GENOMICS, HEALTHCARE AND PUBLIC POLICY

Based on papers delivered at the OHE Conference on Genomics, Healthcare and Public Policy, London, 11 February 1999

Edited by Paul Williams and Sarah Clow

Office of Health Economics
12 Whitehall London SW1A 2DY

ISBN 1 899040 11 0

Printed by BSC Print Ltd, London.

Office of Health Economics

The Office of Health Economics (OHE) was founded in 1962. Its terms of reference are to:

- commission and undertake research on the economics of health and health care;
- collect and analyse health and health care data from the UK and other countries;
- disseminate the results of this work and stimulate discussion of them and their policy implications.

The OHE is supported by an annual grant from the Association of the British Pharmaceutical Industry and by sales of its publications, and welcomes financial support from other bodies interested in its work.

ACKNOWLEDGEMENTS

The OHE conference from which the papers in this book have been drawn was organised in collaboration with the School of Public Policy of University College London, and Pharmaceutical Partners for Better Healthcare (PPBH). The OHE is grateful to PPBH for their financial support in preparing this book.

School of Public Policy, University College London

The School of Public Policy at University College London is an independent source of advice to government and other national and international bodies in the public and private sectors. It aims to achieve a two-way transfer between university-based knowledge and expertise, and government policy requirements. Its purpose is to aid the formation of policies that are conducive to innovation, economic stability, social cohesion and health.

Pharmaceutical Partners for Better Healthcare

The Pharmaceutical Partners for Better Healthcare (PPBH), established in 1993, is a think tank supported by 34 research-based pharmaceutical companies from Europe, Japan and the United States. The member companies of PPBH believe that viable solutions to healthcare issues can be found only if all those involved in the future of healthcare work in partnership. PPBH provides international forums for discussion of issues that cross national borders, sponsors objective research on health care policy, encourages the development of programmes that address key issues, and fosters partnerships among all those involved in providing and using healthcare.

CONTENTS

SPEAKERS

Professor Patricia Danzon
Health Care Department, The Wharton School,
University of Pennsylvania, 3641 Locust Walk,
Philadelphia PA 19104
Tel: +1 215 898 6861 Fax: +1 215 573 2157

Patricia Danzon is the Celia Moh Professor at the Wharton School, where she is Professor of Health Care Systems, and Insurance and Risk Management.

Prior to joining The Wharton School at the University of Pennsylvania in 1985, Dr Danzon held positions as Associate Professor at Duke University, Senior Research Fellow at the Hoover Institution at Stanford, and Research Economist at The Rand Corporation. She has been a Visiting Professor at the University of Chicago and Victoria University (New Zealand).

Professor Danzon is an internationally recognised expert in the economics of healthcare, pharmaceuticals, insurance, and liability systems. She is an elected member of the Institute of Medicine and the National Academy of Social Insurance. She has served as a consultant on international healthcare issues to numerous organisations. Professor Danzon is Associate Editor of the Journal of Health Economics and Research in Law and Economics, and was previously Associate Editor of the Journal of Risk and Insurance. She has published widely on a broad range of subjects related to medical care, pharmaceuticals, insurance, and the economics of law.

Professor John Durant
The Science Museum and Imperial College, London SW7 2DD
Tel: +44 (0)20 7938 8201 Fax: +44 (0)20 7938 8213

John Durant is Director of Science Communication at the Science Museum, and Professor of Public Understanding of Science at Imperial College, London. He is responsible for the construction of a new wing at the Science Museum (The Wellcome Wing) dedicated to contemporary science and technology, due to open in June 2000.

Professor Durant has published widely on the history of the life sciences, the relationship between science and human values, and the public understanding of science. He is the founding editor of the quarterly international journal *Public Understanding of Science*, writes frequently for the popular press, and contributes regularly to radio and television science programmes. Professor Durant has also headed numerous research projects and is currently the co-ordinator of a major European Commission-funded international research project on *European debates on biotechnology: dimensions of public concern*.

Dr Rosalind Eeles
Institute for Cancer Research/Royal Marsden NHS Trust,
Downs Road, Sutton, Surrey SM2 5PT
Tel: +44 (0)20 8643 8901 (x3642) Fax: +44 (0)20 8770 1489

Dr Eeles is Clinical Senior Lecturer and Consultant in Cancer Genetics and Clinical Oncology at the Institute of Cancer Research and the Royal Marsden NHS Trust, London and Surrey, UK. She leads the Cancer Genetics Team there, and is the Head of the Cancer Genetics Clinic at the Royal Marsden.

Her clinical research interests are in the detection and management of carriers of cancer predisposition genes, in particular those with familial prostate and familial breast cancer. Her laboratory research interests focus on familial prostate cancer and the role of germ line mutations in the TP53 gene in Li-Fraumeni and Li-Fraumeni-like families.

Mr Alastair Kent
Director, The Genetic Interest Group, Unit 4D, Leroy House,
436 Essex Road, London N1 3QP
Tel: +44 (0)20 7704 3141 Fax: +44 (0)20 7359 1447

Alastair Kent has been the Director of the Genetic Interest Group (the national alliance for voluntary organizations, charities and support groups for those affected by genetic disorders) since 1993. He has worked in the voluntary sector for the last 15 years with a range of charities concerned with the development and provision of services

to people with a wide range of disabilities. He is also President of the European Alliance of Genetic Support Groups.

Prior to joining this sector, he worked for three Local Education Authorities, initially as a careers officer, but moved to work with school leavers with disabilities and/or learning difficulties. He eventually played a county-wide role in North Yorkshire, UK, where he was responsible for co-ordinating the contributions to meeting the needs of these young people from a range of public, private and voluntary organizations.

Professor Bartha-Maria Knoppers
Faculty of Law, University of Montreal, CP 6128,
Succ Centre-ville, Montreal, Quebec H3C 3J4
Tel: +1 514 343 6714 Fax: +1 514 343 7508

Dr Knoppers is Professor at the Faculty of Law, University of Montreal, Senior Researcher (CRDP) and Counsel to the firm of McMaster Gervais. Currently Chair of the International Ethics Committee of the Human Genome Project (HUGO), she was a member of the International Bioethics Committee of the United Nations Educational Scientific and Cultural Organization (UNESCO) that drafted the *Universal Declaration on the Human Genome and Human Rights*. Her current research and teaching concentrates on genetics, law and ethics, pharmacogenomic research and consent and DNA/tissue banking.

Professor Knoppers has served as an expert to committees of the World Health Organization and the National Institute of Health (Washington). She was a member of the Central Management Committee of the Canadian Genome Analysis and Technology Program, where she also chaired the Medical, Ethics, Law and Social Issues Committee (1992 to 1995). She is consultant to the Ministry of Industry (Ottawa), Co-Director of the Institute for Population Studies (IREP) and of the Quebec Network of Applied Genetic Medicine (RMGA), and a member of the Standing Committee on Ethics of the Medical Research Council of Canada. Professor Knoppers is a member of the board of Genome Canada. In September 1996 she chaired the Organizing Committee of the First International

Conference on DNA Sampling, *Human Genetic Research: Ethical Legal and Policy Aspects*, held in Montreal. In 1997 she was named 'Scientist of the Year' by Radio Canada and by the newspaper *La Presse* and received the medal of the Quebec Bar.

Professor Everett Mendelsohn
Department of the History of Science, Harvard University,
Science Center 235, Cambridge, Massachusetts 02138
Tel: +1 617 495 3741 Fax: +1 617 495 3344

Everett Mendelsohn is Professor of the History of Science at Harvard University, where he has been on the faculty since 1960. He currently chairs the Department of the History of Science.

He has worked extensively on the history of the life sciences, as well as on aspects of the social and sociological history of science and the relations of science and modern societies. He is the founder and former editor of the *Journal of the History of Biology* and a founder of the yearbook Sociology of the Sciences. He serves(d) on the editorial boards of the *Journal of Medicine and Philosophy, Social Science and Medicine, Social Epistemology, Social Studies of Science* and *Fundamenta Scientiae*, among others. He has published widely in the areas of the history and sociology of biology and human genetics, and on the relations between science and modern war.

He is past president of the International Council for Science Policy Studies and was a founder of both the American Association for the Advancement of Science's Committee on Science, Arms Control and National Security, and the American Academy of Arts and Science's Committee on International Security Studies.

Professor Sir Michael Peckham
School of Public Policy, University College London,
29/30 Tavistock Square, London WC1H 9EZ
Tel: +44 (0)20 7504 4966 Fax: +44 (0)20 7504 4969

Sir Michael Peckham is Director of the School of Public Policy at University College London. He is also Chairman of the Office of

Science and Technology's Foresight Panel on Healthcare, and Chairman of the National Education Research Forum.

He was the first Director of Research and Development for the National Health Service and Department of Health from 1991 to 1995. He was responsible for devising and implementing a research and development strategy for the National Health Service which is now receiving international attention.

Between 1986 and 1990 Sir Michael was Director of the British Postgraduate Medical Federation. He was formerly Dean of the Institute of Cancer Research and Civilian Consultant to the Royal Navy. During his clinical career he became an internationally recognised authority on the treatment of Hodgkin's disease and testicular cancer. He was Vice Chairman of the Imperial Cancer Research Fund, President of the Federation of European Cancer Societies, and founder and President of the British Oncological Association. In 1994 he became a member of the National Academy of Sciences, Institute of Medicine in Washington DC.

Sir Mark Richmond
School of Public Policy, University College London,
29/30 Tavistock Square, London WC1H 9EZ
Tel: +44 1(0)20 7504 4966 Fax: +44 (0)20 7504 4969

Sir Mark is a renowned microbiologist. Early in his career he joined the National Institute for Medical Research at Mill Hill, UK, later moving to the Department of Molecular Biology in Edinburgh University. During this period he developed research interests in antibiotics: their modes of action and the susceptibility or resistance to them of clinically relevant bacteria. In 1968 he joined the University of Bristol as Professor of Microbiology, and remained there for 13 years. He was elected Fellow of the Royal Society in 1980.

In 1981, Sir Mark undertook a radical career change, becoming Vice Chancellor of the University of Manchester, UK, for 10 years. In 1990 be was appointed Chairman of the Science and Engineering Research Council, a government-funded agency supporting UK research to the tune of £600 million p.a. In 1993, he was appointed Head of

Research Worldwide for Glaxo.

Since retiring in 1996, Sir Mark has been working as a consultant in the biotechnology and pharmaceutical industries. He is a non-executive director of a number of biotechnology companies and is the Chairman of CRC Technology.

About the Editors

Dr Paul Williams is a Director of Genesis Pharma Strategies (a division of PAREXEL Medical Marketing Services [Europe] Ltd) and Dr Sarah Clow is a Commercial Medical Editor at PAREXEL Medical Marketing Services (Europe) Ltd.

EXECUTIVE SUMMARY

This Conference on Genomics, Healthcare and Public Policy, organised by the Office of Health Economics in collaboration with the School of Public Policy, University College London, and Pharmaceutical Partners for Better Healthcare, examined the status and likely consequences of healthcare applications of genetics. Advances in genetics will open up opportunities for universities and industry, they will induce changes in the practice of medicine, and lead to alterations in the structure and organization of health services in many countries.

Genomics is the study of the genome as a whole – the sequence of DNA nucleotides in the cell and how this provides the information for the cell to function and reproduce itself. An important extension of this is the concept of population genomics, the study of how the genetic constitution of a population is related to health and disease in that population. Genetics is the study of individual genes and their roles in cell functioning and reproduction. Mutations in specific genes often produce, or contribute to, diseases, thus defining the disease as a 'genetic disease'. Therefore, genetic research can be considered a category (perhaps the most critical category) of genomic research.

Public understanding

Despite a steady growth in media coverage over the past decade, levels of public understanding of genomics and genome-related issues in the UK remain fairly low. Data presented by Professor John Durant (see Chapter 2) demonstrate that the British public is relatively supportive of explicitly medical applications of molecular genetics, and tends to distinguish clearly between applications on the basis of their perceived moral acceptability. The general public is increasingly aware of human molecular genetics, and they are increasingly inclined to adopt very different attitudes (based on ethical concerns) towards different applications of human molecular genetics. In general, human genetics currently enjoys a high and positive public profile, and there is strong public support for core applications of genomics in healthcare, provided that there are significant medical benefits to be gained in relation to serious medical conditions. There is considerable public

ambivalence about wider applications and implications of these same technologies. Outside areas of substantial healthcare benefit, people very rapidly become wary. Questions about the moral acceptability of applications are much more important in shaping attitudes to these medical technologies than are questions to do with risk. Where people see benefits and moral acceptability, they will often accept significant risks in order to obtain the benefits. Where people do not see technologies as being morally acceptable, they will rarely tolerate even low levels of risk.

Healthcare and the pharmaceutical industry

Sir Mark Richmond explained the effect of genomics on healthcare and the pharmaceutical industry (see Chapter 3). Advances in genetics are already being used by the pharmaceutical industry to aid drug discovery and genetic technologies are already a main element of the research and development (R&D) programmes of major pharmaceutical companies. Many see the use of genetics and genomics as a way of increasing the size of their markets. Pressures on profit margins will be met by increases in market size and diversity, and companies will evolve from being those devoted to the discovery and exploitation of novel medicines to those that provide a range of therapies and the services to back up their use. Genetic information about pharmacokinetic and toxicity profiles will also allow more accurate dosing recommendations, which will have an impact on drug pricing. This information could also allow companies to give drugs that were previously sidelined, because of toxicity problems, to subgroups of patients who will not have adverse reactions to the drug. Many other companies use genetic technology to develop novel diagnostics. Genetics and genomics are also increasingly involved in product marketing, with managed healthcare programmes and 'market prediction'.

Genetics and genomics will also have a huge impact on the insurance industry. The policies of health insurers will increasingly reflect the mean and variation of the predictability of genetic tests. Issues of confidentiality and access to information will be central to the evolution of this situation. Detailed discussions are needed between government

representatives, the pharmaceutical industry and patient representative groups to investigate how we can move forward. There are enormous advantages for all parties if genetic testing and genotyping can be implemented in a manner acceptable to all interested parties.

Clinical perspectives

Genetic differences may have a role in predisposition to, and behaviour of, disease. As explained by Dr Rosalind Eeles (see Chapter 4), once rapid genetic analysis is available, such analyses will be analogous to blood pressure measurement being used to identify individuals at increased risk of cardiovascular disease. GPs will be able to advise about primary prevention and prescribe preventative drugs to reduce the risk of certain diseases occurring. This proactive rather than reactive style of practising medicine is potentially exciting, but carries with it ethico-legal and social implications for how the data are dealt with.

The main benefit of testing is that once it is known that a patient has a predisposing gene, it is more likely that the disease will be detected at early onset and optimal management strategies can be employed. However, cost-effectiveness models to demonstrate whether genetic testing saves more money than it costs have not yet been conducted.

Patients' perspectives

Recent advances in the understanding of genetics and the contribution that genes make to human health and disease have provided hope for many families affected by hitherto incurable diseases. For those in this position, genetics holds the prospect of effective intervention and ultimately of cure. However, Mr Alastair Kent (see Chapter 5) pointed out that there is a significant gap between the discovery of genes that predispose individuals to develop a particular condition and the ability to intervene in the disease process. Such intervention depends on technical, commercial and social factors. Many patients fear that it will prove to be too technically difficult to bridge the gap between the disease and its cure. Commercial and social issues relate to the successful transfer from the laboratory to the clinic of scientific advances that

enhance prospects of receiving improved services and better diagnostic and/or therapeutic products. Diagnostic and therapeutic tools have been developed, and are made available for treating patients, through the private sector. However, this system, which has produced many remarkable drugs, is driven by attracting investment and delivering a return that is sufficiently attractive to offset the risks. For millions of people at risk from rare disorders, this mechanism is fundamentally flawed, since the mechanisms of the market ensure that promising research will never be translated into effective and affordable products because the costs per case of treatment would be prohibitive.

Ethical and legal implications

Pharmacogenomics focuses on normal genetic variation in the population in order to examine differences between the pathways of action of different drugs so as to understand drug response better. However, Professor Bartha-Maria Knoppers (see Chapter 6) pointed out that the DNA banking required for such studies raises issues of confidentiality surrounding testing for inherited genetic disorders. The socio-economic risks (e.g., unemployment, higher insurance premiums) of participating in a clinical trial as a patient, family member or research participant, distort the rules governing medical confidentiality.

Pharmacogenomic studies seek to use only anonymized samples, so only limited demographic and clinical data accompany the samples. This could create difficulties in that most countries offer a legal right of access to personal information, but there would be no 'person' to be found. Additionally, as the right of the research subject to withdraw cannot be exercised because the subject's sample cannot be identified, and as the subjects cannot be provided with any results, the ethical requirements of the genetic research paradigm cannot be met. There is also a question of whether it is ethical to obtain but withhold information that could be of benefit to a patient. Currently, the 'over-protection' of research subjects in population genetic research, while necessary to redress past grievances or to counteract the lack of universal health insurance, may be harmful to the needs of the population as a whole. Professor Knoppers reviews four approaches to policy-making in genetic research, all with their own advantages and disadvantages.

Is public policy lagging behind the science?

Professor Everett Mendelsohn (Chapter 7) sets the development of human genetics during the 20th century in a historical context, and focuses on the interaction of scientific and technical advances in genetics and the development of social and public policy for human genetics. Early geneticists were convinced that both human physical and mental traits were inherited in law-like fashion. While an extensive social policy of eugenics, to attempt to create a more favourable genetic mix in the populations of Europe and North America, was propounded, the modes for practising the required genetic management were severely limited. Scientists were debarred from experiment in the human field. Two practices which permitted the eugenic vision to be implemented were restrictive immigration (largely limited to the USA) and involuntary eugenic sterilization of certain groups of people.

The process during which genetic science and technique would quickly outrun social policy in the practice of human genetics began with the identification of DNA, the delineation of its chemical composition, its physical structure and its role in protein production. As soon as the techniques seemed useable, there was interest in inserting genes into human cells carrying genetic diseases. Work on gene transfer in mammals proceeded vigorously with increasing, if still limited, technical success, and the lure of recognition and reward pulled experimenters to the edge of socially and ethically accepted practices.

During the past decade and a half, the field of human molecular genetics has been extremely active, and the moves to apply the newly gained knowledge and techniques in genetic screening, somatic therapy, and germ line genetic engineering have become widespread and often controversial. Social analysts are racing to understand the new developments, to develop tools and frameworks for their analysis, and to raise for public and social discussion the myriad implications of the technical achievements. As genetic linkages are established between genes and diseases, genes and physical attributes, and genes and human behaviours, the temptations to simply allow technical capability to guide social judgement is strong. The genetic sciences are robust

and challenging, even if not always wise. In contrast, social and ethical analysis and social and ethical policy-making, while earnest, lack clarity and focus.

The task for the immediate future is to establish a means to integrate the social and moral critique into the decision-making processes of the practising sciences, so that social analysis becomes part of a feedback system to assure wisdom in scientific advance not mere technical achievement. There are potentially significant costs to allowing social policy to lag behind scientific and technical advance. Solving the 'technically sweet' problem before turning to examine the moral and social consequences has proved to be too costly in the past, and may continue to do so in the future.

Economic implications

Professor Patricia Danzon (Chapter 8) examines the economic effects of the various uses of genomics in the diagnosis and treatment of disease, in particular: pharmacogenomics as a tool of drug discovery; gene therapy; pharmacogenetic testing to increase drug specificity; genetic testing of symptomatic patients; and population genotyping. The primary question for payers is whether gene therapies will be cost-effective and affordable. However, the question for private developers of these therapies is whether the prices deemed cost-effective by payers are sufficient to cover costs and yield a reasonable return. Professor Danzon considers the effects of different uses of genomics on the productivity and costs of the pharmaceutical industry, and discusses their effects on the quality, characteristics and prices of therapies available to consumers.

Genomics is already used widely in the pharmaceutical industry, having the potential to reduce R&D costs, increase the rate of new drug introductions, prolong patent protection time, and expand the range of therapies available. In the long run, pharmacogenomics is likely to improve productivity significantly. These advances will result in higher net revenue for each compound developed but also in pressures on payers as more new drugs reach the market. The net beneficiaries will be consumers, who will benefit from a higher rate of introduction of new drugs and lower prices.

There is much clinical uncertainty as to the potential for lasting therapeutic benefits of gene therapy and the risks of severe side effects. Such uncertainties create economic risks, which may require high returns on those products that succeed. If successful, gene therapies would require only infrequent administration, which may be of great benefit to patients, but could raise problems in terms of adequate reimbursement and commercial viability. The number of patients treated per year, at least initially, will be low, and the number of treatments per patient will be low. Both aspects reduce the profitability of gene therapies. The only way they will be able to compete commercially with alternative therapies is if there are significant savings in R&D costs.

Orphan drug status is a possible remedy for the disincentive for companies to invest in therapies for small patient populations. However, the criterion for awarding orphan status[1] is often applied inaccurately or *ex post*. A better approach would be to permit prices that are proportional to expected effectiveness in the target population.

Genetic testing prior to treatment could identify patients who would benefit from particular drugs or those who would develop adverse effects. This would generate social savings by avoiding ineffective treatment and the cost of adverse reactions. The concern from the perspective of industry is that pharmacogenetic testing prior to treatment may result in fewer patients treated and hence lower revenue per drug.

There is some scepticism over whether genetic testing of randomly selected, asymptomatic populations is feasible and useful. Governments do not need to predict with great accuracy the disease mix of their populations. The major determinants of overall demand for medical care are age and other readily observable demographic factors, and unpredictable changes in disease prevalence. The main beneficiaries of population genotyping would be pharmaceutical companies, for whom such information might be useful in drug dis-

1 Orphan drug status may be available in the US for drugs developed for disorders which affect fewer than 200,000 people in the US, or for which there is no reasonable expectation that the costs of R&D could be recovered by sales in the US.

covery and projecting demand. However, genotyping may also entail a range of costs for individuals tested through discrimination in insurance and possibly employment.

Genomics offers great potential benefits, but current reimbursement strategies may be inadequate to encourage appropriate development of long-lived and more specific gene therapies, which are two of the most immediate potential advantageous uses of genomics. Reimbursement needs to be approached much more flexibly in terms of breaking down the silo approach to the drug budget versus other services, thinking in terms of the longer-term benefits and being willing to pay the expected value of future, as well as present-day, benefits.

Chapter 1
Introduction

PROFESSOR SIR MICHAEL PECKHAM
School of Public Policy, University College London, UK

The Conference on Genomics, Healthcare and Public Policy, organized by the Office of Health Economics in collaboration with the School of Public Policy at University College London, and Pharmaceutical Partners for Better Healthcare, examined the status and likely consequences of healthcare applications of genetics. The task of judging what is likely to unfold, even in the short and medium term, is not a trivial exercise. It requires the assembly and analysis of a large body of data from many different sources. The background paper written by Mark Richmond (an expanded version of which has been published in 1999) provided the context for this conference and is an excellent overview of a controversial and fast-moving field of science and technology.

The genome era is certain to bring change. The questions are how, in what form, over what timescale, at what cost and to whom? With hindsight the enthusiasm for gene therapy, for example, now seems premature, and problems that have become apparent were underestimated. Advances in genetics will open up opportunities for universities and industry, they will induce changes in the practice of medicine, and lead to alterations in the structure and organization of health services everywhere. There will be new educational requirements for professionals and the public. The relative certainties of conventional diagnosis will be less black and white as genetic details provide information about risk and the probabilities of developing disease.

There is also likely to be a tension between industrial innovation and government policy. The prospect of commercially-exploited genome research is of obvious interest to industry and to the Department of Trade and Industry. The potential cost of genetic diagnosis and genetic treatments will raise concerns in the Department of Health. Diagnostic tests and pressures for screening are likely to precede major therapeutic advances and in many cases it may be possible to

identify individuals at risk, without being able to do a great deal to lessen their chances of developing disease. Clinically normal people could become pre-patients, perhaps for years, before they develop a condition for which they are at risk, or they may never develop it. It is not known how individuals will respond to a knowledge of risk, and whether this could lead to repeated demands on healthcare systems for reassurance and monitoring.

Population genotyping could reveal hidden disease as well as the epidemiology of future morbidity. Although this could be the route to novel and cost-effective preventative strategies, the shorter term reaction of policy-makers may be determined by fear of an increased burden on health services.

The tension between economic opportunities from commercial development and preventative medicine, and economic pressures from a medicalized population is not new, but it is brought to a head more dramatically in the field of genetics. This should provide a stimulus to re-examine the relationship between technology transfer and industrial R&D on the one hand, and the development of preventative and treatment services on the other.

In medicine, genetic testing has focused primarily on problems that will afflict the next generation through, for example, testing for monogenic disorders such as phenylketonuria and cystic fibrosis. As the genetic component of common chronic disease is better understood, genetic information will be used to determine the susceptibility to disease later in life in the existing generation. Potentially medicine could shift its orientation from late-stage disease to concentrate on early-stage, pre-clinical problems. Currently many doctors are not well-informed about genome research and genetics, and they are not comfortable dealing with concepts of risk and probabilities. The public also have limited knowledge of genetic questions, although the capacity of lay people to understand the issues involved can often be under-estimated.

Both industrial and public policies require an understanding of the issues. The capacity within government to tackle the challenges posed by genetic developments needs to be supplemented by external con-

tributions from specialists. Genetic advances raise social, ethical, economic and legal questions, many of which are not specific to the field but which are heightened by the choices and dilemmas raised by genomics. Even here, ideas and positions are changing rapidly. Germline gene therapy, for example, which was scarcely mentionable two or three years ago, is now more freely discussed. Similarly, cloning of human cells and tissues, which was once out of bounds, is increasingly envisaged in relation, for example, to transplantation.

This conference explored some of these issues and attempted to envisage what is likely to unfold in the medium term. Scientific progress is impressively rapid. The imponderable is the time course for translating discoveries into practical developments. Thus, although the cystic fibrosis gene was identified in 1989, there is as yet no treatment based on gene function. Nevertheless, genome research and genetics are already influencing clinical attitudes. For example, tests for breast cancer genes are a reality, as is a genotypic disease classification for Alzheimer's disease.

REFERENCE

1 Richmond MH. *Human Genomics – Prospects for Health Care and Public Policy*. UK: Pharmaceutical Partners for Better Healthcare, 1999.

Chapter 2
Public understanding of the significance of genomics

PROFESSOR JOHN DURANT
The Science Museum and Imperial College, UK

Abstract

Human molecular genetics and human developmental biology (including cloning) are two of the 'hottest' areas of contemporary scientific research so far as the mass media and the public in the UK are concerned. A steady growth in media coverage over the past decade, particularly in areas such as DNA fingerprinting, may be partially responsible for a marked increase in public awareness of DNA and DNA-related research in the UK in the early 1990s. Nevertheless, levels of public understanding of genomics and genome-related issues in the UK remain fairly low. The most important features of public attitudes towards these areas of research are:

- *The public is relatively supportive of explicitly medical applications of molecular genetics (with the important exceptions of transgenic animal research and xeno-transplantation).*
- *People tend to distinguish clearly between morally acceptable applications (e.g. screening for serious genetic diseases) and morally unacceptable applications (e.g. eugenic attempts to improve human nature). The basis for this distinction has not been adequately investigated, but at present the British public has provisionally classified all forms of human cloning in the 'morally unacceptable' category.*

DNA – a leader in fashion

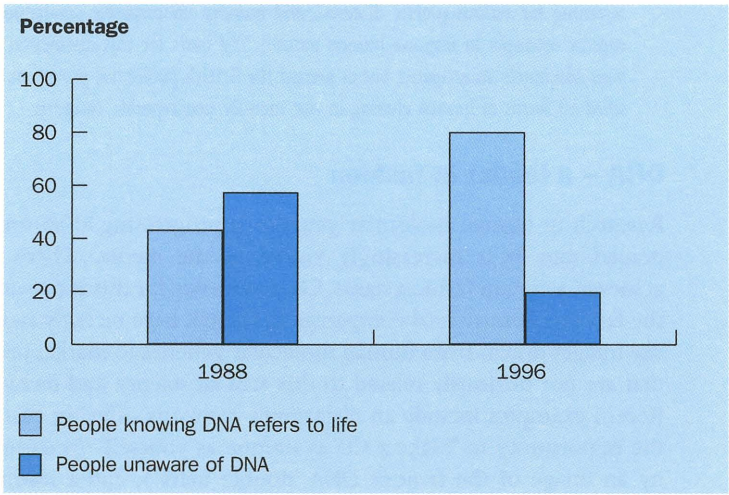
Research in human molecular genetics is progressing at an unprecedented rate. It is increasingly visible in the media, where it has achieved a certain fashion status. Clear evidence for this is provided by the fact that commercial companies in the UK have recently started to use images drawn from human molecular genetics to market products that are not obviously related to this area of science and technology. Recent examples include an electronics company offering customers the opportunity to 'Make a CD as unique as yourself' (accompanied by an image of the famous DNA 'double helix'), and a leading car manufacturer promoting its latest executive saloon by associating it

with DNA, since 'DNA is responsible for the transmission of hereditary characteristics like strength, agility and looks'. In the UK in the late-1990s, DNA has become a glamorous molecule.

Increasing public awareness

The general public is increasingly aware of human molecular genetics, although it is important to remember that awareness does not necessarily convey understanding. In 1988 a random sample of the British public were asked, 'When scientists use the term "DNA" are they referring to: (1) stars; (2) rocks; (3) living things; (4) computers?'. In response to this question, only 43 per cent of respondents were able to state correctly that DNA was something to do with life (Figure 2.1). However, in 1996, when the study was repeated, no less than 81 per cent of people knew that DNA had something to do with

Figure 2.1 **Increasing awareness of DNA over the last decade**



Sources: Durant et al, 1989; Durant and Bauer, 1999.

life. Therefore, in a period of less than a decade, DNA has entered the vernacular of the British. Today, almost everyone has heard of DNA and knows that it is something to do with inheritance. This is a significant change in public consciousness.

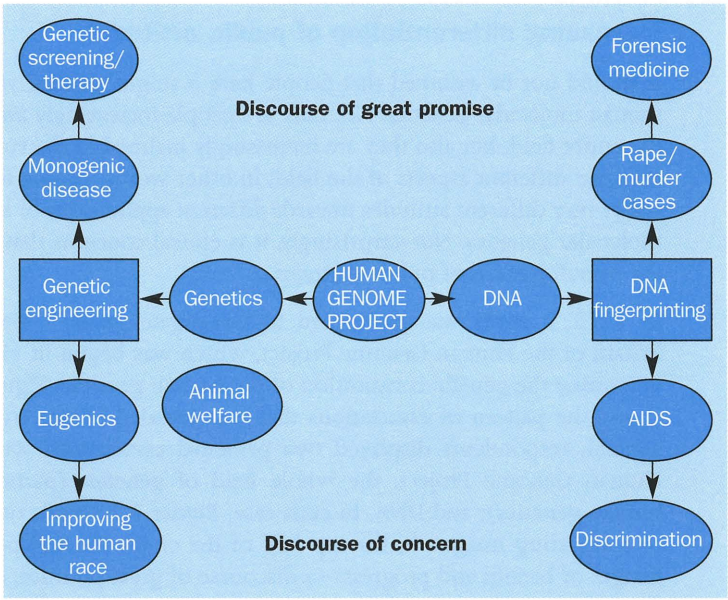
Increasing differentiation of public attitudes

It should not be assumed that people have a single, general view of human molecular genetics. Not only are people increasingly aware of the entire field, but also they are increasingly inclined to discriminate between different aspects of the field. In other words, people tend to adopt very different attitudes towards different applications of human molecular genetics. Not surprisingly, it is ethical concerns that shape the overall pattern of public attitudes.

In 1993, a study was performed to investigate people's views in Britain of the Human Genome Project, which was begun in 1986 to determine the genetic constitution of the human genome. Figure 2.2 shows the pattern of associations that was revealed in this study. In general, respondents displayed two principal associations with the Human Genome Project: the whole field of genetics (particularly human genetics); and DNA. In each case, Figure 2.2 reveals two sets of contrasting images. In the top half of the chart, we find positive images of benefit and progress – a discourse of great promise; and in the bottom half of the chart, we find negative images of actual or potential misuse – a discourse of concern. In the area of human molecular genetics, the ability to diagnose the presence of serious genetic disorders such as Down's syndrome or cystic fibrosis was recognized as an important contribution. However, any attempt to 'improve human nature' had powerful negative associations. Similarly with DNA, there were positive associations with forensic science, but strongly negative associations with HIV testing, which was associated with possible discrimination against individuals on grounds of health status. (This concern is still seen today in debates about the use of genetic testing by insurance companies or employers.)

In 1996, the European Commission funded a major 'Eurobarometer' survey of public perceptions of modern biotechnology in all member

Figure 2.2 **Social representation of the genome project in the UK in 1992, mapping the principal associations organized into two dimensions so as to demonstrate the fundamental tension between the discourses of great promise and concern**



states of the European Union. The total sample size was 16,246 (about 1,000 per EU country). Respondents were asked for their attitudes to six applications of modern biotechnology (Table 2.1, Figure 2.3).

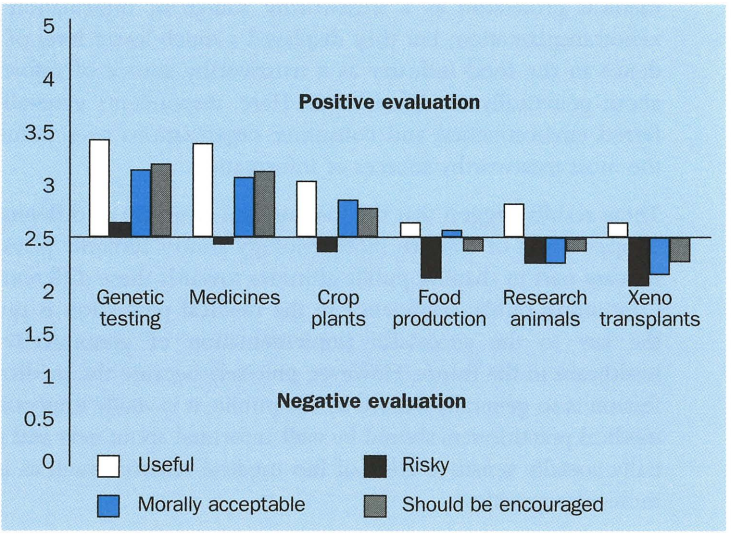
Genetic testing and the production of new medicines and vaccines obtained positive public endorsement in all 15 member states of the EU. The overwhelming majority of respondents believed that both of these applications were useful, morally acceptable and worthy of being encouraged. At the other extreme, the two animal biotechnologies (transgenic animals for medical research, and transgenic animals for human transplantation) were viewed much less favourably. Here, significant numbers of respondents viewed the technologies as being

Table 2.1 **Six applications of biotechnology about which respondents were asked**

- Genetic testing for heritable diseases
- Introducing human genes into bacteria to produce medicines/vaccines
- Transferring genes to produce crop plants that are more resistant to insect pests
- Producing more nutritious foods or foods with a longer shelf-life
- Developing genetically modified animals for research studies
- Introducing human genes into other animals to produce xenotransplants

Source: The Biotechnology and the European Public Concerted Action Group, 1997.

Figure 2.3 **Attitudes in the EU to applications of biotechnology. Perceived use, risk and moral acceptability as determinants of public support using a scale of 0 to 5, where a median score of 2.5 was considered neutral**



Source: The Biotechnology and the European Public Concerted Action Group, 1997.

both risky and morally unacceptable. In the middle were the food biotechnologies, about which there is currently such intense public debate in the UK.

These Eurobarometer data confirm that core medical applications of human molecular genetics for purposes of genetic testing and the production of drugs and vaccines command high levels of public support, whereas many other applications are viewed much less favourably.

The issue of trust – whom does the public believe?

It is important that the public should have confidence in both the individuals and the institutions that are responsible for developing new medical technologies.

In the 1996 Eurobarometer survey, respondents were asked which institutions they would most trust to tell the truth about the development of genetically modified foods and xenotransplants. In general, respondents displayed an extremely high level of confidence in the medical profession as a trustworthy source of information about xenotransplantation; but they displayed a much lower level of confidence in the food industry as a trustworthy source of information about genetically modified foods. Here, respondents generally preferred environmental and consumer organizations over industry as the most trustworthy sources of information.

These results suggest that the institutional structure of different areas of application of modern biotechnology almost certainly plays a significant part in shaping public attitudes towards these different areas. Continuing public confidence in the medical profession is probably the key to the successful implementation of genomically-based healthcare in the future. However, precisely because the medical profession is so generally trusted by the public, it is vitally important that medical practitioners should be well-informed about new and potentially socially sensitive areas of bio-medical research such as human molecular genetics.

Public perceptions around the world

Within the EU, Finland, Greece, Portugal and Spain display the highest levels of public support for various new genetic technologies. By contrast, Austria, Denmark, Germany and Sweden display the lowest levels of support for these technologies. Belgium, France, Luxembourg, the Netherlands and the UK display intermediate levels of support.

The USA is the largest and most significant player in the field of modern molecular genetics and genetic technologies. There is a general sense that the public climate in the USA is more positive towards them than it is in Europe. However, this is only partly true.

Table 2.2 compares results from comparable surveys conducted in the EU and North America in the period 1996 to 1998. For each of three areas of modern biotechnology, respondents are divided into three groups: 'supporters'; 'risk-tolerant supporters'; and 'opponents'. (For the purposes of this analysis, respondents who did not display a clear view are excluded from the table.) In the case of genetically modified food, there were indeed substantial differences between Europe and North America, with American respondents being substantially more supportive. In the case of genetic testing, however, an entirely different pattern emerges. In general, there are not huge differences between Europe and North America in the numbers of 'supporters', 'risk-tolerant supporters' and 'opponents'. Interestingly, however, there are significantly more opponents of genetic testing in the USA than there are in Europe. In the case of xenotransplantation, there are only minor differences between the two sides of the Atlantic.

These results suggest that there are specifically food-related sensitivities towards modern biotechnology in Europe. The existence of such sensitivities is strongly confirmed by the fact that European respondents were more likely than their North American counterparts to possess what might be termed 'menacing images' of genetically modified foods. Thus, 24 per cent of Europeans, but only 8 per cent of North Americans, thought that by eating a genetically modified fruit a person's own genes could be changed. Such images both reflect and reinforce public unease about genetically modified foods in Europe.

Table 2.2 **Global attitudes to biotechnology**

		Percentages of respondents		
		EU n=12,178	*USA n=863*	*Canada n=813*
Genetic testing	Supporters	50	51	48
	Risk-tolerant supporters	33	21	31
	Opponents	7	14	10
Food	Supporters	22	37	38
	Risk-tolerant supporters	21	24	29
	Opponents	30	13	20
Xenotransplants	Supporters	16	23	29
	Risk-tolerant supporters	20	19	31
	Opponents	33	35	26

Supporters: technology is useful, not risky, morally acceptable and to be supported.
Risk-tolerant supporters: technology is useful, risky, morally acceptable and to be supported.
Opponents: technology is risky, morally unacceptable and not to be supported.
(Respondents who did not display a clear view are not shown in the table.)

Source: Gaskell et al, 1999.

Turning to genetic testing, we see no evidence for similar levels of public unease in Europe. On the contrary, it is North Americans who are slightly more likely to express opposition in this area. It is tempting to attribute this difference to the very different healthcare systems on either side of the Atlantic, and in particular to American worries about the implications of genetic testing for the availability of affordable private healthcare insurance. Once again, therefore, we see that culturally specific institutional factors may play a significant part in shaping public attitudes to new genetic technologies.

Conclusions

The main conclusions of this brief review of recent research are as follows:

- Human genetics currently enjoys a high and positive public profile in the UK.
- There is strong public support for core applications of genomics in healthcare, provided that there are significant medical benefits to be gained in relation to serious medical conditions.
- There is considerable public ambivalence about wider applications and implications of these same technologies. Outside areas of substantial healthcare benefit, people very rapidly become wary.
- Questions about the moral acceptability of applications are much more important in shaping attitudes to these medical technologies than are questions to do with risk. Where people see benefits and moral acceptability, they will often accept significant risks in order to obtain the benefits. Where people do not see technologies as being morally acceptable, they will rarely tolerate even low levels of risk.

REFERENCES AND FURTHER READING

1 Durant J, Hansen A, Bauer M. Public understanding of the new genetics. In: Marteau T, Richards M (eds.). *The Troubled Helix: Social and Psychological Implications of the New Human Genetics.* Cambridge, UK: Cambridge University Press, 1996 (paperback, 1999).

2 Durant J, Bauer MW, Gaskell G (eds.). *Biotechnology in the Public Sphere: a European Sourcebook.* London, UK: Science Museum, 1998.

3 Durant JR, Evans GA, Thomas GP. The public understanding of science. *Nature* 1989;**340**:11-14.

4 Durant J, Bauer M. *Public Understanding of Science in Britain: a Report on the 1996 National Survey.* 1999, unpublished.

5 Gaskell G, Bauer M, Durant J, Allum N. Worlds apart? The reception of genetically modified foods in Europe and the United States. *Science* 1999; July 15th.

6 Gregory J, Miller S. *Science in Public. Communication, Culture, and Credibility.* London and New York: Plenum, 1998.

7 Nelkin D, Lindee S. *The DNA Mystique: the Gene as a Cultural Icon*. New York, USA: W H Freeman, 1995.

8 The Biotechnology and the European Public Concerted Action Group. *Nature* 1997;**387**:845-7.

9 Turney J. *Frankenstein's Footsteps: Science, Genetics and Popular Culture*. New Haven, Connecticut: Yale University Press, 1998.

Chapter 3
The effect of genomics on healthcare and the pharmaceutical industry over the next 5-10 years

SIR MARK RICHMOND
School of Public Policy, University College London, UK

Abstract

Advances in genetics are already being exploited by the pharmaceutical industry to aid drug discovery. Apart from concerns about some of the peripheral technologies involved (e.g. animal testing), the general public accepts this and considerable benefit is seen as likely to result. Genetic tests to screen for inherited monogenic disorders in populations seen to be at risk have been used for some years and are well accepted. Screening for monogenic disorders is seen as no different from screening for physiological characteristics as far as anonymization is concerned. Genetic screening of random populations can provide information about future demands for healthcare, and this is of value for governments and the pharmaceutical, insurance and healthcare industries. However, the general public fear that this information may be misused. In particular, there is concern that it may be used by the insurance industry to deny insurance cover, or make it impossibly expensive for certain individuals. Making anonymization foolproof is all but impossible, and ensuring that individuals are informed enough to be able to give 'informed consent' in such a complex area is difficult. Some countries are currently dealing with these problems by establishing voluntary guidelines, but there is little doubt that legislation will soon be introduced to regulate the genetic testing of individuals, and that it will be more restrictive than that which is currently in place. Public discussion of anonymization and informed consent is therefore required urgently.

Genetic sequencing will soon be commonplace

There is a central problem in the reproducibility and accuracy of the technology of genetic sequencing, in that even if the results are 99.9 per cent accurate, that still gives an error of one in 1,000. When determining nucleotide sequences of several hundred thousand genes, inevitably there will be numerous mistakes. This is relatively unimportant when trying to discover the relationship between given mutations and disease, or even when the abundance of given mutations in a population

is in question. These error rates are, however, unacceptable when the treatment of an individual depends on the outcome of the sequencing. Nevertheless, the technology of genetic testing is advancing at a colossal rate and these problems are likely to be solved. Before long, genetic testing as a basis for individual treatment is likely to be commonplace.

Implications for the pharmaceutical industry

The ability to determine genetic sequences on a large scale raises issues of central importance to the future of the pharmaceutical industry and it will, in all probability, be an important driver in allowing the transformation of pharmaceutical companies as we know them today into the healthcare companies of the future.

The pharmaceutical industry is at a watershed in its development. Major pressures on the industry's profit margins are developing. Most of these relate to the world's demographic trends but they manifest themselves in a number of ways:

- The cost of medical treatment is rising. This is partly a consequence of increasing longevity in the population and the resulting complexity of medical conditions to be treated, but is also partly due to an increase in the absolute numbers in any age cohort in the population, particularly the elderly.
- The demands on public funds in developed countries from directions other than the demands of healthcare is beginning to put serious pressure on the availability of funds.
- Advances in medical science are continually increasing treatment possibilities with consequent cost implications.
- Medical advances tend to fragment recognized diseases into subcategories, each of which needs specific therapy. This may give the opportunity to sell a range of medicines rather than a single one, but overall it is a development likely to limit market size without commensurate saving in development costs.
- Public expectations are steadily increasing, with a consequent impact on costs.

- The costs of scientific research, on which drug discovery is ultimately based, are inflating faster than the funds available to meet them.
- Heightened concern over safety is making the development of novel medicines an increasingly expensive business through the demands of increasingly exacting regulatory requirements.

The relevance of these developments is that many companies see the use of genetics and genomics as a way of increasing the size of their markets. Pressures on profit margins will be met by increases in market size and diversity, hence the evolution of companies from being those devoted to the discovery and exploitation of novel medicines to those that provide a range of therapies and the services to back up their use. Furthermore, the application of genetics to all the stages of a company's business is seen as a means of greatly increasing efficiency and effectiveness.

There is no doubt that genomics is already having a major impact on the way in which pharmaceutical companies find and develop novel medicines. The use of genetic technologies for new product discovery is already embraced by the industry as a main element of the R&D programmes of major pharmaceutical companies (Table 3.1).

One very important but neglected area is the genetics of drug distribution in the body. There are enormous opportunities to determine how people will respond – not in terms of their response to the drug clinically, but how they will respond secondarily, in terms of elimination, toxicology, etc. Genetic information about pharmacokinetics and toxicity profiles will also allow more accurate dosing recommendations, which will have an impact on drug sales and hence pricing. This information could also allow companies to give drugs that were previously sidelined because of toxicity problems to subgroups of patients who will not have adverse reactions to the drug. Genetics could play an important role in resolving some of the problems that may have sidelined earlier developments, an activity known as 'drug resuscitation'. Indeed, some companies focus all their activities on using genetic technology to 'resuscitate' problematic drugs.

Table 3.1 **Implications of genomics for the pharmaceutical industry**

- New product discovery
- Development:
  - Clinical trial design
  - Pharmacokinetics
  - Toxicology
- Licensing in and licensing out
- 'Drug resuscitation'
- Diagnostics
- Diagnostic/therapeutic combinations
- Product registration
- Marketing:
  - Managed healthcare
  - Market prediction

Many other companies use genetic technology to develop novel diagnostics. The importance of diagnostic/therapeutic combinations is growing. For example, the Food and Drug Administration (FDA) is becoming increasingly interested in whether a company has a prognostic-diagnostic aid to the therapeutic use of a drug that they are hoping to register. Due to the ease of registration, many feel that the use of genetics in diagnostics is where the impact of genetics will be felt most sharply and most immediately. Genetic-based diagnostics will lead to a more accurate definition of responders and non-responders. If responders can be identified, not only will drugs not be wasted, they will be seen to be much more effective in their use.

Genetics and genomics are also becoming increasingly involved in product marketing, with managed healthcare programmes and 'market prediction'. Not only would genotyping give a guide as to which molecular targets would be worth pursuing (and perhaps more importantly which would not be worth pursuing), it would also make the whole process of drug discovery and development more efficient.

In practice, the widespread development of genotyping outside the pharmaceutical industry is likely to be slowed down by lack of financial support, and pharmaceutical companies are one of the few sources of the necessary funds. Governments want this information (to predict future morbidity and healthcare budgets) but need to consider public perceptions and the impact of these on their voting position in elections. Therefore, governments are unlikely to move very rapidly to support this sort of work. It will be left to the pharmaceutical industry both to provide the cash and to take the lead in turning what should be a very advantageous situation for the population at large and for medical treatment, into an advantage for them. Genotyping studies are likely to be carried out as collaborative efforts between pharmaceutical companies, government agencies, physicians and public interest groups. In order to achieve this, however, the mildly confrontational posture that currently exists between the pharmaceutical industry and some other parts of society and its institutions will need to be replaced with a much closer degree of co-operation.

Implications for the insurance industry

Genetics and genomics will also have a huge impact on the insurance industry. Two areas in which they will be crucial are patient stratification and profiling, and the subsequent question of risk assessment.

The opportunity to carry out population genotyping on a large scale could ultimately lead to a situation where a reasonably accurate assessment of the overall future health of individuals in a society could be gained by routine procedures. The policies of health insurers will increasingly reflect the mean and variation of the predictability of genetic tests. Genetics will have a huge impact on the way in which these businesses are run, and it is important that changes are controlled to protect the public.

Issues of confidentiality and access to information will be central to the evolution of this situation. Widespread population genotyping is not imminent, however, so there is still time to decide the necessary arrangements.

Implications for the public

Currently, genotyping and genetic testing tend to be confined to groups that are known to be at risk. However, if random tests to obtain genetic constitutions of whole populations were performed, this would rapidly lead to patient groups being stratified by genetic make-up. These patients would then be treated according to new practice guidelines and new diagnostic and prognostic testing systems. Such developments would have profound effects on the practice of medicine.

Genetics and genomics will constitute a very important, central element in the whole question of information management in relation to people's lives, whether they are well or ill (Table 3.2).

The inevitable genetic revolution

The pharmaceutical industry is already applying genetics, rapidly and with increasing impact, in the whole of the drug development process. The 'genetic revolution' is inevitable, and the pharmaceutical and

Table 3.2 **Implications of genomics for patients**

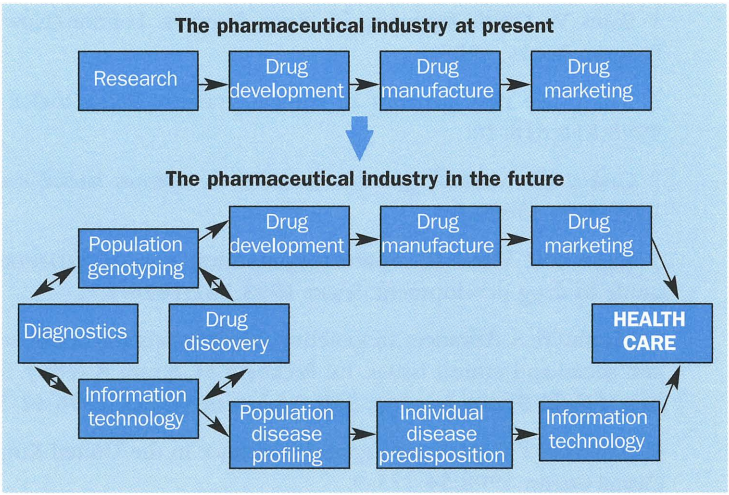
- Patient stratification: the grouping of patients, according to genetic make-up, to help achieve optimal management of their conditions
- Practice guidelines:
  - It is likely that legislation will soon be introduced to regulate the genetic testing of individuals
  - Guidelines regarding 'informed consent' and the intellectual property rights of genetic information collections need to be developed
- Compliance programmes: genetic testing will be used in relation to compliance with various regulations
- Comprehensive diagnostic and prognostic testing: genetic testing will provide a better system for assessing patients at risk of diseases and for diagnosing patients with those diseases
- Patient and provider education: genetic testing will have a significant effect on education and understanding
- Outcomes measurement system: genetic testing will provide a better outcomes measurement system than those already available

insurance industries, the government, the public and public interest groups must begin to prepare and make of it what they can.

The pharmaceutical industry as we now know it will be changed into a healthcare operation which not only performs the conventional activities of the pharmaceutical company, albeit in a more sophisticated way, but will also be associated with disease and population profiling, and the use of that information to set R&D activities (Figure 3.1). The whole research activity of a pharmaceutical company will become a complex area of population genotyping stratification, drug discovery of the classical type, involvement of very sophisticated information management systems, and the use of diagnostics.

It will be very useful for the pharmaceutical company to obtain information about the population into which the drug is being marketed. It may also be useful to offer advice on the effective use of the drug in individual cases, as an aid to both the physician and the patient concerned.

Figure 3.1 **Anticipated changes to the pharmaceutical industry**



Conclusion

A much more cogent, centred discussion is needed between government representatives, the pharmaceutical industry and patient representative groups to try to see how we can move forward. There are enormous advantages for all parties if genetic testing and genotyping can be done correctly.

We should be aiming to obtain a statement from some organizations representing the pharmaceutical industry that they are prepared to help with the exploitation of genetics in a positive, beneficial way, and to begin talking with governments, patient groups and other interested parties to find a way forward. This will not be easy because in general these relationships are mildly confrontational. In relation to the application of this topic, however, there should be co-operation to try to carry forward the development of policy.

REFERENCES

1 Bains W. *Genetic Engineering for Almost Everybody.* London/New York: Penguin Books, 1987.

2 Bell J. The new genetics in clinical practice. *British Medical Journal* 1998;**316**:618-20.

3 Caskey CT. Medical genetics. *Journal of the American Medical Association* 1997;**277**: 1869-70.

4 Kleyn PW, Vesell ES. Pharmacogenomics: genetic variation as a guide to drug development. *Science* 1998;**281**:1820-1.

5 MacIntyre S. Advances in genetics: implications for health services and social and ethical issues. In: Peckham M, Smith R (eds.). *Scientific Basis of Health Services.* London: BMJ Publishing Group, 1996;42-50.

6 Morrison P. Genetic testing and insurance in the United Kingdom. *Clinical Genetics* 1998;**54**:375-9.

7 Rifkin J. *The Biotech Century: Harnessing the Gene and Remaking the World*. New York: Tarcher/Putnam, 1998.

8 Rothstein MA (ed.). *Genetic Secrets: Protecting Privacy and Confidentiality in the Genetic Era*. New Haven and London: Yale University Press, 1997.

9 Rudolph FB, McIntire LV (eds.). *Biotechnology: Science, Engineering and Ethical Challenges for the 21st Century*. Washington DC: Joseph Henry Press, 1996.

10 Silver L. *Remaking Eden: Cloning and Beyond the Brave New World*. New York: Avon Books, 1997.

11 Stephenson J. Ethics Group drafts guidelines for control of genetic material and information. *Journal of the American Medical Association*, 1998;**279**:184.

12 Tudge C. *The Engineer in the Garden: Genes and Genetics from the Idea of Heredity to the Creation of Life*. New York: Hill and Wang, 1993.

13 Wade N. *The Ultimate Experiment: Man-Made Evolution*. New York: Walker & Co, 1997.

Chapter 4
Clinical perspectives

DR ROSALIND EELES
Institute for Cancer Research, UK

Abstract

Genetic differences may have a role in predisposition to, and behaviour of, disease. Genetic models suggest that there are two types of genetic predisposition to disease: high- and low-penetrance genes. Highly-penetrant genes are those with a high risk of causing the disease, although this may not be 100 per cent. Family members may carry the genetic alteration without manifesting the disease, although these individuals can pass the genetic alteration on to their offspring. At present, most of the impact on medicine has been from highly-penetrant genes, which cause 5-10 per cent of common cancers. Low- penetrance genes are often normal variations in genes that result in a slightly increased risk of disease. Once rapid genetic analysis is available for these types of genes, such analyses will be analogous to taking someone's blood pressure in a doctor's surgery to identify individuals at increased risk of cardiovascular disease. Doctors will be able to advise about primary prevention and prescribe preventative drugs to reduce the risk of certain diseases occurring. This proactive rather than reactive style of practising medicine is potentially exciting, but carries with it ethico-legal and social implications for how the data are dealt with.

Introduction

Diversity in the genetic code accounts for differences in phenotypes between populations and it is becoming realized that genetic differences may have a role in predisposition to, and behaviour of, disease. Genetic models suggest that there are two types of genetic predisposition to disease: the so-called high- and low-penetrance genes. Penetrance is the chance that a genetic alteration will have a phenotypic effect.

High-penetrance genes

Highly-penetrant genes are those with a high risk of causing the disease, although this may not be 100 per cent. In general, such genes give rise to familial clustering of disease. Members of families may carry the genetic alteration without manifesting the disease but these individuals can still pass the genetic alteration on to their offspring.

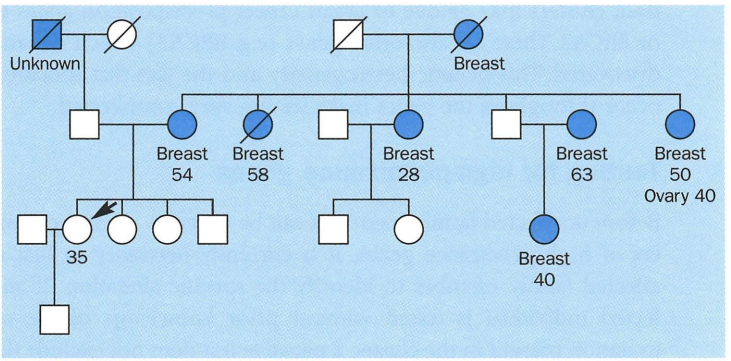
In many cases, alterations in more than one gene predispose families to one type of cancer. For example, familial breast cancer in highly-penetrant clusters may be due to breast cancer predisposition genes BRCA1 or BRCA2. There are also other genes (e.g. BRCA3) which remain to be discovered. This genetic heterogeneity and the fact that mutations can occur throughout the genes make testing very complicated.

Testing for high-penetrance genes

Before unaffected family members can be tested to see if they are carriers of high-penetrance genes, it is currently necessary to first test an affected family member to identify the specific alteration. If an unaffected individual is tested without prior knowledge of the specific mutation present in the cluster, a negative test does not exclude the possibility that the wrong gene has been tested or that a mutation has been missed. This situation will change dramatically with the progression of the Human Genome Project, which aims to clone all of the expressed genes by the second decade of the 21st century. When the technology has advanced so that genetic analysis is faster and more accurate, it may become possible to test many, if not all, of the genes in the human genome. When this happens, previous testing of an affected individual to find the specific mutation in the family may become unnecessary.

Figure 4.1 shows a family tree in which the squares are men, the circles are women, the affected offspring are shaded and diagonal lines represent deceased family members. The types of cancer and age at diagnosis are shown below each affected symbol. Familial clustering is evident. However, if one woman aged 35 enters a clinic with breast cancer (arrowed in Figure 4.1) with no available family history, in many cases, there is currently no way of telling whether she is likely to have a breast cancer predisposition gene or not. There is the probability that she has one, but not the exact certainty. This is where the Human Genome Project will revolutionize medicine. Once all the human genome has been cloned, and provided genetic testing is easy to do, a blood sample could be taken from the individual, the genetic material extracted and put on a chip, thus allowing accurate identification of a genetic alteration. This technology will be available within the next 50 years.

Figure 4.1 **Familial clustering demonstrated in a family tree**

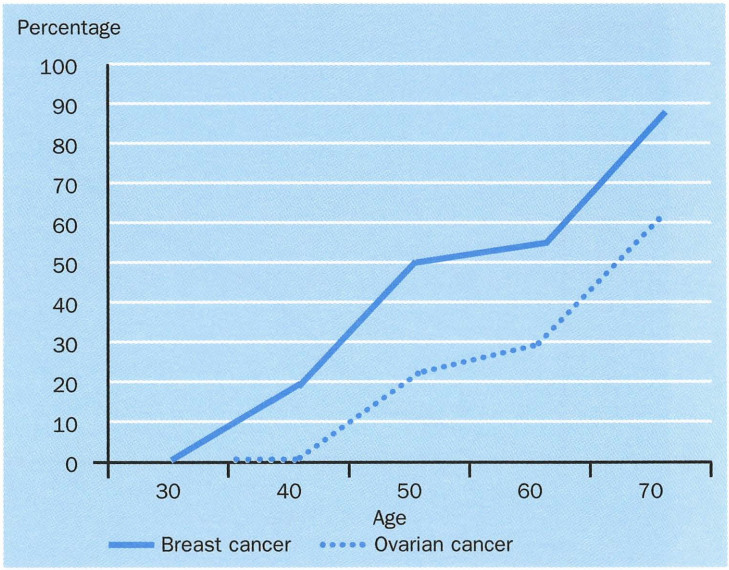


Disease risk levels due to highly-penetrant genes

At present, the greatest impact on medicine has been from highly-penetrant genes. Although they are thought to cause only a small percentage of common cancers, the overall numbers of people affected are still large because these cancers are common. Until recently, about 5 to 10 per cent of breast cancer patients were thought to have a predisposing breast cancer gene, but there is increasing evidence that this estimate is too low. A recent model has suggested that as many as 86 per cent of breast cancer cases occurring in patients younger than 60 could be due to genetic predisposition. A major question is: what component of disease in general is due to a genetic predisposition from both high- and low-penetrance genes?

Figure 4.2 shows the risk profile of the BRCA1 gene. People with the BRCA1 gene have an 85 per cent risk of breast cancer by the age of 80. This is 10 times higher than the lifetime breast cancer risk of the general population, and just over half the risk occurs before the age of 50. The British National Screening Programme is of limited use to these women, because just over half their risk of getting the disease occurs before the screening starts. Additionally, the BRCA1 gene causes other cancers. In particular, it causes a 60 per cent lifetime risk of ovarian cancer, compared with a population risk of about 1 per cent.

Figure 4.2 **BRCA1 breast/ovarian cancer risks**



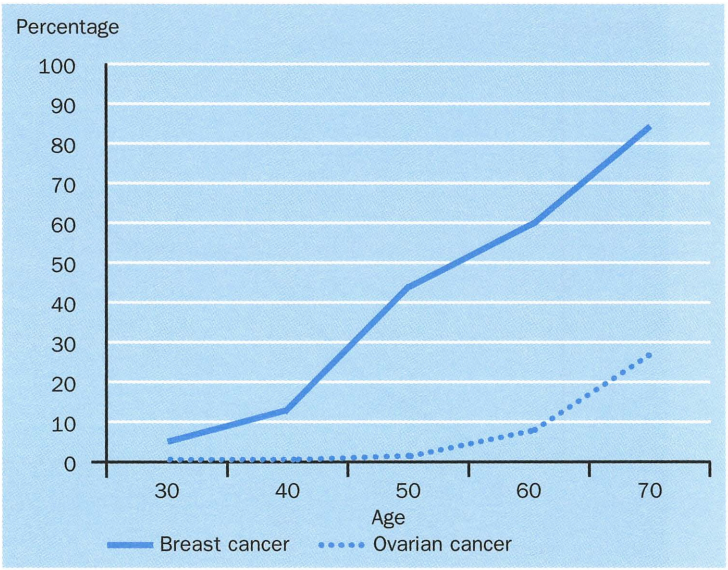
Source: Ford et al, 1998.

Figure 4.3 shows the breast cancer risk profile of BRCA2, which is similar to that of BRCA1. As with BRCA1, BRCA2 confers an increased risk of ovarian cancer, but this risk is not as high as with BRCA1.

The major question is: what about the other 90 per cent of breast cancer cases not due to high-risk genes? Do they also occur due to subtle genetic changes in the germ-line? Should they be classified as being due to a genetic predisposition? In contrast, many genetic changes are not disease-causing. Therefore, once gene alterations have been identified, a number of questions are raised:

- Are the genetic changes causing the disease?
- What is the level of risk?
- Is the disease risk different between different genes that cause the same disease?

Figure 4.3 **BRCA2 breast/ovarian cancer risks**



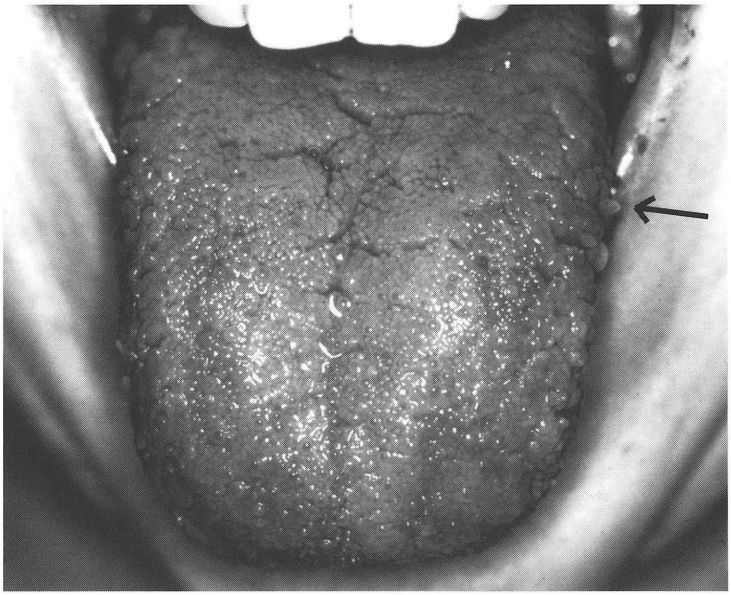
Source: Ford et al, 1998.

Furthermore, does everybody need to have genetic testing? It is possible to tell whether some people have genetic alterations by just looking at the patient. Figure 4.4 shows a very rare syndrome called Cowden's Syndrome. Sufferers have outgrowths on the tongue. This characteristic should tell the physician that the patient has a 30-50 per cent risk of breast cancer by the age of 50. No genetic test is necessary to determine who is a gene carrier in this case.

Genetic testing for BRCA1 and 2

At the moment most laboratories in this country are testing about three-quarters of the BRCA1 gene and in many regions there is no laboratory testing of BRCA2 funded by the NHS – research money funds these tests. The only place in the world where the whole of the

Figure 4.4 **Cowden's syndrome**



Source: Marsh et al, 1998.

coding region of these two genes is tested, where the genetic code is constructed base by base, is at Myriad Genetics in the USA.

Chips will speed up this process, because to test the whole of BRCA1 and 2 can take many months. The DNA will be extracted from the blood, hybridized or matched to the gene sequences on the chip, and mismatches identified. The bases are coloured so mismatches can be seen quickly and easily using a fluorescent reader.

In some instances, genetic testing may alter medical practice. This will become more widespread as testing becomes technologically easier to perform. It is well known that BRCA1 and 2 increase the risk of getting a first cancer, but they also increase the risk of getting it again later. Therefore, if breast cancer is treated on one side, should a pro-

phylactic mastectomy be performed on the other side? This has already been implemented in the USA, and is moving into British practice.

Public risk perceptions

When it is possible to test people for predisposing genes, do they really want to know their risk levels, and what do they perceive about their level of risk? For example, the daughter of someone affected with a BRCA1 gene alteration has a half-chance of inheriting the altered gene. Some people perceive this as a 50 per cent chance that they do not have the gene and some perceive it as a 50 per cent chance that they do have the gene. Risk perception is a very important area of research.

The main benefit of testing is that once it is known that a patient has a predisposing gene, it is more likely that the disease will be detected at early onset and optimal management strategies can be employed. Negative results could prevent prophylactic mastectomies in women whose families are known to possess some form of heritable breast cancer. It could also save money through avoiding unnecessary early mammographic screening. However, cost-effectiveness models have not yet been constructed to demonstrate whether genetic testing saves more money than it costs. Screening of the whole population would be very expensive, and the question is how to target screening for those who are most likely to have a disease.

Finally, not everything is genetic. Many conditions are a result of how the environment interacts with people's genes. Individuals genetically predisposed to certain diseases could potentially alter their lifestyles to prevent undesirable end effects. For example, in women who have genetic alterations in BRCA genes, taking the contraceptive pill lowers their risk of ovarian cancer quite substantially. However, there may be an added risk of breast cancer, although more data are needed to be certain of this.

Low-penetrance genes

Low-penetrance genes will become of increasing interest as genetic testing gets easier. They are often normal variations in genes that result in a slightly increased risk of disease. This is analogous to high blood pressure carrying an increased risk of cardiovascular disease. Once rapid genetic analysis is available for these types of genes, such analyses will be analogous to taking someone's blood pressure in a doctor's surgery to identify individuals at increased risk of cardiovascular disease.

Genetic testing may allow more accurate design of therapies. For example, a patient in the future may enter a doctor's surgery with high blood pressure and undergo a genetic test to see which drug he/she should receive. The genetic test could show that certain drugs would be ineffective for that patient, or that others would give him/her terrible side effects. Therefore, genetic testing could determine specialized prescribing.

This is likely to become a reality in the first half of the 21st century. It will produce a revolutionary change in the way medicine is practised. As genetic analysis becomes faster and more commonplace, GPs will use it to identify risk profiles for their patients, and to advise about primary prevention and even prescribe preventative drugs to reduce the risk of certain diseases occurring. This proactive rather than reactive style of practising medicine is potentially exciting, but carries with it ethico-legal and social implications for how the data are dealt with:

- Is it the right way to go?
- Will we really achieve a benefit in healthcare?
- Will it reduce costs?

We do not yet know the answer to these questions, and there is currently very little research in this area. We need such research to bridge the discoveries and the policy so that we can find out if this is really the right way to proceed.

REFERENCES AND FURTHER READING

1 Eeles RA. Testing for the breast cancer-predisposition gene, BRCA1. *British Medical Journal* 1996;**313**:572.

2 Eeles RA, Ponder BAJ, Easton DF, Horwich A (eds.). *Genetic Predisposition to Cancer.* London, UK: Chapman and Hall, 1996.

3 Ford D, Easton DF, Stratton MR et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *American Journal of Human Genetics* 1998;**32**:676-9.

4 Marsh DJ, Dahia PL, Caron S et al. Germline PTEN mutations in Cowden syndrome-like families. *Journal of Medical Genetics* 1998;**35**:881-5.

5 The Chipping Forecast. *Nature Genetics* 1999;**21**(Supplement).

Chapter 5
Patients' perspectives

MR ALASTAIR KENT
The Genetic Interest Group, UK

Abstract

Recent scientific progress has given insight into the part played by genetics as a predisposing factor to an increasingly wide range of diseases, from rare disorders resulting from mutated highly-penetrant genes to common disorders where risk is enhanced as a result of mutations of one or more predisposing genes. Many of these genetic conditions are, at best, intractable. At worst they are incurable and those affected must live with the risk to them, their families and future generations. For those in this position, genetics holds the prospect of effective intervention and ultimately of cure. Whether or not science will deliver on its promises depends on a number of factors, some of which are examined in this paper, including technical aspects (will the problem of creating effective cures simply prove too difficult?), and commercial and social factors. The latter issues impinge directly on the successful transfer from the laboratory to the clinic of scientific advances that enhance prospects of receiving improved services and better diagnostic and/or therapeutic products. The historical misapplication of genetics, and anxieties about risks and dangers associated with new uses of genetic technology in areas such as food production, play a significant role in defining the acceptability of genetic medicine and its potential contribution to human health.

The Genetic Interest Group

The Genetic Interest Group (GIG) is the UK alliance of charities, voluntary organizations and support groups for families affected by specific genetic disorders. It is an independent charity itself, representing about 130 organizations, many of which fund medical research programmes. Some of these organizations have been responsible for major insights into the biology of genetic disease.

GIG works towards ensuring that after the research has been done, increases in scientific understanding are translated into improved services, support, and eventually treatment for conditions that are currently intractable or incurable. GIG is also concerned with preventing the abuse of genetic information, so that individuals affected by or at risk from genetic disorders do not suffer from unfair discrimination, disadvantage or stigmatization.

Expectations of individuals affected by genetic disorders

Patients affected by genetic disorders, and their families, want cures. Few people would voluntarily choose to have a child affected by a genetic disorder in preference to one that was physically or mentally fit. That does not mean that those born with disabilities are less worthy of full civil and human rights, or that the parents of such children do not value them as much as their healthy, able-bodied siblings. However, it is not an option that would be exercised if there were an acceptable alternative.

Recent advances in the understanding of genetics and the contribution that genes make to human health and disease have provided hope for many families affected by incurable diseases. However, there is a significant gap between the discovery of genes that predispose individuals to develop a particular condition and the ability to intervene in the disease process. Until effective treatment is possible and available, there will always be the fear among affected families that events or circumstances will combine to halt genetic research before cures are found.

The prospect of the failure of science

When gene sequences were first being identified and their functions recognized, there was great optimism that cures would follow quickly. At least 10 years later, effective gene therapy is still a fair distance away. Many patients fear that it will prove to be 'just too difficult' to bridge the gap between the disease and its cure. This is the only genuinely acceptable reason for failing to deliver on today's promise and potential.

Another factor, which is much more within our control, is the issue of funding. A significant factor in funding decisions is the ability of the researcher to attract and hold the attention of fundholders, and to persuade them that the proposed research will be successful and significant. However, an unrealistic expectation of scientists' ability to deliver major breakthroughs in the field of genetics may have been

created. Initial over-optimism, which fails to deliver, produces disenchantment with the result that resources may be diverted elsewhere.

Another issue is the unhappy history of human genetics. This reached a peak in Nazi Germany's eugenics programme, but the misapplication of genetics was widespread in the USA and Europe. Even in a country as apparently liberal as Sweden, there was enforced sterilization of people with learning disabilities as recently as the 1960s and 1970s. The enthusiasm that early protagonists showed for scienceís apparent ability to solve complex problems of human variability has led to a climate of professional and statutory regulation based on ethical and social issues raised by scientific advances.

Opponents of genetic research

Genetics issues raises severe anxiety in the minds of some sections of the community. Concern about genetic issues has united:

- Environmentalists concerned about environmental degradation and loss of biodiversity.
- Consumerists anxious about genetically-modified food.
- Disability activists who see a eugenic agenda designed to eliminate 'people like them'.
- Pro-life groups who use the increased ability to detect severe antenatal abnormalities as a platform in their continuing campaign to end abortion.

Arguments employed by those opposed to genetic research and its alleged potential to cause harm often claim that we should not apply genetic research until we know for certain that it is absolutely safe. However, nothing is without risk. Life, after all, is an ultimately fatal, inherited condition. Failing to intervene when one has the opportunity to do so can be just as unethical as intervening without consideration of the adverse consequences potentially associated with that particular intervention.

About 180,000 pregnancies are terminated each year in the UK. Of these, 2,000 are due to antenatal diagnosis of severe genetic abnor-

malities. Pro-life groups believe that the increased use of antenatal genetic testing will lead to a dramatic increase in the number of abortions carried out for trivial imperfections, such as hair or eye colour. Such claims trivialize the impact on couples who have to choose whether to terminate a pregnancy when a foetal abnormality is detected.

The recent report of the Nuffield Council in Bioethics on genetics and mental health concluded that, excluding very rare disorders such as Huntington's disease or early-onset Alzheimer's, a single genetic change increased the risk of mental health problems by just 2 per cent. When compared with the impact of known predictors of mental health problems such as divorce, redundancy or mourning, the role played by genetics can be seen in context. Nevertheless, disability activists see genetics as a threat to their existence. Tom Shakespeare, writing in the December 1998 issue of *The Splice of Life*, said:

'Many disabled people are fearful that the extension of pre-natal screening will implement a new eugenics, whereby people with impairments are eliminated from the population. Women should be supported to continue with pregnancy and families with disabled children must receive proper educational and welfare services. Above all, we must demand that disabled people are accepted as equal and valuable members of society.'

The implication that we should stop developing and using diagnostics to give families choices rather than chances ignores the fact that the vast majority of disabled people acquire their disability as a result of accident, illness or ageing, and that there is no way we can eliminate disability from society. Shakespeare's demands for respect and equality must be supported, but even if these demands were met in full, having a child with a disability would never be a positive option. Our limited ability to intervene now should not blind us to the absolute goal of achieving effective cures for disorders and diseases of genetic origin. Accepting the fact that the options at the moment are limited, we must not overlook or forget that we will be able to intervene positively in the foreseeable future in an increasing range of disorders. However, even if we cannot, it is questionable whether an imposed

prohibition on antenatal testing for genetic conditions is preferable to the current situation where parents have the choice.

Health economics – a barrier to treating rare disorders?

Academics and clinicians investigating rare single-gene disorders have undertaken much of the fundamental research that has advanced our understanding of genetic disease. Patient support groups raising money from non-statutory sources have often funded this research. Single-gene disorders are rare, but they can often act as a model for more complex polygenic disorders that affect substantial numbers of the population.

Diagnostic and therapeutic tools have been developed, and are made available for treating patients, through the private sector. This system has produced many remarkable drugs. However, it is driven by attracting investment and delivering a return that is sufficiently attractive to offset the risks. For millions of people at risk from rare disorders, this mechanism is fundamentally flawed, since the mechanisms of the market ensure that promising research will never be translated into effective and affordable products because the costs per case of treatment would be prohibitive. Viewing proposals referred to the Gene Therapy Advisory Committee heightens anxieties that patients with rare disorders will not benefit from today's research efforts. With very few exceptions, the proposals are for common disorders such as cancer, with rare conditions not attracting much attention.

The introduction of orphan medicinal product regulations in the EU will go some way towards re-balancing this issue, but a fundamental shift of attitudes is required. The pharmaceutical industry currently benefits from the bargain it has struck with society that says, 'in return for producing a range of safe, effective drugs, we will allow you to make significant profits.' However, industry must acknowledge its responsibilities to all the stakeholders in the healthcare system, not only to those with conditions common enough to be economically attractive. This will ensure not only the long-term health of the industry but will also maintain public trust and confidence in its operations.

Maintaining public support

The scientific progress of recent years has yet to deliver real benefit, at least in the minds of the public, although measures such as the EU's Eurobarometer survey referred to by John Durant (see Chapter 2) shows that the public are broadly sympathetic to R&D in this field. However, the gap between discovering the gene and producing the cure leaves public opinion vulnerable to the efforts of those opposed to genetics and biotechnology. Dr George Poste, Chief Science and Technology Officer at SmithKline Beecham, said recently:

'The biomedical community, academia and industry, will ignore public perceptions of genetics and its clinical applications at their peril. It is not a matter of whether the intellectual and clinical merits of molecular medicine are sound. Unless the public is reassured that the requisite protections are in place to avoid the abusive uses of genetics, public concern and alarm will deflect progress and the full benefit of genetic medicine will be delayed or, worse still, abandoned.'

Proactivity is required to prevent individuals at risk from genetic disorders from continuing to be affected by potentially avoidable ill-health, disability or premature death. When discussing their response to the above statement, the trustees of GIG said:

'We must use every effort to convince those in a position to influence the outcomes of research that the potential benefits for patients and their families outweigh the risks. The only justifiable course of action is to see that science delivers on its promise as quickly as possible.'

Should it fail to do this, it will not only be the families affected today who will have just cause to protest. Those in generations yet to come will have every right to feel robbed of a life free from the threat of genetic disease. The prospect of improving the lives of such families is well worth pursuing vigorously and enthusiastically.

REFERENCES

1 Abbott H (ed.). An interview with Dr George Poste, Chief Science and Technology Officer, SmithKline Beecham. *European BioPharmaceutical Review* 1998.

2 Nuffield Council. *Mental Disorders and Genetics: the Ethical Context*. Nuffield Council in Bioethics, 1998.

3 Shakespeare T. Eugenics? Slipping down the slippery slope. *The Splice of Life* 1998;**5**:4-5.

Chapter 6
The ethical and legal implications of pharmacogenomics

PROFESSOR BATHA-MARIA KNOPPERS
University of Montreal, Canada

Abstract

Pharmacogenomics seeks to tailor drug treatment to genetic variation and susceptibility. Rather than study disease genes, this genotyping research focuses on normal genetic variation in the population in order to examine differences in pathways of action of different drugs so as to understand drug response better. Identifying metabolic differences in patient groups based on genetic polymorphisms will allow for an understanding of the aetiology of common diseases of low penetrance. Such studies require not only classical, clinical drug trials with access to medical records but also DNA banking for the study of normal genetic variation. However, DNA banking brings a paradigm of mistrust based on genetic reductionism and the many issues in the protection of privacy and confidentiality surrounding testing for inherited genetic disorders generally. Can genomic banking, 'piggy-backed' onto clinical trials, escape from these ethical and legal constraints? Do pharmacogenomic studies differ significantly from genetic research in general and so merit different treatment?

Introduction

Pharmacogenomics focuses on normal genetic variation in the population. Drug responses are investigated by examining differences in action pathways of different drugs. Identifying metabolic differences in patient groups based on genetic polymorphisms will lead to understanding of the aetiology of common diseases of low penetrance.

Such studies require classical drug trials with access to medical records and DNA banking for the study of normal genetic variation. However, DNA banking raises a paradigm of mistrust based on genetic reductionism and controversial social, ethical and legal issues. Of particular concern is the protection of privacy and confidentiality surrounding testing for inherited genetic disorders.

Privacy is both the right to be left alone and the right to prevent certain information from being disclosed to others. It is the latter that

stems from the trust relationship between physician and patient known as medical confidentiality. The National Bioethics Advisory Commission (NBAC) in the USA recently concluded:

'It is not enough for NBAC to study the rules currently governing access to human tissue for research; it must also look at the rules governing access to medical records... there is a perceived need to protect medical information, especially information that can be linked to an individual, from the possible negative consequences of research conducted on human biological materials and personal information derived from such materials.'

However, confusion reigns as to the meaning of terms such as anonymous, anonymized, identifiable or coded samples, and what constitutes identifying information. Hence, there is a need to examine the general rules governing confidentiality, in particular those issues relating to pharmacogenomics, before examining potential solutions with an aim to international harmonization.

General rules governing confidentiality in genetic research

Most genetic data are considered to be medical data, providing a strong basis for protection. However, DNA banking raises additional issues, particularly in countries where universal health insurance is not available. In such situations, the socio-economic risks (e.g. unemployment, higher insurance premiums) of participating in a clinical trial as a patient, family member or research participant, distort the rules governing medical confidentiality.

Genetic testing cannot be a condition of employment or insurance, but nothing prevents access to medical records with the 'consent' of the applicant, and 'consent' is inevitably given to obtain the job or the insurance in question. As a result of actual or potential discrimination, certain states in the USA have adopted specific legislation limiting access to genetic information for the purposes of health insurance or employment. Such legislation is also driven by the reductionist notion of 'Genes-R-Us', and by the overall privacy concerns of citizens in an

era when the privacy and security of personal information are generally seen as being under attack.

A waiver of requiring individual consent to the use of DNA samples can be obtained from research ethics boards or committees, provided there is no more than minimal risk of adverse effects on the rights or welfare of participants. However, specific consent to genetic research must be obtained when the sample is identified or coded. Participants must be warned of possible stigmatization and discrimination, and they are also notified of potential commercialization through a renunciation of any intellectual property rights. Finally, they are assured of the confidentiality of the information. No research ethics board approval is necessary if the sample is totally unlinked and the source cannot be identified.

Issues in pharmacogenomics

In the absence of a marker for a particular gene, family pedigree and histories are essential for genetic research. However, since participants risk socio-economic harm, researchers either keep separate records (i.e. they do not mention research participation in the medical record) or, in the USA, they ask for 'certificates of confidentiality'.

At this time, pharmacogenomic studies seek to use only anonymized samples. This means that only limited demographic and clinical data accompany the samples. This could create difficulties in that most countries offer a legal right of access to personal information. However, with anonymized DNA banking, there would be no 'person' to be found. Nevertheless, even anonymized banking could lead to socio-economic harm to the participant due to the very participation in genetic testing and the fact that there cannot be total assurance that an anonymized 'person' cannot be reconstructed by a computer hacker. Additionally, since the right of the research subject to withdraw cannot be exercised because the sample cannot be found, and since the subjects cannot be provided with any results, the ethical requirements of the genetic research paradigm cannot be met.

There is also a question of whether it is ethical to obtain samples and anonymize them but withhold information that could be of benefit to a patient (e.g. diagnosis of a predisposing gene for which preventative

treatment is available). In fact, researchers should not be anonymizing samples if they think that they will be looking for information that would be immediately clinically significant to the patient. Researchers have to choose whether they are anonymizing to get their basic population research data or whether they are doing something more specific in relation to individual results that should eventually return to the individual.

Potential solutions and approaches to policy making

Currently, the 'over-protection' of research subjects in population genetic research, while necessary to redress past grievances or to counteract the lack of universal health insurance, may be harmful to the needs of the population as a whole. Furthermore, at the level of policy making the choice of possible solutions and their advantages and disadvantages are not well understood. Over the past two decades four approaches have emerged in terms of policy making. There are advantages and disadvantages to all four approaches.

1 *A constitutional, human rights approach to circumscribe the applications of new technologies that might otherwise encourage discriminatory or stigmatizing practices.* This approach relies on the interpretation by the highest courts of any country of existing human rights instruments which are then applied to the new technologies. Decisions are strengthened by the fact that public interest groups are often involved, serving to express public values, clarify the issues and set far-reaching precedents. However, the decisions are often ad hoc in nature and achieved after a given technology is already integrated into the healthcare system or research. The process is costly and lengthy and, if the court refuses to go beyond the facts, is a limited recourse.

2 *A statutory-specific approach addressing prohibitions, moratoria, constraints and the implications of scientific advances issue by issue.* This method has the advantage of immediate certainty, clarification and precision, as well as being the expression of political consensus. However, the danger of limited scope and impact beyond the immediate issues remains. Furthermore, if too many technique-specific statutes are adopted in rapid succession, there is a risk of contradictory positions and definitions.

3 *An administrative, regulatory approach concentrating on quality assurance, standardization and monitoring, either through governmental or professional bodies.* This allows for the gradual development of professional codes of conduct, and then licensing, monitoring and quality assurance through regulation, pursuant to already existing broad health legislation. Professionally- and procedurally-oriented, it ensures a 'buy-in' by those involved, so there is greater effectiveness and integration into practice. However, this approach 'administers' technologies and is often lacking in the explicit enunciation of the value-choices underlying their acceptance in the first place, or of explanations why constraints are placed on access, use, and certain forms of research in the standards themselves.

4 *A liberal, market-driven approach maintaining that proper professional practices will ultimately win out and that there is always the threat of litigation to provide a restraining impact on new technologies.* This approach is the most flexible and promotive of scientific research. Subject only to general existing legislation or professional codes, and to funding limitations, a given technology is left to the vagaries of the market and consumer choice. One of the disadvantages of the liberal market approach is the impossibility of achieving the compromise necessary in order to have a broad consensus, leading to private-public oversight through government intervention brought about by legislation.

Conclusions

In the area of pharmacogenomic research and medical confidentiality, the choice between these approaches depends on the degree of public trust in the credibility and effectiveness of such tools and on the state of national and international debate on the issues. The administrative, standardization approach holds the most promise, but it should be an international effort of harmonization, similar to the International Conference on Harmonization (ICH) guidelines for clinical research.

The Human Genome Organization (HUGO) has begun this effort, but the World Health Organization (WHO) and national research bodies should also be involved. Such an international effort is urgent before

the range of current conflicting, largely inapplicable and inappropriate approaches overwhelms population studies. Medical confidentiality legislation needs to be upgraded and should include genetic information, but genetic-specific legislation should not be adopted since this would only lend credence to the idea that genetic difference is abnormal and socially stigmatizing.

Only inclusion of genetic information within the larger category of medical information, and the strengthening of the confidentiality of such information through legislation, can serve to underscore the nature of the physician-patient relationship and so ensure the continuing participation of individuals in genetic and genomic research.

REFERENCES AND FURTHER READING

1 Human Genome Organization (HUGO) Ethics Committee. Statement on DNA sampling: control and access. *Genome Digest* March 1999, 8-9.

2 Knoppers BM (ed.). *Human DNA: Law and Policy.* The Hague: Kluwer Law International, 1997.

3 National Bioethics Advisory Commission. The Use of Human Biological Materials in Research. Draft report, 1 April 1999, Chapter 3, p.71 (http://bioethics.gov/briefings/index.html#January99)

4 Rothstein M (ed.). *Genetic Secrets.* New Haven, Connecticut: Yale University Press, 1998.

Chapter 7
Is public policy lagging behind the science?

PROFESSOR EVERETT MENDELSOHN
Harvard University, USA

Abstract

This paper sets the development of human genetics during the 20th century in a historical context, and focuses on the interaction of scientific and technical advances in genetics and the development of social and public policy for human genetics. The question 'Is social policy lagging behind the sciences?' is examined showing that since the 1970s, the technical advances have outstripped the social policy formation and created important and dangerous strains in the relationship between genetic science and society. The task for the immediate future is to establish a means to integrate the social and moral critique into the decision-making processes of the practising sciences, so that social analysis becomes part of a feedback system to assure wisdom in scientific advance not mere technical achievement. There are potentially significant costs to allowing social policy to lag behind scientific and technical advance. Solving the 'technically sweet' problem first and only then turning to examine the moral and social consequences has, in the past and can in the future, prove to be too costly.

Introduction to genetics and eugenics

William E Castle, the Harvard-based American geneticist, published one of the first genetic texts in the United States, *Genetics and Eugenics*, in 1916. In it he identified what, for him, would be a core problem of human heredity:

'No one can deny that our country's population is increasing fast enough, the only danger is that the biologically poorest elements in the population may increase faster than any other. The declining birth rate is not in itself serious, but the differential character of its decline is serious. The most intellectual and cultured elements in the population breed the slowest. Professor Cattell says that a Harvard graduate [male] has on average three-fourths of a son and a Vassar graduate [female] one half of a daughter. If this continues college graduates may look forward to the early extinction of their line as an element in the American population.'

The social diagnosis was clear to Castle; the scientific tools to remedy the situation were not available.

Castle, like almost all geneticists of his generation, was convinced that both human physical and mental traits were inherited in law-like fashion. He was also aware of, and appreciative of, the eugenic proposals of Francis Galton for dealing with problems like the one cited above – he believed elites and professionals should marry early and have large families. The high level of voluntarism involved in such policy was not lost on Castle, but he was confident of the new scientific information being gathered on human inheritance and the theories being developed around it. He favourably cited two comprehensive studies, one by Karl Pearson (Galton's disciple and director of the Eugenics Laboratory of University of London) and the other by Dr CB Davenport (a former Harvard colleague and director of the Eugenics Record Office at Cold Springs Harbour on Long Island). He took their information and reduced it to a chart.

First, he identified those characteristics that clearly obeyed Mendelian laws, including skin and hair, eyes (cataracts and night-blindness), skeleton, kidneys (including diabetes, considered dominant), alkaptonuria (considered recessive) and nervous system disorders (Huntington's chorea and hereditary feeble-mindedness). Mendelian and sex-linked characteristics included muscular atrophy, haemophilia, and colour-blindness. Characteristics with uncertain Mendelian identity included hare-lip, extra teeth, twinning, left-handedness, and hardness of hearing. Characteristics subject to hereditary laws, but which he listed uncertainly, were general mental ability, memory, temperament, musical, literary, artistic, mathematical and mechanical ability, as well as cretinism, epilepsy, insanity, and longevity.

While Castle's list sounds premature for early century categorization, he was actually cautious compared with Davenport, who confidently identified violence, laziness, worthiness, and matter-of-factness as all dominant Mendelian characteristics, with alcoholism, shyness, and shiftlessness as recessive.

While an extensive social policy of eugenics, to attempt to create a more favourable genetic mix in the populations of Europe and North

America, was propounded, the modes for practising the genetic management called for were severely limited. If the models of genetic manipulation were seen in the relatively successful practices of animal and plant breeding and the rapid growth of experimentation in the new field of genetics, the human geneticists were largely restricted to genetic counselling, exhortation and education. Two practices which permitted the eugenic vision to be implemented were restrictive immigration (largely limited to the United States although proposed by Pearson of the United Kingdom) and involuntary eugenic sterilization of certain groups considered to be genetically impaired (e.g. feeble minded, alcoholics and criminals). The record of involuntary sterilization in North America and Europe has only recently been extensively studied and surprisingly found to have been continued long past the Second World War.

A history of social eugenics

William Castle lamented the situation. While he remained convinced that the same laws govern heredity among humans, plants and animals, the knowledge available in human heredity was 'less accurate'. The reason was simple, scientists were 'debarred from experiment in the human field'. Instead, the practice was largely limited to the observation of traits through the generations and the recording of family trees. Castle expected further cataloguing of human heredity just as fast as the general categories of the phenomena of inheritance were experimentally established for other organisms.

An examination of the early history of human genetics shows that it was closely linked to eugenics which in turn crossed traditional political lines – from socialists to conservatives. The social historians note the close ties of eugenic programmes to professional and middle-class elites. The social policies enunciated and then mapped onto genetic understandings were resolutely middle-class in outlook. One thing is clear: policy proposals, while emboldened by the new genetic science, were definitely in advance of the science. The techniques available for affecting socially desired outcomes were feeble, and severely constrained by other social norms. The crossing of the boundaries of those norms in Germany during the years of Nazi control provide the

counter history to restraint, and serve as one of the reasons for public reaction to later human genetic experimentation and as a source of continuing caution in public response.

However, it is important to recognise that in spite of what post-war human geneticists referred to as the 'lurid and disquieting history' of eugenics in Nazi Germany, and the 'loose thinking' of eugenicists in the United States, the authors of the classic text *Human Heredity* (1954) were able to point to a sounder eugenics re-emerging. Neel and Schull singled out for favourable notice the new 1948 edition of Frederick Osborn's *Preface to Eugenics*. They reported Osborn's proposals to encourage propagation of the 'fit' through marriage and child allowances and preferential housing arrangements. The 'unfit' were to be persuaded to voluntarily limit their families through birth control, induced abortion, and voluntary sterilization. When they turned to human behavioural traits they noted potential problems of upsetting nature's balance (they gave by way of example the introduction of insect pests). They noted that with other organisms one can compensate if mistakes are made, but 'where the organism is man himself, it behoves us to proceed with great caution'.

Neel and Schull recognized that there were clear constraints of method, but they believed research ought to be pushed to identify the genetic control of many biochemical reactions in the human metabolism and to note the inborn errors of metabolism. They pointed to a wide range of genetic diseases that had been identified from afibirinogenemia to xerodermapigmentose. They were laying out the research agenda for the molecular genetics emerging at that time. However, even in their caution, these two geneticists carried a 'eugenic temptation'. Despite their recognition of a lack of good evidence, they did not resist the temptation to examine the genetics of behavioural traits, including intelligence. While they realized the difficulties, they insisted that humans differ more from each other in conscious response to external stimuli than in any other way. Their vehicle for discerning intelligence in humans was the measurement of IQ; clearly imperfect, they said, but quantifiable. The question Neel and Schull posed in 1954 was direct: 'Are there detectable differences in IQ ascribable to heredity?' They turned to the data assembled by

Lewis Terman in 1937, in which 2,904 test scores yielded an almost perfect bell curve. They pointed to foster child and twin studies, and accepted the interpretation that indicated that heredity was an important determinant of intelligence. They noted that caution and care should be taken in using the twin study data and had statistical and biological reservations. Nonetheless, the appeal of a hereditary basis for intelligence kept the issues alive in their text. The use of these judgements for establishing educational and employment policy was widespread in the mid-century and the British reformed their educational system relying heavily on studies of this sort.

Other manifestations of this eugenic potential are found in numerous places in the reflections and programmes of scientists even in the post-war decades of the century. Linus Pauling, twice Nobel Prize winner and the biochemist responsible for spotting the mutant form of haemoglobin associated with sickling of cells, expressed the frustration with human genetic science and its limited ability for intervention. The need for a policy to avoid the mating of sickle carriers was clear:

'I have suggested that there should be tattooed on the forehead of every young person a symbol showing possession of the sickle cell gene or whatever other similar gene...'

His proposal voiced for avoiding mating of two people carrying the same seriously defective gene went beyond the voluntary hope that they would refrain from falling in love to legislation for 'compulsory testing for defective genes before marriage, and some form of semi-public display of this possession...'

Development of genetic techniques

During the first two thirds of the century of modern genetics, techniques for introducing new genetic material into plants and animals was almost completely restricted to the traditional practices of breeding and hybrid crossing – techniques not available for human experimentation. The last third of the century, by comparison, has seen rapid developments in the ability to target gene changes, and in the potential for using this technique on human cells. The identification

of DNA as the hereditary 'stuff', the delineation of its chemical composition, its physical structure, its role in protein production and the recognition of the remarkably simple code governing this production set the stage for the certain break – when genetic science and technique would quickly outrun social policy in the practice of human genetics.

The rather modest tone of the 1953 announcement in *Nature* by James Watson and Francis Crick of a molecular structure for DNA and its implications for gene replication belied the importance this work would have for the very rapid development of molecular genetics, and the strong impetus it would give to efforts to target genetic changes at the molecular level. By the time Watson wrote his autobiographical account of his discovery, *The Double Helix*, 15 years later in 1968, he was able to report a very different tone for the new genetics. Referring to his partner in discovery he opened his account with the claim: 'I have never seen Francis Crick in a modest mood', and it is fair to say that modesty has not been a hallmark of the new genetics nor of its practitioners. Boundaries existed to be broken or challenged. Genetics had entered the fast lane.

In operational terms, the real breakthrough came in the early and mid-1970s with the development of techniques in recombinant DNA work. Even as this work was at the edge of speeding from success to success, some older and wiser heads in the biomedical community were doubting that gene transplanting would be possible. McFarlane Burnet, the important immunologist, put it bluntly in 1973: the desideratum of extracting from a normal human cell the DNA sequence that was missing or distorted in diseased cells and transferring it to cells throughout the body 'would be the crucial and probably impossible...' step. The idea of using a virus vehicle to carry the new gene and 'precisely replace the faulty gene with the right one...' seemed to be in the realm of fantasy. 'I should be willing to state in any company', Burnet proclaimed, 'that the chance of doing this will remain infinitely small to the last syllable of recorded time'. It was a convenient doubt in part, because it delayed the necessity for coming to terms with the numerous implications of gene transfers – scientific, medical, social, and ethical – but this doubt was very quickly overrun.

By June 1973, at a Gordon Research Conference in New Hampshire, Herbert Boyer described the technique he had developed together with Stanley Cohen to put DNA into bacteria. The Boyer-Cohen technique made it possible to make hybrid DNA molecules. A flurry of concern was expressed both in the inside community and soon by a wider group of anxious critics. There was discussion of the immediate impact of the experimentation, but this was explicitly limited to the issue of potential biohazards. The broader social policy implications were consciously excluded from the agenda of the conference held at the Asilomar Conference Center in California in February 1975. The group meeting set in motion the establishment of experimental guidelines for protection from biohazards, and even instituted a temporary moratorium on some forms of recombinant DNA experimentation. The self-regulation, directed from within the scientific community, successfully repelled moves in the United States Congress to enact legal structures regulating recombinant DNA experimentation.

The scientific steps taken involved attempts to transfer genes into numerous micro-organisms, plants, and animals, and has created a whole industry devoted to exploiting the recombinant DNA techniques. The wide involvement of university scientists, in both start-up companies and the restructured major pharmaceutical and chemical firms, reflects a shift in many areas of molecular biology. The movement of critical research out of government-funded laboratories and into private sector firms also had significant implications for the regulation of research and the establishment of social and ethical standards and policies. There has been a variety of responses from the public to the development and use of genetically manipulated organisms and very little attempt to regulate agricultural and industrial applications. Genetically manipulated plant and animal products have been banned in many European markets and widespread distrust of genetic engineering in agriculture is common among the European public. The response in the USA has been more accepting. However, it is fair to say that beyond the health fears expressed toward genetically engineered crops and animals was the latent fear of the transfer of genes into eukaryotic cells, most importantly those of humans.

As soon as the techniques seemed usable, there was interest in inserting genes into human cells carrying genetic diseases. Work on gene transfer in mammals proceeded vigorously with accumulating, if still limited, technical success. Gene therapy for humans was still out of reach in the late 1970s and any thought of trying it experimentally was barred by National Institutes of Health guidelines. However, as often happens in a 'hot' scientific field, some investigators were willing to takes risks that might be seen as crossing acceptable boundaries, hoping that, if successful, the rewards would more than compensate. Martin J Cline, an MD and researcher from the Medical School of the University of California at Los Angeles, broke the rules and took his gene transfer experiments 'off-shore' to Italy and Israel. In July 1980, he administered recombinant DNA to two patients suffering from thalassemia. Cline was subsequently disciplined, his government grants suspended or removed, and his university post redefined, but it was apparent to all reviewers that appropriate guidelines and review procedures for human gene therapy were lagging significantly behind both the technological advances being made and the ethos of active scientists in the field. The lure of recognition and reward pulled experimenters to the edge of socially and ethically accepted practices. At the close of a 1982, conference on gene therapy, one of the organizers, Paul Berg, summed up: 'the consensus of the conference was that genetic approaches to treatment will probably be acceptable eventually; but there are many major technical and social problems that ideally should be solved before this occurs'.

Social implications and regulations

It is interesting to note that recognition of the social implications of the advances in genetic engineering of humans came not only from external critics but also from some of the most active practitioners. 'Will society be prepared?' Marshall Nirenberg asked as early as 1967 in an editorial published in *Science*. Nirenberg realised that technique was coming to outrun social and moral considerations:

'The point which deserves special emphasis is that man may be able to programme his own cells with synthetic information long before he will be able to assess adequately the long-term consequences of

such alterations, long before he will be able to formulate goals, and long before he can resolve ethical and moral problems which will be raised. When man becomes capable of instructing his own cells, he must refrain from doing so until he has sufficient wisdom to use this knowledge for the benefit of mankind. I state this problem well in advance of the need to resolve it, because decisions concerning the application of this knowledge must ultimately be made by society, and only an informed society can make such decisions wisely.'

In 1967, Nirenberg was willing to entertain the idea of self-denial: man should 'refrain from doing so until he has sufficient wisdom...' He was calling for opening a society-wide discussion before making decisions, but not all of his colleagues were equally concerned. As Walters and Palmer reported in their study, *The Ethics of Human Gene Therapy*, Joshua Lederberg feared that Nirenberg might be misinterpreted by the public and 'undercut the very research needed to reach sufficient wisdom'. He worried about over-enthusiastic policing of personal initiative and experimentation. In subsequent Congressional testimony, Lederberg reassured his listeners that geneticists were not going to change the bodies of existing people. Today, more than 30 years later, how would we answer the question: are we socially prepared for human gene therapy? Has the scientific research and experimentation of the intervening years added to the provision of 'sufficient wisdom'?

The Human Genome Project

The 1980s and 1990s have witnessed a proliferation of the identification of genetic bases for a variety of human conditions. The Human Genome Project has become a focal point for much of this effort. When he took over the direction of the American part of the effort (a project financed by the National Institutes of Health and the Department of Energy) JD Watson established a timetable. Arbitrarily setting the starting date as October 1, 1990 (the beginning of the US Government's fiscal year 1991) he proclaimed a completion date of just 15 years later, September 30, 2005. The task was to map and sequence the entire DNA of all 46 human chromosomes, some 50,000-100,000 genes, each containing between 10,000 and 50,000

base pairs per gene or as many as three billion base pairs, of which about 5 per cent were coded for genes. Walter Gilbert had claimed as early as 1985 that 'The total human sequence is the grail of human genetics – all possible information about the human structure is revealed (but not understood). It would be an incomparable tool for the investigation of every aspect of human function'. The designers of the Human Genome Project thought big and had a far-reaching vision.

The project, which includes a large European component, involved a significant scaling up of biological research work and has been described by Francis Collins, now director of the NIH segment, as 'the most important organized scientific effort that humankind has ever attempted... It dwarfs going to the moon'. Certainly hyperbole, but nonetheless indicative of the sense of scope and urgency with which the sequencing and mapping is being conducted. Michael Fortun, an historian of the project, has suggested that to the spatial sense of 'Big Science' (many have recognized that this is certainly 'Big Biology') be added the temporal sense of 'Fast Science' (quoted in Fortun, 1997). The speed vector has been achieved by replacing scientists laboriously sequencing DNA fragments by machines operated by technicians. Gilbert reflected on the problem in 1986 and said that, using sequencing techniques of the time, it would take 'something in the order of 1,000 years, 1,500 years to sequence this amount of DNA' (quoted in Fortun, 1997). To keep public and Congressional support coming Watson noted another imperative, 'We have to get some real results in the next 5 years... find the gene for something which you might not have found if you didn't have the genome mapped'. He also added an ethical dimension. It was known that the Alzheimer's disease gene was located on chromosome 21, and he said that 'it's unethical not to do it [get to it] as fast as possible'. The 'unethical not to do it' theme is repeated on many occasions as gene therapy experiments get under way, but alongside the medical and ethical imperatives Fortun spotted Watson's (as well as Gilbert's) personal imperative:

'People ask why I want to get the human genome. Some suggest that the reason is that it would be a wonderful end to my career... The younger scientists can work on their grants until they are bored and

still get the genome before they die. But to me it is crucial that we get the human genome now rather than 20 years from now, because I might be dead then and I don't want to miss out on learning how life works.'

In addition to the pressures on 'wise decision' making brought by size and speed, the question of financing the Project added a series of factors. As early as 1987, Walter Gilbert proposed establishing a private sector company to pay for the sequencing in return for the sequences being patented and licensed for commercial and medical exploitation and, of course, for the ensuing profits. Instead, the initial financing came largely from government sources on both sides of the Atlantic. Nonetheless, some patenting of sequences occurred amidst continuing controversy. In 1998, a private sector company, Celera, led by the aggressive and entrepreneurial scientist J Craig Venter, entered the race, proposing to complete the sequencing early by 2001 and in turn hold on to control of its sequence data for financial profit rather than releasing it to the world's scientists without restrictions or fees as proposed by the government-funded efforts.

With the important breakthroughs achieved in rapid sequencing procedures, and inventive new means for delivering modified genes to cells, technique had caught up with science in a critical area of human genetics. However, the potential for exploitation of the new knowledge created a series of problems for social and moral policy. Three areas immediately identify themselves for special consideration: diagnosis and screening, gene therapy and genetic modification of behaviour. A fourth area of concern, which is close to human genetic modification, and in which no less spectacular advances have been made, involves human reproduction (e.g. *in vitro* fertilization, postmenopausal pregnancies and the potential for cloning humans).

One theme heard repeatedly in discussions of advances in the study of the genetic basis of human disease is that therapy lags significantly behind diagnosis. In a recent review, Charles Cantor pointed to examples such as sickle cell anaemia, understood molecularly for several decades, or the more recently studied cystic fibrosis, in which therapeutic advances have been very slow. 'Therapeutic and preventive

benefits arising from the discovery of genes for a disease could lag 20 to 50 years behind the diagnostics.' Cantor graphically illustrated his point. In the not distant future, 10 to 15 years, the techniques will be at hand for the application of 'a single multiplex test to foetuses *in utero,* babies at birth, or in many cases, parental carriers...' that will be able to 'detect somewhere between 100 and 1,000 of the most common genetic diseases, disease pre-dispositions, and genetic risk factors for environmental insults, drug dose responsiveness...' Dorothy Nelkin, in her recent book *Dangerous Diagnosis* and in a focused paper, 'The Social Power of Genetic Information', provides even fuller analysis of the social problems derived from the successful race toward genetic diagnosis. She pointed to a clever cartoon from the *New Yorker* magazine illustrating a drive-through testing center on a busy highway advertising tests for 'emissions, drugs, intelligence, cholesterol, polygraph, blood pressure, soil and water, steering and brakes, stress and loyalty'. People, machines, and material are undifferentiated; human physical health and behaviour are treated identically. Most important for the point she is making is that 'most of the tests available in this drive-in station are not intended simply to diagnose manifest symptoms of illness or malfunction; their purpose is... to detect conditions that are latent, asymptomatic, or predictive of possible future problems'. This explosion of diagnostic information taken together with the impotence to therapeutically act on the information, in Cantor's words, 'exposes one of the serious social issues raised by the genome project'.

It is both fair and important to point out that several of the scientists behind the organization of the Human Genome Project suspected that social and moral issues would arise in the course of the Project's work. They built into the American programme design a '3 per cent factor'. A sum equivalent to 3 per cent of the research costs would be allocated to projects examining the ethical, legal and social implications of the research (the so-called ELSI projects). Similar set-asides have marked the several European efforts as well. The outstanding question is whether the pace and direction of the scientific activity reflects the social, ethical, and legal discourse being carried on in parallel. My own initial assessment is that the social and ethical analysis

lags rather than leads the science, and at best slightly slows the pace in several already controversial areas such as germ line interventions, but it is hard to discern any significant feedback loop from social analysis to medico-scientific activity. There has been hot debate over the construction of genetic data bases, but the techniques for developing them and the accumulation of information continues unabated. As Cantor ominously notes in his paper: 'one of the agencies most interested in the genome project is the FBI, a technologically very capable organization'.

Issues brought out by the Iceland project

The Iceland saga is a pertinent, if still not fully understood, effort at the generation of a genetic database of potentially enormous consequences. It throws up a number of the most pressing issues and also demonstrates the very complex problems of decision making. Iceland, an isolated nation of some 270,000 inhabitants, has a very homogenous gene pool that has been largely undisturbed by outside interventions for several centuries. From the geneticist's point of view, this represents a perfect population for the study of genetic variations in diseases and behaviours through many generations and across numerous families. There is also a very well organized national health system with a full national health database.

Kari Stefansson, an Icelandic-born, American-trained geneticist, recognized the potential and, together with American financial backers, established a commercial enterprise deCode Genetics Inc. to collect and process the genetic, health, and personal information of every person in the country, including the genealogical background reaching back through the century. Even more, he wanted the exclusive right to operate the database and sell its information to pharmaceutical companies intent on developing diagnostic tests and therapies. The first such agreement, worth up to US$200 million, has been negotiated with the Swiss company Hoffman-LaRoche to develop and market drugs for some dozen diseases.

The charismatic Dr Stefansson, working together with several associates, including the former Icelandic president Vigdis Finnbogdottir,

brought the proposal to the Parliament. After a relatively brief yet acrimonious debate, legislation was approved by a substantial majority in December 1998. However, the Icelandic Medical Association, the Data Protection Commission and others involved in public health work, individual scientists, and the recently established organisation, Mannvernd, the Association of Icelanders for Ethics in Science and Medicine, are all opposing the project as designed. One of the appeals of Stefansson's proposal is that new scientific and technical jobs would be created stemming the brain drain, consequently reducing the rapidly increasing costs of the Icelandic health system. There was also an appeal to the pride of the local population as contributors of a unique genetic resource to the battle against disease; an argument referred to by one local commentator as a form of 'Genetic Nationalism'.

The issues brought out by the Iceland project are in many ways a microcosm of those being raised in many other venues, such as informed consent. Data from individuals will be included unless the individual explicitly denies the right for her/his data to be included; albeit the dead are automatically included in the longitudinal database. Private sector, exclusive rights have been given to one firm, deCode, and the legislation states that no one, including non-profit organizations, may use the database if their research may be expected to have an adverse effect upon the licensee's commercial interest. Icelandic university-based scientists see this as a limit on the freedom of research, giving deCode a unique advantage in medical and genetic research. Confidentiality will be hard to protect even if encryption is used since the population is so small and it will be difficult to mask much personal information. Harvard geneticist Richard Lewontin in a *New York Times* article (23 January 1999) criticizes the project as another example of the commodification of the human body. Already there is an 'open market for blood, sperm, and body parts... space in someone else's womb...' and soon to some embryos and the tissues grown from them. A veritable 'parts catalogue', he called it. To this list is added the step of Iceland 'making its entire population into a captive biomedical commodity'.

Supporters point to the debate in society, and legislation enacted by a parliament, as representing a clear model of open public/social poli-

cy making, although the segments of society are left badly divided and the acrimonious debate continues. What kind of model does the Icelandic project provide? It represents what is, to date, an example of the broadest possible genetic screening, involving the whole society. While a vote was taken, was it premature in the sense that the longer-term consequences of collecting, managing, and using the genetic knowledge in this way – as a private sector enterprise – are not really understood? In terms of control of the genome of humans, it dwarfs what, in comparison, is the patenting and ownership of sequences being achieved in the established genome projects. All told, the amount of information being gained by the multinational genome project will be many magnitudes greater than that achieved in any previous scientific enterprise. Is the current mode of dealing with this information adequate?

How much do we want to know and what will we do with the information? Thomas Caskey (who isolated the gene for fragile X syndrome, the cause of most mental deficiency in new-borns) put the question forcefully: 'once we can predict disease risk at birth how should we use the information to improve the care provided to the individual?' He had in mind a series of diseases like cystic fibrosis and neurofibromatosis where present therapy is largely symptomatic relief. Clearly a new responsibility is being generated at a rate far in excess of the ability to respond to it.

Genetic information management

There is also the question of gathering and handling information. Wide-scale screening, even if not at the level attained in Iceland, creates problems of confidentiality. In the United States, military organizations are requiring all members to submit to DNA screening. Prenatal screening, which can have clear benefits in identifying disease presence or potential is becoming increasingly widespread. As Dorothy Nelkin notes, tests are becoming ever more 'efficient, inexpensive, accurate, and above all non-intrusive. It would be simple to test every new-born child'. She asks about the implications for privacy, and for potential discriminatory use in such areas as employment and health insurance. Caskey candidly adds, 'I lack sufficient confi-

dence in the security of databanks... and I think that a good deal more public discussion of the subject is required'. Law enforcement agencies in many venues are advocating the creation of national databases for criminals. With the technology available, organizational needs seem to be driving the efforts to enlarge the scope of screening and database construction. Nelkin sees a myriad of situations where agencies, individuals, and institutions may want access to genetic and biological profiles, all with an interest in people in their domains – 'Departments of Motor Vehicles, immigration authorities, creditors, adoption agencies, organ transplant registries, professional sports teams, sexual partners, the military, even university tenure committees'. Obviously, a concern for future health and performance is behind the interest of many of these potential users of genetic profiles, but there is a risk in creating overconfidence in understanding the meaning of a 'genetic basis for...' Discriminatory results from overstatement can obviously be highly detrimental. A number of commentators have pointed to the overlap between genetic disorders and racial and ethnic categories, sickle cell anaemia and Tay-Sachs disease, among others. From another direction, a potentially coercive effort is envisaged. At least one geneticist, Marjorie Shaw, has advocated a strong programme for the use of genetic information: 'the law must control the spread of genes causing severe deleterious effects; just as disabling pathogenetic bacteria and viruses are controlled' (cited in Nelkin, 1992). This attitude would seem to open what Troy Duster has called the *Backdoor to Eugenics*.

The war on human diseases

Although several unorthodox attempts at somatic cell gene therapy have been undertaken in the 1980s, the first sanctioned experiment began in September 1990. A four year old girl was given a dose of her own cells in which a gene had been inserted to replace a malfunctioning gene. It was a rare genetic disease called adenosine deaminase deficiency. Several other similar experiments all had degrees of success. While the techniques being used are derived from the new medical genetics of recombinant DNA and vectors, a focal question is whether this genetic therapy is an extension of, or a significant depar-

ture from, current therapies. In their review, Walters and Palmer contend it is an extension. However, questions remain about when and under what conditions to undertake somatic cell gene therapy experiments. There have now been well over 100 gene therapy procedures carried out in the United States alone and the boundaries have been pushed to the limit, or beyond, on a number of occasions.

It is not yet clear that the success rate is high enough to engender real optimism. Diagnosis of genetic disease still substantially outdistances therapy. Furthermore, current therapeutic techniques tend to be extremely costly, with one estimate of a minimum of $100,000 per patient. Retreatment and constant monitoring are required for all patients, using specialized laboratories able to use very sophisticated techniques. As Walters and Palmer put it, gene therapy 'under these conditions, [will] be of very limited utility in the war on human disease'. However, they note that there are optimists, 'visionaries' who, like W French Anderson, one of the earliest and most persistent proponents of gene therapy, see it becoming routine and widespread, akin to such commonplace techniques as antibiotics and immunizations. Anderson 'dreams of a day when a "magic bullet" will be available that would 'enable healing genes to enter the blood stream and go directly to the cell that needs help' (quoted in Walters and Palmer, 1997).

The enthusiastic researcher and the industrial producer may have conflicting, or at least not fully consistent, goals. The laboratory scientist may want to focus on technically interesting or challenging diseases, while the commercial firm will be directed by the imperatives of the market. Private industry's interest in somatic cell gene therapy is closely tied to diseases prevalent in the United States and Western Europe. The largest trials Walters and Palmer report are in the area of HIV and AIDS. At the time they wrote, about two-thirds of the first 100 protocols had forms of cancer as their target. Cystic fibrosis, the genetic disease most prevalent among Caucasians, received the most attention. Orphan diseases are obviously outside the range of conditions that have large enough markets to be attractive to private sector industry, and therefore do not provide strong incentive for research. In the United States, the commercially organized health care system is

unlikely to invest in these areas and in countries with national health care systems the problem of allocation of resources – monetary and technical – tends to focus on diseases affecting the larger segment of the population. Fundamental issues of access to new technologies and therapies become especially apparent in this new area of medical science. At both the research and therapeutic levels of medical genetics, the policy of social equity is under strain and may well become exacerbated by some of the very successes applauded technically. The answer appears to be to wait for basic reforms in health care systems. The technique may be stunning, but the practice by comparison is flawed.

If the outstanding issues facing somatic cell gene therapy are largely ones of efficacy, utility, and just access, those surrounding germ line gene therapy cut much deeper and evoke fundamental moral and social criticisms. In this form of gene modification, the aim is not only to affect the health of the individual under treatment, but to eliminate the disease-producing genes from being passed to future generations. The focus is on the reproductive cells, to alter the sperm-producing cells in the testes or the eggs in the ovary, or to insert genes into the very early embryo. Experimental work on humans has not yet taken place, although there has been pressure for experiments at the margins, for example with embryonic stem cells.

On the experimental front, work is proceeding using animal models, primarily mice. Some modest success has been achieved on sperm stem cells although the researchers express doubts that the techniques will work for mammalian eggs. There is still a long distance to go because, to date, gene insertion is still considered to be scattershot, with the potential for creating new diseases even as old ones are being treated. The dangers of passing mistakes on to future generations is one obvious detriment to rapid movement now. Only with some dramatic new means of gene transfer permitting precise insertion into the correct site will these problems be overcome. The arguments for proceeding with experiments on gene therapy adopt an essentially public health model – reducing the incidence of inherited diseases in the human gene pool. This would be seen as extending to new generations the success gained from somatic cell gene transfers. However,

elimination or even great reduction of defective genes will not occur by treating the individual sufferers from genetic diseases. By far the largest numbers of defective genes are carried in heterozygous individuals who are themselves asymptomatic. Therefore, it would be important to achieve large scale gene intervention. The question returns to wide scale screening, an ever more likely prospect, but having screened and identified defective genes, then what?

A molecular basis for a new eugenics was seen early, and enunciated with clarity, by one of the makers of the new molecular biology, Joshua Lederberg. Even as Francis Galton had proclaimed much earlier that eugenics could do kindly and rapidly what the Darwinian 'survival of the fittest' would do with much greater pain over a longer period of time, so Lederberg in 1963 saw an analogous role for the new genetics:

'The recent achievements of molecular biology strengthen our eugenic means to achieve [human survival]. But do they necessarily support proposals to transfer animal husbandry to man? My own first conclusion is that the technology of human genetics is pitifully clumsy, even by the standards of practical agriculture. Surely within a few generations we can expect to learn tricks of immeasurable advantage. Why bother now with somatic elections, so slow in its impact? Investing a fraction of the effort, we should soon learn how to manipulate chromosome ploidy [number of sets of chromosomes], homozygosis [the union of gametes that are identical for one or more pairs of genes], gametic selection, full diagnosis of heterozygotes, to accomplish in one or two generations of eugenic practice what would now take ten or one hundred.'

Thirty years on, the techniques are by no means in place to achieve Lederberg's goals, but the extensive work done with somatic cell interventions, and the pace of current research on gene transfer procedures, coupled with the explicit germ line experimentation with animals and the boundary work envisioned for the next year or two with human embryonic stem cells, suggests that it is not too early to open a sustained social and moral policy examination on this sensitive front. The postponement of this discussion, often urged by

researchers anxious to deflect the overflow of criticism to other more benign experimentation, should not stand in the way of an informed, serious discussion.

Many authors have pointed to the issues they believe deserve discussion now, in preparation for decisions in what may be the near future. There seems to be general agreement that, at this stage, human germ line therapy is too risky. This is primarily because of the inability to target gene insertion precisely. This is an area where intense research may bring useful procedures in the near future. How low should the risk be when dealing with human embryos? How mistake-free should the procedure be required to become before use? The financial costs will certainly be high at the beginning and the mode by which these costs are covered could force acute decisions for both private sector health insurance programmes, and state systems which balance some general gain with the support of small population high cost therapy. This could become another area in which social inequalities are increased by new medical techniques.

One area where contentious debate can be expected focuses on whether germ line intervention is necessary, or whether other preventative or therapeutic means can be used instead. Somatic cell gene therapy, traditional metabolic or drug therapy, selective abortion and embryo discard are alternatives that vary in cost, moral acceptability, and known efficacy. How widespread would the use of germ line therapy have to become to be considered successful? A single individual genetic disease sufferer? Broad use against the most debilitating diseases? Wide scale use to eradicate most genetic diseases? Coupled with these questions is the issue of whether the procedures should be voluntary or mandatory. Health systems, whether private or public, may insist that insurance and care will be given only if a gene therapy regimen is accepted thus protecting against the expenses involved in children carrying treatable diseases into the next generation.

While recognizing the very negative connotations of the word 'eugenics', Walters and Palmer opt for using a different description for the ends they have in sight: 'a voluntary programme to reduce the incidence of genetic disease through germ line genetic intervention'.

They bolster their acceptance of this restrained germ line procedure by pointing to public responses in opinion polls conducted by Louis Harris in 1986 and 1992. There was a majority (52 per cent) strongly supporting germ line intervention to prevent 'children inheriting usually fatal genetic disease....' This fell to 24 per cent for a non-fatal birth defect. Majority support was also registered for using joint somatic and germ line treatment in 'usually fatal diseases... likely [to] be inherited'. Interestingly, expert opinion (both medical and ethical) was more restrained in its attitudes toward germ line therapy.

Some commentators raise the moral issue of whether humans, or particularly small groups of humans, should have the degree of control over their futures which germ line therapy could provide. Are we ready to accept this form of responsibility for such directed choice? Assuming that malevolence is not a factor, are we confident in the quality of the knowledge and judgement of the medical professionals who would be counted on for these decisions? Whose concepts of health and diseases would govern the choices?

What is in some ways surprising is how often scientific literature returns to models of a benevolent eugenics aimed not only at excluding disease-forming genes but otherwise enhancing human capabilities. For example, Robert Sinsheimer, one of the more responsible members of the molecular biology community writing in 1969, explores a new eugenics that 'could at least in principle be implemented on a quite individual basis' (quoted in Keller, 1992):

'The old eugenics was limited to a numerical enhancement of the best of our existing gene pool. The new eugenics would permit in principle the conversion of all the unfit to the highest genetic level. It is a new horizon in the history of man. Some may smile and may feel that this is but a new version of an old dream. It is that, but it is something more. The old dreams of the cultural perfection of man were always sharply constrained by his inherent, inherited imperfections and limitations... To foster his better traits and to curb his worse by cultural means alone has always been, while clearly not impossible, in many instances most difficult... We now glimpse another route – the chance to ease the internal strains and heal the internal flaws directly,

to carry on and consciously perfect far beyond our present vision this remarkable product of two billion years of evolution.'

Writing even before the successes of recombinant DNA experimentation, Sinsheimer dreamed of a molecular future where the human genetic make-up would be much more plastic in the hands of science then had been previously envisaged. He shares something of the optimistic spirit shown by his colleague Joshua Lederberg a half dozen years earlier. It was a spirit, however, which others picked up. Robert Nozick, the philosopher, liked the potential voluntarism the new genetics seemed to offer and, in 1974, speculated about a 'genetic supermarket in which parents, rather than the state, could choose the genetic make-up of their children' (quoted in Reiss and Straughan, 1996).

As the potential for effecting germ line genetic engineering became greater, some tough questions arose, most particularly confronting the issue of boundaries. At least two fronts became clearer – disease elimination or modification and the genetics of human behaviours. The report of a conference sponsored by the Institute of Medicine and the National Academy of Sciences in 1986 tried its hand at distinctions. They decided that somatic cell gene therapy raises no ethical issues beyond those of any new therapy, but that germ line gene therapy, enhancement genetic engineering and eugenic genetic engineering raise scientific and ethical issues beyond those associated with other medical technologies (Nichols, 1988). Aside from the fact that the tools for these forms of genetic manipulation did not exist and 'may never be possible because of the extreme complexity of the systems involved', the 1986 report was anxious to decouple somatic gene therapy from any of the germ line forms. They went so far as to say that many diverse groups 'have concluded that it would be unethical to withhold somatic cell gene therapy from severely ill patients solely because other forms of genetic engineering might be misused in the future'.

Within three years, in a 1989 article, 'Human Gene Therapy: Why Draw a Line', W French Anderson (one of the staunch advocates of therapeutic uses of genetic engineering) drew a clear line separating gene therapy aimed at curing or preventing disease – of which he was

in favour – and genetic engineering intended to enhance the capacities of otherwise healthy humans – which he opposed (quoted in Walters and Palmer, 1997). He claimed the focus must be on genuine medical problems, but is the line that clear? By 1995, Sir Walter Bodmer, a distinguished British human geneticist and former president of the Human Genome Organization, (writing with science journalist Robin McKie) was not sure and asked ëwould it really be so bad if we added genes for height to small people, or for hair to the bald, or good eyesight to the myopic? Probably not.' Should we draw the line at genes for intelligence and athleticism? Would the very notion of the sanctity of human individuality be badly compromised? 'Just where we get off the slippery slope is therefore a matter for society to choose', but Sir Walter suggested we could be relaxed. The time scale to achieving technical capacity is such that 'we have plenty of time to debate the issues and resolve them'. To conduct this discussion properly, he claimed, what is needed is a DNA literate public.

The philosopher John Harris picked up several of these themes in his 1992 book, *Wonderwoman and Superman: the Ethics of Human Biotechnology*. As with a number of others, noted above, he asked whether having the technique makes us duty bound to use it. He set out what be believed to be proper guidelines (quoted in Reiss and Straughan, 1996):

'We must not act positively so as to cause harm to those who come after us, but we must also not fail to remove dangers which, if left in place, will cause harm to future people. Thought of in this light, there is a clear dilemma about genetic engineering. On the one hand we must not make changes to the genetic structure of persons which will adversely affect their descendants. On the other hand we must not fail to remove genetic damage which we could remove and which, if left in place, will cause harm to future people.'

The emerging consensus, if it is that, is to stress the need for a good deal of further ethical and social examination before embarking on the 'slippery slope' of germ line genetic intervention. While accepting the argument that in principle it may be acceptable to cure diseases when possible, the Archbishop of York, John Habgood, in 1995, urged his readers to be extremely 'suspicious about improving human

nature; and be even more suspicious of those who think they know what improvements ought to be made' (quoted in Reiss and Straughan, 1996).

Ethics of enhancement therapies

While there is certainly not a vigorous current campaign to engage in enhancement therapies, there is a steady stream of experimentation focused on aspects of enhancement and on the genetic bases of human behaviour characteristics. The enhancements discussed include the physical, some of which are medically related, for example children with growth hormone deficiency who may potentially be treated through genetic intervention. Currently such children are treated with a human growth hormone produced using recombinant DNA methods. Genetic modification of dwarfism has created debates within the dwarf community, with some objecting to the imposition of norms which casts them in a position of abnormality. A variety of sports contexts come to mind every time physical enhancement is broached. Many non-genetic medical regimens are currently used, even if they are regulated in some sports. Ageing is another area discussed. Genetic techniques, Walters and Palmer note, may be used to extend the length of life. If such techniques are efficacious this enhancement will have profound social policy implications. Current experiments on human reproduction using in vitro fertilization techniques have already made it possible for post-menopausal women to carry a foetus to term in their own uterus.

The bioethicist/physician Tristam Engelhardt operating under the thesis that 'nature does not know best', identifies a number of other human characteristics recommended for germ line genetic engineering: near-sightedness, menopause and the concomitant osteoporosis, and the shortened life expectancy of males as compared to women due in part, he notes, 'to genetically determined increased risk of diseases' including myocardial infarction and cancer of the prostate (quoted in Walters and Palmer, 1997).

Physical enhancement through eugenic genetic engineering raises questions enough, but the potential for behaviour eugenic engineer-

ing is surely more sensitive. Philip Kitcher, a philosopher of science, in a recent highly informed commentary on the implications of the new genetics for humans identified the work of Dean Hamer of the National Cancer Institute as representing important trends. Hamer and his colleagues, in a much talked about 1993 paper, discovered, 'A linkage between DNA markers on the X chromosome and male sexual orientation', homosexuality. Kitcher lauds the caution which Hamer showed when he indicated that he is not able to ëestimate the frequency with which those who bear the 'gay' alleles develop same-sex preferences...' Hamer's work opens up the way to further study of the genetics of behaviour.

However, Hamer is not nearly so cautious in a new popular book *Living With Our Genes* (1998), written together with Peter Copeland. With the full enthusiasm of someone overcoming great hurdles, he pointed to a wide variety of 'behaviours determined largely by heredity'; an obese gene; the genetics of gender ('men are programmed to seek more partners and sexual novelty; women are serial monogamists'); addictions to alcohol, tobacco, and dangerous drugs; and violence and aggression... 'The evidence that IQ is largely inherited is overwhelming.' Hamer recounts that, since the discovery of the genetic link to male homosexuality, his lab is now looking at sexual orientation in women. In addition, he claims his researchers have now found genes for two other personality traits: novelty seeking and worry. Further, he notes shyness is inherited at birth. Indeed, Hamer's broad claim is that 'the emerging science of molecular biology has made startling discoveries that show beyond a doubt that genes are the single most important factor that distinguishes one person from another'. The image he projects: 'We come in large part ready-made from the factory'.

The implications of the new knowledge gained and the contexts of its discovery seem straightforward enough to Hamer: 'the stampede to map the genome plus the decisive role of genes in behaviour means that, whether anyone thinks it's a good idea or not, we soon will have the ability to change and manipulate human behaviour through genetics'. He identifies this with the new field – 'functional genomics' – figuring out what genes do and linking it to the new technologies

of intervention. The manipulations are at present restricted to animals, 'Dolly the sheep being the first well-known example, but *humans are just a few steps away*' [my italics]. The project is being vigorously driven – 'Lives are at stake. Money is at stake... That's a powerful combination anywhere, and in America it's invincible'.

Even with the allowance for hyperbole (molecular biology has not been a modest enterprise) and a lengthened time line, Hamer has given ample warning and asked the questions his warnings demand: 'It's too late to wonder whether we are going to genetically tinker with human behaviour. We need to decide very quickly how we are going to do it. How will we distinguish 'good' genes from bad? What traits will be valued and what will be discarded? Who gets to choose?' In much more restrained tones, Walters and Palmer reached very similar conclusions: '...at some point in the near or more distant future, the technical capability to enhance at least some human characteristics [physical, intellectual, moral] will be developed'. In measured tones, they argue for the ethical acceptance of some changes in human nature. Disease and disability are 'evils that should be overcome as quickly and efficiently as possible'. Similarly, they argue that there are problems in the intellectual and moral sphere which in part at least should be addressed 'through the judicious use of genetic technologies'. The human race should not be 'fated to accept the current state of affairs'. In the same Harris poll cited above, Walters and Palmer record that majorities of the public polled opposed genetic manipulation to improve physical characteristics and opposed manipulation to improve intelligence of children. They also note the vigorous opposition to genetic enhancement from both the British and Canadian advisory committees, with the Canadians emphatically rejecting further work in this field: 'No research involving the alteration of DNA for enhancement purposes will be permitted or funded in Canada'.

Conclusions

During the past decade and a half, human molecular genetics has been extremely active and the moves to apply the newly gained knowledge and techniques in genetic screening, somatic therapy, and germ line

genetic engineering have become widespread and often controversial. Social analysts, from ethicists to legal scholars, historians, philosophers, economists, and sociologists are racing to understand the new developments, to develop tools and frameworks for their analysis, and to raise for public and social discussion the myriad implications of the technical achievements. Old boundaries are being challenged concerning what is ethical, what is normal, what is human? As genetic linkages are established between genes and diseases, genes and physical attributes, genes and human behaviours, the temptation to simply allow technical capability to guide social judgement is strong. Or, the temptation to seek to alter, make better, human health, human social and psychological behaviour, to engage in a eugenic quest for an improved human and a more satisfactory human condition, takes hold a step at a time. The genetic sciences are robust and challenging, even if not always wise. By contrast, social and ethical analysis and social and ethical policy making, while earnest, lack clarity and focus. Technical developments are taking place in a recognizable range of institutions guided by a mix of scientific enthusiasm, institutional imperative, search for rewards (both monetary and professional) and an honest attempt to put science to work. Social and moral discourse, by comparison, seems scattered, unfocused and at times quixotic – how many times is the paradoxical identified? This lack of disciplined analysis and lack of firm institutional bases has weakened the sometimes important questions asked and proposals made. The science seems strong (too strong?) and goal-oriented and quite prepared to ignore important caveats. The task for the immediate future is to establish a means to integrate the social and moral critique into the decision-making processes of the practising sciences, so that social analysis becomes part of a feedback system to assure wisdom in scientific advance not mere technical achievement. There are potentially significant costs to allowing social policy to lag behind scientific and technical advance. Solving the 'technically sweet' problem first and only then turning to examine the moral and social consequences has, in the past and can in the future, prove to be too costly.

REFERENCES AND FURTHER READING

1 Bodmer W, McKie R. *The Book of Man, the Human Genome Project and the Quest to Discover Our Genetic Heritage*. New York: Scribner & Welford, 1995.

2 Broberg G, Roll-Hansen N (eds.). *Eugenics and the Welfare State, Sterilization Policy in Denmark, Sweden, Norway, and Finland*. East Lansing, Michigan: Michigan State University Press, 1996.

3 Burnet M. *Genes, Dreams and Realities*. Cambridge, UK: Harmondsworth Press, 1973.

4 Cantor C. The challenges to technology and informatics. In: Kevles D, Hood L (eds.). *The Code of Codes, Scientific and Social Issues in the Human Genome Project*. Cambridge, MA: Harvard University Press, 1992.

5 Caskey CT. DNA-based medicine and prevention from therapy. In: Kevles D, Hood L (eds.). *The Code of Codes, Scientific and Social Issues in the Human Genome Project*. Cambridge, MA: Harvard University Press, 1992.

6 Castle WE. *Genetics and Eugenics: a Text Book for Students of Biology and a Reference Book for Animal and Plant Breeders*. Cambridge, MA: Harvard University Press, 1916.

7 Collins F. *New York Times* 1999; May 22.

8 Duster T. *Backdoor to Eugenics*. New York: Routledge, 1990.

9 Fortun M. Projecting speed genomics. In: *The Practices of Human Genetics. Sociology of the Sciences Yearbook* 1997;21:25-48.

10 Fortun M, Mendelsohn E (eds.). *The Practices of Human Genetics. Sociology of the Sciences Yearbook* 1997;21:25-48.

11 Gilbert W. A vision of the grail. In: Kevles D, Hood L (eds.). *The Code of Codes, Scientific and Social Issues in the Human Genome Project*. Cambridge, MA: Harvard University Press, 1992.

12 Hamer D et al. A linkage between DNA markers on the X chromosome and male sexual orientation. *Science* 1993;261:321-327.

13 Hamer D, Copeland P. *Living With Our Genes, Why They Matter More Than You Think*. New York: Doubleday, 1998.

14 Keller EF. Nature, nurture, and the Human Genome Project. In: Kevles D, Hood L (eds.). *The Code of Codes, Scientific and Social Issues in the Human Genome Project.* Cambridge, MA: Harvard University Press, 1992.

15 Kevles DJ. *In the Name of Eugenics, Genetics and the Uses of Human Heredity.* New York: Harvard University Press, 1985.

16 Kitcher P. *The Lives to Come, The Genetic Revolution and Human Possibilities.* New York: Touchstone Books, 1996.

17 Krimksy S. *Genetic Alchemy, The Social History of the Recombinant DNA Controversy.* Cambridge, MA: MIT Press, 1982.

18 Lederberg J. Biological future of man. In: Wolstenholme G (ed.). *Man and His Future.* London: Churchill Livingstone, 1963.

19 Mehlman MJ, Botkin JB. *Access to the Genome, The Challenge to Equality.* Washington DC: Georgetown University Press, 1998.

20 Neel JV, Schull W. *Human Heredity.* Chicago: University of Chicago Press, 1954.

21 Nelkin D. The social power of genetic information. In: Kevles D, Hood L (eds.). *The Code of Codes, Scientific and Social Issues in the Human Genome Project.* Cambridge, MA: Harvard University Press, 1992.

22 Nichols EK (Institute of Medicine, National Academy of Science). *Human Gene Therapy.* Cambridge, MA: Harvard University Press, 1988.

23 Nirenberg M. Fine structure of RNA codewords recognized by bacterial, amphibian, and mammalian transfer RNA. *Science* 1967;157:633.

24 Paul DB. *Controlling Human Heredity, 1865 to the Present.* Atlantic Highlands, NJ: Humanities Press International Inc, 1995.

25 Pauling L. Reflections on the New Biology. *UCLA Law Review* 1968;15:269.

26 Reilly PR. *The Surgical Solution, a History of Involuntary Sterilization in the United States.* Baltimore: Johns Hopkins University Press, 1991.

27 Reiss MJ, Straughan R. *Improving Nature? The Science and Ethics of Genetic Engineering.* Cambridge, UK: Cambridge University Press, 1996.

28 Sigurdsson S. The databank takeover of Iceland. *Committee on Intellectual Correspondence: Newsletter* (summer 1999), in press.

29 Thompson L. *Correcting the Code, Inventing the Genetic Cure for the Human Body.* New York: Simon & Schuster Inc, 1994.

30 Walters L, Palmer GJ. *The Ethics of Human Gene Therapy.* New York: Oxford University Press, 1997.

31 Watson JD. *The Double Helix.* London, Atheneum, 1968.

32 Watson JD, Tooze J. *The DNA Story, a Documentary History of Gene Cloning.* San Francisco: Freeman, 1981.

Chapter 8
The economic implications of genomics

PROFESSOR PATRICIA DANZON
The Wharton School, University of Pennsylvania, USA

Abstract

This paper examines the economic effects of the various uses of genomics in the diagnosis and treatment of disease, in particular: pharmacogenomics as a tool of drug discovery; gene therapy; pharmacogenetic testing to increase drug specificity; genetic testing of symptomatic patients; and population genotyping. The positive analysis considers the effect of genomics on the productivity of, and costs to, the pharmaceutical industry and discusses effects on the quality, characteristics and prices of therapies available to consumers. Private sector responses depend on public sector policies on insurance reimbursement, public subsidies to R&D, and patent rights. The policy analysis here considers the design of these public policies to promote appropriate private sector investments in genomics. In particular, the appropriate incentives to develop gene therapies with long-lasting benefits and pharmacogenetic-based improvements in drug specificity will require careful design of reimbursement policies and possibly orphan drug provisions.

Science defines opportunities, economics defines which opportunities are addressed

The primary question for payers is whether gene therapies will be cost-effective and affordable. However, the question for private developers of these therapies is whether the prices deemed cost-effective by payers are sufficient to cover costs and yield a reasonable return. This paper considers the effects of different uses of genomics on the productivity of, and costs to, the pharmaceutical industry and discusses their effects on the quality, characteristics and prices of therapies available to consumers.

Pharmacogenomics as a tool of drug discovery

Pharmacogenomics is already used widely in the pharmaceutical industry, having the potential to reduce R&D costs, increase the rate of new drug introductions, prolong effective patent protection time, and expand the range of therapies available. However, early predic-

tions that genomic information would permit precise and specific targeting may have been overly optimistic. Many genes correlated with specific diseases are not causative and may be 'blind alleys'. Nevertheless, in the long run, pharmacogenomics is likely to improve productivity significantly.

These advances could result in higher net revenue for each compound developed but also in pressures on payers as more new drugs reach the market. There may be some opportunities for displacing spending on other areas of medical care (e.g. inpatient costs), but this depends on whether the new drugs are truly new, offering improvements in quality or quantity of life; are cost reducing; or are just more drugs in crowded therapeutic categories. If it is the last, then competition and regulation will drive down prices. Increased numbers of new drugs per year, with no change in average prices and volumes, will counter efforts to limit drug spending to a roughly constant share of gross domestic product (GDP). Both competitive and regulatory pressures may lead to lower prices or volumes until opportunities for above-normal expected profits from these technologies have been exhausted.

The net beneficiaries will be consumers, who will benefit from a higher rate of introduction of new drugs and lower prices. En route to this equilibrium, those companies that excel in improving R&D productivity are likely to enjoy above-normal profitability. This is consistent with standard models of dynamic competition in innovative industries.

The only special policy issue relating to pharmacogenomics as a tool of drug discovery (and not other discovery technologies) is that use of genomic information may be inappropriately low due to the fragmentation of patent rights. Use of genomics to develop gene therapies (see below) may be particularly difficult due to the number of patents that may have to be assembled and the uncertainty over who holds which patents. The existence of proprietary patents has been cited as an obstacle to development by academic researchers, and lack of technology transfer from academics to small commercial companies in the UK has been cited as a policy failure to be remedied. However,

patent structure is complex and optimal configurations cannot be determined until the uses of genomic information are better known.

Gene therapy

There is a lot of clinical uncertainty as to the potential for lasting therapeutic benefits and the risks of severe side effects from gene therapies. Such uncertainties create economic risks, which may require high returns on those products that succeed.

On the other hand, projecting long-term health benefits on the basis of short-term clinical endpoints is often problematic for new drugs of all kinds, whereas gene therapies may face fewer problems in extrapolating such data. If the gene therapy achieves persistent expression of the desired protein in trials and this is sufficient for an improvement in health, certainty of long-term health benefits of *in vivo* gene therapies could be greater than for many drugs for which the trial endpoints are only loose correlates of the desired health outcome. However, clinical learning curves may adversely affect the initial cost-effectiveness of gene therapies. Moreover, if the benefit of some gene therapies is to offer improvement in quality of life rather than reduced costs to the medical system, this may not be adequately recognized in measures of effects. Therefore, proving cost-effectiveness may be difficult for gene therapies.

If successful, gene therapies would require only infrequent administration, rather than the once-daily regimes for most pharmaceuticals. While the potentially long-lived effects of in vivo gene therapies are of great benefit to patients, they could raise problems in terms of adequate reimbursement and hence commercial viability. For example, payers may be willing to pay £5,000 per year for continuous treatment, but if the benefits of a single administration of a therapy were to last five years would they be willing to pay £25,000 in a single payment? This may not be a problem if gene therapy is reimbursed as a service like surgical intervention or other costly one-off treatments with long-term benefits. However, if gene therapy is allocated to drug budgets and has to compete with other pharmaceutical products with a much lower price per daily dose, distortions could arise.

Reimbursement could be difficult due to component-based, annual budgeting in some healthcare systems, which often fail to reimburse for long-lived benefits, particularly when benefits accrue elsewhere in the healthcare system or economy.

Nevertheless, there is always a price at which gene therapy is cost-effective from a payer perspective. The question for commercial feasibility is whether this price will allow companies developing the therapy to break even. A new gene therapy will be considered cost-effective by payers if:

$$(C_g - C_0)/(E_g - E_0) < k$$

where:

$$C_j = P_j + C_j^d + C_j^i \text{, for } j = g, 0$$

and where:

$_g$ and $_0$ = gene therapy and existing alternative treatment, respectively

P_j = the price of the drug used in the gene therapy, or existing alternative treatment

C_j^d = other direct treatment costs

C_j^i = indirect costs

E_j = quality-adjusted life years (QALYs) produced by each therapy

k = threshold cost per QALY at which an intervention is considered cost-effective.

Payers are interested in the difference between the costs and the effects of gene therapy and existing therapy. Assume that the maximum they are willing to pay for one QALY is threshold value k. The maximum price at which gene therapy is cost-effective is the price of the existing therapy, plus any savings in other direct and indirect costs, plus the difference in QALYs evaluated in monetary terms:

$$P_g^{max} = P_0 + \Delta C^d + \Delta C^i + k\Delta E$$

where:

$$\Delta C^d = C^d_0 - C^d_g$$

$$\Delta C^i = C^i_0 - C^i_g$$

$$\Delta E = E_g - E_0$$

From the producer's perspective, the break-even minimum acceptable level of profit (in discounted present value terms) on the investment in gene therapy is Π, where:

$$\Pi = \Sigma[(P_g - M)\ Q^t\ N^t\ (1 + r)^{-t}] - F(r,L)$$

The profit per treatment is found by taking the difference between the price of gene therapy (P_g) and variable cost per treatment to the producer (M). This is multiplied by the number of treatments per patient per year (Q) and the number of patients treated (N) in each year for the T years of the product's market life, discounted using the minimal discount rate (1+ r) and summed. This is where the long-life therapies are distinctly different, in that there are many fewer treatments per patient. This overall treatment revenue generated net of costs must be sufficient to cover the R&D fixed costs (F = average R&D cost per compound launched; r = risk-adjusted cost of capital; L = average lag in years from discovery to launch).

Some of the benefits of gene therapy will be through lower indirect costs and higher quality of life for patients, which may not be recognized by payers. Variable costs of treatment are likely to be high, however, which tends to reduce profitability. The number of patients treated per year, at least initially, will be low, and the number of treatments per patient will be low, both also reducing profitability. Therefore, the only way that gene therapy will be able to compete with alternative therapies is if there are significant savings in R&D costs. It is not yet known how this will work out, but it is clear that, at least on the revenue side, there may be significant impediments to adequate reimbursement.

One implication of this is that private investment is likely to be skewed towards short-acting therapies, leaving public sector investment to take care of the longer-life therapies. The other issue is the adequacy of orphan drug legislation, which in the USA is currently

defined in terms of a threshold number of patients with the disease (200,000). The implicit assumption is that those patients would be treated every year. However, with long-life gene therapies, patients would not need to be treated every year. The orphan drug threshold should be modified in order to adjust it for the relative infrequency of these treatments, if it is to be neutral between short and long-lived therapies, including gene therapies.

Pharmacogenetics

Genetic testing prior to treatment could identify patients who would benefit from particular drugs or those who would develop adverse effects. This would generate social savings by avoiding ineffective treatment and the cost of adverse reactions. However, these savings are balanced by the potential fragmentation of therapy markets. Two questions arise:

- When is the use of pharmacogenetic testing beneficial from a social perspective?
- Is the private incentive of drug manufacturers consistent with this social benefit?

The concern from the perspective of industry is that pharmacogenetic testing prior to treatment may result in fewer patients treated and hence lower revenue per drug. In addition, the costs of diagnostic screening may reduce the net price the payer is willing to pay for the drug. If there is no offsetting decrease in cost of R&D per drug, this fragmentation of the patient population due to pharmacogenetic testing would reduce the incentive to develop new drugs, other things being equal.

Let n_1 be the number of patients who benefit from the drug and n_2 the number who do not benefit but who can only be identified by testing. Assume that the producer of the drug also develops and sells the test. Let R_1 be the producer's profit with no testing and R_2 the profit with testing:

$$R_1 = (n_1 + n_2)(P^d - M) - F_1$$

$$R_2 = n_1(P^d - M) + (n_1 + n_2)(P^t - C) - F_1$$

where:

P^d = price of the drug

M = variable cost of the drug

P^t = price of the test

C = cost of the test

F = R&D cost of the drug

The producer's profit is greater with the test than without, $R_2 > R_1$, only if:

$$(n_1 + n_2)(P^t - C) + (F_1 - F_2) > n_2(P^d - M)$$

Thus if the test must be competitively supplied, such that $P^t = C$, the monopoly producer of the therapy has no incentive to invest in pharmacogenetic testing in development that leads to a narrower indication unless there are significant savings in R&D cost. Such savings may be possible if, for example, genetic testing permits Phase III trials to be targeted to fewer patients who are more likely to benefit. Thus, efficacy may be demonstrated with much smaller trials. It is also possible that, with genetic testing, the drug could be designed such that it is effective for a larger fraction of the patient population. In that case, the tendency for pharmacogenetics to shrink the average size of the target population per drug would be mitigated. Without such benefits, a drug producer has no financial incentive to invest in pharmacogenetic testing that simply shrinks the target population.

Of course, if there is free entry to the business of developing genetic tests to determine which population subgroups will benefit from a specific drug, then pre-treatment tests are likely to be developed where there is a net saving to the payer (that is, the treatment savings exceed the cost of the test). Drug producers would then face smaller populations and some drugs may not be developed, where the population fragmentation would reduce expected revenues below the level necessary to cover the costs of R&D. However, to the extent that genetic testing does permit savings in clinical trials or modification of the molecule such that it treats more patients, it is likely that the drug

producers will have incentives to do this testing themselves as part of drug development, rather than wait for others to do it after drugs reach the market, in which case the producer suffers the loss of sales but gets none of the possible benefits of smaller trials or better designed drug.

Consider now the social planner/payer perspective. Let B_1 denote the social benefit with no test, B_2 the social benefit with testing, S the cost of the drug, X the cost of the test, and Q the monetary value of the benefit per patient who benefits. For simplicity, assume there are no side effects:

$$B_1 = n_1Q - (n_1 + n_2)S$$

$$B_2 = n_1(Q - S) - (n_1 + n_2)X$$

The necessary condition for testing to be beneficial, $B_2 > B_1$ implies:

$$n_2S > (n_1 + n_2)X$$

Thus testing is socially beneficial if the savings from avoiding treatment for the n_2 patients who do not benefit exceed the cost of testing all patients. This can be rewritten:

$$n_2 / (n_1 + n_2) > X/S$$

Thus, testing is worthwhile from a social perspective if the ratio of non-responders to the total population exceeds the ratio of the cost of the test to the cost of the drug.

The analysis so far demonstrates that the private incentives to develop and use pharmacogenetic testing may differ from the socially optimal incentive. If tests can only be developed by the pharmaceutical firm that develops the drugs – for example, if the necessary information is proprietary – then there may be sub-optimal testing. It seems more realistic to expect competitive entry into the supply of tests, in which case drug producers would face smaller target populations. In some cases, the target population may now be too small for the drug to be commercially viable, in which case those patients who would have benefited will forego treatment. The primary reason for this conflict between social and private incentives is that drug expenditures on

patients who do not benefit are pure waste to the payer but are revenue to the manufacturer.

The analysis so far assumes that the price of the drug is the same, regardless of the expected benefits to the average patient who takes the drug. If instead the price is proportional to the expected benefits, then the price of the drug would increase as specificity increases and the risk of zero benefit (or even harm) declines. If price increases in proportion to the expected benefit per patient who takes the drug, the producer's revenues are unaffected by genetic testing that narrows the size of the population treated.

In the USA, orphan drug status is a possible remedy for the disincentive for companies to invest in therapies for small patient populations. By granting market exclusivity, orphan drug status does permit higher prices for small populations. However, the criterion for awarding orphan status – a target population of 200,000, or fewer, patients in the USA – is quite arbitrary and often turns out to be inaccurate ex post. A better approach, which is roughly consistent with current cost-effectiveness norms, would be to permit prices that are proportional to expected effectiveness in the target population. This rewards producers in proportion to the social savings from more specific targeting, hence it would encourage appropriate investment in the use of pharmacogenetics to develop drugs with greater specificity that reduce waste to payers.

Genetic testing of symptomatic patients

Genetic testing of individuals who are symptomatic or at high risk of developing a disease is no different, from a policy perspective, from other forms of diagnostic testing. However, there are issues of confidentiality of medical records and prevention of their use for purposes other than treatment of the patient. Since patients who are tested can expect to benefit directly from more appropriate treatment or prevention of the disease, they have an incentive to give informed consent to the testing when they perceive that the benefits exceed the risks.

Genotyping of random populations

There is some scepticism over whether genetic testing of randomly-selected, asymptomatic populations is feasible and useful.

Two social benefits are claimed for such testing. Firstly, it would enable researchers to understand better the relationship between genetic make-up and disease, which in turn would aid drug discovery. Secondly, governments might be able to predict better, and hence provide for, the future healthcare needs of their populations, which would benefit consumers.

In theory, multivariate analysis applied to large populations could enhance our understanding of the correlation between genotypes and disease. The practical issue is the precision of the resulting estimates and how much of disease patterns would be explained. If the relationships between genes and diseases are complex, with most diseases involving several genes as well as environmental and patient-specific factors, then such analysis could yield many significant coefficients but low overall explanatory power. Results could be sensitive to choice of functional form and all the usual pitfalls of multivariate analysis. Thus, it is unclear how much such analysis would add to the information obtained from clinical trials – failures and successes – and other means of understanding the genetic basis of diseases.

Even if there were some significant gain in knowledge of the genetic basis of disease from random population genotyping, it is questionable whether this would be necessary or even useful to governments in planning healthcare expenditures. In order to predict future health needs of a population, the government would need to know that the future populationís genetic makeup would resemble that of the population used in the testing. Given population mobility, this could not be assumed, even if the test population were randomly selected. In fact, such random sampling could not be preserved if informed consent were required as a condition of participation and/or compensation offered to participants.

More generally, governments do not need to predict with great accuracy the disease mix of their populations. The major determinants of

overall demand for medical care are age and other readily observable demographic factors, and unpredictable changes in disease prevalence, such as HIV or the emergence of drug-resistant TB. The major shocks to health expenditures on the supply side have come from development of new technologies. Knowing the future disease mix without knowing the technologies that may be available to treat it might not help government very much, even if they did engage in long-term planning.

Thus, the major short-run beneficiaries of the information that might be available from population genotyping would be pharmaceutical companies, for whom such information might be useful in drug discovery and projecting demand. Note that the pharmaceutical company is concerned primary with global demand, which might be easier to project, whereas government needs to know location-specific demand, which would be much harder to predict given population mobility.

In the long run, benefits might accrue to consumers if reduced costs of drug discovery are passed on in lower prices and/or more innovations. However, genotyping may also entail a range of costs for individuals tested, through discrimination in insurance and possibly employment. There may be a case for providing compensation to those consumers who undergo testing by subsidizing their insurance rates if they fall into a high-risk class, since they are incurring risks, costs and inconvenience for the sake of the social good. Without such compensation, obtaining a random sample of volunteers to participate in population genotyping seems unlikely.

Since the information obtained through population genotyping is likely to be of most immediate value to the pharmaceutical industry, it would make sense to say that they should pay for it. However, this would raise issues about who would have access to the information, if participation by individual firms is voluntary.

Conclusions

Genomics offers great potential benefits, but current reimbursement strategies may be inadequate to encourage appropriate development

of long-lived and more specific gene therapies, which are two of the most immediate potential advantageous uses of genomics. Reimbursement needs to be approached much more flexibly in terms of breaking down the silo approach to the drug budget versus other services, thinking in terms of the longer-term benefits and being willing to pay the expected value of future, as well as present-day, benefits.

Genetic testing prior to treatment may fragment markets for medicines and lead, in effect, to more orphan drugs. One approach to overcoming this disincentive to invest in developing such therapies would be to permit new medicine prices that are proportional to their effectiveness.

The feasibility and usefulness of population genotyping remains to be demonstrated. However, in the short-term at least, the information it could yield would be of most value to the pharmaceutical industry: in drug discovery and projecting demand.

FURTHER READING

1 Kettler HE. *Updating the Cost of a New Chemical Entity.* Office of Health Economics, London, UK, 1999.

2 Marshall A. Getting the right drug into the right patient. *Nature Biotechnology* 1997;**15**:1249-52.

3 Martin PA, Thomas SM. The commercial development of gene therapy in Europe and the USA. *The STEEP Special Report* #5, Science Policy Research Unit, University of Sussex, UK, 1996; Chapters 5-6.

4 Martin PA, Thomas SM. The commercial development of gene therapy in Europe and the USA. *Human Gene Therapy* 1998;9:87-114.

Chapter 9
Panel discussion

Chairman: PROFESSOR EVERETT MENDELSOHN

Panel: PROFESSOR PATRICIA DANZON,
DR TREVOR JONES (Association of the British Pharmaceutical Industry)
MR ALASTAIR KENT

What should the government be doing?

MR KENT Governments need to define their long-term intentions. If governments shift responsibility for long-term health, wealth and welfare onto the individual, then the insurance industry needs to provide mechanisms to allow us to make arrangements. The implication of genetics, however, seems to be that the pool will be subdivided into cheap pools and expensive pools. If such a policy is to work, there must be mechanisms to support those who find themselves in expensive pools because of genetic predispositions. It is a matter of social justice and common sense.

PROFESSOR MENDELSOHN What do we want governments to do *in this specific area?* The easy answer is funding, avoiding discriminatory policies, and some degree of regulation where there are potential populations at risk, or risky activities being carried out. However, I am not sure that this provides the full answer of what we want governments to do at this stage.

PROFESSOR DANZON The question of how you deal with high-risk individuals in insurance pools is one that has already come up in a lot of different insurance markets. There are a number of pooling and cross-subsidy mechanisms for dealing with this. It is not something totally novel, just a new application.

The conflict between anonymity and the need to let individuals know potentially useful information

AUDIENCE COMMENT Perhaps one way of doing an anonymized study would be in the form of a census, sending out anonymous

questionnaires and cheek swabs. If we really want data for genomics, we have to separate it from the patients at the first instance. Only when we have the data will it be feasible for patients to get information from that. It will be difficult to do it in any other way.

DR JONES Various groups seek to use a database of that nature for different reasons: the discovery scientist or the academic for a very different reason perhaps than the pharmacovigilance person, the pharmacoeconomics person, or the carer group. We seem to be at a loss to create a database with sufficient encryption to allow proper and reasonable access on the known rules, in a way that allows us access to a broad enough database. The community has to determine what the basic unit of scrutiny would be and what breadth of study we would like to have and then, as more functions of the genes come through, make that available in different ways in a totally encrypted fashion.

MR KENT If we wait until we have a perfect system we will never move forward. It is important that we do not allow ourselves to be dazzled by what might be possible, or allow that to stop us from taking the first steps towards achieving at least measurable improvement for people who are currently sick and dying.

Is genetic information really different from medical information?

AUDIENCE COMMENT Genomics is moving quickly and there are tremendous opportunities there. If there are good products for the patients, then the patients will want them. Why do we think that there is a problem?

PROFESSOR DANZON It is not so much a problem as an opportunity for gaining information about the relationship between genetic code and disease. This would be a significant step forward. The question that has not been addressed is how much do we gain by population genotyping rather than by trying to get the same sort of information through other means?

DR JONES The drug industry is not giving up other kinds of research while it is trying to find out function in terms of genomes. However, if we knew more about the basis of the genomic variation in a particular disease we have heard about – breast cancer – it could allow us to think what we might do: (a) intervene; (b) counsel; and (c) choose therapy more accurately.

AUDIENCE COMMENT I do not see the distinction between genetic information and medical information. I am not sure what the new problem is, except that maybe genetic information potentially affects more people, but per individual the impact is the same. We had family histories before, so I do not see any substantive difference that genomics has raised that you did not have through family history.

MR KENT I would like to agree with you that, although in many instances genetic information is perceived to be different in practice it is not. Part of the problem is to do with the perception. To give an example, when the Association of British Insurers was developing its code for the handling of genetic data in insurance, it defined genetic data as that which arises from either a DNA-based or a chromosome-based analysis. If you arrive at a diagnosis as a result of an MRI scan, the condition is the same, the genetic implications are the same, but it falls outside the scope of the code. There is this almost mythical power given to DNA diagnostics. We need to break down the barrier; we need to demystify genetics, and take away some of its assumed power to predict.

AUDIENCE COMMENT There may be two reasons why genes are seen to be different. One is the way people perceive them. This is an important issue if we are talking about public policy consequences. The other reason is quantity – the type of scientific leaps we are talking about and the potential to transform the way we tackle illness are of a quantitatively different order to the way in which people talk about other things.

Orphan drugs

DR JONES The issue of orphan drugs is one of very significant consequence. A consortium of institutions has recently come together to work in partnership with industry on malaria, to bring candidate drugs through a virtual development process into a not-for-profit endeavour. This is a valuable model for areas where the pharmaceutical companies will not do the work because it diverts resources from more common diseases of mankind. It is not about having the cash; but is rather about having the resource and diverting it to another area. We are likely to find that genomic diversity identifies subsets of populations that we will not work on – for the same reason: the diversion of resources elsewhere. However, it will be some time before we are able to be that specific and identify these orphan diseases on the basis of genetics. At the moment we are doing it on the basis of simple numbers.

MR KENT From the patient's perspective, whether a rare disease or a common disease affects you, you have the same hope for health. All families want to benefit from advances in understanding the molecular basis of disease and the contributions that might make to the development of cures. There is a very important question of social justice that politicians are very keen to talk about but have yet to do something practical about achieving.

AUDIENCE COMMENT As some of these new therapies enter the market, we are beginning to see that they have somewhat higher costs than others. They also treat a specific population. To what extent do you think that this could increase the stigmatization of people with rare diseases? For example, if you have a rare disease that costs $30,000 a year and people become aware that this small group of patients is consuming a disproportionate amount of healthcare resources, does this force an explicit debate on rationing or does it create discrimination and problems within the social fabric?

MR KENT There is a risk that information about the genetic basis of disease may be used to stigmatize some sections of the population,

particularly if the condition that results from that genetic change is one that carries stigmatization with it (e.g. mental health problems). On the other hand, the last 20 or 30 years have seen a huge change in the way in which society responds to and perceives disabled people or people who are chronically sick. I see no evidence that advances in understanding of genetics will reverse that. As to the rationing question, there needs to be a debate to take into account not just the direct costs of the medication but also the indirect costs to the individual, the health service and to society of failing to provide that medication. It is a much more complicated equation than simply saying 'the price of the pill is the cost to society'.

The status of the market

PROFESSOR MENDELSOHN The market has been defined as a mover, shaker and shaper. What is the market good at? What things is it weak at? What areas need to be supplemented? Does the market deliver the best science, or is it a science they can convince people is good enough at the cost that is affordable? What other kinds of differentiations are there when we think of what we expect the market to be able to do? At one level we talk about an area of human activity that is highly rational and of high skill – pharmaceutical sciences, genomic sciences. At another level we talk about something that is amorphous and that we think has self-regulating powers. What does it look like to those of you who bear down hard on what it can and cannot do?

PROFESSOR DANZON On the question of how well markets take care of R&D: small companies actively engaged in gene therapy research demonstrate impressive growth. Having said that, the market is selective in financing only those activities where there is a reasonable chance of covering the costs of capital. There will be some conditions that are either too unusual, or too infrequently treated, or where the science is just too uncertain, and the market will not take care of it. That is where we should rely on public funding.

PROFESSOR MENDELSOHN In a sense you are saying we should leave the profit to the private sector companies, and ask the public to bear the cost for the non-profitable. US universities have decided they want their cut of the profitable research. Otherwise, as soon as an area becomes profitable, the scientists involved in pursuing it are snatched away.

DR JONES The genome revolution, whether pathogenomic or human genomic, opens up more specific targets and perhaps allows the market to be more discriminating about what it is prepared to focus on. The will and the motivation of the individual scientist, and the level of science at the moment, are not quite that clever – but we are getting there.

PROFESSOR DANZON There seem to be implications that profit for industry is bad, but it is because companies are pursuing profit incentives that these things are brought to market. However, the commercial viability will not be there for some of these technologies and this is where we know that the public sector will need to step in -– not necessarily public funding for specific indications, but making sure that the basis of public funding to things like the genome project or orphan drug legislation encourages appropriate levels of activity.

PROFESSOR MENDELSOHN In the computer industry, large companies fostered smaller ones to take the risks and then, when they proved good, bought them out. In a sense, you allow a 'nursery' to be created in which there is just enough capital put in, some of which is clearly lost, in order to keep the innovative capacity.

DR JONES This pattern has been matched in the pharmaceutical world. Most big pharmaceutical companies are liasing with 30 to 50 platform technologies or small-to-medium enterprises: some by direct equity ownership, some by sharing expertise, by access to facilities. That is a very healthy way forward. In a sense there is a 'risk altruism' out there.

GLOSSARY

Alleles: One of two or more alternative forms of a gene, only one of which can be represented in a chromosome.

Bases: The genetic information of DNA is contained in the sequence of four bases – adenine, guanine, thymine and cytosine – along the molecule. RNA contains the base uracil instead of thymine.

BRCA1 and BRCA2: Genes predisposing the carrier to the occurrence of breast cancer.

Chromosomes: The self-replicating genetic structures within cells. They are made up of a linear array of genes.

Cloning: The process of asexually producing a group of cells (clones), all genetically identical, from a single ancestor.

Coding: The process whereby the sequence of nucleotide bases that constitute the backbone of DNA are used to specify the structure of RNAs and proteins.

Codon: A group of three bases in a nucleic acid, coding for a particular amino acid or acting as a signal to stop or start a gene being ëreadí. Sometimes referred to as triplets.

Cystic fibrosis: A clinical condition caused by mutation in the CFTR gene – a gene that determines the production of a chloride channel in cells. The condition is characterized by the defective function of a number of organs, notably the lungs.

DNA (deoxyribonucleic acid): The material that encodes genetic information. It consists of a pair of chains made up of polynucleotides.

DNA banking: DNA banking involves storing some of a person's DNA, which is usually obtained from blood and then frozen. This DNA can be stored for many years.

DNA sequence: The relative order of codons in a piece of DNA.

Enzyme: A protein that catalyzes chemical reactions, primarily in one direction.

Eugenics: The use of genetic knowledge to implement racial policies.

Eukaryotic cells: Organisms made up of eukaryotic cells include plants, animals, fungi, and many unicellular organisms. These cells contain membrane-bounded compartments (organelles) with specialized functions, and a mesh of protein fibres (cytoskeleton) that contributes to cell shape and the management of intracellular traffic.

Familial: More common in a given family group than in the general population.

Functional analysis: The process whereby the function of the protein product of a given gene is elucidated.

Gene: The fundamental functional unit of heredity. It consists of DNA.

Gene expression: The process whereby the coded information contained in genes is transcribed into mRNA and then translated into protein within the cell.

Gene mapping: The determination of the relative positions of genes on a DNA molecule, usually a chromosome.

Gene product: The product, either RNA or protein, which results from the expression of a gene.

Gene therapy: The insertion of functional genes into a cell in which they are absent or defective.

Genetic code: The sequence of triplets of nucleotides in DNA which specify analogous nucleotide triplets in RNA and single amino acids in proteins.

Genetic counselling: The procedure by which patients and their families are given advice about the nature and consequences of inherited disorders.

Genetic sequencing: Determination of the order of the bases in a strand of DNA.

Genetics: The study of the pattern of inheritance of specific traits.

Genome: All the genes that constitute the genetic make-up of an organism.

Genomics: The study of the genome.

Genotype: The genetic make-up of the organism.

Genotypic disease classification: Identifying the genes responsible for causing certain diseases.

Germ line gene therapy: Gene therapy targeted at sex cells (sperm or eggs), such that genetic defects are not passed on to future generations.

Human Genome Project: The project, begun in 1986, to determine the genetic constitution of the human genome.

Marker: An identifiable physical location on a chromosome whose inheritance can be followed.

Mendelian laws: There are two copies of each allele in somatic cells, but the pairs separate when forming gametes so that each gamete contains only one copy. In sexual reproduction the alleles from two individuals are combined in all possible combinations in the offspring.

Microchips: Silicon-based micro-arrays for carrying out chemical reactions in large numbers and on a minute scale.

Monogenic disorder: A condition determined by a mutation in a single gene.

mRNA: Messenger or mRNA is a copy of the information carried by a gene on the DNA. The role of mRNA is to move the information contained in DNA to the 'translation machinery'.

Mutation: A chemical modification in the structure of a gene that leads to coding for altered, or no, product.

Nucleotides: The 'building blocks' from which nucleic acids are composed; each comprises a base, a sugar and a phosphate group.

Penetrance (of a gene): The extent to which a gene is implicated as a cause of a disease.

Pharmacogenomics: The use of genomics to facilitate and improve the predictability of clinical trials and other aspects of drug development.

Pharmacokinetics: The study of the movement of a drug through the body, from absorption, through distribution and metabolism, to elimination.

Phenotype: The reflection of the genome of an individual in the characteristics of the whole organism.

Polygenic disorder: A condition caused by the interaction of mutations in more than one gene.

Polymorphism: A condition in which a chromosome or genetic character occurs in more than one form, resulting in the coexistence of more than one morphological type in the same population.

Polynucleotides: Long chain of linked nucleotides, which make up DNA and RNA.

Population genomics: The study of the genetic make-up of entire populations.

Recombinant DNA: DNA that contains genes from different sources that have been combined by the techniques of genetic engineering rather than by breeding experiments.

RNA (ribonucleic acid): A nucleic acid, occurring in the nucleus and cytoplasm of cells, concerned with the synthesis of proteins.

Sequencing: The determination of the order of nucleotides in a gene or in an mRNA molecule, or the order of amino acids in a protein.

Somatic gene therapy: A way of introducing copies of 'healthy' genes into body cells. The disease will be controlled if the introduced genes work normally. The patient's DNA is not permanently changed.

Toxicology: The study of poisonous materials and their effects upon living organisms.

Recent OHE publications

Doctors, Economics and Clinical Practice Guidelines: Can they be Brought Together?
by David Eddy, 1999 (price £5.00)

Leadership, Change and Primary Care Groups
ed. Louise Locock, 1999 (price £5.00)

Public Involvement in Priority Setting
ed. Lisa Gold, 1999 (price £5.00)

Risk and Return in the Pharmaceutical Industry
eds. Jon Sussex and Nick Marchant, 1999 (price £10.00)

The New NHS: What Can We Learn from Managed Care in New Zealand and the US?
ed. Nick Goodwin, 1999 (price £5.00)

Trade Mark Legislation and the Pharmaceutical Industry
by Shelley Lane with Jeremy Phillips, 1999 (price £10.00)

Organisational Costs in the New NHS
by Bronwyn Croxson, 1999 (price £7.50)

Disease Management, the NHS and the Pharmaceutical Industry
by Anne Mason, Adrian Towse and Mike Drummond, 1999 (price £7.50)

Updating the Cost of a New Chemical Entity
by Hannah Kettler, 1999 (price £7.50)

Controlling NHS Expenditure: the Impact of Labour's NHS White Papers
by Jon Sussex, 1998 (price £5.00)

GP Commissioning Groups – the Nottingham Experience
by Stephen Earwicker, 1998 (price £5.00)

Our Certain Fate: Rationing in Health Care
by Alan Maynard and Karen Bloor, 1998 (price £5.00)

Competition through Innovation, Innovation through Competition
by Hannah Kettler, 1998 (price £7.50)

Biotechnology and the Economics of Discovery in the Pharmaceutical Industry
by Helen Simpson, 1998 (price £7.50)