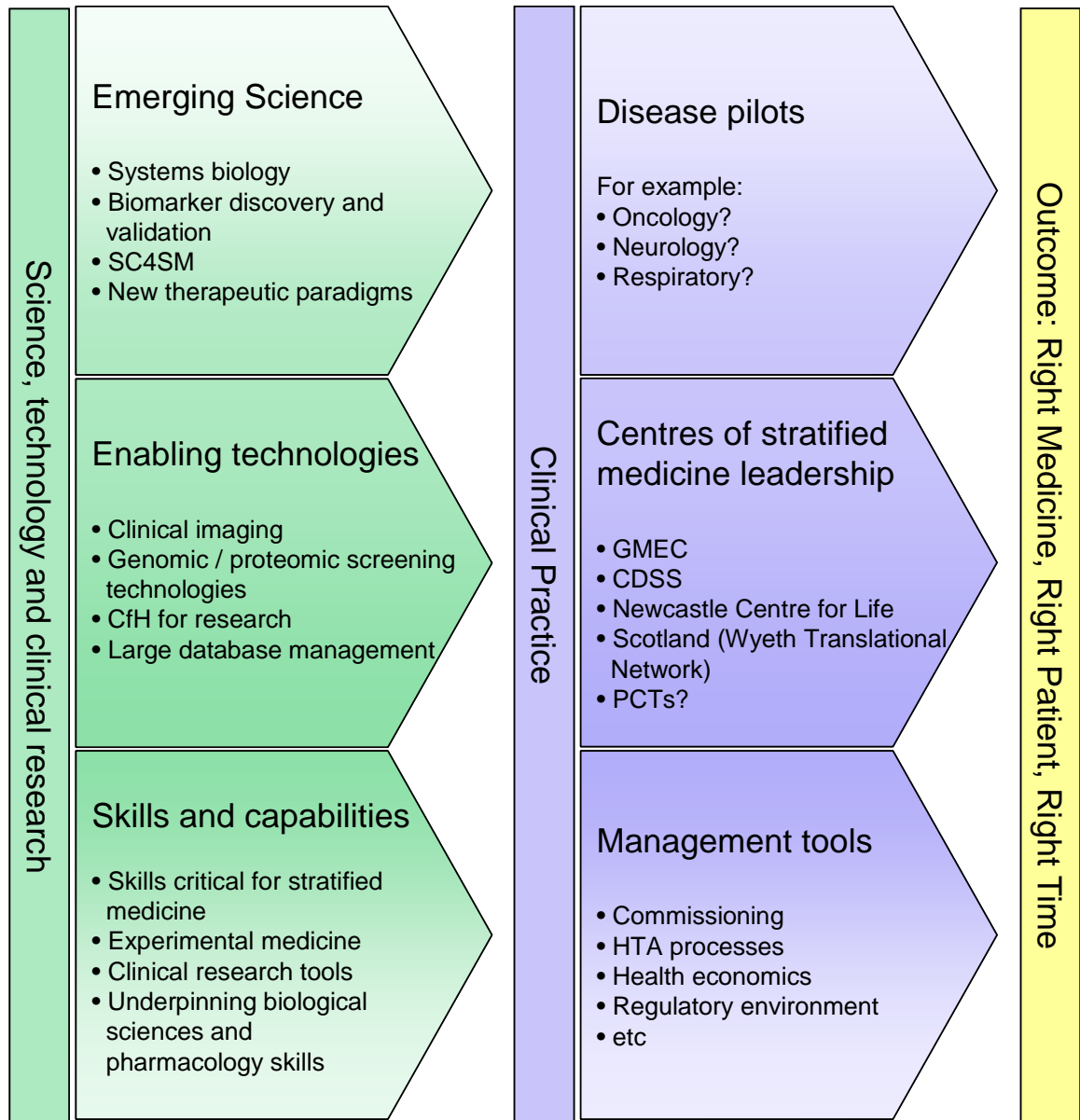
⁶ <http://en.wikipedia.org/wiki/Genomics>

⁷ <http://en.wikipedia.org/wiki/Pharmacogenetics>

⁸ <http://en.wikipedia.org/wiki/Pharmacogenomics>

⁹ <http://www.innovateuk.org/ourstrategy/innovationplatforms.ashx>

FIGURE 1: ELEMENTS OF AN INTEGRATED STRATIFIED MEDICINES STRATEGY



RESPONSE TO SPECIFIC QUESTIONS

Policy Framework

- *Who is in charge of setting and reviewing policy in this area?*
 - *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?*
 - *Does the existing regulatory and advisory framework provide for optimal development and translation of new technologies? Are there any regulatory gaps?*
 - *In what way is science and clinical policy decision-making informed by social, ethical and legal considerations?*
 - *How does the framework compare internationally?*
14. Genomic medicine covers a wide range of healthcare applications and as such, policy setting is, and should remain, an activity undertaken by a range of stakeholders. The challenge is therefore integration.
 15. The Office for the Strategic Coordination of Healthcare and Research (OSCHR) and its Translational Medicine Board is the obvious point of leadership and coordination for translational medicine R&D policy, of which genomic medicine is a part. Other players include the Wellcome Trust and Research Councils.
 16. On the whole, the current regulatory and advisory framework is good - the use of pharmacogenetic information to improve the risk:benefit profile of a drug is beginning to be recognised by drug regulatory agencies around the world and the ICH¹ have agreed definitions to facilitate further efforts in this arena which have already been transposed into regional guidelines of the EU, US and Japan.
 17. There are a number of stakeholders interested in the regulatory framework, for example: the pharmaceutical and diagnostic industries, key bodies such as the Academy of Medical Sciences, MHRA, the Department of Health and the NHS itself.
 18. For the future, an integrated regulatory framework for the co-development of a medicine with a diagnostic or predictive test should be a priority.
 19. The pharmaceutical and diagnostic industries are global. Any regulatory developments should be considered in this context and vehicles such as ICH used to develop agreed, internationally recognised regulations. Pharmaceutical companies and regulatory agencies from around the world contribute collaboratively through the ICH process.
 20. Pharmaceutical companies constantly develop their policies in light of the evolving social, ethical and legal environment. Such policies need to be global in application and respect national and regional differences in ethics as much as possible. All pharmaceutical companies support the concepts of free and fully-informed consent as a framework for requesting donation of samples during clinical studies.
 21. The Nuffield Council on Bioethics produced a report called "*Pharmacogenetics: ethical issues*"¹⁰ in 2003 that provides a good summary and recommendations from the situation at that time and its discussions and conclusions remain relevant today.
 22. It should also be remembered that pharmaceutical research is carried out to the strictest guidelines including research ethics committees and legislation such as Clinical Trials Directive that enshrine Good Clinical Practice into regulatory requirements. Additionally, in the UK the Human Tissue Act and the Data Protection Act provide additional frameworks for good practice. We do not believe therefore that further regulation is required, but companies continue to seek out new and evolve existing good practices in all aspects of their genomic and genetic research.

¹⁰ http://www.nuffieldbioethics.org/go/ourwork/pharmacogenetics/publication_314.html

Research and Scientific Development

- *What is the state of the science? What new developments are there? What is the rate of change?*
23. The sequencing of the human genome in 2001, led to significant hope that this would bring a rapid change in treatment of patients with debilitating disease. In reality this was only a step in the process of moving towards the application of genomic medicine. Many companies had already invested heavily during the 1990's, utilising genomic research to help identify the underlying causes of or susceptibility to disease.
 24. Since that time a number of medicines have been developed that target specific genetic profiles of patients, such as Herceptin and Gleevec, yet these are based on single gene disorders. The major step-change will be integrating genetic (e.g. single nucleotide polymorphisms (SNPs)) and other biomarker information to allow stratification of populations. This is not, however a trivial task as it requires an understanding of the interaction of multiple genes, their protein products and of drug metabolism and how this relates to patients in the clinical environment.
 25. However, advancements in pharmacogenetics are clearly reflected by the increasing number of drug labels that now include validated genomic biomarkers markers as an integral component of prescribing information for a range of indications including HIV, cancer, psychiatry, cardiovascular and hypertension. Examples include the labelling for Kivexa (abacavir) and other abacavir containing products due to the risk of abacavir hypersensitivity reaction¹¹. The FDA has produced a "Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels"¹².
 26. Emerging platform technologies, including diagnostics and imaging, analytical methodologies and clinical trial design are all important in developing genomic medicine into the clinic. Such changes are part of an evolutionary process rather than a revolution. Genomic medicine is one piece of the jigsaw in delivering stratified medicines to patients and added value for healthcare systems.
 27. The application of genomic medicine will undoubtedly accelerate when whole genome sequencing becomes rapid and affordable; a number of companies have a goal of providing a whole genome analysis for less than £500 per person.
 - *Who is taking the lead in the consideration and co-ordination of research and the development of new technologies?*
 - *How effective is the policy and investment framework in supporting research in this area?*
 - *How does research in the UK compare internationally? How much collaboration is there?*
 - *What are the current research priorities?*
 28. Innovation in the whole healthcare sector is clearly high on the Government agenda. The ABPI had a substantial input into the review led by Sir David Cooksey on UK Health Research in 2006 and has already contributed strongly to Lord Darzi's Health Innovation Council and his recent review of the NHS. These are important initiatives that will contribute to making the UK a more innovative home market for biomedical advances, if concrete proposals emerge to stimulate innovation across the NHS.
 29. In particular OSCHR has a key role to play, overseeing and coordinating healthcare research strategies across the National Institute of Healthcare Research (NIHR) and the Medical research Council, as well as other stakeholders such as the Technology Strategy Board. OSCHR has only just started its work, but momentum must be maintained.
 30. Any initiative must embrace particular UK strengths and opportunities, such as Biobank and Connecting for Health, and develop initiatives that complement international efforts. In

¹¹ <http://emc.medicines.org.uk/>

¹² http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

particular companies are already engaged with the European *Innovative Medicines Initiative*³ (along with UK research institutions) and the FDA's *Critical Path*⁴ and will not wish to duplicate investments across the globe.

31. In genomic medicine there are two broad priorities:
 - first, in genomics – that is the characterisation of DNA and RNA¹ – to understand the underlying causes of disease to identify potential new targets against which drugs can be developed;
 - second, through understanding genetic variation¹ of patient populations it is possible to: identify susceptibilities to disease; identify those likely to respond to a specific medicine by knowledge of the underlying cause; and understand how particular patients metabolise medicines in order to identify the appropriate dose to improve both safety and efficacy.
- *What is the role of industry? How much cross-sector collaboration takes place?*
32. Pharmaceutical companies already play a vital role in genomic medicine. Analysis of genetic information is routinely undertaken throughout the drug discovery and development pipeline. Cross-sector collaboration is extensive, both nationally and internationally and collaborations also exist in the form of public-private partnerships, perhaps the best known of these being the SNP (Single Nucleotide Polymorphism) Consortium, established in the late 1990's, that helped map 1.5 million SNPs and included 13 pharmaceutical and technology companies. More recently the International HapMap project is mapping SNP variation across the world.
33. More recently research programs that focus on serious drug-related adverse events (e.g. LQT, hepatotoxicity, Stevens Johnson Syndrome) that occur within or across various classes of pharmacological agents have been initiated through collaborative ventures such as the International Serious Adverse Events Consortium, a consortium of pharmaceutical companies, academic institutions, and the FDA.
34. The UK is developing its collaborative framework. Although collaborative research between industry and academe has historically been strong in the UK, an ABPI survey has noted the volume of collaborations has declined between 2003 and 2007. The reasons for the decline in UK collaborations are complex and include escalating cost, increasing international competition for research funds, difficulty in contract negotiation and lack of incentives available for academics to collaborate more closely with industry. If the UK is to have the best chance to lead in genomic medicine, these issues should be addressed.

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?*
 - *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?*
35. Genetic information, including annotated sequences and SNP maps are held in a number of publicly available databases. The Human Genome Project, the SNP Consortium and HapMap Project have developed consistent standards that are transparent and quality checked.
 36. In the UK there are a number of initiatives that could prove useful: Biobank; and Connecting for Health, the NHS electronic records initiative that has an objective and advisory group on utilising data within a clear ethical framework.
 37. OSCHR and its Translational Medicine and e-Health Boards also have roles to play in overseeing the utilisation and translation of this data to improve patient outcome.
 38. Internationally, drug regulatory agencies have established both informal and formal evaluation frameworks – some now involve international collaboration between regulators in the US, EU

and Japan. This helps to ensure consistency and high quality of data collection for submission to the regulators.

39. Genetic information needs to be collected with relevant, accurate and consistent medical data to allow for useful analysis and interpretation. High quality clinical collection and analysis with good electronic medical/health record management is essential if research, and more importantly patients, are to benefit from the full potential of such information

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

40. It is worth noting that the Nuffield Council of Bioethics report¹¹ stated that: “Genetic information does not necessarily raise different ethical issues from other types of medical information. We believe that the most important aspect to consider is the information that a test reveals and its implications for the patient, not whether the information is directly genetic”

41. Pharmaceutical companies take the security and management of genetic information very seriously. Rigorous ethical review takes place in all UK clinical studies, encompassing the collection and use of samples and any accompanying medical information.

Translation

- *What opportunities are there for diagnostics, therapeutics and prognostics - now and in the future?*
- *Who is responsible for translation to clinical practice?*
- *Given the pace of technological advance, how “future-proof” is healthcare investment in this area?*
- *How does the UK compare to other countries and what lessons can be learnt?*
- *How meaningful are genetic tests which use genome variation data? What progress has been made in the regulation of such tests?*

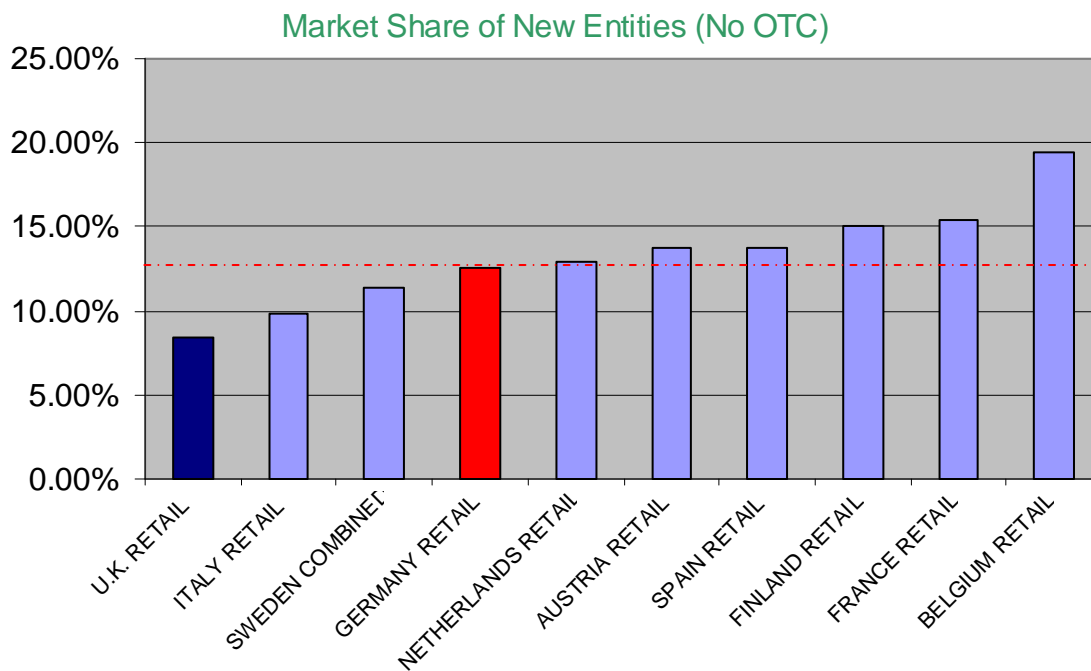
42. The UK should be well placed to accelerate the translation of genomic medicine from early discovery research to bedside under the auspices of OSCHR. This should be considered in the broader context of the application of biomarkers in stratified medicines. Within this context there is unlikely to be a single model of delivery of genomic medicine, but rather a framework for targeting of medicines to stratified patient populations.

43. There are also a number UK and European initiatives that should facilitate translation, including:

- The proposed Centre for Drug Safety Science centred at Liverpool and Manchester Universities that is still awaiting funding approval from the Medical Research Council – this initiative involves the Department of Health/NHS’ Chair in Pharmacogenetics at Liverpool University.
- The UK Global Medical Excellence Cluster (GMEC) incorporating Oxford, Cambridge and key universities in London, such as Imperial, UCL and KCL.
- In Europe industry and the Commission have been working together on removing bottlenecks in drug discovery and have established a Joint Undertaking called the *Innovative Medicines Initiative*³. A Strategic research Agenda has been developed for a 7 year research programme, with the first call for proposals to be published at the end of April 2008.
- In the USA the *Critical Path Initiative*, led by the FDA, is also addressing key factors to enhance productivity in drug discovery and development. All the major pharmaceutical companies are engaging with this process.

- The ICH¹ also has a role to play in developing globally accepted standards for key issues in regulation, already having developed definitions for pharmacogenetics and pharmacogenomics.
44. The ABPI believes that the OSCHR should take leadership in developing a UK national strategy on stratified medicines as previously discussed, which would need to encompass a number of facets in a coordinated and joined up approach, including:
- emerging science in drug discovery and diagnostics;
 - e-Health;
 - clinical application;
 - regulatory environment; and
 - health economics.
45. Overall, we believe that the UK compares favourably against other countries in Europe, but this does not mean to say there is not room for improvement. In particular the UK has a poor record on the uptake of innovative medicines when they first enter the market (Figure 1)

FIGURE 1: Uptake of new medicines in the UK, compared to other leading European nations.



46. The Government has a strong commitment to increasing industry investment in clinical trials in the UK. While there are encouraging signs of industry using the clinical trial networks set up under UKCRC and NIHR, there are still major challenges. Such issues must be addressed if the UK is to translate the opportunities from genomic medicine from the research base through to clinical benefit.
47. The first challenge is the slow start-up of trials and recruitment of patients. Yet of greater concern is the negative impact that restrictions on the availability of current 'gold-standard' treatments have on the ability to place phase 2 and phase 3 clinical trials on the next generation of treatments in the UK. In 2007, a survey of ABPI members identified (see Annex 2):
- 10 late clinical development studies that could not be placed in the UK owing to the lack of NICE guidance on comparator medicines used in other countries;
 - 5 studies that could not take place because of restricted uptake or implementation of NICE guidance; and

- one case study where an international benchmark of care was not implemented in the UK.
48. If this poor support and recognition of innovative medicines is sustained in the marketplace, then it is difficult to see how genomic medicine could be successfully translated to the clinic and benefit patients.
 49. Translational research is integral to the conversion of scientific knowledge into patient healthcare benefits. The Department of Health and professional medical organisations are in key positions to collaborate with industry to identify and address potential hurdles to the acceptance of genetics into clinical practice.

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?*
 - *What impact will genomic data have on data emerging from projects such as UK Biobank, Generation Scotland and other biobanks?*
50. There are various strategies for identifying biomarkers of which genome-wide association studies are one. Others include more specific genetics analysis (e.g. restricted to only biological pathways involved in drug metabolism), proteomic analysis, and other physiological markers.
 51. The ABPI has brought together pre-clinical safety scientists and experimental medicine experts (in early clinical pharmacology and research) in a Safety Biomarkers Working Group. This has surveyed reasons for failure in clinical trials and is now developing strategies in pre-competitive research that will aid in the identification of safety biomarkers – both pre-clinical and clinical – to reduce the risk of adverse events and aid in early compound selection. Such work is feeding into the research programmes of the European *Innovative Medicines Initiative* and the strategy of the UK's Translational Medicine Board. This is early days, but such initiatives should assist with the translation of biomarkers into research and clinical application.
 52. The UK Biobank, Generation Scotland, as well as the cancer tissue bank in Wales, could all provide valuable resources for the development of new biomarkers of disease and disease susceptibility. However the information is only as valuable as the quality of the samples and the information contained therein.
 53. In the UK, the electronic patient records initiative, Connecting for Health and the associated ethical framework for utilising such large scale epidemiological data in biomedical research also provides a real opportunity to create UK competitive advantage and enhance outcomes for patients. The e-Health panel reporting the OSCHR should play a leadership role in ensuring that the opportunities for UK patients and the research base are optimised.

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?*
 - *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?*
 - *Should there be a regulatory code (mandatory or voluntary) covering the provision of this advice?*
 - *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?*
54. Genomic information, in conjunction with proteomic and physiological biomarkers, will help to diagnose diseases and predict disease susceptibility according to the underlying

pathophysiology rather than the manifestation of symptoms alone. This will allow pre-symptomatic treatment of some diseases and more focused treatment of others– that is *the right patient, the right medicine, the right time*. Undoubtedly we will find that some diseases (defined by symptoms) will sub-segment into different root causes.

55. Patients should be provided with relevant information about any medical test used in provision of their own healthcare and genomic medicine and genetic tests are no exception to this – appropriate care should be taken in explaining such tests and the reasons for their use in prescribing medicines. The Nuffield Council on Bioethics report on pharmacogenetics stated that genetic information does not necessarily raise different ethical issues to any other forms of medical information. Nevertheless genetic testing does raise concerns among some patients that need to be addressed.
56. The integration of genomic medicine, and indeed other biomarkers in the clinical environment will require appropriate training and support of medical students, as well as practising GPs and consultants and other healthcare professionals.
57. In addition consideration should be given as to how to incorporate basic knowledge and information in to the school curriculum, to educate the next generation. This should be done through, in the long term, science curricula, dialogue, education and debate, and “patient friendly” materials and resources. “Patient friendly” materials and resources should also be made available in the clinic.

Closing Comments

58. Industry is continuing to invest in genomic medicine, genomics and genetics. Genomic medicine offers a real opportunity for patients to benefit from better targeting of medicines increasing patient safety and drug efficacy.
59. However, coordinated action within the research and regulatory environments is needed to allow the co-development of diagnostic and prognostic tests to ensure the realisation of *the right medicine, the right patient, the right time*.