Bioethics and the reinforcement of socio-technical expectations

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Abstract

Over the past few years, considerable interest has been paid to the way in which social expectations (hopes, hypes, fears) about new genomic technologies help shape, and in themselves are shaped by, emerging technologies, regulatory regimes and social concerns. In comparison, little attention has been paid to the role of expectations in related, but non-scientific discourses, such as bioethics. Drawing on a review of publications addressing the ethical issues associated with pharmacogenetics, this paper presents a detailed critique of bioethicists' contribution to these debates. The review highlights how, almost a decade after bioethical debate around pharmacogenetics started, and in contrast to the professions' self-perception as a form of regulator, bioethicists still largely restrict themselves to reviews of possible ethical issues raised by this technology, rather than critiquing others' positions and arguing for specific points of view. In addition the paper argues that bioethicists tend to: accept unquestioningly scientists' expectations about the development and ethical issues raised by pharmacogenetics; ignore contributions from bioethicists who *do* question these expectations; and engage in an ethical debate, the boundaries of which have been laid down and defined by academic and industry scientists. The paper concludes by offering some possible explanations for why the bioethical discourse has taken this form.

Introduction

Over the past few years sociologists have become increasingly interested in bioethics. At one level, this interest centres on the ways in which social science research can contribute to how bioethics goes about its business, what Ray DeVries calls 'sociology in bioethics' (De Vries, 2003. See also Hoffmaster, 1992; DeVries and Conrad, 1998; Kleinman, 1999) and what others have labelled 'critical bioethics' (Hedgecoe, 2004). But taking this interest further, a number of authors have taken bioethics as an actual site for sociological study (Bosk, 1999; Evans, 2000; Stevens, 2000; Wolpe, 2000; Messikomer, Fox and Swazey, 2001; Evans, 2002). This article aims to contribute to this latter area of research by exploring the bioethical discourse surrounding a new technology, called pharmacogenetics, and proposing sociological explanations for why this discourse has taken the form it has.

Pharmacogenetics, the use of genetic tests to help develop and prescribe drugs, has generated a great deal of interest over the past few years, both on the part of pharmaceutical companies (Roses, 2002; Lindpaintner, 2003a/b) – who are thought to be channelling billions of dollars into research in this area (Lehman Brothers, 2001; PriceWaterHouse Coopers, 2005) – and academic scientists (Evans and Relling, 1999; Mancinelli, Cronin and Sadée, 2000; Persing and Cheek, 2000; Weinshilbourn, 2003; Burkee and Psaty, 2007; Piquette-Miller and Grant, 2007). Unsurprisingly, this topic has generated considerable debate over the ethical issues that might be raised by the increased use of genetic testing that would result from the expansion of pharmacogenetics and it is this literature that this article will examine. Going further, if, as one author has claimed, 'pharmacogenetics serves as a battlefield *par excellence* for the bioethicists' (Sutrop, 2004: v), this study we may in turn reveal some wider facets of bioethics as a way of thinking about new science and technology.

Theoretical Background

Since it appeared as a term in the early 1970s (Potter, 1971) bioethics has taken a number of forms. While general definitions describe it as 'the systematic study of the moral dimensions – including moral vision, decisions, conduct and policies – of the life sciences and health care, employing a variety of ethical methodologies in an

interdisciplinary setting' (Reich, 1995 quoted in Jonsen, 1998: vii), there are other ways of classifying and defining bioethics, not least those places where bioethical debate take place. This approach underpins John Evans' useful distinction between Foundational, Clinical and Public bioethics. Foundational bioethics focuses on how topics of concern relate to issues such as theoretical systems of ethics or democratic values. Clinical bioethics, in comparison, which concerns interactions with patients or research participants, tends to take place within healthcare settings while public bioethics which is concerned with setting policies about bioethical topics to apply to all members of a particular society, is located in the public space, encompassing regulators, government sanctioned advisory commissions, as well as the media, academics, pressure groups and face to face discussions between individuals (Evans, 2006: 214).

In these terms, this article focuses on debates within public bioethics; although the protagonists are (largely) academics and bioethicists are defined in terms of their disciplinary background (philosophy for example) or affiliation with departments or research centres that define themselves as bioethics related (rather than through membership of public bioethics commissions) the focus of the debate around pharmacogenetics is not on basic bioethical theory or principles (as foundational bioethics would be) but rather on the broader policy and public responses that might arise with the development of this technology. And in this context, 'public bioethics' can be seen as serving two distinct, though often complementary roles: as a form of regulation, and for scanning the 'ethical horizon'.

What is Bioethics for?

The first role for bioethics concerns the identification and elucidation of possible ethical issues associated with new technologies, what we might call ethical 'horizon scanning'. As Magrit Sutrop notes in a guest editorial for the journal *Bioethics*, 'ethicists have an important job in identifying potential problems before they will actually emerge in reality' (Sutrop, 2004: vi). The aim here is to prepare society for newly developed/ing technologies and the challenges they bring. This, slightly speculative aspect to bioethics has a long tradition, evolving out of bioethics' origins in concerns raised by new technologies in the 1960s, although it has not gone unchallenged, with Ruth Clayton, in her review of Jonathan Glover's classic text

What sort of People should there be? noting that she was 'irritated…by his inclusion of all imaginable outcomes; wholesale extrapolations from current techniques without consideration of the biological realities and the contexts in which biological systems operate' (Clayton, 1986: 163). While Clayton was a biologist, similar concerns about bioethicists' uncritical acceptance of scientific futures have been expressed more recently from within the bioethics community (Elliott, 2005). Despite these cautions, a key role for bioethics remains the identification and exploration of the ethical problems raised by new and emerging technologies, such as human cloning, stem cell research and nanotechnology.

The second role for bioethics is as a form of regulation. A good statement of such an approach might be:

> 'Bioethics is an important non-legal regulatory feature in areas such as reproductive and end of life issues…as well as genetic testing, manipulation, and data storage. Its norms also attempt to regulate the conduct of scientific research, access to and quality and safety of technology, medical services, essential medicines, and other preconditions for health' (Faunce, 2005: 173)

While the idea of bioethics as regulation is not often explicitly proposed by bioethicists themselves, one can detect a strong element of this approach in, for example, the words of Daniel Callahan – co-founder of one of the earliest bioethics institutions The Hastings Centre – from 1977:

> 'Doctors want...to make all the choices. Well, we're saying to them no. There are some public interests at stake here and some general principles you have to abide by...You're playing in a public ball-park now...and you've got to live by certain standards...like it or not' (cited in Stevens, 2000: 52-53).

While bioethicists may be unwilling to explicitly adopt the mantel of regulators, previous social scientific research in this area highlights how easily they slip into this role. For example Lewins has outlined how, in debates over euthanasia, bioethics serves as a form of social control over the medical profession (Lewins, 1998). On a broader stage, Brian Salter has explored how, in the wake of a collapse in public trust of technocratic scientific opinion, bioethics (mainly in the form of public bioethics commissions) has become a form of political legitimation for decision-making around controversial technologies (Salter and Jones, 2002,, 2005; Salter, 2007).

Perhaps the most detailed evidence of bioethics' regulatory impulse is provided in Renée Fox and Judith Swazey's historico-ethnographic study of the origins and development of American bioethics and its institutions. They note the way in which traditional histories of bioethics centre on the discipline's emergence in the 1960s in the context of the social challenges presented by new technologies (such as organ transplantation) as well as perceived bad behaviour on the part of medical professionals. The consequent need to control and regulate the behavior of others' reached its peak in the symbiotically close relationship between specific academic bioethicists and the committee drawing up federal regulations for the oversight of human subjects research (Fox and Swazey, 2008).

A key part of the bioethical toolkit in its role as regulator is philosophical argument, the taking and defence of a particular intellectual position, the analysis and critique of alternative points of view. Without making an argument for a particular point of view, it becomes very hard for a bioethicist to tell other people what it is they should, or should not, be doing. This is, of course, a very broad position, and does not presume that there is any one correct way to make such a bioethical argument: it may involve the application of a bioethical theory (such as principalism), but then again, it may not. It may be as straightforward as unpicking the logic underpinning other people's positions. What matters is that, while acting as an informal regulator, a bioethicist has to argue for a particular position and, probably, disagree with alternatives.

Of course, the roles of regulation and horizon scanning are not mutually exclusive, and they can be seen as feeding into or influencing each other. For example, in their critique of horizon scanning – what they call 'prophetic bioethics' – Guyer and Moreno chastise bioethicists for lazily accepting science fiction scenarios in place of realistic science, and as a consequence of 'ignoring the biological red flags of cloning in favour of ethical ruminations that lead nowhere useful, bioethicists disavow their role in providing oversight…to contemporary science and medicine' (Guyer and Moreno, 2004: W16). The remainder of this article explores how bioethicists have gone about fulfilling these two roles in the case of one specific technology, pharmacogenetics .

Sample

Using database searches on Pubmed and Web of Science, supplemented by manual searches of the literature 52 English-language articles were identified which were primarily about the (bio)ethics of pharmacogenetics or pharmacogenomics.[1] It is important to note that these articles are bioethics articles (i.e. excluding health economics or policy) *about* pharmacogenetics, rather than reviews of pharmacogenetics which happen to mention ethical issues at some point. This latter category of article is interesting and is an important way for scientists to discuss the ethics of this technology (Hedgecoe and Martin, 2003) but is outside the scope of this article. Similarly, the articles have pharmacogenetics/omics as their focus, rather than broader topics such as 'post-genomic medicine' or 'personalised medicine' which practice runs showed produced large numbers of irrelevant material, and few articles not covered by the chosen search terms. In addition, this approach avoids edited collections (such as Rothstein, 2003) and the reports of bioethics commission (e.g. Nuffield Council, 2003) since their length, multi-authored nature, and non-peer reviewed status makes comparison with journal articles difficult.[2]

Method and Analysis

Methodologically this paper provides a critical literature review of articles explicitly addressing the ethics of pharmacogenetics, sharing some methodological features with Anne Kerr's comprehensive analysis of debates around the genetics of cystic fibrosis (2000) or Hedgecoe and Martin's (2003) previous work on pharmacogenetics. To aid analysis a form of broad qualitative textual analysis was used focusing on the presence, extent and manner in which specific ethical topics are discussed in relation to pharmacogenetics. The aim was not to count every instance of a particular word, phrase or theme prior to statistical analysis, but rather to assess more impressionistically how fully a particular ethical topic has been handled in a particular paper. The articles reviewed in this analysis are listed in the annex to this paper. When these articles are referenced, [square brackets] are used, to distinguish from articles in the bibliography.

Article content is classified according to a mixed-scale which incorporates both the extent to which the article discusses a particular topic, and whether an argument or specific recommendation is made. Any single article can obviously contain a mixture of categories if it covers a number of different topics in varying depth. At the bottom

end of the scale is a 'mention', a brief appearance by a topic with no further discussion. For example the underlined text below counts as a 'mention' of stigmatisation:

> 'The social consequences that arise from new disease labels and their legitimization would obviously involve interpersonal stigmatization or identity issues. In addition, a wider range of possible societal concerns, such as those related to access to insurance, employment and health-care resources, will probably emerge' [Issa, 2002: 306].

The ethical topic, in this case the possibility that pharmacogenetics might lead to the stigmatisation of some people, is mentioned in the text but there is no discussion or presentation of possible issues and the author moves onto the next topic (insurance) immediately.

This is followed on the scale by an 'overview', which provides more information on a topic, often in the form of a series of questions. For example, an overview of the issues raised for family members is provided in the following text:

> 'If family members were then to request testing, should testing be made available to them? Or should information be disclosed only on the condition that they agree not to be tested? If they were tested and found to be homozygous for the E4 allele, indicating possible susceptibility, what would be the consequences of reclassifying surrogate decision makers as 'at risk'? Such questions are not easily resolved' [Issa and Keyserlingk, 2000: 920]

It is typical of such an 'overview' that while questions might be asked, little or no attempt is made to answer them.

Text that 'reviews' a topic provides more information than an overview, discusses the pros and cons of particular positions but, crucially, tends not argue for a particular point of view. For example, March, Cheeseman and Docherty [2001] provide a detailed review of national and international laws and regulations concerning data protection as they relate to pharmacogenetic research. Yet by and large they avoid drawing critical conclusions regarding the effectiveness or otherwise of these different regulations, aside from some broad warnings at the end of the paper about such regulations not delaying or preventing potentially beneficial research.

Finally texts that make 'arguments' take a particular position with regard to some aspect of pharmacogenetics and often criticise other positions. One of the best examples in this sample comes from Weijer and Miller who argue for a position (concerning community informed consent), dispute the views of others (a group called the Pharmacogenetics Consortium) and make a number of recommendations:

> 'we think it essential that communities be extended protections that allow for their respectful involvement in research...Regrettably, the Pharmacogenetics Consortium's treatment of communities is deficient in a number of respects...' [Weijer and Miller, 2003: 3. Emphasis added]

Occasionally more policy minded authors will make a series of 'recommendations', which suggest particular courses of action but which tend to lack the detail of 'arguments'. When such recommendations are based on closely worded analysis this is not a problem [e.g. Clarke, English, Harris, and Wells, 2001]. But when they are based on a more stripped-down 'wish-list' of ethical goals [e.g. Temporary Committee on Human Genetics and Other New Technologies of Modern Medicine, 2002] the putative value of such an article is perhaps harder to argue for.[3]

This classification scheme fits the two central roles for bioethics identified above. Arguments and recommendations are crucial to bioethics' regulatory role, since they are essential in analysing situations, dilemmas and technologies and advising people on right and wrong decisions. Articles which provide information about ethical issues arising from this new technology are fulfilling the horizon scanning role, with an implicit assumption that more detail and discussion is better. An article which identifies and discusses new ethical issues is fulfilling a role (horizon scanning) as much as one that argues for a particular position does (regulation), so the classification scheme does not necessarily prioritise 'Arguments' over 'Reviews'. And of course these classifications can occur in the same articles; an article consisting largely of a detailed review of specific issues may lead up to a well constructed argument.

When it came to classifying the authors of these articles, a simple scheme classing them as 'scientists', 'social scientists', or 'ethicists' was used. 'Scientists' includes clinicians, pharmacists and even, in the case of Tom Wilkie [Spallone & Wilkie, 2000], a physicist and former science journalist, and social scientists were few in

number and clear in their disciplinary affiliation. Ethicists (which for the purposes of this article includes lawyers and policy researchers) is a more contentious act of classification. The obvious problem is, as Carl Elliot has wryly noted, that no one wants to be called a bioethicist (Elliott, 2002). For the purposes of this analysis, people were categorised on the basis of disciplinary training (a Ph.D. in philosophy designates an ethicist for example), and/or departmental affiliation (someone who works in a centre for bioethics, is classed as a bioethicist). But, as STS has long taught, such classifications are not cut and dried. For example, Amalia Issa wrote some of the first papers on the ethics of pharmacogenetics [2000; 2001] was trained in neuroscience with a Ph.D. in Neurology and Neurosurgery at McGill University. Yet in 2000, when two of her papers were published, she held a postdoctoral position in the Biomedical Ethics Unit at McGill University and she had completed a fellowship in Medical Ethics from the Division of Medical Ethics at Harvard Medical School. For the purposes of this article, she counts as an ethicist. A similar issue was raised by Sandra Soo-Jin Lee, who has a background in Anthropology, but who is based at the Stanford Center for Biomedical Ethics, and who is classed as a bioethicist.

Results

In terms of the general characteristics of the sample, of the 51 articles where authors could be clearly identified[4], 38 of them were authored, or co-authored by bioethicists, with 11 of these being co-authored with scientists and only 2 with social scientists. Thus, as we might expect, bioethicist (co-)authored articles make up a majority of those sampled, although with 24 articles – 12 of them (co-)authored with other scientists and 11, as previously mentioned with ethicists – scientists have also contributed to this literature in a noticeable way. In terms of the nature of their contribution, it is clear that when bioethicists write about pharmacogenetics, articles consisting almost solely of 'mentions' are rare [i.e. Mordini, 2004]. Rather they tend to offer broad overviews [e.g. Issa, 2000; Rothstein & Epps, 2001; Alcalde & Rothstein, 2002] or reviews [e.g. Robertson, 2001; Buchanan, Califano, Kahn, McPherson, Robertson, & Brody, 2002; Vaszar, Cho, and Raffin, 2003; Lushoff and de Wert, 2004; Morely and Hall, 2004; Lee, 2005b; Lushoff, 2006] of a number of ethical topics which might arise with the application of this technology.

One justification for this comes from Weijer and Miller who note that such broad summaries are 'essential for defining the range of issues that ought to be addressed, [and] the time has come for detailed investigation of specific [ethical] problems' [Weijer & Miller, 2003: 1]. If this is the case, we might expect such 'broad brush' approaches to these issues to change over time, with a steady increase in articles that argue for specific positions and recommendations. This does not seem to have happened. The 20 articles containing arguments or recommendations identified as being (co-) authored by ethicists are spread fairly evenly between 1999-2008, with one incidence in each year apart from 2001 and 2004 (4 and 5 articles respectively), 2003 (3 articles) and 2005 (2 articles). The past 3 years (2006-2008) have had only 1 'argument' article each. [Chadwick, 1999; Issa, 2000; Thomas, 2001; Renegar, Rieser and Manasco, 2001; Issa, 2001; Rothstein and Epps, 2001; Freund and Wilfrond, 2002; Paul and Roses, 2003; Williams-Jones and Corrigan, 2003; Weijer and Miller, 2003; Morely and Hall, 2004; Mordini, 2004; Netzer and Biller-Andorno, 2004; Shubert, 2004; Neil and Craigie, 2004; Lunshof, 2005; Lee, 2005a; Joly and Knoppers, 2006; Marx Stöting, 2007; Bolt et al, 2008] There does not seem to have been an increase in the numbers of articles by bioethicists arguing for specific positions, as the possible range of ethical topics has been 'mapped out'. Thus while there are a number of excellent, argumentative bioethics papers present in the literature [e.g. Chadwick, 1999; Weijer & Miller, 2003; Schubert, 2004] this does not seem to be part of a growing trend.

The next two sections discuss in detail how this review relates to the two roles for bioethics identified earlier.

Crowded Horizons

One obvious way of assessing horizon scanning is to explore whether, when bioethicists perform this role, they reveal possible ethical problems with a technology that have not been mentioned before. Thus one aspect of horizon scanning is the identification of novel ethical issues. Yet in the specific case of pharmacogenetics, there is already some evidence that, at the very least, bioethicists are not the only ones involved in horizon scanning. In their review of the scientific literature on pharmacogenetics, Hedgecoe and Martin noted that:

> ‘discussion of the ethics of pharmacogenetics is mainly organized within the scientific community... 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. (Hedgecoe and Martin, 2003: 351)

It is clear that the overviews and reviews provided by ethicists and scientists are largely interchangeable in terms of their concerns, the issues raised and way in which problems are framed. Bioethicists tend not to introduce ethical theories – often seen as the hallmark of bioethical thinking – in their reviews/overviews of these topics. For example, comparing the following two overviews of privacy/confidentiality, by an ethicist and scientist respectively, little difference can be seen between the overall tone or detail:

> - ‘Keywords are privacy and confidentiality, and the means for safeguarding that are various modes of de-identification, the option of withdrawl, strict limitation of access, storage, and use of data’ [Lunshof, 2006: 188]
> - ‘The distinctive DNA content of an individual has been likened to a ‘future diary’, containing potentially deterministic information regarding the health and well-being of a person…large consequences may result for the usefulness of genotypic data in a pharmacogenomic context if complete anonymization is required’ [Landon, 2006:30].

Analysis of the ethics literature around pharmacogenetics suggests that where it is hard to find an ethical feature of pharmacogenetics discussed by a bioethicist that has not first been discussed by a scientist (see Table 1), this is in large part because, as has been noted, scientists have written about the ethics of pharmacogenetics in both scientific review articles and in papers specifically focussed on the ethics of pharmacogenetics.

Table 1: Common ethical topics in pharmacogenetics

Topic	**1st mentioned by scientist:**	**1st mentioned by ethicist:**
Race	[Motulsky, 1978]; Lindpaintner, 1999	[Issa, 2000]

Privacy	[Motulsky, 1978]; Lindpaintner, 1999	[Issa, 2000]
Stigmatisation	[Motulsky, 1978]; Anderson, Fitzgerald & Manasco, 1999	[Issa, 2000]
Orphan drugs	Maitland van der zee , de Boer and Leufkens, 2000	[Thomas, 2001]

Exceptions are the topic of the overlap between disease genes and pharmacogenetic indicators which was introduced in 1999 by both Ruth Chadwick [1999] and the pharmacist Wolfgang Sadee (1999) and informed consent which was discussed by both non-ethicists [Spallone & Wilkie,, 2000] and ethicists [Issa, 2000] in 2000. Even setting aside the remarkable foresight of Arno Motulsky's 1978 paper, it is clear that scientists are responsible for setting the parameters of the bioethics debate surrounding pharmacogenetics. Because scientists can discuss ethical issues in scientific review articles as well as bioethics papers, they have managed to gain an early presence in the ethical discourse in this area. One might expect bioethicists following in scientists' footsteps to engage in a process of 'sifting' or 'high lighting' those concerns they feel ought to be prioritised. Yet ethicists cover the same topics as scientists, and do not seem to draw out specific issues as worthy of notice. And it is not that these are the only ethical issues to do with pharmacogenetics; there is the option that bioethicists could 'forge ahead' of the scientists' view of the ethical issues, pushing the limits of what counts as an ethical issue in pharmacogenetics. There are a number of obvious ethical issues in pharmacogenetics which have not been addressed, including: the nontherapeutic nature of pharmacogenetic trials where DNA is sampled and stored for some unspecified future use or problems over the clinical validity of experimental pharmacogenetic tests. While these may be topics of debate in bioethical discussion of other technologies (DNA banks for example), this is not the case in pharmacogenetics. For some reason the topics that bioethicists' discuss tend to remain within the discursive limits previously laid down by scientists.

One possible explanation for this lies in the relationship between bioethics and the kinds of socio-technical expectations that scientists create to garner support for their work. A growing body of research has documented how such expectations or promissory claims are created, sustained and developed, and how, in turn, they shape the kinds of technologies that actually come to fruition (Martin, 1999; Brown, Rappert and Webster, 2000; van Lente and Rip, 1998; Hedgecoe, 2003; Nerlich and Halliday, 2007). While I accept that it is a contentious claim, I wish to suggest that because

bioethicists tend to buy into scientists' expectations about the development of a technology – not least of all because they too have an interest in that future, with all its tricky ethical problems coming to pass – there is also the chance of 'slippage', with bioethicists also accepting scientists claims about the *ethical* future, i.e. the ethical issues raised by pharmacogenetics. Of course to suggest that it is in a particular group's interests to hold a particular position does not imply that there is some kind of conscious, grand conspiracy on the part of members of that group to promote that point of view. SSK has long shown how groups promote intellectual positions that bolster their own interests without the need to posit conspiracies. The same is true in the case of bioethics and the promotion of scientists' visions of how the pharmacogenetics will develop.

In an attempt to support this claim, it is not unreasonable to suppose that one aspect of bioethics' 'horizon scanning' role is the creation of expectations about the development of technology, specifically the creation of expectations that include a space for bioethics. Thus in the case of pharmacogenetics, there is a need for bioethicists to suggest that pharmacogenetics be seen as a real, serious technology, and thus something worthy of ethical debate. This is why bioethics articles on pharmacogenetics tend to echo the way in which *scientific* review articles bolster expectations around this technology, assuming that it will come into everyday clinical use. It is not that bioethicists are incapable of taking a critical position regarding the science of pharmacogenetics, see Ruth Chadwick's work for example [Chadwick, 1999], yet this kind of approach, which is sceptical about the *scientific* expectations being generated around pharmacogenetics is not widely represented among bioethicists.

A good example of the way in which bioethicists mirror scientific expectations around pharmacogenetics can be seen in the way in which the topic of Adverse Drug Reactions (ADRs) is discussed. The idea that pharmacogenetics will reduce the incidence of adverse drug reactions is crucial to some scientists' visions about how this technology will develop (Anderson, Fitzgerald and Manasco, 1999; Lau and Sakul, 2000; Meyer, 2000; Ginsburg and McCarthy, 2001; Akhtar, 2002; Eichelbaum, Ingelman-Sundberg and Evans, 2006) and these authors frequently cite a particular

review article (Lazarou, Pomeranz and Corey, 1998) which emphasises the serious nature of ADRs for healthcare systems.

The same pattern can be found amongst bioethicists who cite this paper in support of pharmacogenetics' potential public health benefits, and hence an ethical reason for its development [e.g. Issa, 2000; Rothstein & Epps, 2001; Thomas, 2001; Issa, 2002; Lee, 2003; van Delden, Bolt, Kalis, Derijks, & Leufkens, 2004; Mordini, 2004; Neil and Craigie, 2004; Joly and Knoppers, 2006; Lee, 2007; Peterson-Iyer, 2008].[5] Thus while some bioethicists are sceptical in their discussions of this topic [Chadwick, 1999; Williams-Jones & Corrigan, 2003; Vaszar, Cho, & Raffin, 2003], a large number uncritically accept a key vision of this technology which centres on the public health problems presented by ADRs and pharmacogenetics' potential in their solution. For ethical debates, the ADR issue is an important support for arguments in favour of this technology, underlining the direct public health benefits that will result from the introduction of pharmacogenetics. If pharmacogenetics stops direct physical harm to large numbers of people, then its ethical status is obviously bolstered.

Not only do they propose the same expectations, bioethicists also mirror scientists' reluctance to question the role of ADRs in the phamacogenetic future. Like scientists, bioethicsts ignore the lack of an obvious link between Lazarou and colleague's study and the idea that pharmacogenetics will provide a solution to the public health problems raised by ADRs. The study itself never mentions pharmacogenetics, genetics or genomics and a cursory reading of the scientific literature reveals that, as things currently stand, *we do not know* what proportion of common ADRs could be avoided with the widespread use of pharmacogenetics (Phillips, Veenstra, Oren, Lee & Sadée, 2001). Bioethicists ignore more recent research which suggests that around two-thirds of current ADRs could be avoided with improved prescribing practice, without the need to introduce pharmacogenetic testing (Pirmohamed, et al, 2004).[6]

Even if one does not think that it is bioethics' job to critically question the content of science – something that is open to debate given that there are a number of examples where this has happened (Schüklenk, Mertz and Richters, 1995; Robert, 2000; Kahn, 2006) as well as the previously noted internal critique that opposes 'buying into' scientific futures unchallenged – it is hard to ignore the way in which bioethicists'

discourse around the future development of pharmacogenetics strongly mirrors that of scientists engaged in promoting positive expectations about this technology. Indeed on occasion, bioethicists go beyond what scientists themselves might claim. For example, Mordini [2004: 375] suggests that 'We are rapidly advancing towards the post-genomic era in which genetic information will be a part of our everyday life' and Issa [2002: 300] that pharmacogenetics 'will also profoundly change the way in which clinical drug trials are conducted'. Yet compared to Klaus Lindpaintner of Roche, *a man paid to promote this technology*, their expectations seem somewhat over the top: 'pharmacogenetics and pharmacogenomics...are commonly touted as heralding a 'revolution' in medicine, yet as soon as one begins to probe more carefully, little substance is yet to be found to support these enthusiastic claims' (Lindpaintner, 2003a: 142). While Lindpaintner might have some strategic reasons for moderating expectations around the development of this technology (cf Hedgecoe, 2001: 893-898 on the genetics of Schizophrenia) there are other critical voices in the scientific literature, casting doubt on fundamental of aspects of pharmacogenetics, which are entirely absent from bioethical debates (Coats, 2000; Sam, 2004. For a critique of the structures involved see Nightingale and Martin, 2004).

Because bioethics needs to reinforce the *technical* expectations around a particular technology, for without the impending appearance of a new technology what need is there for pressing discussion of the ethical issues it raises, it becomes relatively straightforward for slippage to occur and for bioethicists to uncritically adopt scientists' *ethical* expectations about the kinds of issues that this technology will raise, thus undermining their role of 'horizon scanning'. One consequence of this is the odd situation where bioethicists' discussions of the ethics of pharmacogenetics are not obviously written by people with specific skills or training in ethical analysis, a situation resulting from the structural aspects of bioethics publications (at least on pharmacogenetics); for whatever reason, the bioethics literature is tilted towards the production of these reviews (rather than articles that argue for specific positions), resulting in an emphasis upon horizon scanning, and scanning a horizon that has already been mapped out by scientists at that

Limited arguments

Of the 20 out of 38 articles authored or co-authored by bioethicists that engage in some sort of argument, 13 could be said to make more than a cursory attempt to make a particular case [Chadwick, 1999; Issa, 2000; Renegar, Rieser and Manasco, 2001; Issa, 2001; Freund and Wilfrond, 2002; Paul and Roses, 2003; Williams-Jones and Corrigan, 2003; Weijer and Miller, 2003; Netzer and Biller-Andorno, 2004; Shubert, 2004; Lunshof, 2005; Lee, 2005a; Joly and Knoppers, 2006]. An example of the kind of detailed argument contained in one of these 12 can be found in one of Sandra Soo-Jin Lee's articles [Lee, 2005a] which moves from introducing genomics and the drivers of pharmacogenomics to a critical review of the factors producing what she calls an 'infrastructure of racialization'. Focusing on the role pharmacogenomics might play in this racialization of medicine she highlights the disputed nature of race within medicine, leading onto criticism of various regulatory authorities (e.g. the FDA in the case of BiDil) and arguing for a need to balance market interests with distributive justice. In contrast, a cursory argument is provided by Mordini [2004] who after a brief outline of orphan drug legislation suggests that 'We need new regulatory measures to encourage the development of clinically desirable but economically unprofitable medicines' [p.378]. While they may argue for the same point, there are noticeable differences between these articles in terms of the range of sources drawn upon, the case made to support a particular argument and the attention paid to competing positions.

There is no way of knowing whether with around a third of their articles making decent arguments, bioethicists are fulfilling their role as informal regulators in the ethical debates around pharmacogenetics, yet these minority of arguments could be contrasted with the seeming way in which when scientists make ethically provocative claims, bioethicists tend not to challenge them. Most ethics articles written by scientists cover the same sorts of topics as bioethicists' and in the same sorts of ways (i.e. mentions, overviews and the occasional review). Yet some scientists make very strong arguments for particular ethical positions, points which, while one might not agree with, certainly contribute to the intellectual debate surrounding this technology. For example, Klaus Lindpaintner of the pharmaceutical company Roche accepts that there is an overlap between pharmacogenetic and 'traditional' disease genetic testing. Yet he concludes that 'Rather than treating genetic information as a special form of medical information, standards of confidentiality and individual choice regarding the

use of all types of medical data need to be established and/or redefined. Ultimately, society will benefit most by simultaneously acting to protect not so much the privacy of medical information, but the way it is used*'* (Lindpaintner, 1999: 488). His point, not so much challenging genetic exceptionalism but rather seeking to redefine standards of medical confidentiality to make pharmaceutical research easier is clearly open to challenge by bioethicists yet seems to have been overlooked. Similar points could be made about academic pharmacist Julie Johnson's claim that while 'There are also myriad ethical, social and legal considerations...these fields need to keep in step with the scientific advances so that once the scientific data support wider use of pharmacogenetics information in the clinical setting, these nonscientific issues do not present barriers to its actual application' (Johnson, 2003: 665). One interpretation of this position is that Johnson is suggesting that ethical and legal concerns are irrelevant, once the science of pharmacogenetics has got it right. This seems, at the very least, open to question from a bioethical position; that it has not been addressed, may just be a feature of bioethics publications, that they take longer to write and publish, or suggestive of a wider reluctance on the part of bioethicists to actually engage with others' positions, at least with regard to pharmacogenetics.

In addition, it is clear that that even some of those articles which make a long and sustained argument for a particular position could be seen as problematic in terms of originality. The clearest example of this can be found in Netzer and Biller-Andorno's paper in the pharmacogenetics special issue of *Bioethics* [2004]. In many ways this is an excellent example of bioethics; a collaborative paper between a scientist and an ethicist which covers the scientific ground with confidence. The problem comes with this paper's core claim to originality:

> 'So far little attention has been paid to the possibility that the routine application of pharmacogenetic testing could result in considerable harm to patients...*We have emphasised* that they [i.e. pharmacogenetic tests] will sometimes contain important secondary information as well' [p. 345 & 350 emphasis added].

While they do not explicitly claim to be the only people who have argued this, it is peculiar, disingenuous even, not to point out that this same point about disease gene/pharmacogenetic overlap has been widely discussed by scientists (Bell, 1997; Lichter and Kurth, 1997; Persidis, 1998; Anderson, Fitzgerald and Manasco, 1999;

Moyses, 1999; Lindpaintner, 1999 & 2003a; Lindpaintner, Foot, Caulfield, and Hall, 2001) [Vaszar, Rosen, and Raffin, 2002], bioethicists [Chadwick, 1999; Robertson, 2001; van Delden, Bolt, Kalis, Derijks, & Leufkens, 2004] and sociologists (Hedgecoe and Martin, 2003). Netzer and Biller-Andorno actually cite an article (Lindpaintner, 2003a) which makes this point about secondary information, yet at no point do they acknowledge this.

Similar weak referencing can be found in other papers in the sample – for example Neil and Craigie [2004] who appear unwilling to cite previous literature on pharmacogenetics [e.g. Chadwick, 1999] published in the same bioethics journal – raising the question whether simple repetition (often without citation) of what others have already argued counts as an original argument. The point is not to single out these authors for criticism but rather to suggest that bioethics debates around pharmacogenetics are characterised by limited citation of previous authors' contributions and a general acceptance of repetition as a form of originality. These authors are simply at one end of the spectrum.

A core theme in bioethicists' self perception is as the profession that advises the public on issues having to do with science and medicine. Yet, despite that claim, in the case of pharmacogenetics, only a minority of bioethicists' articles actually engage with making a considered argument, and of a number that do, concerns can be raised about the originality of their claims. It is not clear whether these issues around citation of previous authors' work are limited to the discourse around pharmacogemnetics or are characteristic of wider bioethics debates.

Discussion

The nature of bioethicists' discourse around pharmacogenetics does not conform to the idea that somehow they regulate or challenge scientific discourse and practice, or that they identify new ethical issues associated with this technology. Rather, it seems as if bioethicists have tended to provide broad but 'thin' reviews of potential ethical issues within the boundaries of ethical discourse set by academic and industry scientists, and have tended to avoid putting forward arguments for or against particular ethical positions. The question remains why this should be the case.

One possible element is pharmacogenetics itself, an expectation-heavy, industry-rich research topic coming to prominence in the late 20th Century. In the wake of the human genome project and controversies such as GM Food, scientists are acutely aware of the importance of ethical debates around new technologies. As a result, scientists have seen the need to discuss and debate the ethical issues surrounding pharmacogenetics from the very beginning of recent interest in this area in the mid- to late-1990s. They also have the advantage of being able to discuss these issues in scientific reviews as well as bioethics articles, giving them considerable influence over the shape of the discourse. One consequence of this is that by the time bioethicists became aware of this new research area and began to think about the issues it might raise, scientists had already 'mapped out' limits to the ethical discourse, leaving bioethicists trailing in their wake.

This explanation has much to recommend it, fitting neatly with industry scientists' acute sensitivity to the need to distance pharmacogenetics from the GM food debacle (e.g. Roses, 2000: 1361. See also Millstone, 2000) and with the important role ethics seems to be playing in the creation and maintenance of expectations in this area (Hedgecoe and Martin, 2003). Yet it does not explain why bioethicists are willing to accept without question scientists' statements about the future development of pharmacogenetics. It is quite clear that bioethicists can be sceptical of these scientific claims. It is just that they are not. Nor is it clear why bioethicists seem to be content for their discourse to remain within its current parameters, and are so unwilling to think in novel ways about the ethical issues raised by pharmacogenetics.

It is possible that aspects of bioethics as a discipline have also contributed to the way in which the ethical discourse around pharmacogenetics has developed, for example the unclear nature of what counts as an original contribution in bioethics. Of course, it would be relatively easy for bioethicists writing about pharmacogenetics to decide to actually argue for particular positions, to see what others have said, analyse their arguments, point out the weaknesses and make a case for a particular point of view, and as has been made clear, some authors have done this. Journals could encourage this by asking authors to clearly state, either in their cover letter or the article itself, what their original contribution is. In addition, a comprehensive review would help 'horizon scanning' in that it would identify the issues that have already been raised by

other authors and highlight possible 'gaps'. In addition, review articles should not be dismissed in themselves as unoriginal, since it is clear that, in the scientific literature at least, they produce original arguments and interpretations of results (Myers, 1990, 1991; Sinding, 1996). The point is to attempt a degree of comprehensiveness to the review, detecting themes that run through it and providing a critical appraisal, rather than simply cherry-picking a few references (if at all). A critical review of this literature does exist [Moldrup, 2001]; almost inevitably it is written by a scientist.

From this single case study, it *cannot* be argued that these features of bioethics' scholarly standards are true of the discipline as a whole (although they are true of articles on pharmacogenetics published in mainstream bioethics journals), nor is it clear where these standards originate. It may be a feature of bioethics' putative interdisciplinarity and relative youth, that standards have not had the time to develop, and that no one discipline's scholarly standards dominate. Alternatively, perhaps bioethics' standards *are* rooted in a single discipline, philosophy, where perhaps there is no tradition of formal literature reviews, and where the making of a case from scratch (even a case that has been made before), counts as original. Interestingly, the current debate within bioethics over the discipline's quality places the blame squarely at the feet of those who seek to move bioethics *away* from its philosophical roots towards a more interdisciplinary character, a move that threatens, it is claimed, the philosophical rigour of bioethical debate (Benatar, 2006; Schüklenk, 2006; Williamson, 2008). It is paradoxical then that it is those authors who most obviously conform to this philosophical ideal (in terms of background and approach) who offer the least in terms of rigour, originality and depth when it come to discussing the ethics of pharmacogenetics.

Finally, beyond the limited realm of pharmacogenetics and the internal features of bioethics as a discipline lie explanations that derive from bioethics' status as a form of non-legal regulation, most obviously, the concept of 'regulatory capture', the almost inevitable process by which over time, regulators begin to share the ideas, beliefs and goals of the group they are meant to be regulating. This need not be the result of financial control, though this may be a powerful factor in the case of bioethics as whole (Elliott 2004). As Tina Stevens has shown, the Hasting's Center itself, the institution co-founded by Daniel Callahan to tell scientists and doctors that 'You're

playing in a public ball-park now...and you've got to live by certain standards...like it or not', underwent just such capture early in its existence (Stevens, 2000. See also Stemerding and Jelsma, 1996).

While financial muscle is a powerful driver for regulatory capture, it is not clear it has explicitly driven the shape of bioethics' discourse around pharmacogenetics, since the funding of bioethicists' work in this area is varied (i.e. not always from government funding agencies). Rather, it seems as if in the case of pharmacogenetics, the regulatory capture taking place is *intellectual*. As John Evans has pointed out, bioethics as a discipline, and much of its reasoning, was created to serve the interests of scientists working on human genetic engineering (Evans, 2000). This kind of intellectual regulatory capture is clear when, for example, the bioethicst John Robertson suggests that 'Proper attention to informed consent and the privacy of PGx [pharmacogenetic] test samples and results is essential for the smooth assimilation of PGx into clinical practice', with no question that there *should* be a 'smooth assimilation of PGx into clinical practice' [Robertson, 2001: 209].

Bioethics' tendency to avoid fundamental debates about the construction of technologies leads to its inherent interest in the *application* of technologies. In the case of pharmacogenetics, this has led to an acceptance of scientists' technical and ethical expectations, however easily open to question such expectations are (for example the role of pharmacogenetics in dealing with ADRs as a public health threat). This need for technologies to exist, even if only in a promissory sense, before their ethical aspects can be debated, has led bioethicists to avoid discussion of issues beyond the pre-constructed discursive boundaries.

While the argument in this paper remains restricted to debates around a specific technology, I wish to suggest that thinking in terms of socio-technical expectations may help explain recent features of wider bioethical thinking. As Carl Elliott notes:

> 'It was not that long ago that the default stance of bioethics was a suspicion of medical and institutional authority. As new medical technologies appeared in hospitals…bioethicists asked whether these technologies…were actually a means of dehumanization…[Yet]…More and more often we hear from

> bioethicists who are not just pro-technology but much more fervently pro-technology than the public at large' (Elliott, 2005:21).

I would like to speculatively suggest that the changes in bioethics noted by Elliott are, partly at least, driven by socio-technical expectations, bioethics' apparent need for such expectations to come to fruition (to justify the need for ethical debate), and the way in which acceptance of scientists' expectations smooths the way for acceptance of scientists' beliefs about the **ethical** impact of such expectations.

Be that as it may, in the case study presented here, the confluence of these three themes – the timing of pharmacogenetics, the internal issues around quality in bioethics, and regulatory capture – has produced a debate about the ethics of pharmacogenetics that sticks within strict boundaries and which serves to support the kinds of expectations being generated about this technology by industry and academic scientists. Drawing on wider ideas within STS, we can place bioethicists at the bottom of Donald MacKenzies' 'certainty trough' with those people 'committed to the institutional and research programme' who are not directly involved in research but who may well use, comment on or mange its results, people who have low uncertainty about the technology concerned (MacKenzie, 1990). MacKenzie drew up the certainty trough in an attempt to outline people's attitudes in his research on nuclear missile guidance systems, and nuclear weapons provide a useful way of thinking about bioethicists and the role they should play with regard to scientists' expectations and hopes. In his contribution to the 1992 conference on the 'Birth of Bioethics' the medical historian Daniel Fox drew a comparison between bioethicists and civilian academics researching arms control:

> 'In both defense and health...there has been a tension between professional and civilian control. Arms control intellectuals and bioethicists have been crucially important mediators between the ideologies and the technical fantasies of the professional on the one hand, and the most adamant and uninformed advocates of civilian control on the other' (Fox, 1993: S13).

The point of this paper has been to suggest that, in the case of pharmacogenetics, bioethicists are no longer questioning the 'ideologies and technical fantasies of the professional', but have largely bought into their claims, both technical and ethical. Whether this is a welcome state of affairs, and if not, how it can be remedied, are beyond the scope of this paper, yet at its best, bioethics provides a rigorous, critical

engagement with scientific ideas, helping policymakers, doctors and researchers think about the kinds of futures we can live in. A return to these values would be welcome.

[1] On the difference between the two terms see: Hedgecoe, 2003. This article will use the term pharmacogenetics..

[2] One possible omission from my sample are debates around the heart disease drug BiDil, which is licensed in the US for African Americans, supposedly because of their differing genetic make up. The widespread criticism of this drug centres on the way in which patients' race has become a shorthand (and an inaccurate, misleading one at that) for their genotype. In line with this position, since there is no genetic test associated with the prescription of BiDil I reject the idea that BiDil is an example of pharmacogenetics (as opposed to 'racial medicine', or 'personalised medicine' or some other vague term), a position which is hard to argue with unless one seriously thinks that the question: 'are you African-American?' counts as a genetic test. As a result, I have excluded articles that are specifically focused on the BiDil case, while at the same time acknowledging that ethics articles which discuss the possible racializing impact of pharmacogenetics may well mention BiDil in a broader debate.

[3] In terms of coding, truly banal recommendations (e.g. 'there needs to be more research on the impact of stigmatisation') were ignored. Borderline cases of banality, mainly the need to 'educate' professionals about pharmacogenetics *were* included in the coding.

[4] One article, [Temporary Committee on Human Genetics and Other New Technologies of Modern Medicine 2002] listed its authors' backgrounds as: 'medical and social backgrounds', and was excluded from this count as too vague.

[5] Although neither Thomas [2001] nor Peterson-Iyer [2008] actually cite Lazarou and colleagues 1998 paper, their phrasing – Thomas writes of ADRs being the 'fourth leading cause of death' a direct echo of Lazarou's paper – suggests that they are thinking of the 1998 meta-review of ADRs.

[6] This last paper has been largely overlooked by both scientists and bioethicists interested in the ethics of pharmacogenetics, with only one bioethicist – [Lunshof, 2006] – citing it, and that in a way which fails to acknowledge that it does not support the idea of pharmacogenetics as the solution to ADRs

Acknowledgements

I would like to thank Richard Aschcroft, Tim Caulfied, Paul Martin and three *SSS* reviewers for their helpful comments on this paper.

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Annex 1: Articles reviewed organised chronologically. Author affiliations in brackets:

Article

2008

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