

## Context, ethics and pharmacogenetics

Article (Unspecified)

Hedgecoe, A. M. (2006) Context, ethics and pharmacogenetics. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*, 37 (3). pp. 566-82. ISSN 1369-8486

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Context, Ethics and pharmacogenetics

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## **1. Introduction**

Since the rise of modern bioethics, the usual approach to an assessment of the ethical issues relating to any new technology involves debates over the meanings of particular terms (for example, the differences, if any, between therapeutic and reproductive cloning), speculation as to the possible harms that may arise, and the application of various ethical theories to help decide how to use the technology in question. While this article is not the place to rehearse the problems with this kind of approach (Fox and Swazey 1984; Hoffmaster 1992, 1994), I want to show how an alternative, empirically based, take on the ethics of a particular technology (pharmacogenetics) strengthens the case made by those who claim that the social sciences have an important role to play in exploring the ethical issues surrounding new technologies (Haimes 2002; DeVries and Conrad 1998; Zussman 2000).

The core theme of this kind of research is that the ethical problems associated with a particular technology can only be seen in the context in which that technology is actually used. Since most bioethical reasoning ‘strips away’ the, supposedly extraneous, background and context to any particular case, the kinds of ethical issues raised bear little relation to the actual problems faced by clinicians. As a result, having presented the ethical problems linked to pharmacogenetics, as seen by scientific commentators and bioethicists, this article then presents interview data with clinicians and researchers from Alzheimer’s disease and Breast cancer, to show how they view the ethics of pharmacogenetics.

The broad theoretical structure for the research project this article comes from is a constructivist approach to the sociology of technology, summed up as the ‘social shaping of technology’ (Bijker, Hughes and Pinch 1987; Bijker and Law 1992). But in the case of this particular article, the ideas underpinning my approach are derived from the work of James Lindemann Nelson and Robert Zussman, who raise important issues for how we assess the ethical impact of particular technologies. In essence, this article is written in

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reaction to the 'linear model' of bioethics decision making, where social scientists provide accurate and interesting descriptions of the lived clinical world, which philosophers then 'programme' into their ethical theories, to produce the finished 'right' (in two sense of the word) answer (Nelson 2000). In such a model, the social scientist becomes "a junior partner to the philosopher, someone who responds to ideas generated elsewhere but who generates few if any of his or her own" (Zussman 2000:10).

The alternative is a contextual approach, which assumes that ethical decisions are not made in some sort of vacuum, but arise in particular social, technical and cultural situations. From this point of view, the place to start any enquiry into healthcare ethics is at the clinical 'coalface', where ethical decisions about, in this case, the use of genetic tests to govern the prescription of pharmaceutical products, are made. By rooting analysis in the decisions that clinicians actually make, we can avoid the feeling that sometimes occurs with more philosophical bioethics, that clinicians exist in some sort of amoral desert until the bioethicist turns up to tell them what they should be doing. The danger of the kind of approach used in this article is that one might lose the critical 'teeth' that bioethics brings when it comes from outside a particular situation. If our ethical assessment is rooted in a particular context, then we run the risk of conservatively simply supporting current clinical practice, regardless of its ethical impact (Zussman 2000: 10). The trick is, as in so many cases, a question of balance.

## **2. Pharmacogenetics: Science And Ethics**

### **Commentators**

One interesting part of the debate around pharmacogenetics and pharmacogenomics is the large number of review articles, or commentaries, written by academic and industry scientists. These articles do not present new research results, but rather act as a forum to discuss the direction this new technology is going in and the challenges that have to be faced if pharmacogenetics is to make its way into the clinic (Hedgecoe 2003).

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One important element of these commentaries is discussion of the ethical issues raised by pharmacogenetics; while not all these articles refer to ethical issues, it is not unusual to find a pharmacologist or senior pharmaceutical company scientist, writing in a science journal, speculating about the ethical impact the use of pharmacogenetics may have on clinical practice.

For the biotechnology and pharmaceutical industries the ethical issues associated with genetic testing are more than just simple talking points, elements of a background discourse. Since the backlash against genetically modified food in Europe, industry has become painfully aware of the possible problems that might arise from failing to take public opinion seriously. In the case of a new genetic technology like pharmacogenetics, the ethical debate is an integral part of bringing a product to market (Hedgecoe and Martin, 2003). One commentator goes so far as to suggest that the reasons why industry has been resistant to adopting pharmacogenetics as part of drug development lie with “the major societal and ethical considerations of DNA analysis and the regulatory impact of genetics analysis” (Jazwinska 2001: 202).

The consistent theme in scientists’ discussion about the ethics of pharmacogenetics is the need to distinguish pharmacogenetics from other, usually more problematic, technologies. The first distinction is between genetic testing as a whole and more controversial technologies with the word ‘genetic’ in their name. As Allen Roses, Glaxo-SmithKlines’s Vice-president for Genomics, and a major proponent of pharmacogenetics puts it: “This is not gene therapy or genetically modified foods or genetic engineering” (Roses 2000: 1361). An important element of this distinction is the need to educate the public: “The lessons learned from the public’s outcry to genetically modified food may help refine strategies...that are used to educate both the public and the healthcare professionals alike” (Akhtar 2002:299).

This process of distinction continues as commentators seek to separate pharmacogenetics from ‘traditional’ genetic testing which focuses on disease risk and susceptibility. It is regarded as “important to make a clear distinction between the ethical implications of

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testing for disease predisposition...and those surrounding tests whose goal is simply to predict the effectiveness of therapies for existing conditions” (Pfof, Boyce-Jacino and Grant 2000:337). Sir Richard Sykes, Chairman of Glaxo-SmithKline, is clear about this when he suggests that “Pharmacogenetics applications will only measure how a patient will respond to a medicine. Thus they are quite distinct from those [genetic] tests considered over the past two decades” (Sykes 1999).

The means by which distinction is most clearly drawn is on the grounds of novelty. Firstly, one can substitute a term like ‘pharmacogenomics’ for the more old fashioned (coined in 1959) ‘pharmacogenetics’. While there are no *intrinsic* differences between the two terms, the ‘-omics’ in pharmacogenomics implies novelty and a separation from what has gone before (Hedegco 2003). In addition, many of these review articles discuss the new technologies that will make pharmacogenetics cost effective and clinically practical: Single Nucleotide Polymorphisms (SNPs), DNA arrays and bio-informatics. The exact nature of these new technologies is less important to the current argument than the fact that they are presented as revolutionary, novel spin-offs from the Human Genome Project.

As in the previous case of distinguishing testing from GM crops, the motivation is a need to clarify issues for the public, lest they become confused, or panic: “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 2000: 1361). And this is a viewpoint that has already been tacitly accepted by, at least some regulators. The European Medical Evaluation Agency (EMA) suggests that “It is important to distinguish between genetic testing for the diagnosis or prognosis of disease and the form of genetic testing performed for pharmacogenetics...generally carries a different magnitude of social, legal and ethical considerations for the patient” (EMA 2000).

Of course, one alternative to this is to accept that there may be important ethical problems with pharmacogenetics, but that they are over-ridden by the benefits that will arise: “the

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great potential gains from pharmacogenomics, in terms of both patient well-being and cost of healthcare, heavily outweigh the risks” (McLeod and Evans 2001: 115). Linked to this is the idea that current restrictions on genetic information are preventing such benefits coming about: “Requirements for confidentiality and limitation of using this [genetic] data...place major constraints on our ability to generate meaningful data...Clearly the need for education, information, and teaching about genetics is large and evident, to put risks in perspective and illuminate the potential benefits of our growing knowledge” (Lindpaintner 1999: 487). One obvious ethical result of the benefits brought by pharmacogenetics is that “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, Smith and Smith 2000: 989)

But it is important to note that some scientific commentators take quite different views and accept that “The pharmacogenomic approach is not without its challenges, not the least of which are the ethics questions surrounding the privacy of genetics data” (Anderson, Fitzgerald and Manasco 1999:267). One point made by these writers is that it is not necessarily the case that a clear line can be drawn between a pharmacogenetic test, and a test for disease susceptibility: “After all, polymorphisms relevant to drug response may overlap with disease susceptibility, and divulging such information could jeopardise an individual” (Sadée 1999:3). Such overlaps may well be the exception rather than the rule. After all “in pharmacogenomics we are normally only looking at genes in relation to a drug’s metabolism or mechanism of action” but this does not rule the possibility that “polymorphisms related to drugs could also be related to diseases” (Rioux 2000:896).

### **Ethicists**

Although the ethical debates around pharmacogenetics are largely being set by scientific and commercial considerations (Hedgecoe and Martin 2003), this is not to say that bioethicists have not begun to explore some of the potential problems that may arise with this new technology. As a result, there are a number of articles focusing specifically on the possible ethical, issues raised by pharmacogenetics, as well as at

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least one edited collection (Rothstein 2003), and two reports by committees, one in the US (Buchanan et al 2002.) and one in the UK (Nuffield Council on Bioethics 2003).

Most of these pieces emphasise the ethical issues involved in pharmacogenetic research, specifically, debates surrounding informed consent. Given that informed consent is a 'classic' issue in clinical trials of all kind, this makes a great deal of sense. In the case of pharmacogenetics, the worries are that participants may not understand the reason their DNA is being sampled, or that the imprecise nature of much pharmacogenetic research means that by definition, it is not possible to give participants full information about the uses to which their DNA may be put. Related to this is the concern that if participants in a clinical trial are not given adequate privacy, then their genetic data may 'leak' into the broader community; even if this information is not relevant for disease diagnosis, it may still lead to social or financial stigmatisation (Rothstein and Epps 2001). One solution to this is to ensure that the participants' DNA, personal and medical data are encoded or encrypted in such a way to prevent any infringement of privacy. But 'full anonymisation' (i.e. the removal of all identifiers, making tracing the participant all but impossible) prevents researchers feeding-back results to patients. Since "it could be argued that researchers have an obligation to pass useful research findings to study participants" (Clarke et al. 2001: 91), there is clearly a tension between two different sets of values. Researchers need to protect participants' anonymity, while at the same time ensuring that any positive results from the trial can be fed back. This tension between the needs of the researchers and the protection of confidentiality or privacy crops up in a number of recent ethical reviews (Robertson, 2001; Issa, 2000; Vaszar, Rosen and Raffin 2002; The Consortium on Pharmacogenetics, 2002).

Ethicists have also, to a lesser degree, discussed the potential problems that may arise from the clinical application of pharmacogenetics. Although some authors do emphasise the possible personal implications of clinical pharmacogenetics such as the impact on insurance (e.g. Robertson, 2001; Clarke et al. 2001), most focus on the broader, systemic issues that will arise, such as physician (and pharmacist) education, the direct marketing



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of pharmacogenetic tests to the public and possible issues of legal liability (The Consortium on Pharmacogenetics, 2002; Brushwood 2003; Palmer 2003).

The aim of the rest of this paper is to explore the degree of overlap between the issues raised by bioethicists and scientific commentators, and the problems of pharmacogenetics faced by those clinicians who are beginning to use this technology. By comparing and contrasting the experiences, attitudes and values of those who are using pharmacogenetics with the opinions of those speculating about it, I hope to be able to orient ethical debates around this new technology towards clinical reality. At same time, although there are good reasons for focusing on the two case studies presented here, we should be cautious about thinking that these two instances will highlight all the ethical problems that will come with the clinical adoption of this new technology. Pharmacogenetics has to be seen as an extremely heterogeneous technology, and as a result, drawing sweeping generalisations about its social impact is rather difficult.

### **3. Two Cases: Alzheimer's Disease And Breast Cancer.**

The two case studies I explore in the rest of this article involve Alzheimer's disease and Breast cancer. More specifically, they revolve around: a family of drugs called AcetylCholinesterase Inhibitors and the APOE gene, in Alzheimer's; and the drug Herceptin and the HER2 gene in the case of breast cancer. These two cases cover a number of features that scientific commentators suggest occur in pharmacogenetics. In the case of Alzheimer's, pharmacogenetics involves the retrospective application of genetic testing to already licensed products, an overlap between a 'pharmacogenetic' gene and a more traditional 'disease gene', with different companies having the rights to the drugs and the genetic test. In contrast, Herceptin is a drug specifically designed to interact with a particular gene product, where the manufacturer of the drug also licenses the test and where the drug concerned has made it through the drug approval process as a pharmacogenetic product. In addition both disease are widespread, and incur significant treatment costs. If pharmacogenetics becomes commonly used in the clinic, it will be in these kinds of cases.

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Alzheimer's disease (AD) is a progressive neurological disorder characterised by a slow, steady deterioration in cognitive skills, such as language and memory, leading to depression, psychosis or other behavioural disturbances, and finally death. The risk of developing AD increases proportionally with age, with one estimate suggesting a prevalence of between 0.82 and 1.08% in over 65s in Europe, with the number of AD sufferers in the UK put at around half a million people and the current total cost in the US put at \$100 Billion per year (Johnson, Davis and Bosanquet 2000).

Although there are three clear familial types of AD, they account for less than 5% of all cases (Richard and Amouyel 2001). The vast majority of Alzheimer's cases are 'sporadic' in that the cause is unknown although possible risk factors have been listed as: age, previous head injury, ingesting Aluminium and particular versions of the protein apolipoprotein E (Richard and Amouyel 2001). This protein is coded for by the gene APOE on chromosome 19, and is involved in the regulation of cholesterol levels in the body. Three versions (or 'alleles') of the APOE gene have been identified (E2, E3 and E4) with APOE E4, which occurs in 15% of the population, associated with an increased risk of developing sporadic Alzheimer's disease.<sup>1</sup>

Although the exact mechanism is still a mystery, it is widely accepted among medical professionals and geneticists that homozygotes for E4 (i.e. people who carry two copies) have an increased of developing AD when compared to non-E4 carriers, as do heterozygotes for E4 (i.e. one copy) although to a lesser extent. There are also claims that when APOE E4 carriers develop Alzheimer's disease, they do so earlier, and with a greater age-related decline than other cases of AD (Saunders et al 1993; Noguchi, Murakami and Yamada 1993; Smith 2000).

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<sup>1</sup> Terminology around APOE can vary, but the convention seems to be that the protein, apolipoprotein E is shortened to apoe (i.e. lower case) while the gene involved is always uppercase APOE, with its different alleles referred to as E, or epsilon, or  $\epsilon$ .

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At the same time as researchers were connecting APOE4 to increased risk of Alzheimer's disease, the pharmaceutical company Warner-Lambert was preparing to launch the first Alzheimer's drug treatment. Tacrine, as the product was called, is one of a family of compounds called acetyl cholinesterase (AChE) inhibitors, which act as symptomatic treatment for Alzheimer's disease. Since Tacrine's launch in 1993, three more drugs from the same family have been licensed: Donepezil (marketed as 'Aricept' by Pfizer); Rivastigmine ('Exelon'; Novartis); and Galantamine ('Reminyl': Janssen).

In 1995, a research team headed by Judes Poirier at McGill University announced that they had discovered a link between APOE status and response to Tacrine (Poirier et al. 1995). It had always been a problem with Tacrine (and the other acetyl cholinesterase inhibitors) that there was a wide range of response to the drug, with up to 50% of patients not improving significantly when treated (Farlow et al 1992). What the McGill group had done was stratify the response rates from a clinical trial of Tacrine according to APOE status. They found that ">80% of apoE4-negative AD patients showed marked improvement after 30 weeks" whereas "60% of apoE4 patients were unchanged or worse after 30 weeks" (Poirier et al 1995: 12260 & 12263). As a result, APOE E4 status "may be a useful predictor to clinical outcome of...therapies" (Poirier et al 1995:12264).

The Poirier paper has proved to be extremely popular with commentators on pharmacogenetics, described as "one of the most widely cited pharmacogenomic studies" (Evans and Johnson 2001: 27), and with the ISI science citation index showing that the 1995 Poirier article has been cited over 265 times, including over 100 citations since the beginning of 2000. With some authors even suggesting that pharmacogenetic testing for APOE4 is currently in use in the clinic (Ensom, Chang and Patel 2001), Alzheimer's disease would seem to be a good example to test clinicians' attitudes towards the ethics of pharmacogenetics.<sup>2</sup>

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<sup>2</sup> This story is complicated by the fact that very few of the clinicians I spoke to believe that there is a link between APOE status and response to Tacrine. There are a number of reasons for this, including replication failures, the phasing out of Tacrine in clinical treatment, and ethical worries on the part of clinicians. However the Poirier paper has stimulated a great deal of interest in this area, and all new Alzheimer's drugs are tested for a pharmacogenetic link to E4 in clinical trials, with a number of possible candidates coming through.

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My second case study, that of breast cancer, is rather different from Alzheimer's disease. To start with, the drug involved, Herceptin, was developed with the intention of being prescribed to a genetically identified sub-group of patients; Herceptin was always seen as a pharmacogenetic drug. Initially developed by the biotech firm Genentech, Herceptin is now marketed in Europe by Roche, and currently has sales of £460 million a year, making it Roche's fifth biggest selling drug (Guardian 2003). As the first pharmacogenetic drug licensed in the US (in 1998) and the UK (a year later), Herceptin is often cited as a pharmacogenetic success story, although such a claim rather glosses over the number of times the drug was almost cancelled during development (Bazell 1998).

Initially, some industry scientists balked at the idea of Herceptin being described as pharmacogenetics, or pharmacogenomics. For them, the fact that HER2 testing measures, in the first instance at least, protein levels, and that the genetic component (HER2 over-expression) is not an inherited genetic difference makes Herceptin as case of "not quite pharmacogenomics" (Haseltine 1998; Rusnak et al 2001: 304). Others have described this as "a difficult argument to follow" suggesting that it is "neither helpful [n]or meaningful" (Lindpaintner et al 2001: 77). An increasing number of scientists seem quite happy to cite Herceptin as an example of pharmacogenetics (e.g. Sadee 1999; Shi, Bleavins and Iglesia 2001; Ginsburg and McCarthy 2001; Akhtar 2002). And it is clearly a good enough example of pharmacogenomics to be so described in an editorial by the editors of *Nature Biotechnology* (Anon, 1998).

Herceptin is designed to neutralise large amounts of a protein called Human Epidermal growth factor Receptor 2, or HER2. This protein, and the gene that codes for it (also called HER2) are present in normal human tissue, and play a vital role in controlling cell division and growth. In upto 30% of breast cancers, the body appears to making far too much HER2 protein, which in turn stimulates tumour growth and produces a more aggressive form of cancer, associated with more relapses and worse prognosis. Herceptin interferes with HER2 over-expression and stimulates the immune system to attack HER

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overexpressing cells, and though not a cure, the drug reduces tumour size and improves live expectancy.

Exactly why some people's HER2 genes begin to over-express is not clear, but it seems to be the result of an external factor: HER2 over-expression is not an inherited feature of people's genomes, and is thus not something that can be passed from mother to daughter. Because HER2 status is a feature of the tumour, HER2 testing involves use of breast biopsy material (usually taken upon initial diagnosis). The first line of testing, immunohistochemistry (IHC) uses antibodies to detect HER2 protein levels in a slice of biopsy material. If this test is unclear, then Fluorescent In-Situ Hybridisation (FISH), which detects levels of the HER2 gene is used.

#### **4. Themes**

##### **What do you tell people?**

Respecting patients' autonomy in making decisions over treatment, and getting their 'informed consent' is at the core of modern medical ethics. Both in terms of the rules laid down for ethical clinical practice (Levine 1988; Smith, 1999) and in philosophically based medical ethics (e.g. Beauchamp and Childress 2001), the need to get informed consent from patients is crucial. Yet a considerable amount of empirical research suggests just how hard it is to decide exactly what counts as 'informed' consent (see Sugarman et al 1999 for a bibliography). And this is certainly a question raised by my interviews. More importantly, what happens when informed consent comes up against other values, which are perhaps equally deeply rooted in a particular clinical community?

Even before I began interviewing, I could spot a possible ethical problem to do with the use of APOE4 testing in the clinic for pharmacogenetic purposes. Since the elucidation of the link between APOE4 and increased risk of late-onset AD, the professional community surrounding Alzheimer's has been extremely resistant to the use of APOE testing in the clinic. The argument goes that the test is only for a risk factor: there are

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many people, between 23 – 68%, with Alzheimer’s who do not carry the APOE4 allele, and many E4 carriers who never develop Alzheimer’s, the test can play no useful part in clinical diagnosis or treatment (Ritchie and Dupuy 1999). Over the years there have been a number of professional consensus meetings which have re-affirmed this point (Farrer, Brin, Elsas et al. 1995; Brodaty, Conneally, Gauthier, et al. 1995; Relkin, Kwon, Tsai and Gandy 1996; Post, Whitehouse, Binstock, et al. 1997; McConnell, Koenig, Greely and Raffin 1998; The Ronald and Nancy Reagan Research Institute of the Alzheimer’s Association and the National Institute on Aging Working Group 1998). For most professionals working in Alzheimer’s disease, the clinical use of APOE 4 testing is irresponsible and unethical.

Yet despite the high profile nature of this consensus position, the ethical issues involved in introducing a pharmacogenetic test for APOE4 into the clinic seem to have escaped the notice of most of those commentators only too happy to cite Alzheimer’s disease, APOE and Tacrine as a good example of pharmacogenetics.<sup>3</sup> From talking to clinicians involved in the treatment and care of, as well as research into, Alzheimer’s patients, it is clear that these ethical problems have not escaped their notice. This is perhaps best illustrated by the mini-scenario painted for me by my interviewee Clinician-Researcher 4, who acted out both sides of the following conversation:

“Supposing you know that lack of APOE4 predicts response, if you do this, and depending on what age group etc. you do their APOE4 and you find out they’re 3/4, or 2/4 or 4/4:

‘Right, sorry you’re not getting treatment.’

‘Well, why am I not getting treatment?’

‘Because of your genotype that doesn’t respond.’

‘Well, what is that genotype?’

‘OK, so it’s 4/4.’

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<sup>3</sup> An exception to this is Patrice Rioux, who notes that “a person’s apolipoprotein E genotype could have an impact on drug treatment by acetylcholinesterase inhibitors but also seems to be a risk factor for early onset of Alzheimer’s disease” (Rioux 2000: 896). On the bioethics front, Issa and Keyserlingk (2000) provide a detailed discussion.

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‘What does that genotype mean then?’

You won’t get this from the patients. Sometimes when it’s Alzheimer’s, you get it from the family

‘What does that mean then?’

‘APOE4 is associated with a worse vascular outlook and, really, worse prognosis in AD’

Even if you don’t tell them, if they know the genotype, the family will be away [mimes typing at computer], downloading from whatever [web]site. And we see that and you can’t blame them for that’.

And it is this threat to the families of patients that seems to underpin this kind of resistance to pharmacogenetics. As another interviewee puts it: “once you genotype somebody for APOE4, for pharmacogenetics, they would then have access to that result...and then that information becomes known to the rest of the family. And they then, from that information can infer some element of risk” (AD Researcher 1). But why should we be concerned if the families of Alzheimer’s patients learn something about their parent’s genotype, and hence, possibly about their own genetic risk? And how much information could a family member get from such a test?

To answer the second question first: if “you test patient X and you find he’s E4/E4, well then you immediately know that all his children are carrying an E4 allele. So you immediately know they’ve all got a 4 times increased risk of getting Alzheimer’s Disease” (AD Clinician Researcher 1). The trouble comes when one tries to interpret what the idea of a ‘four times risk’ means. It would be easy to see clinicians’ resistance to allowing access to this kind of information as paternalistic, if not patronising, towards the capabilities of members of the public. It may well be just that, but if, so it is an attitude they also have with regard to their medical colleagues:

“it’s difficult for me to even impart the information to psychiatrists. In fact, just before you came, someone said ‘oh, I’ve got someone who’s got a family history, can we do their E4?’ And I said ‘well, why?’ Literally they’ve got the blood in

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their hand and I said ‘well why are you doing it?’ And I’d just given a talk on this, a week ago. They can’t work it out, they can’t work out why I’m saying it’s of no value...” (AD Clinician Researcher 7)

In addition to this, a number of interviewees mentioned difficulties that would arise if insurance companies were to get hold of the results of these pharmacogenetic tests. It is quite conceivable that if APOE4 testing was used to guide treatment decisions, then companies might pay attention to the offspring of people with Alzheimer’s who did not receive acetylcholinesterase inhibitors. The assumption would be that their parent is at least an APOE4 heterozygote, if not a homozygote, and thus their children are at increased risk of carrying the E4 allele themselves, and hence of developing Alzheimer’s. The issue of genetic testing and insurance has a long history in the bioethics literature, and these clinicians’ concerns obviously tie into this. They are also at odds with the perspective of those scientific commentators who claim that pharmacogenetic testing is ‘not like’ disease gene testing, and that it needs to be assessed in different ways.

In contrast to this, the breast cancer clinicians I spoke to expressed no particular concern over the use of HER2 testing, and did not feel the need to inform their patients of exactly what was going to happen. When asked whether they told patients about Herceptin, prior to tissue being sent to the pathology lab for IHC screening, many of the clinicians I spoke to stated that they did not: “The current procedures are that if you’ve got a tumour, the pathologist can do what he wants to it, no one ever suggests that he should ask the patient for permission to do it” (Her2 Clinician Researcher 12 ).

The point is that when a tumour biopsy is done, patients are told that a number of different tests will be run on this material. The question is, why should a HER2 test be singled out for specific attention? One answer might be that HER2 status is known to be a prognostic factor, and that patients may wish to know that such a ‘predictive’ test is being carried out. The problem is, that most of the tests carried out on tumour material have some prognostic role:



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“At the moment we look at lymph-node status, we look at tumour size, we look at tumour grade, of course we know the age of the patient, so in there we’ve got quite a lot of prognostic information and we discuss treatment plans with the patient in the light of that prognostic information” (HER Clinician Researcher 8). In that sense, information on HER2 “will just be added into the equation, trying to make a more accurate determination of what that individual’s prognosis is” (HER Clinician Researcher 1).

While much of the literature about Herceptin suggests that HER2 over-expression is a powerful predictor of disease outcome, it seems to play a much lower-key role in the decision-making processes of these clinicians:

“it’s not like the difference between being node-negative and node-positive, or having a grade 3 rather than a grade 1 tumour, I think it [giving HER2 status] is a needless complication of managing people who are already over-loaded with information. Information over-loading in cancer patients is beginning to be a big issue, I think” (HER Clinician Researcher 6).

This is in direct contrast to what little writing there has been on the ethics of Herceptin which has tended to highlight the special nature of HER2 testing:

“as soon as a patient with breast cancer submits her trastuzumab [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, Foot, Caulfield, and Hall 2001: 81)

For clinicians in the UK’s National Health Service, at least, there is little support for this kind of exceptionalism in the case of HER2 testing, which is seen as just adding more information to the prognostic process, rather than being a make-or-break test. Rather than assuming that ethical theory can settle this debate, perhaps coming down on the side of those commentators who feel that HER2 testing is somehow privileged, a contextual perspective will try and see the problem from ‘inside-out’. We could claim that the

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clinicians' attitudes towards what they tell patients are a simple example of good old fashioned paternalistic medical practice, exactly the kind of thing that medical ethics has been fighting against for the past few decades. Alternatively we could see things from the clinicians' perspective; by not informing their patients about the nature of the test their tissue is about to undergo, their ethical position is underpinned by both practical and epistemological considerations.

Epistemologically, a HER2 test, although a genetic test, is not a test for a gene like APOE4. HER2 over-expression is not inherited, and the result of an individuals' test tells us nothing about their relatives' chances of developing HER2 over-expressing breast cancer. APOE4 is inherited, and thus carries with it quite different ethical concerns. Given this status, quite understandable practical considerations result: if HER2 does not carry with it particular ethical problems, then why should clinicians single it out from the range of other tests run on breast tissue? If it is not singled out then either nothing is said at all, or alternatively, clinicians ought to give their patients in-depth information about each and every test that is going to be performed on their biopsy. This in turn raises issues about how clinicians should best use their time. In the light of these practical considerations, current clinical practice, where patients are informed that some test will be run on their material, but the specific nature of these tests is not spelled out begins to make more 'ethical sense'.

Beyond this, the ethical status of a test is tentative and contingent, dependent in part on whether there is a form of intervention that could be used. For clinicians and others working with Herceptin, such as Pharmacists, one of the most important justifications for the use of HER2 testing is that it then leads onto an intervention. Simply testing a tumour for HER2 status, without access to Herceptin, is of little use:

“there's a world of difference between testing something which might predict the likelihood of a disease or course of that disease when you can't do anything about it, and testing for something because it dictates how you treat something, so it is interesting...it still does have implications; things like insurance and people's

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mental well-being, suddenly changes when you actually have an intervention you can make” (Her2 Pharmacist 2).

Viewed from within the clinic, the availability of an intervention changes the moral status of a diagnostic test:

“in the UK [testing] just hasn't [taken off]... because people can say well we don't really think it makes a difference to management, then there wasn't the mentality to do it. Now I think we have to because you need to know whether that patient down the road is someone who might benefit from the licence indication of the drug” (Her2 Clinician-researcher 4).

Yet even the ethical role of interventions depends upon the context. In the case of Alzheimer's disease, even if the test aids the use of an intervention, the professional ethical consensus still resists it's application.

### **Trust in Numbers:**

The second theme that comes out of empirical research into the ethics of pharmacogenetics, is who gets access to new treatments, and how are these decisions made. In the case of Alzheimer's disease, a major reason for resistance to pharmacogenetics offered up by Alzheimer's professionals is the weakness of the link between APOE4 and non-response to Tacrine. The original Poirier study found that 60% of APOE4 carriers failed to respond to Tacrine after 30 weeks, which means that 40% the carriers did respond. Since E4 carriers make up between 55-70% of Alzheimer's patients, using genetic testing to screen-out E4 carriers as 'non responders' could deny what are still the only licensed drugs for this condition to two-thirds of all patients, when 40% of them (perhaps 28% of the total) may respond.

As far as the clinicians I spoke to were concerned, these kinds of odds are not good enough to deny someone treatment: “Even if there was a 20%, a 10% chance of someone going to get a benefit, well if you were that individual, or closely related to that individual, you'd probably take your chance” (AD Clinician Researcher 5). Having to

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rule patients out on statistical grounds is not a phenomenon new to medicine of course, and as such, we have to set pharmacogenetics within the larger context of current clinical practice:

“We already know there are people who are 20% less likely to respond to all sorts of things but we always give the hope that they might. So at what point does it become clinically acceptable not to give a drug to somebody who is marginally less likely or even significantly less likely to respond?” (AD Clinician Researcher 3)

Of course prescribing policies get set by healthcare providers and funders, and my interviewees accept that “if there were definitive tests that would predict response on a genetic basis, you would get a pressure on from above, at health authority and government level to focus prescribing” (AD Clinician Researcher 4). And such decisions, made at the population level, “needn’t necessarily be congruent with the wishes and needs of the individual, or people closely related to that individual” (AD Clinician Researcher 5). In this sense, the needs of the individual patient are in conflict with those of society at large.

In the case of Herceptin, the pharmacogenetic product is currently being prescribed by clinicians, so in many ways it is subject to the kinds of bureaucratic pressures these interviewees are talking about. These go beyond the issues involved in any normal expensive treatment; the point about pharmacogenetics is that a test will be required for the drug to be prescribed properly. As a result, the current devolution of budgets within healthcare providers can cause problems: “although the Trust has given us funding for the drug, they haven’t given us any funding for the HER-2 testing so... we’re struggling at the moment to try and get some funding for our pathology department to go on to do the HER-2 testing which is not something that’s being done routinely” (HER2 Clinician Researcher 1). It is of course ironic that in this case there is enough money for the relatively expensive treatment, but no budget for the test.

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There are several levels at which Herceptin is controlled and limited, largely on economic grounds. For reasons of both space and the focus of this article, I will concentrate on one particular, clinician lead, approach, which is that of the ‘named prescriber’. In this approach, only a limited number of clinicians in a specific area (covering hospitals sharing the same budget) are deemed expert enough to actually prescribe Herceptin:

“Within [our area], we’ve actually said that the only two people who should instigate prescribing are Dr. Parker and Dr. Cassidy [pseudonyms]. So, we’re actually trying to control the initiation of Herceptin so that we make sure that people are actually FISH 3 positive, have been properly tested, have been through the other options” (Her2 Pharmacist 1).

For the clinicians, this is a solution still allowing their patients access to an expensive drug (£20,000 per year), but displaying a degree of financial responsibility, and forestalling potential attempts from healthcare managers to restrict Herceptin prescription on other grounds. This strategy has echoes of Robert Zussman’s assessment of the tension between financial and medical duties in US based Managed-care organisations, often deemed as morally suspect in bioethical literature:

“physicians do not, for the most part, act as the profit-maximising individuals beloved of classical economic theory...financial incentives...become important only within a collective context as networks of physicians elaborate those incentives into a culture of practice” (Zussman 2000: 9).

Here the problem is the inverse of that in Alzheimer’s disease: rather than clinicians being resistant to a new technology, breast cancer clinicians are keen to prescribe Herceptin, though they realise this needs to be done in such a way as to be acceptable to healthcare funders.

## **Conclusions**

What this small selection of data from my interviews suggests is that introducing pharmacogenetics into the clinic maybe a far more complicated procedure than most commentators seem to admit. The central point is that there is always a context to a

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pharmacogenetic test when it enters a clinical situation. In the case of Alzheimer's disease, this context includes a decade's-worth of debate and restriction on the clinical use of APOE testing, as well as broader medical debates over rationing and evidence based medicine. Herceptin has had a smoother ride, and has made it into the clinic; the ethical problems are very different, partly because of the nature of the genetic test, but also because breast cancer clinicians use significantly more testing than old age psychiatrists. The clinical culture, and thus the ethical issues raised, is quite different. Yet to read most of the literature on pharmacogenetics, while there might be ethical problems with developing products and the storage of genetic material, the actual clinical use of testing is presented as relatively unproblematic.

The contextual approach to ethical issues that I advocated at the beginning of this article turns traditional bioethics on its head: rather than coming to a technology with a set of concepts or an ethical theory in hand, this approach starts from the clinical experience, looking at the ethical aspects of pharmacogenetics as seen by those people beginning to use this new technology. We then need to move outwards, beyond the particular case, to see whether these cases have anything to teach us about theory.

The strongest theoretical element that comes out of this discussion is the role of clinicians' 'resistance' to various aspects of pharmacogenetics. In this context, I am borrowing Beeson and Doksum's development of Foucault's ideas, with resistance being a political terms referring to "elements of discourse that seem to conflict with or evade more dominant assumptions and priorities" (Beeson and Doksum, 2000: 155). In the case of Alzheimer's disease, clinicians resistance centres on the actual introduction of the technology itself, while in Breast Cancer, clinicians are largely welcoming of Herceptin as a new weapon in their armoury against cancer. In this case, the resistance focuses on the nature of the Her2 test, with clinicians rejecting the notion that it is in some way special or different. But both sets of professionals are extremely knowledgeable about the treatment being proposed, and it is this aspect of 'knowledgeable resistance'.

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When faced with professional resistance to new technologies, a common response from supporters of genomics is to suggest that there is need for ‘education’ on the part of doctors and other medics (this obviously echoes the need to inform the public about the different and safe nature of pharmacogenetics). For example, when faced with research that claims that GPs are distinctly unexcited about the introduction of genetic testing into the clinic because of time constraints and the limited occurrence of Mendelian genetic disease (Kumar 1999; Kumar and Gantley 1999) supporters of technology claim that more complex genetic technologies (led by pharmacogenetics) will inevitably enter primary care, and there is thus a need for GPs “to become genetically literate” (Emery and Hayflick 2001: 1027).

But this cry for genetic literacy looks a bit odd in the light of my research data. All the clinicians and clinician-researchers I interviewed were extremely genetically literate. Some of the people I spoke to had been involved in the early studies of APOE and Alzheimer’s risk. Yet these people were also highly resistant to aspects of pharmacogenetics. At the very least this undermines the, frankly simplistic, idea that to get professionals to engage with a new technology, we just have to educate them about it. Professional resistance, if it is to be overcome, can only be dealt with by actually engaging with those ethical and structural issues that professionals are concerned about.

When we think about how new technologies get implemented in the clinic, and the ethical problems that may arise, we need to bear a number of points in mind. In the same way that pharmacogenetics is a reaction against the ‘one-size-fits-all’ approach to pharmaceutical prescription, it may make sense to accept that the varied and contingent nature of different clinical cultures means that a similar approach to the ethical problems raised by pharmacogenetics may not be that productive. To assume that a broad and heterogeneous technology like pharmacogenetics will be problematic in the same way, where ever it is used, is a touch simplistic. Even the theoretical concept of ‘resistance’ cannot be unequivocally applied to all examples of the technology. Will clinicians resist pharmacogenetics when it is used to avoid potentially lethal adverse drug reactions? Maybe, but it is hard to say for sure.

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As a result, we need to approach the ethical issues raised by pharmacogenetics on a case by case basis, mapping out the kinds of problems that arise when the technology is used, rather than adding to the already expansive speculations surrounding this technology.



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