The Drugs Don't Work: Expectations and the Shaping of Pharmacogenetics

Adam Hedgecoe and Paul Martin

Social Studies of Science 2003; 33; 327
DOI: 10.1177/03063127030333002

S|S|S

ABSTRACT This article examines one particular set of technologies arising from developments in human genetics, those aimed at improving the targeting, design and use of conventional small molecule drugs – pharmacogenetics. Much of the debate about the applications and consequences of pharmacogenetics has been highly speculative, since little or no working technology is yet on the market. This article provides a novel analysis of the development of pharmacogenetics, and the social and ethical issues it raises, based on the sociology of technological expectations. In particular, it outlines how two alternative visions for the development of the technology are being articulated and embedded in a range of heterogeneous discourses, artefacts, actor strategies and practices, including: competing scientific research agendas, experimental technologies, emerging industrial structures and new ethical discourses. Expectations of how pharmacogenetics might emerge in each of these arenas are actively shaping the trajectory of this nascent technology and its potential socio-economic consequences.

Keywords expectations; genetics; genomics; biotechnology; pharmaceutical; bioethics

The Drugs Don't Work:

Expectations and the Shaping of Pharmacogenetics

Adam Hedgecoe and Paul Martin

> 'Like it or not, we will soon have the ability to predict the variation in drug responsiveness of large numbers of individuals . . . A dramatic change in the practice of medicine over what we know today is certain. Each patient will have to be treated as the individual we already know he or she is.' Charles Cantor (1999: 288)

Introduction

Much of the discussion surrounding the promise of the Human Genome Project revolves around its effect on clinical practice and the development of 'genomic medicine' (Bell, 1998). The biggest impact so far has been on drug discovery and development, and this article examines the rise of one particular set of technologies aimed at improving the targeting, design and use of conventional small molecule drugs – pharmacogenetics.

Social Studies of Science **33/3(June 2003) 327–364**

[0306-3127(200306)33:3;327–364;033243]
www.sagepublications.com

In the business press over the past five years, there has been increasing discussion of pharmacogenetics and 'designer drugs', their potential impact on the pharmaceutical industry and clinical practice, as well as the social and ethical issues they raise (Cookson, 1997; Carr, 1998; Shook, 2001). Pharmacogenetics may have a number of important consequences, most notably the development of new commercial strategies based on the targeting of particular drugs to patient sub-populations, patient stratification and the geneticization of common diseases, as well as raising the traditional problems associated with genetic testing (discrimination, confidentiality, etc.). However, much of the debate about the consequences of the introduction of pharmacogenetics has been highly speculative and has approached questions in a piecemeal manner, since little or no working technology is yet on the market. In contrast, we aim to outline a novel analysis of the development of pharmacogenetics, and the social and ethical issues it raises, based on what might be called the sociology of technological expectations (see Brown et al., 2000). This will emphasize the co-construction of particular scientific visions of the development of the technology, novel research agendas and experimental technologies, emerging industrial structures and new ethical discourses. Expectations of how pharmacogenetics might emerge in each of these arenas are actively shaping the trajectory of this nascent technology and its potential socio-economic consequences.

Conceptual Approach

In trying to understand many of the developments in genetics and biotechnology social scientists, bioethicists and policymakers are faced with major problems as few, if any, technologies are widely used. In fact, one of the major criticisms levelled at the emerging field of genetic medicine is that it is surrounded by too much 'hype', speculation and unsubstantiated claims (e.g. Richards, 2001). As a consequence, the lack of any real substance to developments in this area makes it very difficult to accurately assess what might occur in the future and the ethical, social and legal consequences of different scenarios.

A novel approach will therefore be taken in this paper, based on a more critical understanding of how new technologies 'come into being'. Instead of seeing the speculative claims made about the future of pharmacogenetics as ephemeral and irrelevant, we argue that they are fundamental to the dynamic processes that create new socio-technical networks. Understanding the formation, mobilization and shape of these expectations or 'visions' is therefore central to the analysis of an emerging biotechnology.

A process of great uncertainty marks the early development of most new technologies and the search for formats, designs and applications which will both 'work' in technical terms and command support from potential developers and users. The analysis presented here will examine the key role of one kind of expectation, which we have called 'visions', in socially shaping emerging technological options and the design of physical

artefacts and commercial products. Three groups of actors are particularly important in this respect: researchers whose visions guide the design of clinical experiments and prototype technologies; commercial firms who embed these visions in business strategies and potential products; and bioethical commentators who discuss the potential future social and ethical problems raised by different applications.

Previous work on the sociology of technological expectations has looked at the activities of researchers and technicians (van Lente, 1993), policymakers (de Laat, 2000) and, to a lesser extent, the activities of firms (Martin, 1999). However, almost no attention has been paid to the role of bioethicists in constructing future scenarios and possible social problems. This paper will argue that the creation of a bioethical discourse around a controversial technology is important as it both provides a negotiation space to explore the socially acceptable limits of the technology and acts as a means of enrolling support from key actors. In this particular case, leading advocates of the technology have attempted to construct options which distance pharmacogenetics from the serious ethical problems which surround other forms of genetic testing.

We therefore focus not just on technical and commercial issues, but also on the way in which ethics discourses are an integral part of the construction and shaping of technology. The contingency of technological development means that the impact and consequence of a new technology will depend on which set of technological options are adopted – some will be rejected as being too controversial. In the social negotiation that shapes emerging options, ethics may be a decisive factor. As a result, our focus will be on the way in which new technologies, new industries and new ethical, legal and social problems are co-constructed during the process of technical change through the creation of competing visions.

Conceptual Framework and Methodology

In the last 15 years a new sociology of technology has emerged, based on a critique of technological determinism (Bijker et al., 1987; MacKenzie & Wajcman, 1999). Instead of innovation and technological change being driven by an innate technical logic, the development of new technologies is seen as a fundamentally social process open to sociological analysis.

A number of different theoretical perspectives have been used to examine the creation of new technologies, including actor-network theory (ANT) (Callon, 1987), the social construction of technology (SCOT) (Bijker, 1995) and the analysis of large technical systems (Hughes, 1987). Although each takes a distinct approach they share several common features, notably the idea that the development of a new technology involves a range of heterogeneous social, technical, economic and political processes. In addition, these approaches argue that new knowledge is co-produced at the same time as new technologies and new socio-technical relations, through a process of mutual shaping. This paper will draw on the following concepts from within the sociology of technology:

The construction of socio-technical networks – Successfully introducing new technologies into routine use requires the alignment of a range of heterogeneous human and non-human actors and artefacts into stable socio-technical networks (Callon, 1987; Bijker, 1995). To achieve this, network builders might be involved in, for example, the creation of new social practices, new companies and new forms of state regulation, which emerge together during innovation. Network formation therefore requires the enrolment of various actors, the formation of alliances and the mobilizing of different social, technical and economic resources.

The social shaping of technology – As an integral part of the creation of stable socio-technical networks the emerging technology is socially shaped to reflect the activities and interests of the groups involved in the innovation process. This is mediated through the design, testing, selection and redesign of the various technological options and may result in the physical form of the technology changing dramatically over time. For example, as new groups of actors join the emerging network, they may favour particular options over others and shape the future direction of research and design (Bijker, 1995). Through an examination of the competing technological options, the changing designs and applications, and the role of the various groups involved, it thus becomes possible to analyse the physical development of a new technology in sociological terms.

The creation of visions and the enrolment of support – An important process in the formation of networks is the creation of particular promises, 'visions' or expectations for how the technology might be used in practice and sold as a commodity (van Lente, 1993; Martin, 1999; Brown et al., 2000). For example, in van Lente's study of the development of Tenax, a new paper for insulating high-voltage cables, the scientists involved in the project created the expectation that the technology was a way of solving technical questions of electricity transmission, coping with increased electricity demand and improving market share for their company. These expectations subsequently shaped the behaviour of key actors and their development of the technology.

During the early stages of the introduction of a radically new technology a number of competing expectations for how it might be used often coexist (Pinch & Bijker, 1984). These may be associated with the formation of different network configurations and the emergence of alternative designs or technological options. With respect to the formation of these networks, van Lente has asked 'What is the role of expectations in the alignment of heterogeneous elements that together shape technology?' (van Lente, 1993: 34). Using case studies of three 'promising technologies' he demonstrates that expectation statements are a resource for actors involved in innovation, in that they can help to:

- *legitimize*, justify, back their arguments, give reasons in general;
- *mobilize* funds, attention of other actors;
- allow decision-making and *reduce the uncertainty* inherent in technological developments (van Lente, 1993: 187, original emphasis).

Expectations therefore simultaneously act as a means of enrolling support and resources into the emerging socio-technical network, enabling interactions between actors and guiding the physical design of artefacts. They may also form part of a new set of cognitive structures that both enable and affect the development of the technology (Bijker, 1995).

In general, most of the work on the sociology of technological expectations has focused on what might be called the articulation of visions or promises. For van Lente these are statements uttered in public or written down. Other authors have analysed the representation of expectations (Grin & Grunwald, 2000; Michael, 2000), their narrative construction (Deuten & Rip, 2000) and metaphors of the future (Wyatt, 2000). In contrast, our emphasis will be on both the articulation of expectations in scientific and bioethical discourse in the form of specific visions, and their embodiment in the design of experiments and the formation of new biotechnology companies as a result of the decisions made by innovators. Visions therefore constitute a particular class of expectation which both project and anticipate how the future might emerge, and provide a strategic framework for actors as they attempt to construct particular socio-technical networks. The deployment of this concept will help us to examine the way in which expectations are translated from discursive structures into a heterogeneous set of professional practices, social organizations and physical artefacts.

Much of the current discussion concerning both the science and economics of pharmacogenetics is speculative and differing options for its development can be clearly identified. This provides a good opportunity to chart the way in which an emerging discipline, set of technologies and industrial structures are being shaped by different visions during their early development (van Lente & Rip, 1998; Guice, 1999).

An important technique in the building of these visions is the formation of 'coalition[s] representing various elements of a prospective technical order' (Guice, 1999: 82). Such coalitions can clearly be seen in the alliances being formed between various industry actors and the collaborations between drug companies and academic researchers. Some commentators suggest that pharmacogenetics is the testing grounds for a new research paradigm which revolves around 'the collaboration between biotechnology companies, academic researchers and clinicians' (Pfost et al., 2000: 334). As a consequence, the development of this technology provides a good site for analysing the dynamic relationship between visions and network formation.

We use these theoretical tools to analyse the development of pharmacogenetics as a scientific concept, an experimental research practice, an emerging industrial sector and a bioethics discourse. The next section provides a brief history of pharmacogenetics from the 1950s until the present day and is based on a historical review of the scientific literature in this field. Then we describe the two main visions for pharmacogenetics being articulated by the scientific proponents of the technology. One is focused on the genetic basis of adverse drug reactions and the other

revolves around the role of disease-related genes in determining drug response. Next we examine the industrial development of pharmacogenetics within the biotechnology and pharmaceutical industry, and the articulation of the two visions already identified. Finally we describe the bioethics discourse emerging around these two main technological options and outline the different ethical, legal and social problems associated with each. The conclusion draws together the different strands of the argument and offers some sociological reflections about the role of visions in shaping technologies, industries and ethical problems.

From Pharmacogenetics to Pharmacogenomics

Origins and Early Development

Traditionally pharmaceutical companies have adopted a 'one-size-fits-all' principle with regard to different people's reactions to drugs (e.g. Liggett, 2001). Although acknowledging variations in dosage (because of age, sex and body size) the general approach has been the development of mass-market therapies based on the assumption that everyone responds in the same way. Yet research scientists have long acknowledged genetic variation in drug response. Friedrich Vogel first introduced the term 'pharmacogenetics' in 1959, following groundbreaking work by Arno Motulsky two years earlier (Nebert, 1997; see Weber [2001] for a detailed historical review).

Around this time, a number of important discoveries were made, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency in 1956 and the genetic variation in ethanol metabolism in 1964 (Kalow, 1990). Until the late 1980s, pharmacogenetics expanded slowly as a discipline, with specific drug–gene relationships becoming clear as and when investigators came across them, rather than there being any active search for such links. To a large extent, this was the result of relying on methods from classical genetics: individual studies followed by family and population analysis (Meyer, 1990).

Despite this long history, at an industry level there has been a profound reluctance to admit the extent of genetic variation and its effect on drug response (Corrigan, 2002; Glaser, 1998). This may be due to the fact that very little could be done, but another reason is the understandable unwillingness of the industry to admit to the huge scale and very real risks posed by genetically based adverse drug reactions (ADRs) (Abraham, 1997).

The Molecular Turn

This situation started to change with the emergence of molecular biology, which provided the means for improved investigation of the genetics of drug response. The 'molecular turn' in pharmacogenetics can be dated to 1988, when Frank Gonzalez and his colleagues isolated several alleles of

the human CYP2D6 gene, part of the P450 cytochrome complex of genes responsible for drug metabolism in the liver (Gonzalez et al., 1988). This study opened the field up to the 'new genetics'; alleles of the P450 complex are associated with adverse drug reactions caused by several products, and have thus become a popular focus for contemporary research. Coming into the 1990s, a number of new technologies such as polymerase chain reaction and high-throughput sequencing gave scientists greater understanding of genetic variation and increased the interest in pharmacogenetic studies. In addition to these technical developments, there were also ideological changes which, in the wake of the Human Genome Project, started to reconstruct medicine in terms of genetics (Bell, 1998). Perhaps most importantly, pharmacogenetics finally aroused the interest of the pharmaceutical industry, perfectly combining the promise of the new genetic technologies with a focus on drug discovery and development. Around this time a new term began to be used to describe the discipline: pharmacogenomics. This concept has a variety of meanings, although most centre on the use of genome-wide screening for pharmacogenetic reactions (Hedgecoe, 2003). In order to avoid confusion, this article tends to use the term pharmacogenetics, although many of the authors cited prefer pharmacogenomics.

Following the genome project and the development of powerful new gene sequencing and analysis technologies, a new form of research known as association genetics has started to transform the study of the relationship between genes and disease. Proponents claim that this new 'functional genomics' has enabled the unravelling of diseases at the genetic level and the identification of disease-associated genes. In addition, association studies allow the study of the relationship between particular genetic markers and specific reactions to drugs, without having to do traditional family-based linkage analysis.

In terms of testing, new technologies such as DNA arrays (also called 'gene chips') are being developed to allow the cheap, fast and large-scale screening of populations for genetic markers which are correlated to either positive or negative reactions to specific drugs (Evans & Relling, 1999).[1] Although still in its infancy, one such DNA array targeting the pharmacogenetically important cytochrome P450 complex is already commercially available (Sadée, 1999) and in the next few years more are expected to enter the market. For many in the field this will open the door to the routine use of pharmacogenetic tests in the clinic. However, before this can be done the validity and clinical utility of the technology will have to be demonstrated, and commercially attractive products and services will need to be developed. Although the general promise of pharmacogenetics became apparent in the mid-1990s, working applications have remained elusive. The following section will examine a number of specific visions for the scientific and clinical development of pharmacogenetics and explore how these are being used to design clinical experiments and construct future applications.

Scientific Visions of Pharmacogenetics

During the development of new medical technologies, researchers are involved in both designing and testing particular technical options and seeing if they can be incorporated into routine clinical practice (Martin, 1999). This process often takes a long time and involves heavy investment in human testing before even a prototype can be developed. The creation of visions for how a new medical technology might be used to treat patients can play an important part in this process. In particular, advocates of new technologies use visions to get access to funding, design research agendas and clinical experiments, and start the development of new drugs (Martin, 1999). An examination of the different visions surrounding the early stages of innovation can therefore shed light on these dynamic processes of enrolment and alignment. In terms of van Lente's ideas, these scientific visions 'legitimize' the concept of pharmacogenetics, justifying the research that has been carried out and providing a rational basis for further work. Whether it is because pharmacogenetics will reduce the harm caused by ADRs, or because it reveals the true mechanism of the underlying pathology, the visions painted in the scientific literature provide the starting point for any further developments.

Following a detailed review of the scientific and clinical research literature we have identified two main visions for the development of pharmacogenetics, with different authors trying to shape the discipline as a whole along different lines. In the first vision, pharmacogenetic variations are focused on drug metabolism and are independent of disease-causing genes. Here the emphasis is on the safety of a drug. In the second, the introduction of pharmacogenetics is centred on the genes associated with disease and will lead to changes in how common diseases are classified. Here the emphasis is on drug efficacy. The following sections examine each of these in more detail, describing how they are being articulated and embodied in practice with respect to both the use of established (already licensed) pharmaceutical products and the development of new medicines.

It might be tempting to view these visions in terms of 'controversy studies', which are such a reliable approach to the sociology of science and technology. We think this would be a mistake, since it would overstate the antagonism or competition between the two visions and their proponents. Both these visions rely on many of the same technologies (sequencing, DNA arrays, SNP analysis), and they overlap to a certain degree; there are many articles that discuss both approaches (e.g. Akhtar, 2002; Ensom et al., 2001; Evans & Relling, 1999; Ginsburg & McCarthy, 2001; Ingelman-Sundberg, 2001; Kleyn and Vesell, 1998; Mancinelli et al., 2000; Marshall, 1997; Norton, 2001; Persing & Cheek, 2000; Rusnak et al., 2001). However, while these visions can coexist, they are analytically and discursively discrete, are embodied in different research practices, shape firm strategies in distinct ways and have particular ethical features. Our point is

to show that these differences exist, and suggest that they can best be explained in terms of constructing one of these two visions.

A Vision of Classical Pharmacogenetics – ADRs and Disease Independence

The first vision is based on the notion that pharmacogenetics is mainly concerned with understanding how drugs are metabolized, rather than understanding the genetic basis of a particular disease (Housman & Ledly, 1998; Kalow, 2001; Meyer, 2000; Roses, 2000a, 2000b; Sadée, 1999; Schmitz et al., 2001; Steimer & Potter, 2002; Weber, 2001; Wolf et al., 2000). It therefore focuses on adverse reactions to compounds, the genetic variations in genes responsible for drug metabolism (pharmacokinetics and toxicology) and the use of this data as a means of improving the safety of medicines.

Articulating the Vision. A vital actor in this vision is the set of genes that code for the cytochrome P450s, a family of enzymes that operate in the liver. These enzymes are responsible for the initial metabolism of many prescription drugs, and variations in the DNA (genotype) coding for them result in wide differences in how drugs are metabolized. For example, patients with an amplification of one of the P450 genes (CYP2D6) are classed as ultra-rapid metabolizers. This means that their body processes some drugs so quickly that no therapeutic effect is gained; in the case of some treatments, they might have to be prescribed 50 times the dose given to other patients (Wolf et al., 2000: 988). CYP2D6 alone is thought to be involved in the metabolism of about one-quarter of all prescription drugs, and alterations in this gene can lead to therapeutic failure, adverse effects and toxicity in particular subgroups of patient undergoing treatment. This is a major problem as over 30% of drugs that enter clinical trials are withdrawn from further development due to unfavourable drug metabolism. The P450s are widely cited by proponents of this vision (without exception; their well-researched nature makes them a reliable basis for the construction of this vision.

Another example used in articulating this vision are polymorphisms in the gene that codes for the enzyme thiopurine methyltransferase (TPMT), which is involved in the metabolism of a number of drugs commonly used to combat childhood leukaemia. Slow metabolizers of these drugs require up to one-fifteenth of the normal dose (to avoid a potentially fatal ADR), while fast metabolizers require much higher doses for effective treatment (Krynetski & Evans, 1999; Meyer, 2000).

What links the authors promoting this vision of pharmacogenetics is the focus on pharmacokinetics (drug metabolism) and in particular the P450 genes, as well as an emphasis on improving the safety of prescribing. For these authors: 'The aim of pharmacogenomics is to decrease adverse responses to therapy through determining new therapeutic targets and genetic polymorphisms that effect drug specificity and toxicity' (Wieczorek & Tsongalis, 2001: 1).

From a purely practical viewpoint, it is not hard to see how pharmaceutical companies could have an interest in developing a technology which, in a litigious environment like the US healthcare sector, may reduce the number of patients who have cause to sue drug manufacturers. Of course, the identification of pharmacogenetic reactions may also lead to a situation where companies that do not employ this technology are sued for endangering patients. This has already happened in the class action brought against SmithKline Beecham in late 1999, which alleges that the LYMErix vaccine for Lyme's disease reacts with the HLA-DR4+ polymorphism (present in up to 30% of the population) to produce autoimmune arthritis. The claimants suggest that the company knew about this pharmacogenetic reaction, but marketed the drug regardless (Wortman, 2001).

A key element of this vision is the separation of disease genetics from drug genetics; a genetic test in this case does not reveal anything about the prognosis or even the cause of the condition treated by the drug concerned. This serves a central purpose, as it roots the emerging discipline of modern pharmacogenetics in a well-tested and widely recognized biological effect: the metabolism of drugs by the P450 genes. Even sceptics about the role of genes in medicine would have difficulty casting doubt on the idea that many aspects of drug metabolism are genetically influenced.

How Might this Option be Integrated into Clinical Practice? In practice many large pharmaceutical companies already classify participants of their clinical trials as fast, slow or normal drug metabolizers using P450 genotyping, but in the clinical setting such testing is still very rare (Sadée, 1999). Clinical testing might involve the diagnostic genotyping of patients before they are prescribed drugs; those with the 'wrong' genotype would not be given that therapy, or would be prescribed an alternative dose. Genotyping of this sort has already become a practice in some (mainly cancer) centres, to reduce the risk of ADRs (Sadée, 1999).

Various proposals exist for the organization of testing, including third-party services, local hospital-based testing and 'desktop' devices in the physician's office. If such technology was available to identify those at risk of an ADR from a given drug, regulatory authorities might come under pressure to change the labelling of the drug to restrict its use to particular groups. In general, however, the introduction of this option for pharmacogenetics would not necessarily have a significant impact on established medical practices, but would simply bring in an element of pre-prescribing diagnosis. The UK Department of Health has recently carried out a study suggesting that P450 screening could be implemented in the near future, and would be cost effective if targeted at high-risk groups and key clinical areas (DoH, 2000).

The Development of New Drugs. Within this vision less attention has been given to how pharmacogenetics might be used to help develop new drugs. Instead the main focus here has been on the 'rescue' of drugs in development which have failed in late stage (phase II/III) clinical trials. Some

commentators have suggested that if an effective drug fails to get marketing approval because it induces a genetically based ADR in a small percentage of patients, the trial could be redone using a pre-screening of the patient population to eliminate people at risk of ADRs (Regalado, 1999). If it was shown to be safe and effective in this group, the drug could then be licensed for use only with that particular genotype and with a clear warning on the label that people with the 'wrong' genotype could not be given the product. This might significantly increase the chance of drugs gaining marketing approval, but at the expense of restricting their use and a compulsory tie into diagnostic genotyping.

The way in which this vision is being articulated by its scientific advocates therefore involves the simultaneous construction of particular problems to be solved (i.e. drug safety), the solution of the ethical problems associated with genetic testing, and how the technology might be used to increase the profitability of the pharmaceutical industry through drug rescue. It therefore provides a rhetorical justification for the pursuit of a particular research strategy, but also offers a means of overcoming potential resistance and guides the development of business strategy.

A Vision of Disease Dependent Pharmacogenetics

The 'disease dependent' vision of pharmacogenetics aims to identify associations between genetic markers for drug response and those genes directly involved in the development of different forms of pathology (e.g. Anderson et al., 1999; Bell, 1997; Lichter & Kurth, 1997; Lindpaintner, 1999; Lindpaintner et al., 2001; Moyses, 1999; Persidis, 1998a, 1998b).

Articulating the Vision. If a central theme of the ADR vision of pharmacogenetics is a concern with drug metabolism and safety, then the core of the disease dependent view is 'patient stratification' and improved efficacy. This is based on the idea that many common diseases are, despite their phenotypic or clinical homogeneity, caused by a number of different genetic changes:

> There is little doubt that many of our current disease definitions such as cancer, diabetes and heart disease are actually very different diseases at the molecular level that manifest themselves phenotypically in similar ways. (Persidis, 1998a: 210)

Conditions can therefore be reclassified in terms of specific genes or gene defects, linking variation in disease progression to variation in drug reaction, ensuring that one 'outcome from the pharmacogenetics approach is a redefinition of what a disease is at the molecular level' (Persidis, 1998a: 210).

Since diseases can be split into a number of sub-conditions (on the basis of different genetic factors), patients can be separated into different groups according to this new classification, focusing on finding those people who can be classed as 'good responders'. In this vision, such division or patient stratification does not happen only at the level of the

clinic, but further back in the drug development process, 'allowing more specific trials for single disease entities, eliminating some of the problems associated with enrolment of heterogeneous patients' (Kurth, 2000: 227). Stratification therefore offers the prospect of a reduction in the numbers of patients entered for clinical trials, and hence a financial saving for companies (Anderson et al., 1999).

How Might this Option be Integrated into Clinical Practice? In practical terms this particular technical vision might be integrated into the clinic by much greater use of gene-based diagnostics to help classify the disease suffered by a patient at a molecular level. In effect a 'molecular diagnosis' would be made, which would then form the basis for clinical management, including drug therapy, as a means of improving the efficacy of treatment. As with the first vision, genotyping might be organized in a number of ways, but the effect on diagnostic practice would be much more profound than simply screening for ADRs. In this case, genetic analysis would become a central and routine part of the treatment of many common diseases:

> A pharmacogenomic model of drug prescription . . . would start with the analysis of the patient's . . . DNA . . . A limited genome scan using preselected SNPs markers would be run . . . The patient's marker pattern would be compared with patterns of efficacy established for drugs that are generally prescribed for the disease being treated . . . [This] . . . would result in selection of a drug and dose which would be optimal for the patient. (Anderson et al., 1999: 266–67)

Painting such a scenario brings this vision into sharper focus, allowing clinicians and policymakers to see how pharmacogenetics might operate in the clinical encounter.

Proponents of this vision claim that because of such molecular diagnosis, doctors will be able to treat patients' 'real' illness, instead of simply dealing with a vague collection of symptoms that could correspond to a number of distinct conditions. This reclassifying role seems likely, especially since it has already occurred in a number of conditions, most notably diabetes (Bell, 1998; Hedgecoe, 2002).

Furthermore, there have already been a number of clinical research studies designed to emphasize the potential for pharmacogenetics to significantly redefine common diseases in relation to established drug therapies. In the same way as the previous vision heavily cited studies of the cytochrome P450s to root itself in solid research, so the disease-centred vision tends to cite some of the following studies, to 'prove' that pharmacogenetics can tell us something about underlying disease mechanisms.

A key point to note about some of these examples is not just that pharmacogenetics can lead to the stratification of disease along genetic grounds (e.g. asthma, schizophrenia), but that these stratifications can also map onto divisions in prognosis and clinical development of disease (e.g. Alzheimer's, heart disease and cancer). For example, in a widely cited study Kuivenhoven et al., 1998) showed that variations in the genetic locus

responsible for the cholesteryl ester transfer protein (CETP) were related to variations in response to the drug prevastatin, commonly used to treat high cholesterol levels. However, the most important finding was that the mutation associated with the greatest risk of heart attack (TaqIB) is also associated with the most positive response to treatment. This means that a genetic test to decide on whether to prescribe prevastatin is also a prognostic test for the type and severity of heart disease a patient might develop. In this way some pharmacogenetic tests overlap with diagnostic genetic tests.

TABLE 1
Clinical Studies where Disease-Associated Markers Indicate Drug Response

Disease	Gene marker	Drug	Comments	Reference
Alzheimer's	APOE	Cholinesterase inhibitors	Carriers of APOE4 allele have reduced effect from drug	Poirier et al., 1995*
Atherosclerosis	Cholesteryl ester transfer protein (CETP) gene	Prevastatin	Mutation TaqIB associated with greatest risk of heart attack also associated with most positive response to treatment	Kuivenhoven et al., 1998
Ovarian cancer	P53	Common anti-cancer drugs	P53 makes tumours chemoresistant: more aggressive treatment required	Shelling, 1997
Asthma	ALOX5 promoter locus	ABT-761	Carriers of certain variations in gene showed improved response	Drazen et al., 1999
Breast cancer	HER2 overexpression	Herceptin	Herceptin, a monoclonal antibody, only effective in tumours overexpressing the HER2 protein, which have a worse prognosis	Cobleigh et al., 1999
Schizophrenia	Serotonin neurotransmitter receptor 2A	Clozapine	Certain alleles (carried by ~50% of pop.) lead to improved response to drug	Arranz et al., 2000

* We are aware that the link between Tacrine and APOE4 is regarded with suspicion by many psychiatric geneticists, and the results of this particular paper have been largely rejected. Yet this research is still cited in reviews of the literature, and thus plays an important role in the construction of this vision.

In the overall strategy associated with this vision of pharmacogenetics, research does not therefore have to chase after comprehensive explanations of the mechanisms underlying common diseases in order to redefine those diseases in genetic terms, provide a prognosis or predict the likely effect of therapy. If a strong correlation between a genetic marker and drug response or disease prognosis can be demonstrated, then this will have immediate clinical value, even if the biology of this link remains a mystery. This opens up the prospect of the rapid introduction of routine clinical genetic testing based on nothing more than a statistical association between a marker and the response to a particular drug.

The Development of New Drugs. In terms of new drug development, the stratification of diseases at the molecular level might enable the possibility of designing new drugs aimed at specific genotypes. In this way companies may be able to develop therapies for highly targeted patient groups, which may be unresponsive or react adversely to current treatments.

> In the context of drug development, the segmentation of patient populations according to genotype has the potential to define groups of individuals with the most beneficial therapeutic ratio. Since the size of clinical studies is affected by the magnitude of the therapeutic effect, increasing the proportion of responders should allow smaller and faster trials. Such small 'smart' studies will provide a counterbalance to the large 'dumb' studies used to detect small treatment effects in large populations. (Moyses, 1999: 199)

One consequence of such an approach would be the segmentation of drug markets and the creation of specific therapeutic niches. While this might improve therapy for some people, it could also lead to a situation where it becomes commercially unattractive to create new drugs for small numbers of people with rare 'unresponsive' genotypes.

Rather than being based on the construction of new problems to be solved (i.e. ADRs) the way in which this vision is being articulated by its scientific supporters focuses on the potential for creating a new type of medicine. Here the emphasis lies on new and powerful ways of seeing and diagnosing disease, the creation of a more scientific medicine, potential improvements in patient care and reducing the costs of drug development. As with the previous example, this vision provides a rhetorical justification for the pursuit of a particular research agenda, but also offers a guide to the way in which health services and professional practice should evolve, and strategies to improve the profitability of the pharmaceutical industry.

The creation of these two visions is not just a discursive or cognitive phenomenon, but is also embodied in research agendas and the design of clinical experiments. A commitment to a particular vision not only implies a judgement about the benefits of a certain scientific strategy, but also a commitment to: specific types of research questions (safety vs efficacy; prescribing practices (screening for ADRs vs a 'molecular diagnosis'; drug development strategies (drug rescue vs targeting new drugs at specific genotypes; and even definitions of disease (e.g. disease stratification).

The successful demonstration of the utility of these new ways of using and developing drugs in research settings gives weight to the initial claims made for the development of pharmacogenetics in general. However, these visions will only translate into widespread clinical practice if the pharmaceutical industry embraces them and if the important ethical, legal and social problems they raise can be successfully negotiated. The next section will examine the way in which pharmacogenetics has stimulated the creation of a new industrial sector and how these different visions are guiding the formation of company strategies for the commercialization of particular technical options.

The Creation of a Pharmacogenetics Industry: The Integration of Genomics into the Drug Development Process

The success or failure of pharmacogenetics will ultimately depend on how well it is integrated into the pharmaceutical industry. Drug companies drive the development and adoption of new medicines and constitute the most powerful group supporting the creation of this technology. They have already committed considerable investment to this area, with advocates predicting that the rise of pharmacogenetics will be beneficial to industry, clinicians and patients (Regalado, 1999). For the patient, it is claimed that pharmacogenetics will allow doctors to prescribe drugs more effectively and reduce the chances of adverse reaction. However, the greatest promise is for industry, where it is hoped that the technology will result in increased sales, cheaper and faster clinical trials and the 'rehabilitation' of drugs which have been removed from the market after being considered dangerous (Sadée, 1999).

Companies are therefore involved in developing commercial plans to exploit the promise of pharmacogenetics and translating the scientific visions described above into business and technology strategies for the creation of new products and services. We identify distinct commercial strategies based on each of the two main visions, which have been used to guide internal investment decisions, create inter-firm collaborations and attract finance from investors. Furthermore, these visions are also embodied in the physical design of the products and services being developed by firms. In this sense, visions serve as strategic resources to 'mobilize' funds and enrol the support of other actors to the technology. While the visions articulated in the scientific literature legitimize pharmacogenetics, the actions of industry bring those visions to life, both in terms of actual (or future products) and in the corporate literature and business plans based around these competing approaches.

The Structure of the Pharmacogenetics Industry

As with many other biomedical technologies, such as diagnostic imaging or gene therapy, the development of a new technology has both resulted in, and depended on, the creation of a new set of industrial actors (Blume, 1992; Martin, 2001b). In this sense, new industries are co-constructed

during the process of innovation and socio-technical network formation. The destiny of an emerging biotechnology depends on the existence of firms which have invested heavily or been established solely to exploit it, as only companies have the financial, managerial and commercial resources to bring new drugs to market. At the same time, the fate of these firms is intimately tied to the success of the technology. If a technology fails, so do many firms aligned with it.

Pharmacogenetics is no exception to this general pattern and a new industrial sector has been created in the last five years to exploit the commercial opportunities promised by the technology. The results of a comprehensive survey of the North American and European biotechnology industries[2] identified two distinct groups of companies involved in the development of pharmacogenetic technology: small biotechnology firms dedicated to creating 'platform technologies' for the analysis of the genetic basis of drug response, and large pharmaceutical companies involved in clinical drug development. Tables 2 and 3 summarize the results of this survey and give a list of both these groups of companies. This classification is, of course, well known within the pharmaceutical industry and is used by annual reviews of the industry as a useful way of comparing different kinds of firms. Our point is that these differences do not just represent firms' age, size or cash flow, but also their research strategies and attitude towards the two visions outlined above.

In total, some 48 biotechnology firms and 12 large pharmaceutical companies have started to develop pharmacogenetic technology. American firms dominate and the majority of the biotechnology start-ups have been founded in the last five years. Most firms are pursuing a range of different strategies and it is beyond the scope of this paper to analyse them all in detail. However, six of the leading biotechnology firms in the field of pharmacogenetics have been identified (three European, three US) and information about their strategies, products/services and collaborations is presented in Table 4; all are using large genetic databases and the techniques of association genetics in combination with SNPs to locate markers correlated with particular drug responses.

Visions of Pharmacogenetics Embedded in the Strategies of Leading Firms

Closer examination of the leading firms' technology and business plans shows how the two visions described above are being embedded in firm strategies for the commercial development of pharmacogenetics. Analysing a range of publicly available documents, including annual reports, websites, press releases, US Securities and Exchange Commission (SEC) filings and press stories, it was striking how important the articulation of a commercial strategy based on one or other of these visions was to these companies. Just as scientific investigators use the creation of expectation to enrol support and resources, firms appear to deploy visions of how their technology might be made profitable in order to attract investors, collaborators and customers. The creation and marketing of these visions is an

important part of the work involved in starting a new biotech firm (Martin, 2001b).

Firm Strategies Focusing on Finding Genetic Markers Associated with ADRs. Four of the leading firms described in Table 4 are involved in developing technology based on the ADR-centred vision of pharmacogenomics with

TABLE 2
Biotechnology Firms Developing Pharmacogenetics Technology

US (41 firms)	Acadia	InforMax
	Affymetrix	Interleukin
	Celera	Lynx
	Clingenix	MassTrace
	CuraGen/454 Corporation	Molecular Innovations
		Molecular Simulations
	DiaDexus	Myriad Genetics
	EmerGen	Nanogen
	Exelixis	Orchid BioSciences
	First Genetic Trust	Millennium Predictive Medicine
	Genome Therapeutics	
	Genomica	Pharmagene
	Genaissance Pharmaceuticals	PharmaSeq
		PPD Pharmaco
	Genelabs Technologies	Quintiles Transnational
	Genelex	Rosetta Inpharmatics
	Gene Logic	Sequenom
	GeneticXchange	Signalgene
	Genome Pharmaceuticals	Third Wave Technologies
		Transgenomic
	Genometrix	Variagenics
	Illumina	WITA Proteomics
	Incyte	
Europe (7 firms)	DeCODE Genetics	Genset
	ExonHit	Oxagen
	Gaifar	Oxford Glycosciences
	Gemini Genomics	

TABLE 3
Large Pharmaceutical Companies Developing Pharmacogenetics Technology

US	Europe
Abbott	Amersham Pharmacia
Bristol Myers Squibb	AstraZeneca
Genzyme	Bayer
Janssen	Glaxo SmithKline
Pfizer	Hoffman-La Roche
Warner Lambert	Novartis

TABLE 4
The Strategies of Leading Biotechnology Firms Developing Pharmacogenetics

Name	Location	No. of staff	Strategy	Products/services	Alliances related to pharmacogenetics
CuraGen	US	300	Identification of genetic markers linked to drug response – emphasis on safety (ADRs)	Sell data to improve clinical development (trials) of new drugs – aim to reduce negative response/ toxicity. Develop diagnostics to detect ADRs	Bayer, Ono Pharmaceuticals
DeCODE Genetics (Encode subsidiary)	Iceland	500	Identification of genetic markers linked to drug response – emphasis on safety (ADRs)	Develop diagnostics to identify patients most at risk of ADRs to commonly prescribed medicines	Affymetrix, Hoffmann-La Roche
Gemini Genomics	UK	N/a	Identification of genetic markers linked to drug response – emphasis on safety (ADRs)	Sell data to improve clinical development (trials). Patents on CYP alleles and licensing use for development of diagnostics to detect ADRs	–

Genaissance Pharmaceuticals	US	120	Identifying genetic markers linked to response to commonly prescribed medicines – emphasis on efficacy (good responders)	Sell data to improve clinical development (trials) of new drugs aimed at good responders and develop diagnostics to improve marketing of licensed products to good responders	AstraZeneca, Gene Logic, Janssen, Pfizer, Seqenom
Genset	France	530	Identifying genetic markers linked to drug response – emphasis on safety (ADRs)	Sell data to identify people at risk of, and co-developing diagnostics to screen for, ADRs from licensed drugs. Selling data to target new drug development at people at low risk of ADRs	Abbott, Pharmacia and Upjohn, Sanofi-Synthelabo
Variagenics*	US	N/a	Identifying genetic markers linked to drug response – emphasis on efficacy (good responders)	Sell data to improve clinical development (trials) of new drugs and develop diagnostics to target new medicines to responsive genotypes	Amgen, Boehringer Ingelheim, Covance, Isis, Quintiles

* As a sign of how quickly the pharmacogenetics industry is moving, and of the fragile nature of many of these companies, we note that at the end of January 2003 Variagenics merged with the 'biopharmaceutical' company Hyseq, to form a new firm: Nuvelo Inc. From the company website, Nuvelo seems focused on the development and marketing of new drugs, and thus, Variagenics' pharmacogenetic goals seem to have fallen by the wayside.

its emphasis on drug safety. The French firm Genset was the first biotechnology company to move into the field of pharmacogenomics (i.e. large-scale industrial pharmacogenetics) when it established a landmark US$23 million research collaboration with Abbott in 1997. Under the terms of the agreement, Genset aims to discover genes and markers associated with particular drug responses and Abbott will then produce tests using this information for diagnostic purposes. In particular, the collaboration focused on Abbott's asthma drug Zileuton, which causes liver damage in a small number of patients. In July 1999 Genset identified genes associated with Zileuton-induced liver toxicity and has subsequently filed patent applications covering these markers. The intention is to develop a genetic test to pre-screen asthma patients so that those with the 'wrong' genotype are not given Zileuton. The company hopes that this might increase the use of the drug.

In early 2001 CuraGen became one of biggest players in the field when it established a US$124 million collaboration with the large pharmaceutical company, Bayer. They aim to evaluate Bayer's preclinical 'pipeline' of new drugs early in development in order to reduce the cost of development, decrease the time to market and create 'safer and more efficacious products'. In particular, the firm intends to compile a database of gene-based markers and information that will enable scientists to predict potential drug toxicities early in their development. According to the company website:

> Through the application of this knowledge, CuraGen scientists can identify patients as being negative responders or as having a high susceptibility for a toxic reaction, prior to their enrolment into clinical trials. This knowledge can ultimately prevent toxic side effects and even catastrophic failures of potential blockbuster therapeutics. This same knowledge can also be applied in the development of diagnostics for use in personalized medicine. By determining in advance which drugs are safest and most efficacious for patients, CuraGen is helping to ensure that the most appropriate drugs are prescribed at the most opportune times, reducing side effects and limiting adverse reactions.[3]

Gemini Genomics' approach is also based on classical pharmacogenetics in that it involves studying the genetic basis of drug metabolism. In particular, the firm is involved in identifying polymorphisms in the cytochrome P450 (CYP) enzymes. In 2000 Gemini was granted a patent describing polymorphisms in the CYP2D6 and CYP2C19 genes, which can identify individuals with ultra-rapid drug metabolism. It plans to create diagnostic tests using this information. These polymorphisms' importance is highlighted by another small firm, Genelex, which has started marketing genetic testing for CYP2D6 variants direct to the public and medical practitioners. It claims that ADRs are the fourth leading cause of death and the single largest source of malpractice payouts in the US and urges doctors to 'be one of the first healthcare practitioners to enter the era of personalized medicine.'[4]

DeCODE Genetics, through its subsidiary Encode, has also taken a similar approach that emphasizes the benefits of this vision for improving the safety of prescription medicines. To this end, it plans to:

- use genetic information to determine proper dosage levels and establish which drugs patients should avoid because of possible side-effects;
- develop clear descriptions for individuals – perhaps in the form of a smartcard that can be carried in a wallet or purse – stating their most likely response to common drugs. By making such information easily and immediately available to individuals and physicians, the chances of drug treatments leading to dangerous reactions and side-effects should be significantly reduced.[5] As a means of trying to realize this vision of a 'smartcard', DeCODE has established a collaboration with Affymetrix to develop a 'gene chip' that will predict the responsiveness of individual patients to treatments for common diseases.

These examples suggest that the vision of pharmacogenetics based on the reduction of ADRs is shaping the commercial strategies of a number of leading firms in terms of the research they are undertaking, the intellectual property they are creating, their choice of collaborators, and the products and services they plan to sell. The focus is both on improving the safety of already licensed products and the development of new compounds.

Firm Strategies Focusing on the Identification of 'Good Responders'. In contrast to the significant commercial interest in identifying ADRs, only two of the leading companies – Genaissance and Variagenics – are currently (January 2002) developing their commercial strategies around the disease dependent vision of pharmacogenetics as applied to both new and approved drugs. For new medicines, both Genaissance and Variagenics aim to examine the genetic variation among patients in clinical trials to create 'smarter' trials through the design of protocols that result in the inclusion of those patients most likely to benefit from the proposed therapeutic product. Here the emphasis is on finding good responders, rather than those at risk of ADRs, by identifying polymorphisms in disease-associated genes. This might reduce the size and, hence, the cost, of late-stage clinical trials.

In relation to drugs already on the market, Genaissance seeks to maximize pharmaceutical company product sales by first creating diagnostic tests that predict drug response and which might be used in tandem with the prescribing of a medicine. Second, the company is looking to integrate genetic variation information into drug marketing strategies to enhance a market leading position or to address problems such as poor market penetration, competitive pricing, risk of therapeutic substitution, and limited patent life. Finally, the firm hopes to use pharmacogenetic data to target new markets and obtain approval for new drug indications.

In particular, the firm hopes to find genetic markers that identify individuals who will respond better to a particular drug within a particular

class of compounds, compared to other drugs in the same class, or who will respond better to one class of drugs compared to another class. It is attempting to demonstrate the potential of this approach with the statins, which are used to treat patients with high cholesterol and lipid levels, and who are at an increased risk of cardiovascular disease. According to the firm:

> This is a highly competitive market with multiple approved products seeking to gain increased market share. Currently, the market is approximately $11 billion worldwide and is forecast to at least double in size by 2005. Identification of genomic markers that would allow the right drug to reach the right patient would allow a company to further differentiate its product and may improve patient compliance, which are both particularly important factors when maximizing profit from drugs that are taken over the course of a lifetime.[6]

Genaissance is currently organizing clinical trials to test the predictive power of its genetic markers for a number of already licensed statin drugs. It then intends to auction this information to pharmaceutical firms involved in marketing these drugs to give the highest bidder a significant advantage over its competitors. Interestingly, this approach is at odds with the conventional wisdom about pharmacogenetics, which claims that the era of 'blockbuster' drugs (single compounds marketed to large populations) is ending. Instead, some have argued that the arrival of pharmacogenetically based 'minibusters' (McCarthy, 2000) might allow companies to 'segment and grow' particular markets (Anderson et al., 1999: 268).

As with the 'ADR vision', this idea of how pharmacogenetics might develop is embodied in the plans, strategies and activities of companies and is playing a major role in shaping the behaviour of these key actors. In particular, commercial strategies based on this vision aim to help improve the marketing of already licensed drugs to good responders and the development of new drugs aimed at highly profitable genotypes. However, while there are important differences between the commercial realization of each of these two visions, they share some common objectives, most notably, a reduction in the time and cost and improvement in the success rate of clinical trials, and the expansion of markets for established drugs through proprietary tests and an expansion of indications.

Integration of Pharmacogenetics into the Mainstream Pharmaceutical Sector

The success of these visions in creating interest in pharmacogenetics has fuelled mergers and close working relationships between large drugs companies and smaller firms specializing in diagnostics, platform technologies and the creation of genetic databases (Persidis, 1998b). Already over 150 pharmacogenetics alliances between large and small firms have been created since 1997.[7] Furthermore, prior to the widespread introduction of pharmacogenetics, most large drug companies are already preparing themselves for the impact of this technology on their core activities by collecting DNA samples from the participants of their clinical trials (Martin, 2001a).

Even if a trial is not intended to investigate the pharmacogenetic effects of a particular drug, companies reason that such samples may be useful in the future if the drug has problems later in its development.

In terms of our explanatory framework, this review of the pharmacogenetics industry shows how the two visions articulated in the scientific literature have become embodied in the policies, structure and products of individual pharmaceutical companies and biotechnology firms. This has involved the translation of particular discourses into a heterogeneous range of artefacts, organization structures, work practices and material investments. In this way visions provide the strategic framework for actors to change the present in order to build the future.

Despite the large sums being invested in pharmacogenetics, there is still a high degree of contingency and uncertainty surrounding this technology, perhaps best represented by the tension between placing the emphasis on ADRs (which the industry is very worried about making public) and strategies aimed at identifying 'good responders'. Furthermore, very few pharmacogenetics products or services are actually on the market. Only with time will it be possible to assess if either of these visions translates into commercially viable tests and drugs.

Critically, the extent to which companies are able to realize the benefits offered by pharmacogenetics will depend on a range of social and technical factors, including: how well genetic testing is able to predict drug response in practice; how commercially attractive a particular application is; the ability to integrate the technology into routine clinical work; and the social, ethical and regulatory issues raised by each option. In particular, the resolution of the controversial ethical issues raised by pharmacogenetics will be a prerequisite for the successful creation of new markets. The way in which these bioethics debates are being constructed is explored in the next section.

The Social Problems Raised by Pharmacogenetics: Bioethics as a Form of Expectation

As is the case with many other novel genetic technologies, bioethicists, the media and some scientists claim that there are pressing social and ethical problems associated with pharmacogenetics (Chadwick, 1999; Clarke et al., 2001; Issa, 2000; Issa & Keyserlingk, 2000; Kreeger, 2000; Rothstein & Griffin Epps, 2001). Issues raised in this context include the general concerns posed by genetic testing (data privacy, informed consent, discrimination by insurers and employers), access to healthcare and the safety of drugs developed for particular genotypes. However, the focus of this analysis will be on the way in which the two visions discussed above are reflected in the bioethics discourse surrounding pharmacogenetics, and the way in which that discourse is shaped to support these visions. To what extent does bioethical discourse play a role in creating expectations and constructing particular technical options?

Initially, bioethics might seem peripheral to the eventual outcome of technological developments, but we believe that this would ignore important changes that have taken place within bioethics as an academic discipline over the past few years and what one might call the creeping 'corporatization of bioethics'. There is growing concern among some bioethicists that: 'the pharmaceutical and biotechnological industries are funnelling more and more cash into the pockets of academics who teach and study ethics' (Elliott, 2001; see also Callahan, 2000). While Carl Elliott's concerns about the effect of this money on the erosion (both perceived and actual) of bioethics' reputation are beyond this paper, he lists several examples of the way in which firms have engaged with bioethics discourse, ranging from the withdrawal of funds[8] to the support for academic bioethics departments.[9]

The pharmaceutical industry is increasingly concerned about debates in professional bioethics. One of the clearest statements of this comes in Rahul Dhanda's recent book *Guiding Icarus*: *Merging Bioethics with Corporate Interests*. Dhanda is in charge of bioethics at Interleukin Genetics, a pharmacogenetic biotechnology company. He suggests that as biotech start-ups become more successful, it will not be 'enough for a company to have faith in its technology anymore; the company must also be responsible for it . . . As biotechnology progresses, it must do so hand in hand with ethics' (Dhanda, 2002: 5–6). Dhanda contradicts worriers like Elliott and suggests that, rather than companies using bioethics as a form of PR, to legitimize decisions already made, biotechnology firms need bioethicists' impartial analysis, and that over time '. . . bioethics can become a seamless part of the corporate landscape. Standard operating procedures and corporate culture will each require reconception' (Dhanda, 2002: 7–8). He cites a report by PriceWaterhouse Coopers on the future of health care which recommends that biotech companies develop a bioethical framework within which to make decisions, and that they consult with professional bioethicists (PriceWaterhouse Coopers, 1999).

Added to this is the role that bioethics has played as a 'political broker' in debates over biotechnology regulation in the European Union (Salter & Jones, 2002) and the claim that pharmaceutical companies have, compared with academics, been reluctant to explore pharmacogenetics, largely because of the possible ethical issues involved (Jazwinska, 2001). When we claim that bioethics may be the decisive factor in deciding whether or not a particular vision becomes reified in scientific and company practice, we are simply building on a well-documented trend in the relationship between bioethics and the pharmaceutical industry.

To examine the bioethics discourse surrounding pharmacogenetics, we searched both the scientific and bioethics literature for articles dealing with the ethics of pharmacogenetics, using the definitive bibliographic database covering bioethics, *Bioethicsline*, which has now been incorporated into the National Library of Medicine's *PubMed* database (www.ncbi.nlm.nih.gov/entrez/query.fcgi). We found a total of 29 English language journal articles on *PubMed*, which included the terms 'ethics' and 'pharmacogenetics' or

'pharmacogenomics' in either their heading, abstract or keywords.[10] Strikingly, only one of these papers was in a non-scientific journal, and this was contained in a specialized law and science publication (*Law and Human Genome Review*). Fifteen papers focused on a discussion of the ethical issues specifically raised by pharmacogenetics. Of these, bioethicists (mainly lawyers) wrote six, academic scientists or clinicians four, with four papers coming from commercial sources and one from a journalist. The majority of the other 14 articles touched on this topic, but only as part of more general discussions of post-genomic medicine. Three more papers were found using the Science, Social Science and Arts and Humanities Citation Indices, one of which dealt with technical issues to do with clinical trials (Rioux, 2000), one with the organization of DNA databases (Lavori et al., 2002) and one which focused on the possible problems raised by pharmacogenetics and the use of ethnic groupings (Foster et al., 2001). All three were published in technical scientific journals rather than the bioethics literature.

In addition to the use of electronic databases, a manual search was also undertaken of the scientific literature described in the earlier sections of this paper to find articles which discussed the ethics of pharmacogenetics, but which were not indexed as covering this topic in *PubMed*. A further 20 articles were found which covered this area, although in almost all cases they were written by scientific researchers and the discussion of ethics was part of broader discussions of either the technical or commercial development of the technology.[11]

From this review of the literature a number of features can be clearly identified. First, this early discussion of the ethics of pharmacogenetics is mainly organized within the scientific community through publications in scientific journals. Very little debate has taken place within dedicated bioethics journals. Furthermore, it is also noteworthy that almost no social science work has been done on the ethical, legal and social issues raised by pharmacogenetics. Second, the discussion seems to be dominated by researchers involved in developing the technology, with independent professional bioethicists being in a minority. Third, with most of the articles not explicitly about just the ethics of pharmacogenetics, the debate is often closely tied to other discussions on the scientific, clinical and commercial prospects for the technology. It therefore appears that the construction of a bioethics discourse around pharmacogenetics is mainly being shaped by researchers advocating the development of the technology and is closely tied to the creation of scientific and commercial expectations.

The papers found in this search were then examined to see if they referred in any way to the visions identified above. While much of the discussion was of a generic nature and covered general problems raised by genetic testing, the two technical options were clearly visible in the discussion of the bioethics of pharmacogenetics. In van Lente's terms, explicitly constructing these visions in terms of ethical debates reduces the uncertainty associated with developing a potentially controversial technology. What we see here are authors using the discursive space provided

by ethics debates to clarify the potential ethical issues associated with their particular vision, and in turn to influence possible future response on the part of regulators and the public.

Ethical Expectations Associated with the ADR Vision of Pharmacogenetics

Commentators who discussed the 'ADR approach' to pharmacogenetics often drew an ethical distinction between testing for genetic diseases and testing for drug reactions, and claimed a reduction in the ethical problems in this context. For example, Housman and Ledley note that:

> Pharmacogenomics is not aimed at achieving seminal insights into proximal causes of disease, but rather simple improvements in patient care. Pharmacogenomics should not be confused with predisposition or predictive testing. (Housman and Ledley, 1998: 492)

Allen Roses, a senior scientist at Glaxo SmithKline, takes this further by arguing that 'Pharmacogenetics is not really about disease diagnosis' (Roses, 2000b: 1358) and insists on the need to separate public perception of the ethics of pharmacogenetics from disease testing: 'Clear language and differentiation of respective ethical, legal and societal issues are required to prevent inaccurate vernacular usage creating a confused public perception of "genetic testing"' (Roses, 2000a: 857–65; or see McCarthy, 2000: 142).

It therefore appears that supporters of this vision are making strenuous efforts to distance it from ethical controversies, claiming that this type of testing will reveal nothing about prognosis or disease susceptibility. But ethical issues are not simply passive; they reflect back on the visions and influence the practices being proposed. For example, Roses accepts that to avoid the possibility of ADR/disease SNP overlap, it would make sense to 'select polymorphisms with no known relationship to any disease diagnosis'. But even if there were some overlap, 'if the magnitude and severity of drug-induced [ADRs] is considered, the benefits far out-weigh the costs' (Roses, 2002: 547).

Alternatively, when the ethical issues surrounding the technology are mentioned, they are sometimes discussed in terms of the ethical duty to use pharmacogenetic testing, as a way of reducing harm to patients: 'One day it may be considered unethical not to carry out such tests routinely to avoid exposing individuals to doses of drugs that could be harmful to them' (Wolf et al., 2000: 989). Similarly Roses calls possible over-regulation of pharmacogenetic tests a 'tragedy' (Roses, 2000b: 1361).

While many in the pharmaceutical industry view this application of pharmacogenetics, which aims to reduce the numbers of ADRs, as being ethically responsible, there are some who seriously doubt the wisdom of applying the ADR vision to the rescue of drugs which fail late-stage trials. For example, Bill Haseltine of Human Genetic Sciences:

> sees a big problem in developing drugs that might work wonderfully in 75% of the population but be extremely harmful to the other 25% . . .

> [Pharmacogenetics] . . . means manufacturing and producing a drug that could either kill or severely harm a substantial number of people. And the only thing that stands between your drug and that harm is a diagnostic test that has to be interpreted correctly. (quoted in Regalado, 1999: 47)

The ethical discourse around this particular vision creates a specific set of expectations about the problems associated with the future development of pharmacogenetics. In particular, advocates argue that testing for ADRs is quite distinct from genetic testing in general, and that the technology does not therefore raise significant ethical, social and legal problems. In this sense, it is being constructed as relatively problem-free. In contrast, the rescue of drugs which have failed late-stage trials because of serious ADRs is highly problematic.

Ethical Expectations Associated with the Disease Dependent Vision of Pharmacogenetics

While it may be true to say that the ADR-centred vision of pharmacogenetics does not imply particular ethical problems, this is not the case for many disease-centred pharmacogenetic tests. Some leading scientific advocates of this option acknowledge that the distinction between pharmacogenetics and genetic testing in this context cannot be maintained: 'there is little reason to assume that pharmacogenetic data for common complex disorders will differ significantly from primary disease susceptibility data in their potential to raise these issues' (Lindpaintner et al., 2001: 81; see also Anderson et al., 1999; Chamberlain & Joubert, 2001).

In the case of the disease-centred vision, a test for a pharmacogenetic reaction may also become a genetic test for the disease itself, with all the attendant ethical problems such as confidentiality, consent, use of test results, etc. For example, 'as soon as a patient with breast cancer submits her *trastuzamab* [Herceptin] prescription, the pharmacist and the cashier, as well as the data entry clerk, the claims adjuster, and any number of additional personnel involved in health care administration and reimbursement will, by inference, know that patient's HER-2-expressor status' (Lindpaintner et al., 2001: 81).[12]

As a consequence of this position, the ethical expectations raised as part of this vision are more problematic and might imply many of the same responses (e.g. genetic counselling, tight regulation) used to manage traditional genetic testing. This might make it harder to integrate this option into clinical practice. As in the previous vision, ethical issues are used to propose changes to practice, in this case to 'structures of confidentiality and individual choice regarding the use of all types of medical data' which may need to be 'redefined' in the light of the widespread use of pharmacogenetics (Lindpaintner, 1999: 488).

This brief discussion of the ethical debate surrounding these two visions highlights a number of key points. In particular, the way in which advocates are constructing the ADR-centred vision allows the insulation of pharmacogenetics from public disquiet about genetic testing and the

misuse of information by third parties such as insurers and employers. If, as claimed, pharmacogenetics tells such people nothing about a person's current (or future) state of health, then it might be far simpler both in terms of the ethics of its use, winning public support and how it should be regulated. Yet this is in direct contrast with the alternative vision, which requires pharmacogenetic tests to be seen in the same light as more 'traditional' genetic testing. These ethical positions reinforce core aspects of the two visions: that the ADR-centred one focuses on drug metabolism and the disease-centred one 'unveils' the true causes of diseases. In this way these ethical positions help construct the visions, but also attempt to overcome likely barriers to the introduction of the technology and stress the potential benefits of pharmacogenetics.

The way in which scientific advocates of pharmacogenetics are playing a leading role in constructing particular bioethical discourses around the technology highlights another key point. Debates over the bioethics of controversial genetic technologies provide what might be called a 'negotiation space' which can be used to explore the socially acceptable limits of their use and how they might be governed. Through a process of creating a series of imagined scenarios or bioethical expectations for the application of a technology it is possible to examine the potential ethical, social and legal issues raised and gauge the extent to which a particular technical option will meet popular resistance. Given that public and professional support is essential for the adoption of biomedical technologies, these anticipatory debates serve a vital role in the construction of stable socio-technical networks and shape the creation of governance regimes.

The history of gene therapy well illustrates this point. The controversy surrounding proposals to clinically develop gene therapy in the US in the 1980s only subsided, and clinical trials were allowed to start, once a regulatory regime had been put in place which commanded widespread support (Martin, 1998). However, this was the final outcome of nearly a decade of bioethical debate and social negotiation, and initially placed severe restrictions on the technical options that could be developed (Martin, 1998). Some potential applications of gene therapy, most notably germ line therapy which involves the modification of future generations, were widely opposed and specifically excluded by the political settlement that underpinned the regulatory regime.

Bioethics debates therefore play a central role in creating visions which can form the basis for the enrolment of social support from key groups of actors, mobilizing resources and translation into practice. At the same time they influence the selection and shaping of technical options through a process of anticipatory negotiation over what is acceptable and how particular applications should be regulated. In this way the creation of particular bioethical discourses should be seen as an integral part of the socio-technical processes involved in the shaping of artefacts, and the construction of applications and markets for emerging genetic technologies.

Conclusions

Controversial early stage genetic technologies are difficult to analyse, both in terms of the direction of their development and the social and ethical issues they raise. In this paper we have drawn on insights from the sociology of technological expectation to provide evidence about the different ways in which pharmacogenetics is currently moving, how its development might be shaped, and the ethical problems different options might raise. In particular, the concept of competing technological visions provides a powerful framework for organizing the analysis of early stage innovation, giving guidance about the potential trajectory of the technology, but without losing sight of the highly contingent nature of technical change.

Heterogeneous Expectations and the Formation of Socio-Technical Networks

The preceding sections have described the construction of different types of expectation in three distinct social locations: within scientific practice through publications and the design of experiments; within the biotechnology industry through the creation of companies and the articulation of business plans; and within bioethics discourse. As we have shown, the creation of these two visions is not just a discursive or cognitive phenomenon, but is embodied in a range of heterogeneous artefacts, actor strategies and material practices. A commitment to a particular vision not only implies a judgement about the benefits of a certain scientific technique, but also a commitment to specific types of research questions (safety vs efficacy), prescribing practices (screening for ADRs vs a 'molecular diagnosis'), drug development strategies (drug rescue vs targeting new drugs at specific genotypes), commercial products (diagnostic tests vs selling data on efficacy), business relationships (collaborations on ADRs vs efficacy) and even definitions of disease (e.g. disease stratification). Visions provide a framework within which the future shape and application of a technology are constructed, as they act as both an aid for decision-making and a focus for the mobilization of actors and resources. In this way, new technologies, new industries and new ethical, legal and social problems are co-constructed and mutually shaped.

Instead of seeing the speculative claims made about the future of pharmacogenetics as ephemeral and irrelevant, this paper has argued that they are fundamental to the dynamic processes that create new socio-technical networks. The development of particular options for a new technology requires the construction of socio-technical network around them through a process of enrolment and alignment. Visions of these different options play a central role in organizing such networks. In addition to getting particular technologies to work in both experimental and clinical settings, four main groups of actors are required to create stable networks which will allow the introduction of a new medical technology into practice: industry, clinicians, patients and regulators. Visions provide industry with ideas about how profits might be made,

clinicians with a guide to how a new technique can be integrated into practice, patients with the hope of improved care, and regulators with a framework for governing an emerging technology.

In the future, new groups of actors may become involved in the creation and use of pharmacogenetic technology and might be associated with the construction of new technical options, new visions and new ethical problems. This could take the development of the technology in new directions. However, we believe that the early formation of particular socio-technical networks around specific visions and applications will have a major impact in creating particular trajectories and could shape all subsequent activity. In extreme cases the formation of robust stable networks may lock a technology into a fixed niche and make some new visions and applications impossible to realize.

However, it should be stressed that this is not simply a one-way process, as the manner in which each group problematizes different technical options, and the extent to which their support can be enrolled, will ultimately decide the fate of a particular vision. If a key actor cannot be 'won over' then that vision will have great difficulty being successfully translated into material and social reality. In order to enrol support and develop stable socio-technical networks around particular options it will be essential to overcome any major difficulties that a group might have with a given application. This is especially important in the area of human biotechnology, which has proved to be highly controversial and where promising technologies have been killed off by public hostility.

Bioethics, the Expectation of Social Problems and the Shaping of Technical Options

It is in this context that the role of bioethics as a form of expectation and a means of social negotiation must be understood. The work of researchers and bioethicists in anticipating the likely social problems raised by pharmacogenetics might help ensure that either options are chosen for the development of the technology which are less controversial or safeguards that reassure the public are put in place before the technology is widely used. The creation of bioethical scenarios associated with particular visions which can act as a negotiation space is instrumental in the process of socio-technical alignment.

Such alignment enables the formation of new markets, as these require users, such as doctors and patients, to adopt new forms of practice. A central task in the enrolment of end users is the creation and maintenance of confidence about the risks and benefits of treatment. In the medical domain such risks are socially managed through both statutory regulation and professional governance processes, and bioethical debates play an important role in shaping these frameworks. Tight regulations controlling controversial technologies can be seen as embodying the outcome of social and political negotiations conducted through bioethical debates. They help ensure the acceptability of a specific set of options for a new biotechnology

and underpin its diffusion into widespread use. Furthermore, a stable and widely supported regulatory framework also gives commercial developers the confidence to commit the heavy investment required to create new drugs and therapeutics. This is particularly important in biotechnology where product lead times can be as long as 10–12 years before a product reaches the market and investment has to be sustained throughout this period in anticipation of success.

Given the importance of ensuring social acceptability for new medical technologies, engagement with bioethics by researchers and companies may be seen as just as important to the creation of a new technology as getting particular techniques to 'work'. The increasing prominence of bioethics within biotechnology is clear. A similar reflection might also be made about scientific support for the funding of social science research on bioethical problems through the US National Institutes of Health ELSI programme and the UK Wellcome Trust's Medicine in Society programme.

By creating a more complete picture of the process of technical change in biotechnology, as well as carrying out empirical research on the ethical, legal and social issues raised by emerging genetic technologies, social scientists such as ourselves are also helping construct a set of future expectations. It is therefore impossible to maintain the long-established view that public policymakers and commentators such as bioethicists and social scientists are simply responding to the consequences of technical change. Through the anticipation of social and ethical problems and a critical engagement with the process of innovation, they are also helping construct and shape the future. The implications of this reflexive point have perhaps still to be digested by many who are working on the social studies of science and technology.

Acknowledgements

The authors would like to thank Brian Rappert, Graham Lewis, Andrew Smart and Andrew Webster for their input and feedback, as well as four anonymous *SSS* referees. Both authors are supported by grants from the Wellcome Trust: Paul Martin by grant #018381 ('The Clinical and Commercial Development of Pharmacogenetics') and Adam Hedgecoe by a Postdoctoral Training Fellowship #GR061491MA ('Pharmacogenetics and Genetic Reclassification of Disease').

Notes

1. The basic principle behind genetic association studies is the statistical correlation between specific DNA sequences and particular diseases or drug responses. Instead of trying to make disease–gene associations using raw sequence data, researchers are using single-nucleotide polymorphisms (SNPs) (Evans & Relling, 1999: 488). Human populations are to some extent genetically heterogeneous; i.e. the exact sequence of a particular gene varies within a population. The variation is generally limited to a relatively small number of such single base-pair changes, which are stable and inherited across generations. The hope is that specific SNPs will be found to closely correlate with the particular disease or drug reaction being investigated. Specific genes that react to particular drugs will tend to be inherited with certain SNPs. Thus, screening for those SNPs will indicate a person's reaction to a drug, regardless of whether the gene

involved has been identified. This is a technically demanding procedure involving high-speed DNA screening on a huge scale, coupled to complex statistical analysis using massive data processing.

2. This survey was conducted using commercial databases (Genetic Engineering News Company Database, BioSpace) the biotechnology trade press (*GEN, Genome News, Nature Biotechnology*) and web searches. Company documents and news stories were then collected and used to classify and group firms. The most well-established companies in the field were analysed in greater detail.
3. CuraGen website, January 2001, <*http://www.curagen.com/technology/frameApps.htm*>
4. Genelex website, December 2001, <*http://www.healthanddna.com/drugreactiontest.html*>
5. Encode website, January 2002, <*http://www.encode.is/main_english.asp?group_id=42&page_id=12*>
6. Genaissance website, January 2002, <*http://www.genaissance.com/our_solutions/bus_models.html*>
7. Dr Andy Smart, personal communication, January 2002.
8. In 2000 Eli Lilly cancelled its support for the independent bioethics institute, the Hastings Center, because of a special issue of *The Hastings Center Report* (30[2] March/April 2000) which was critical of Prozac (a Lilly drug) and other antidepressants.
9. The University of Pennsylvania Center for Bioethics is supported by, among others, Monsanto, DeCode Genetics, Geron, Pfizer, AstraZeneca, and Human Genome Sciences. Elliott also lists: the Sun Life Chair in Bioethics at the University of Toronto; Stanford University's Center for Biomedical Ethics' $1 million gift from SmithKline Beecham; and the Midwest Bioethics Center's 'Research Integrity Project' funded by a $600,000 donation from Aventis Pharmaceuticals (Elliott, 2001).
10. Ameen et al. (2002); Broder et al. (2002); Issa (2002); Weinshilboum (2002); Anderlik & Rothstein (2001); Carroll & Coleman (2001); Davis & Long (2001); Francke (2001); Jones (2001); Kozma (2001); Nebert & Bingham (2001); Oestreicher (2001); Renegar et al. (2001a, 2001b); Robertson (2001); Rothstein & Griffin Epps (2001); Thomas (2001); Arledge et al. (2000); Fujiki (2000); Issa & Keyserlingk (2000); Lea (2000); van Ommen (2000); Kaplan & Junien (2000); Myers (2000); Hinde (2000); Emilien et al. (2000); Issa (2000); Motulsky (1978); Stern (1971).
11. Lindpaintner (1999); Chadwick (1999); Housman & Ledley (1998); Kreeger (2000); Roses (2000a, 2000b); McCarthy (2000); Regalado (1999); Wolf et al. (2000); Lindpaintner et al. (2001); Jazwinska (2001); Chamberlain & Joubert (2001); Ginsburg & McCarthy (2001); Anderson et al. (1999); Phillips et al. (2001); Sadée (1999); Clarke et al. (2001); Roses (2002); McLeod & Evans (2001); Akhtar (2002).
12. Not all commentators accept that Herceptin and HER2 testing is an example of pharmacogenetics: see Haseltine (1998); Rusnak et al. (2001).

References

Abraham, John (1997) 'The Science and Politics of Medicines Regulation', in Elston (1997): 151–82.

Akhtar, Saghir (2002) 'Pharmacogenomics: Are Pharmacists Ready for Genotyped Prescribing?', *The Pharmaceutical Journal* 268 (2 March): 296–99.

Ameen, M., Catherine H. Smith, and Jonathon N.W.N. Barker (2002) 'Pharmacogenetics in Clinical Dermatology', *British Journal of Dermatology* 146(1) (January): 2–6.

Anderlik, Mary and Mark Rothstein (2000) 'Privacy and Confidentiality of Genetic Information: What Rules for the New Science?', *Annual Review of Genomics and Human Genetics* 2: 401–33.

Anderson, Wayne, Craig Fitzgerald and Penelope Manasco (1999) 'Current and Future Applications of Pharmacogenomics', *New Horizons: Science and Practice of Acute Medicine* 7(2) (April): 262–69.

Arledge, Teresa, Andrew Freeman, Julian Arbuckle, Michael Mosteller and Penelope Manasco (2000) 'Applications of Pharmacogenetics to Drug Development: The Glaxo Wellcome Experience', *Drug Metabolism Reviews* 32(3–4): 387–94.

Arranz, Maria J., J. Munro, J. Birkett, A. Bolonna, D. Mancama, M. Sodhi, K. Lesch, J. Meyer, P. Sham, D. Collier, R. Murray and R. Kerwin (2000) 'Pharmacogenetic Prediction of Clozapine Response', *The Lancet* 355 (6 May): 1615–16.

Bell, John (1997) 'Genetics of Common Disease', *Philosophical Transactions of the Royal Society of London* 352: 1051–55.

Bell, John (1998) 'The New Genetics and Clinical Practice', *British Medical Journal* 316: 618–20.

Bijker, Wiebe (1995) *Of Bicycles, Bakelites and Bulbs: Towards a Theory of Sociotechnical Change* (Cambridge, MA: MIT Press).

Bijker, Wiebe, Thomas Hughes and Trevor Pinch (1987) *The Social Construction of Technological Systems* (Cambridge, MA: MIT Press).

Blume, Stuart (1992) *Insight and Industry: on the Dynamics of Technological Change in Medicine* (Cambridge, MA: MIT Press).

Broder, Sam, Arthur Caplan and William Evans (2002) 'Therapeutic Horizons – The Human Genome', *Journal of the American Pharmaceutical Association* 42(5 Suppl 1): S22–23.

Brown, Nik, Brian Rappert and Andrew Webster (eds) (2000) *Contested Futures: A Sociology of Prospective Techno-science* (Aldershot: Ashgate Press).

Callahan, Daniel (2001) 'Doing Good and Doing Well', *The Hastings Center Report* 31(2): 19–21.

Callon, Michel (1987) 'Society in the Making: The Study of Technology as a Tool for Sociological Analysis', in Bijker et al. (1987): 83–103.

Cantor, Charles (1999) 'Pharmacogenetics Become Pharmacogenomics: Wake Up and Get Ready', *Molecular Diagnosis* 4(4) (December): 287–88.

Cardon, Lou, Rammana Idury, Timothy Harris, John Witte and Robert Elston (2000) 'Testing Drug Response in the Presence of Genetic Information: Sampling Issues for Clinical Trials', *Pharmacogenetics* 10: 503–10.

Carr, G. (1998) 'Survey: The Pharmaceutical Industry', *The Economist* 345 (21 February): 1–16 of supplement.

Carroll, A. and C. Coleman (2001) 'Closing the Gaps in Genetics Legislation and Policy: A Report by the New York State Task Force on Life and the Law', *Genetic Testing* 5(4) (Winter): 275–80.

Chadwick, Ruth (1999) 'Criteria for Genetic Screening: The Impact of Pharmaceutical Research', *Monash Bioethics Review* 18(1) (January): 22–26.

Chamberlain, John and Pieter Joubert (2001) 'Opportunities and Strategies for Introducing Pharmacogenetics into Early Drug Development', *Drug Development Today* 6(11) (June): 569–74.

Clarke, Angus, Veronica English, Hilary Harris and Frank Wells (2001) 'Report on Ethical Considerations', *International Journal of Pharmaceutical Medicine* 15: 89–94.

Cobleigh, Melody, Charles Vogel, Debu Tripathy, Nicholas Robert, Susy Scholl, Louis Fehrenbacher, Janet Wolter, Virginia Paton, Steven Shak, Gracie Lieberman and Dennis Slamon (1999) 'Multinational Study of the Efficacy and Safety of Humanized Anti-HER2 Monoclonal Antibody in Women who have HER2-overexpressing Metastatic Breast Cancer that has Progressed after Chemotherapy for Metastatic Disease', *Journal of Clinical Oncology* 17: 2639–48.

Cookson, Clive (1997) 'Personalised Treatment', *Financial Times* (12 August 1997): 10.

Coombs, Rod, Ken Green, Albert Richards and Vivien Walsh (2001) *Technology and the Market: Demand, Users and Innovation* (Cheltenham: Edward Elgar).

Corrigan, Oonagh (2002) 'A Risky Business: The Detection of Adverse Drug Reactions in Clinical Trials and Post-Marketing Exercises', *Social Science and Medicine* 55: 497–507.

Davis, Alison and Rochelle Long (2001) 'Pharmacogenetics Research Network and Knowledge Base: 1st Annual Scientific Meeting', *Pharmacogenomics* 2(3) (August): 285–89.

De Laat, Bastiaan (2000) 'Scripts for the Future: Using Innovation Studies to Design Foresight Tools', in Brown et al. (2000): 175–208.

Department of Health (2000) *Harnessing the Potential of Gene Science: A Strategy for the DH* (London: Strategy and Planning, DoH).
Deuten, J. Jasper and Arie Rip (2000) 'The Narrative Shaping of a Product Creation Process' in Brown et al. (2000): 65–86.
Dhanda, Rahul (2002) *Guiding Icarus: Merging Bioethics with Corporate Interests* (New York: John Wiley & Sons).
Drazen, Jeffrey, Chandri Yandava, Louise Dube, Natalie Szczerback, Richard Hippensteel, Antonino Pillari, Elliot Israel, Nicholas Schork, Eric Silverman, David Katz and Jeffrey Drajesk (1999) 'Pharmacogenetic Association between ALOX5 Promoter Gnotype and the Response to Anti-Asthma Treatment', *Nature Genetics* 22: 168–70.
Elliott, Carl (2001) 'Pharma Buys a Conscience', *The American Prospect Online* 12(17), September 24(96)October 8, www.prospect.org/ Accessed 27 January 2003.
Elston, Mary (ed.) (1997) *The Sociology of Medical Science and Technology* (Oxford: Blackwell).
Emilien, G., M. Ponchon, C. Caldas, O. Isacson, and J.M. Maloteaux (2000) 'Impact of Genomics on Drug Discovery and Clinical Medicine', *Quarterly Journal of Medicine* 93(7): 391–423.
Ensom, Mary, Thomas Chang and Payal Patel (2001) 'Pharmacogenetics: The Therapeutic Drug Monitoring of the Future', *Clinical Pharmacokinetics* 40(11): 783–802.
Evans, William and Mary Relling (1999) 'Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics', *Science* 286 (15 October): 487–91.
Foster, Morris W., R. Sharp and J. Mulvihill (2001) 'Pharmacogenetics, Race and Ethnicity: Social Identifiers and Individualized Medical Care', *Therapeutic Drug Monitoring* 23(3): 232–38.
Francke, Uta (2001) 'The Human Genome Project: Implications for the Endocrinologist', *Journal of Pediatric Endocrinology and Metabolism* 14 Suppl 6: 1395–408.
Fujiki, Norio (2000) 'A Biography and Bibliography: The Recent Trends in Bioethics and Medical Genetics in Japan (Part II)', *Law and Human Genome Review* (13): 183–210.
Ginsburg, Geoffry and Jeanette McCarthy (2001) 'Personalized Medicine: Revolutionizing Drug Discovery and Patient Care', *Trends in Biotechnology* 19(12) (12 December): 491–99.
Glaser, Vicki (1998) 'Pharmacogenomics: Laying the Foundation for Prescriptive Medicine', *Genetic Engineering News* 1 January 1998: 1, 9, 31 and 39.
Gonzalez, Frank J. et al. (1988) 'Characterization of the Common Genetic Defect in Humans Deficient in Debrisoquine Metabolism' *Nature* 331(6155) (4 February): 442–46.
Grin, John and Armin Grunwald (2000) *Vision Assessment: Shaping Technology in 21st Century Society* (Springer: Berlin).
Guice, John (1999) 'Designing the Future: The Culture of New Trends in Science and Technology', *Research Policy* 28: 81–98.
Haseltine, William (1998) 'Not Quite Pharmacogenetics' letter, *Nature Biotechnology* 16: 1295.
Hedgecoe, Adam (2002) 'Reinventing Diabetes: Classification, Division and the Geneticization of Disease', *New Genetics and Society* 21(1) (April): 7–27.
Hedgecoe, Adam (2003) 'Terminology and the Construction of Scientific Disciplines: The Case of Pharmacogenomics', *Science, Technology and Human Values* 28(4) (in press).
Hinde, Annabel (2000) 'Evolution, not Revolution', *Trends in Biotechnology* 18(6): 230–31.
Housman, David and Fred Ledley (1998) 'Why Pharmacogenomics? Why Now?', *Nature Biotechnology* 16: 492–93.
Hughes, Thomas (1987) 'The evolution of Large Technical Systems', in Bijker et al. (1987): 51–82.
Ingelman-Sundberg, Magnus (2001) 'Pharmacogenetics: An Opportunity for a Safer and More Efficient Pharmacotherapy', *Journal of Internal Medicine* 250: 186–200.
Issa, Amalia (2000) 'Ethical Considerations in Clinical Pharmacogenomics Research', *Trends in Pharmacological Science* 21: 247–49.

Issa, Amalia (2002) 'Ethical Perspectives on Pharmacogenomic Profiling in the Drug Development Process', *Nature Reviews Drug Discovery* 1(4) (April): 300–08.
Issa, Amalia and Edward Keyserlingk (2000) 'Apolipoprotein E Genotyping for Pharmacogenetic Purposes in Alzheimer's Disease: Emerging Ethical Issues', *Canadian Journal of Psychiatry* 45: 917–22.
Jazwinska, Elizabeth (2001) 'Exploiting Human Genetic Variation in Drug Discovery and Development', *Drug Discovery Today* 6(4) (February): 198–205.
Jones, Judith K. (2001) 'Pharmacogenetics and Pharmacoepidemiology', *Pharmacoepidemiology and Drug Safety* 10(5) (August/September): 457–61.
Kalow, Werner (1990) 'Pharmacogenetics: Past and Future', *Life Sciences* 47: 1385–97.
Kalow, Werner (2001) 'Pharmacogenetics in Perspective', *Drug Metabolism and Disposition* 29(4) (April): 468–70.
Kaplan, Jean-Claude and Claudine Junien (2000) 'Genomics and Medicine: An Anticipation. From Boolean Mendelian Genetics to Multifactorial Molecular Medicine', *Comptes Rendus de l'Academie des Sciences (Paris) Series III* 323(12) (December): 1167–74.
Kleyn, Patrick and Elliot Vesell (1998) 'Drug Variation as a Guide to Drug Development', *Science* 281 (18 September): 1820–21.
Kozma, Chahira (2001) 'Genetic Testing and Disease State Management', *Managed Care Interface* 14(11): 54–57.
Kreeger, Karen Young (2001) 'Scientific, Ethical Questions Temper Pharmacogenetics', *The Scientist* 15(12) (11 June): 32.
Krynetski, Eugene and William Evans (1999) 'Pharmacogenetics as a Molecular Basis for Individualized Drug Therapy: The Thiopurine S-Methyltransferase Paradigm', *Pharmaceutical Research* 16: 342–49.
Kuivenhoven, Jan Albert, J. Wouter Jukema, Aeilko Zwinderman, Peter de Knijff, Ruth McPherson, Albert Bruschke, Kong Lie and John Kastelein (1998) 'The Role of a Common Variant of the CETP Gene in the Progression of Coronary Artherosclerosis', *New England Journal of Medicine* 338(2) (8 January): 86–93.
Kurth, Janice (2000) 'Pharmacogenomics: Future Promise of a Tool for Identifying Patients at Risk', *Drug Information Journal* 34: 223–27.
Lavori, P., H. Krause-Steinrauf, M. Brophy, J. Buxbaum, J. Cockroft, D.R. Cox, L. Fiore, H. Greely, H. Greenberg, E. Holmes, L. Nelson and J. Sugarman (2002) 'Principles, Organization, and Operation of a DNA Bank for Clinical Trials: A Department of Veterans Affairs Cooperative Study' *Controlled Clinical Trials* 23(3) (June): 222–39.
Lea, Dale (2000) 'A New World View of Genetics Service Models', *Online Journal of Issues in Nursing* 5(3) (September): 5.
Lichter, Jay and Janice Kurth (1997) 'The Impact of Pharmacogenetics on the Future of Healthcare', *Current Opinion in Biotechnology* 8: 692–95.
Liggett, Stephen (2001) 'Pharmacogenetic Applications of the Human Genome Project', *Nature Medicine* 7(3): 281–83.
Lindpaintner, Klaus (1999) 'Genetics in Drug Discovery and Development: Challenge and Promise of Individualizing Treatment in Common Complex Disease', *British Medical Bulletin* 55(2): 471–91.
Lindpaintner, Klaus, Elizabeth Foot, Mark Caulfield and Ian Hall (2001) 'Pharmacogenetics: Focus on Pharmacodynamics', *International Journal of Pharmaceutical Medicine* 15: 74–82.
McCarthy, Alun (2000) 'Pharmacogenetics: Implications for Drug Development, Patients and Society', *New Genetics and Society* 19(2) (August): 135–43.
MacKenzie, Donald and Judy Wajcman (1999) *The Social Shaping of Technology* (Buckingham: Open University Press. Second edition).
McLeod, Howard L. and William E. Evans (2001) 'Pharmacogenomics: Unlocking the Human Genome for Better Drug Therapy', *Annual Review of Pharmacology and Toxicology* 41: 101–21.
Mancinelli, Laviero, Maureen Cronin and Wolfgang Sadée (2000) 'Pharmacogenomics: The Promise of Personalized Medicine', *AAPS Pharmsci* 2(1) (7 March), Article 4.

Marshall, Andrew (1997) 'Getting the Right Drug into the Right Patient', *Nature Biotechnology* 15: 1249–52.
Martin, Paul (1998) 'From Eugenics to Therapeutics: The Impact of Opposition on the Development of Gene Therapy in the USA', in Wheale et al. (1998): 139–58.
Martin, Paul (1999) 'Genes as Drugs: The Social Shaping of Gene Therapy and the Reconstruction of Genetic Disease', *Sociology of Health and Illness* 21: 517–38.
Martin, Paul (2001a) 'Genetic Governance: The Risks, Oversight and Regulation of Genetic Databases in the UK', *New Genetics and Society* 20(2) (August): 157–83.
Martin, Paul (2001b) 'Great Expectations: The Construction of Markets, Products and User Needs During the Early Development of Gene Therapy in the USA', in Coombs et al. (2001): 38–67.
Meyer, Urs (1990) 'Molecular Genetics and the Future of Pharmacogenetics', *Pharmaceutical Therapies* 46: 349–55.
Meyer, Urs (2000) 'Pharmacogenetics and Adverse Drug Reactions', *The Lancet* 356(11) (11 November): 1667–71.
Michael, Mike (2000) 'Futures of the Present: From Performance to Prehension', in Brown et al. (2000): 21–39.
Motulsky, Arno (1978) 'Bioethical Problems in Pharmacogenetics and Ecogenetics', *Human Genetics* Supplement 1: 185–92.
Moyses, Chris (1999) 'Pharmacogenetics, Genomics, Proteomics: The New Frontiers in Drug Development', *International Journal of Pharmaceutical Medicine* 13: 197–202.
Myers, Martin (2000) 'Use of Polymorphism Analysis Required Ethical Guidelines', *British Medical Journal* 321 (12 August) 12: 453.
Nebert, Daniel (1997) 'Pharmacogenetics: 65 Candles on the Cake', *Pharmacogenetics* 7: 435–40.
Nebert, Daniel and Eula Bingham (2001) 'Pharmacogenomics: Out of the Lab and Into the Community', *Trends in Biotechnology* 19(12): 519–23.
Norton, Ronald (2001) 'Clinical Pharmacogenomics: Applications in Pharmaceutical R&D', *Drug Development Today* 6(4) (February): 180–85.
Oestreicher, Paul (2001) '4th Annual Pharmacogenomics and Medicine Lectures', *Pharmacogenomics* 2(3) (August): 291–96.
Persidis, Aris (1998a) 'The Business of Pharmacogenomics', *Nature Biotechnology* 16: 209–10.
Persidis, Aris (1998b) 'Pharmacogenomics and Diagnostics', *Nature Biotechnology* 16: 791–92.
Persing, Brady and Denis Cheek (2000) 'Pharmacogenomics', *Nursing Clinics of North America* 35(4): 975–80.
Pfost, Daniel, Michael Boyce-Jacino and Denis Grant (2000) 'A SNPshot: Pharmacogenetics and the Future of Drug Therapy', *Trends in Biotechnology* 18: 334–38.
Phillips, Kathryn, David Veenstra, Eyal Oren, Jane Lee and Wolfgang Sadée (2001) 'Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review', *Journal of the American Medical Association* 286(18) (14 November): 2270–79.
Pinch, Trevor and Wiebe Bijker (1984) 'The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology Might Benefit Each Other', *Social Studies of Science* 14: 399–441.
Poirier, Judes, Marie-Claude Delisle, Isabelle Aubert, Martin Farlow, Debmoi Lahir, Siu Hui, Phillipe Bertrand, Josephine Nalbantoglu, Brian Gilfix and Serge Gauthier (1995) 'Apolipoprotein E4 Allele as a Predictor of Cholinergic Deficits and Treatment Outcome in Alzheimer Disease', *Proceedings of the National Academy of Sciences* 92: 12260–64.
PriceWaterhouse Coopers (1999) *Healthcast 2010: Smaller World, Bigger Expectation*, www.pwchealth.com. Accessed 27 January 2003.
Regalado, Antonio (1999) 'Inventing the Pharmacogenomics Business', *American Journal of Health System Pharmacy* 56: 40–50.

Renegar, Gaile, Patricia Rieser and Penelope Manasco (2001a) 'Family Consent and the Pursuit of Better Medicines Through Genetic Research', *Journal of Continuing Education in the Health Professions* 21(4) (Fall): 265–70.
Renegar, Gaile, Patricia Rieser and Penelope Manasco (2001b) 'Pharmacogenetics: The Rx Perspective', *Expert Reviews in Molecular Diagnosis* 1(3) (September): 255–63.
Richards, Tessa (2001) 'Three Views of Genetics: The Enthusiast, the Visionary and the Sceptic', *British Medical Journal* 322 (28 April): 1016–17.
Rioux, Patrice (2000) 'Clinical Trials in Pharmacogenetics and Pharmacogenomics: Methods and Applications', *American Journal of Health System Pharmacy* 57(9): 887–98.
Robertson, John (2001) 'Consent and Privacy in Pharmacogenetic Testing', *Nature Genetics* 28(3): 207–09.
Roses, Allen (2000a) 'Pharmacogenetics and the Practice of Medicine', *Nature* 405 (15 June): 857–65.
Roses, Allen (2000b) 'Pharmacogenetics and Future Drug Development and Delivery', *The Lancet* 355 (15 April): 1358–61.
Roses, Allen (2002) 'Genome-based Pharmacogenetics and the Pharmaceutical Industry', *Nature Reviews Drug Discovery* 1: 541–49.
Rothstein, Mark and Phyllis Griffin Epps (2001) 'Ethical and Legal Implications of Pharmacogenomics', *Nature Reviews Genetics* 2: 228–31.
Rusnak, James, Robert Kisabeth, David Herbert and Denis McNeil (2001) 'Pharmacogenomics: A Clinician's Primer on Emerging Technologies for Improved Patient Care', *Mayo Clinic Proceedings* 76: 299–309.
Sadée, Wolfgang (1999) 'Pharmacogenomics', *British Medical Journal* 319 (13 November): 1–4.
Salter, Brian and Mavis Jones (2002) 'Human Genetic Technologies, European Governance and the Politics of Bioethics', *Nature Reviews Genetics* 3(10): 808–14.
Schmitz, Gerd, Charalampos Aslanidis and Karl Lackner (2001) 'Pharmacogenomics: Implications for Laboratory Medicine', *Clinica Chimica Acta* 308: 43–53.
Shelling, Andrew (1997) 'Role of p53 in Drug Resistance in Ovarian Cancer', *The Lancet* 349 (15 March): 744–45.
Shook, David (2001) 'The Personalized Future of Medicine', *Business Week Online* 16 August 2001.
Steimer, Werner and Julia Potter (2002) 'Pharmacogenetic Screening and Therapeutic Drugs', *Clinica Chimica Acta* 315: 137–55.
Stern, Curt (1971) 'The Place of Genetics in Medicine', *Annals of Internal Medicine* 75(4): 623–29.
Thomas, Sandy (2001) 'Pharmacogenetics: The Ethical Context', *Pharmacogenomics Journal* 1(4): 239–42.
van Lente, Harro (1993) *Promising Technology: The Dynamics of Expectations in Technological Development* (Enschede: Department of Philosophy of Science and Technology University of Twente).
van Lente, Harro and Arie Rip (1998) 'The Rise of Membrane Technology: From Rhetorics to Social Reality', *Social Studies of Science* 28(2): 221–54.
van Ommen, G. (2000) 'Human Genetics in Health Care', *European Journal of Pediatrics* 159 Suppl 3: S170–72.
Weber, Wendell (2001) 'The Legacy of Pharmacogenetics and Potential Applications', *Mutation Research* 479: 1–18.
Weinshilboum, R. (2002) 'The Genomic Revolution and Medicine', *Mayo Clinic Proceedings* 77(8): 745–46.
Wheale, Peter, Rene von Schomberg and Peter Glasner (eds) (1998) *The Social Management of Genetic Engineering* (Ashgate Publishing, Ashgate).
Wieczorek, Stacey and Gregory Tsongalis (2001) 'Pharmacogenomics: Will It Change the Field of Medicine?', *Clinica Chimica Acta* 308: 1–8.
Wolf, C. Roland, Gillian Smith and Robert Smith (2000) 'Pharmacogenetics', *British Medical Journal* 320 (8 April): 987–90.

Wortman, Marc (2001) 'Medicine Gets Personal', *MIT Technology Review* January/February http://www.technologyreview.com/articles/wortman0101.asp.
Wyatt, Sally (2000) 'Talking About the Future: Metaphors of the Internet', in Brown et al. (2000): 109–26.

Adam Hedgecoe is Senior Lecturer in the Institute for the Study of Genetics, Biorisks and Society (IGBiS), University of Nottingham. He undertook postgraduate training in molecular biology and gained experience of health policy analysis before moving to SPRU, University of Sussex, where he studied a range of emerging genetic technologies. He currently holds grants on *The Clinical and Commercial Development of Pharmacogenetics* and *The Impact of Genomics on Innovation in the Pharmaceutical Industry*. His main research interests focus on the development, commercialization and regulation of emerging biotechnologies.

Address: Department of Sociology, University of Sussex, Falmer, Brighton, BN1 9RH, UK; email: A.M.Hedgecoe@sussex.ac.uk.

Paul Martin is a Lecturer in the Department of Sociology at the University of Sussex, where he is completing a Wellcome Trust Postdoctoral Research Fellowship. For his Ph.D. and the early parts of his fellowship he was based at the Department of Science and Technology Studies, University College London, and he is interested in the social construction of disease, the representation and regulation of genetic technologies and the relationship between bioethics and the social sciences. His current research investigates the role of pharmacogenetics in the genetic reclassification of common disease.

Address: Institute for the Study of Genetics, Biorisks and Society (IGBiS), University of Nottingham, Nottingham, UK.