Patents and non-invasive prenatal testing: Is there cause for concern?

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Abstract

Intellectual property rights are key to the translation of discoveries into clinical use in personalised medicine. This paper explores the interaction of intellectual property rights, specifically patents, with the field of genomic personalised medicine, through empirical work investigating the role that patents play in the development and delivery of non-invasive prenatal testing. Single gene testing and non-invasive prenatal testing represent examples of two different types of innovation likely to be important in personalised medicine, and which operate differently in terms of how the law is applied in practice. In single gene testing, on the one hand, previous studies demonstrate that patents have little impact on practice for those developing genetic tests in the public sector in the UK, because they are largely ignored. In contrast however, the present qualitative interview study finds that law and law-in-practice in non-invasive prenatal testing are much more convergent than found in single gene testing. Those involved in the development and delivery of non-invasive prenatal testing are more aware of patents, and balance the costs and benefits of greater engagement or compliance with patent law, in relation to factors such as freedom to operate, litigation and licensing, in favour of compliance. Compliance can take different forms; licensing is compliance, as is forbearance from using a patented invention in the absence of a patent licence. This paper explores the factors relevant to patent law compliance in non-invasive prenatal testing, and further considers the implications for the field of personalised medicine. It argues that as the prevalent means to promote openness, access and affordability in biomedicine are founded on the existing legal structures of intellectual property rights, such solutions will only be effective and adopted when these existing legal structures of intellectual property law are recognised and respected in the relevant field. It is therefore essential that such solutions only be deployed with a nuanced understanding of the operation of the law-in-practice.

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Introduction

Personalised medicine relies on the translation into clinical practice of the discoveries of genomic research. Intellectual property rights can be key to this translation, and this paper explores the interaction of intellectual property rights, specifically patents, with the field of genomic personalised medicine, through empirical work investigating the role that patents play in the development and delivery of non-invasive prenatal testing (NIPT).

"Openness" is often promoted as an important means to enhance access to biomedical innovations. However, it is rare that innovative products and tests in biomedicine are developed and translated into clinical use in the absence of some form of intellectual property, and patents are still core to the biomedical innovative process. Therefore, discussions about openness in debates about access to medical innovation often focus on licensing models, the exploitation of statutory exceptions and exclusions, or compulsory licensing. All of these techniques to advance access and affordability are founded on the existing legal structures of intellectual property rights. This paper argues that such solutions, which are founded on existing law, will only be effective and adopted when these existing legal structures of intellectual property law are recognised and respected in the relevant field; that is, where there is convergence between the law and the law-in-practice. It is therefore essential that such solutions only be deployed with a nuanced understanding of the operation of the law-in-practice in the relevant industry.

The ways in which the intellectual property system might operate in practice in personalised medicine is the focus of this paper. This paper postulates that single gene testing (SGT) and non-invasive prenatal testing (NIPT) represent examples of two different types of innovation which are emblematic of the innovations likely to be important in personalised medicine, and which operate differently in terms of how the law is applied in practice. In SGT, on the one hand, previous studies demonstrate that patents have little impact on practice for those developing genetic tests in the public sector in the UK, because they are largely ignored (Hawkins 2011). In contrast however, the present study finds that law and law-in-practice in NIPT are much more convergent than found in SGT. Those involved in the development and delivery of NIPT are more aware of patents, and balance the costs and benefits of greater engagement or compliance with patent law, in relation to factors such as freedom to operate, litigation and licensing, in favour of compliance. Compliance can take different forms; licensing is compliance, as is forbearance from using a patented invention in the absence of a patent licence. This paper explores the factors relevant to patent law compliance in NIPT, and further considers the implications for the field of personalised medicine, drawing on data from a qualitative interview study.

Personalised medicine - SGT and NIPT

Two early clinical applications of genetics and genomics research, SGT and NIPT, will be examined in this paper, because they represent useful case studies of the role that patent law plays in translation of research into clinical use, at different times in the 'genomics revolution'.

Single gene testing

SGT represents probably the earliest clinical application of the human genome project; indeed, many singe gene tests became available before the first draft of the human genome was published. Since the early identification of genes causative of diseases, clinical genetics laboratories have conducted tests to search for disease-causing mutations in those genes in individuals, usually for diagnostic purposes. A common task for a diagnostic laboratory is to check the entire sequence of a gene for disease-causing mutations. This sequencing was traditionally conducted by Sanger sequencing methods, but laboratories increasingly use next generation sequencing to sequence all coding regions (whole-exome sequencing), the entire genome (whole genome sequencing) or by targeted sequencing of particular areas (with large gene panels)(Broendberg et al. 2018). However, sequencing has not always been the method of choice, and many other methods may be employed. Whatever the technology used, SGT involves the identification, through technical means, of one or more mutations in the genetic code of an individual, for the purposes of medical diagnosis or treatment.

Non-invasive prenatal testing

Prenatal screening for fetal anomalies has long formed part of prenatal care. However, traditional screening tests which use blood tests and ultrasound are suboptimal as they have high false positive rates (Nicolaides 2011), leading to anxiety and over-referral for diagnostic testing. Prenatal diagnostic tests, such as chorionic villus sampling or amniocentesis are invasive procedures which carry a small risk to the fetus (Akolekar et al. 2015). NIPT,[1] described as a the 'vanguard of genomic medicine' (Hui & Bianchi 2017), allows for safe screening for fetal genetic abnormalities from a maternal blood sample, and utilises the presence of cell free fetal DNA (cffDNA) in the maternal circulation from as early as 5 weeks gestation, with testing possible from around 10 weeks. NIPT has low false positive rates, and therefore fewer patients are referred for follow-up diagnostic testing than with previous screening tests (Taylor-Phillips et al. 2016). Although the presence of fetal DNA in maternal circulation was demonstrated in 1997, the mixture of maternal and fetal cell free DNA posed a significant technical challenge and it was not until advances in genomic techniques that a viable method of prenatal testing was developed (Chiu & Lo 2011), with the first clinical tests becoming available in 2011(Allyse et al. 2015). There are different technical means of carrying out NIPT, and multiple commercial providers, who rely on slightly different mechanisms of testing (Bianchi & Wilkins-Haug 2014). NIPT may be offered to high risk pregnancies, as a contingent screen (following a higher risk first trimester screening result) or as a first line test, and different countries and professionals currently follow different practises in this regard (Benachi et al 2019).

[1] The terminology used is not yet the subject of consensus; the literature also uses the terms cell-free DNA-based screening or non-invasive prenatal screening using cell-free DNA among other variations on the same theme. In this paper, I use 'NIPT' to refer to prenatal screening of cell-free fetal DNA from a maternal blood sample.

Personalised medicine?

There are key similarities and differences between these two types of tests which are relevant and important to this discussion. Both tests take DNA as their subject matter, and both fields have patents which have the potential to affect the freedom of providers to operate. Both types of test share similar imperatives in terms of access to technology/medicine, and those who develop and deliver these tests are concerned to satisfy this need for access to medicine or public health. Finally, at least in public healthcare systems, the key actors who develop and deliver these tests are the same or similar: laboratory researchers, technicians and managers and to a lesser extent clinicians. On the other hand, there are important differences. NIPT has relevance to a much broader group of patients than SGT; pregnancy is not a rare disease. Perhaps relatedly, the role played by commercial entities in developing and delivering NIPT is much more prominent than for SGT. Differences in demand mean that there will likely be a higher volume of testing than for SGT, with associated changes in laboratory workload, and issues of scaling and workflow for this increased volume.

NIPT highlights a change in the way in which genetic testing is conducted. With advances in technology, next generation sequencing has become a key platform technology on which much genetic testing is based. With this technology has come an increased reliance on Illumina, as the current market leader in genomic sequencing technology, for supply of sequencing machines, reagents and know-how. It is therefore evident that there has been a shift towards an increasing role for commercial entities in this field in recent years.

Patent law and personalised medicine

The intersection of patent law with the field of genomics has generated significant public interest and concern. This trend was evident in Europe from the mid-1990s, and continues with the advent of NIPT.

Single genes

The law relating to SGT has been extensively rehearsed in various publications, so will not be discussed in depth here.[2] Of note for the purposes of this paper is that there were multiple patents (Hopkins et al. 2006; Jensen & Murray 2005), with no successful challenges to their validity or enforceability in the courts until the mid to late 2000s, although there were some partially successful oppositions at the EPO which narrowed patent scope (Matthijs et al 2013). However, despite extensive publicity, public and academic concern proved largely groundless, in that there was little to no demonstrated effect on patient access to genetic testing for most diseases in most of the world (Caulfield et al. 2006; Hawkins 2011; Nicol & Liddicoat 2013; Skeehan et al. 2010).

[2] There is extensive discussion in the literature of the law, ethics and politics of gene patents, and this paper does not seek to revisit that debate. For a summary, see for example: (Ayme et al. 2008; Bostyn 2004; Hawkins 2010; Merrill et al. 2006; Nuffield Council on Bioethics 2002; Organisation for Economic Co-operation and Development 2002).

However, more recently, following a series of cases in the USA and Australia, the law has been reshaped. In Europe, gene product patents remain permitted, as are patents on genetic diagnostics, subject to the normal patentability criteria. In contrast, in the USA and Australia, some gene patents have become more limited in scope. The US Supreme Court held that a naturally occurring DNA segment is a product of nature and is not patentable merely because it has been isolated.[3] Similarly, although on slightly different grounds, the Australian High Court held that isolated gene sequences were not patentable, because they were not something made or brought about by human action; the substance of the claims was the information embodied in the sequence, which is not made but discerned.[4] However, there are ways of inventing around the limits of the *Myriad* decisions (Aboy et al. 2017), leaving some scope for gene product patents, and moreover, there remain diagnostic method patents that are valid, with arguably more impact on freedom to operate in diagnosis (Huys et al. 2009). As a result, the limitations of the Myriad decisions on product patents for diagnostic testing are likely small (Hawkins 2016; Schwartz & Minssen 2015; Wales & Cartier 2015).

NIPT

The research underpinning NIPT was conducted in the late 1990s at the University of Oxford by Dennis Lo, and was patented by Isis Innovation (now Oxford University Innovation) in key jurisdictions. It is this patent, the so-called '540 patent' (after its US number, with corresponding patents in major jurisdictions), which has been the subject of the greatest attention in the press and literature.[5] The patent, which was exclusively licensed, then assigned to Sequenom (Oxford University Innovation 2014) claimed certain methods of using cffDNA, was very broad, and arguably covered practically every method of performing NIPT using cffDNA analysis. However, it was invalidated in the USA, on the basis that the relevant claims did not disclose an inventive concept sufficient to transform the claimed naturally occurring phenomena into a patent eligible application.[6] In contrast, in Europe, the patent[7] has survived better to date, although not entirely unscathed. It was unsuccessfully opposed at the European Patent Office, on the grounds of lack of inventive step and insufficiency of disclosure, rather than subject matter eligibility, but was upheld in opposition proceedings and on appeal to the Technical Board of Appeal.[8] The patent is now being enforced by Illumina in national proceedings in various European countries.[9] The only litigation in Europe yet to result in a

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[3] *Association for Molecular Pathology v. Myriad Genetics, Inc.,* 569 U.S. 576 (2013).

[4] *D'Arcy v Myriad Genetics Inc* [2015] HCA 35 at [6].

[5] U.S. Patent No. 6,258,540. This patent application was filed in 1997 and granted in the USA, Australia, and various European countries in broadly identical terms. The term '540 patent' is used to refer to this patent family in this paper.

[6] *Ariosa Diagnostics v Sequenom* 788 F.3d 1371 (2015). The Supreme Court of the USA declined to grant certiorari, so the patent remains invalid: *Sequenom v Ariosa Diagnostics, Inc* 136 S.Ct. 2511 (2016).

[7] The patent corresponding to US '540, European Patent No 0994963, was granted by the European Patent Office, with terms that are substantively similar to the corresponding US patent.

[8] Case T0146/07- 3.3.08 13 Dec 2011.

[9] Illumina (which now controls the patent through the patent pool arrangements agreed with Sequenom in 2014) is suing various alleged infringers in England, Switzerland, Germany and Poland. A preliminary injunction was granted in Germany against molecular diagnostic company Amedes MVZ Trägergesellschaft performing NIPT

judgment on patent validity is in England, where a judgment, was delivered in November 2017.[10] This litigation considered patents in three families,[11] and the parties argued a broad range of issues, including obviousness, priority, sufficiency and whether the claims relate to a discovery as such. The court held the Lo 1 patent valid in part: a number of claims were invalidated for lack of priority due to lack of enablement and lack of disclosure. In contrast to the US approach however, the subject matter challenge was unsuccessful. The patent was not held to be invalid as a discovery as such, because the claims are not directed to information about the natural world, but rather to a practical process, the detection method.[12] The other patents (Quake and Lo 2 and 3) were all held to be valid. Premaitha was held to be infringing all patents with its current Iona test. The Harmony test was held not to infringe the Lo 1 patent. Although the decision was initially appealed, the parties have now settled their dispute, and Premaitha (now Yourgene Health) has been granted a licence (Yourgene Health 2018).

In addition, other patents which cover narrower aspects of NIPT, such as those which cover certain types of sequencing techniques or technologies, have been granted, and some of these are also being litigated. In the USA, for example, a patent dispute between Stanford University and the Chinese University of Hong Kong is ongoing,[13] and Illumina and Natera are involved in litigation over a patent for NIPT library preparation ('Illumina Sues Natera Over NIPT Library Prep Patent | 360Dx' 2018), amongst other patent disputes between different players in the NIPT market (such as 'Illumina Files IP Suit Against Ariosa, Roche Over Array-Based NIPT | GenomeWeb' n.d.).[14] At least one further claim for infringement of a different patent was filed in England.[15]

In December 2014, Sequenom and Illumina, key players in the development and delivery of NIPT, settled their outstanding patent disputes by 'pooling' their patents ('Illumina, Sequenom Pool NIPT Patents, Settling IP Disputes' 2014). Through the agreement, Illumina obtained exclusive worldwide rights to use the pooled patents for kit tests for NIPT and to license third-party laboratories to develop and deliver their own laboratory-developed NIPT, and Illumina

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called Fetalis (at the time based on Ariosa technology): Genome Web, German Court Issues Preliminary Injunction Against Amedes for NIPT, https://www.genomeweb.com/sequencing/german-court-issues-preliminary-injunction-against-amedes-nipt (accessed 1 June 2018). The Fetalis test is now offered by Amedes based on Illumina Veriseq technology: https://www.fetalis.de/fuer-aerzte/ (accessed 1 June 2018)

[10] *Illumina v Premaitha* [2017] EWHC 2930.

[11] The patents in issue in these proceedings fall into three families: European Patent (UK) 0 994 963 (Lo 1); European Patent (UK) 1 981 995 and its divisional, European Patent (UK) 2 385 143 (Quake patents); and European Patent (UK) 2 183 693 (Lo 2) and its divisional, European Patent (UK) 2 514 842 (Lo 3).

[12] *Illumina v Premaitha* [2017] EWHC 2930 at [189].

[13] The Board Of Trustees Of The Leland Stanford Junior University v The Chinese University Of Hong Kong Appeal from the United States District Court for the Northern District of California in No. 3:12-cv-00865-SI, Judge Susan Y. Illston (27 June 2017)

[14] For example Illumina Inc et al v Ariosa Diagnostics Inc et al, ILLUMINA, INC., et al., Order granting defendants' motion for Summary Judgment, United States District Court for the Northern District of California Case No. 18-cv-02847-SI Judge Susan Y Illston (24 December 2018).

[15] *Illumina v Premaitha* [2018] EWHC 615 although this dispute was settled.

has aggressively defended those rights through litigation. Thus, multiple patents, held by multiple parties, are the subject of litigation in multiple jurisdictions.

Freedom to operate in personalised medicine

In order to avoid potential liability for infringement, those working in a field where there are granted patents should survey the patent landscape in order to determine their freedom to operate, and this principle applies equally in the field of personalised medicine. If patents which appear to cover the area in which those conducting genetic testing wish to work exist, then decisions need to be made as to how to proceed. If the patent appears to be valid, and the conduct in question would clearly infringe it, a patent may be licensed. Questions as to patent validity or infringement may provide leverage in bargaining the terms of the licence. If the validity of the patent is open to question, then one of two courses might be taken. First, an active challenge to the validity of the patent may be taken, through proceedings seeking revocation, either in the national courts, or, if within nine months of grant, by opposition proceedings at the EPO. Alternatively, the conduct in question could proceed, and a counterclaim for revocation could be made should the patent proprietor issue proceedings for infringement. This course of conduct would however result in potential exposure to damages for the infringer should the patent be found to be valid.

In these respects, gene patents operate no differently from patents in other areas of technology. There are however some particular issues that arise because of the nature of genetic testing, which have generated significant concern in the literature (Heller & Eisenberg 1998; Kaye et al. 2007). First, there is the potential for 'patent thickets' to arise. A patent thicket may arise where a multitude of patents is held by a multitude of owners (van Overwalle 2009; Shapiro 2001). Patent thickets can arise on either the technology for genetic testing (such as polymerase chain reaction or PCR, which is useful for a broad cross-section of disease tests) or in diagnosis-specific patent protection. In the case of diagnosis-specific patent thickets, there are potentially two forms: vertically oriented and horizontally oriented gene patent thickets (Verbeure 2009). Vertical patent thickets may arise where there is a broad patent granted over the gene-disease link, and later additional patents on specific mutations within that gene. Horizontal thickets may arise where a disorder is caused by multiple genes, either independently or cooperatively, and multiple genes need to be examined in a test. The transaction costs of investigating the patent situation, including identifying relevant patents, determining whether the conduct in question falls within the scope of the claims, and then negotiating necessary licences, or defending infringement proceedings, are high for individual patents. When multiple patents are held by multiple owners, the cost increases accordingly (Heller & Eisenberg 1998). A related problem which arises from patent thickets is 'royalty stacking'. If many patents need to be licensed, and each requires the payment of a royalty, then the resulting test may become very expensive (Verbeure et al. 2006). There is the potential for patent thickets and royalty stacking in both SGT and in NIPT.

There are some obvious similarities between the NIPT and SGT patent landscapes. In NIPT, there are numerous patents, and the landscape appears to have all the hallmarks of the potential for patent thickets and royalty stacking that caused such concern in relation to SGT patents, but which proved ultimately irrelevant in clinical application. There are also some important differences however. There is more litigation over these patents than in relation to gene

patents,[16] and some patents have been invalidated in some jurisdictions.[17] Moreover, a number of different patents are the subject of litigation. Perhaps significantly, there are a few key entities which hold a number of important patents, in contrast to SGT, where patent holders were numerous and diffuse, as the patents often arose from academic research.

These are significant potential problems, which could have a considerable impact on the delivery of genetic tests to patients. If patents do in fact have a negative impact on patient access to genetic tests and subsequent clinical care, then action should be taken to ameliorate this effect. Given the relative infrequency with which patent disputes reach the courts, it is important to examine how the law operates in practice, in order to determine how best to target any necessary intervention.

Law in practice – a study of NIPT

This section of the paper examines the ways that those working in the development and delivery of genomic medicine interact with patent law, taking NIPT as a case study, which can then be compared to previous work in relation to SGT. Empirical work is relevant and necessary to uncover the law-in-practice in this space. Case law in this field is sparse, and reflects only a small percentage of the field. This work seeks to explore awareness of the law, together with the balancing of the costs and benefits of greater engagement with patent law (termed 'compliance' in this article)[18] amongst those working in the field of non-invasive prenatal testing in Europe.

Methods

This paper reports a qualitative interview study conducted with stakeholders in the translational research process in NIPT in Europe. Participants were recruited from three groups; genetics laboratory staff and management, commercial NIPT providers and researchers and clinicians, although there was some overlap between these categories. The study focused primarily on those working in, or interacting with, the public sector in Europe. This is because, in Europe, the public sector is the primary vehicle for the delivery of genomic medicine. Moreover, at least in Europe, the vast majority of women will access their prenatal care through the public sector. The role that patents play in influencing the prenatal care pathway is therefore important, and affects questions of justice and equity of access.

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[16] Although there were opposition proceedings in relation to BRCA and other gene patents at the European Patent Office, those proceedings were on the whole unsuccessful in invalidating patents, and had relatively little impact on the clinical practice of testing.

[17] Although the Myriad BRCA 1 patents were ultimately partially invalidated in some jurisdictions, they were unusual in this, and most single gene patents were never litigated.

[18] The term compliance is used for consistency with other literature in this field, including Ayres & Braithwaite 1992; Ehrlich et al. 2002; Ellickson 1991; Murphy et al. 2009; Tyler 2006; Winter & May 2001 among others. Compliance as used in this paper is further discussed below under 'Analytical Framework'.

Targeted sampling was employed, to ensure an appropriate spread of interviewees. The sample was approximately two thirds constituted by public laboratory senior staff and directors (many of whom were also research active), with the remaining one third being clinicians (also mostly research active) and those working in a commercial context. The majority of interviewees were based in Europe, although some were previously based in Europe and had relocated to other countries. Interviewees were recruited through approaches by the author at scientific conferences, email contact and through personal recommendation of those working in the field. A final method of identification of potential interviewees was through 'snowball sampling'. At the end of each interview, an interviewee was asked to identify other individuals whom he or she thought would be suitable for the candidate to interview. This method identified a small number of additional interviewees.

Forty interviews of approximately one hour each were conducted (25 between July 2014 and April 2015; 15 between April 2016 and August 2017). The interviews were conducted face-to-face or by telephone. Interviews were recorded on a digital voice recorder and professionally transcribed, and analysed using grounded theory methodology, using NVivo. The interviews were conducted as semi-structured qualitative interviews, and the topics were addressed in roughly the same order, but in differing degrees of detail, depending on the interests and expertise of the interviewees. Relevant quotations from interviews are used below to illustrate the points made. These quotations have been edited to remove extraneous filler words (such as um, er and you know) and repeated words unless they were repeated for emphasis, but are otherwise verbatim, except as shown with ellipses.

Background – this study in context

In the field of SGT in Europe, previous research has indicated that those working in the development of diagnostic tests were instead in many cases working almost in ignorance of the law (Gaisser et al. 2009; Hawkins 2011). On the whole, patents were not causing difficulties, but this was because they were generally ignored, rather than because any problems were optimally managed. With very few exceptions, those developing and carrying out genetic tests did not conduct freedom to operate searches and did not license patents. They did not experience any negative consequences of this failure to take account of existing IP rights, they had not been approached by patent holders either informally or formally, and they had not been sued for patent infringement. Awareness of patents was generally very low. Where there was some awareness of patents, there was a rudimentary balancing of the costs and benefit of compliance as against non-compliance. Those working in developing and delivering SGT weighed factors such as the risk of being sued (perceived to be low) as against the costs of licensing (perceived to be high) and the harm to patients (perceived to be high) and came to the view that the balance was in favour of ignoring patents (Hawkins 2011).

This study explores the relevant differences in the field of NIPT. At the outset of the study, all indications were that there were differences in the ways in which those in the field of NIPT were aware of, and balancing questions of compliance and non-compliance with patent law. This study has explored these questions in detail.

Patent law does not exist merely in the abstract. Rather, it should have a practical relevance for the process of developing a diagnostic test. Conversely, the social world is relevant to law.

Where law violates conventions and understandings expressing social relations, then the social world will influence the use of law, and can restrain and modify law, 'even to the point of marginalisation or suspension' (Galligan 2007). This study examines not only what people do in relation to NIPT patents, but also the factors that influence their behaviour.

Analytical framework

The notion of compliance is contested in law. It has different meanings in different bodies of literature, and is often not the subject of precise definition. In this paper, compliance is used in its broadest sense to connote engagement with the legal system. It implies that the parties are aware of the private rights that are conferred by the law and that they respect those rights. In patent law, compliance implies that parties would conduct due diligence searches, and arrange their affairs in accordance with the results of those searches, and licensing patents, contesting them through legal process or engaging in rational infringement, that is, deciding to risk being sued on the basis that they consider the patent invalid, or that they are not infringing it. In this sense, perhaps the term 'engagement' with law would be more appropriate, but the term compliance is used for consistency with other fields of legal scholarship (Ayres & Braithwaite 1992; Ehrlich et al. 2002; Ellickson 1991; Murphy et al. 2009; Tyler 2006; Winter & May 2001). On a conceptual level, a number of factors are likely to influence whether relevant actors comply with the law. Firstly, the actor must be aware of the law. Secondly, the actor should perceive that the costs of compliance with the law are lower than the costs of non-compliance (Becker 1968; Winter & May 2001). 'Costs' in this sense is used in its very broadest sense, encompassing not only economic costs, but also costs of a personal and moral nature (Ayres & Braithwaite 1992).

Awareness that a law exists alone may not be sufficient; it is important that the person knows the content of the law in question. One who is aware that there is a law with which he or she should comply, or a private right which he or she should respect, but who deliberately refuses to find out what he or she must do to comply with the law or respect that right, cannot be said to be truly aware of the law in question. Common sense implies that where someone does not know of the existence, or of the necessary detail, of a law that applies to their conduct, then, whilst they may obey the law by chance, they cannot take active steps to ensure that their conduct complies with the law. This is particularly relevant for laws which impose positive duties to act in a particular way. There are likely to be varying levels of awareness of a law among members of any community to which the law applies.

If a person has some level of awareness of a law, then there are various factors which might influence their decision about whether or not to comply with it. On some level, a balancing exercise may be carried out: do the costs of compliance outweigh the costs of non-compliance (Murphy et al. 2009)? This exercise may be subconscious. Factors potentially influencing the perception of relative costs of compliance and non-compliance will be such things as the likelihood of enforcement of the law and the possible penalty should the law be enforced. However, deterrence through punishment forms only part of the motivation for compliance or non-compliance (Murphy et al. 2009; Tyler 2006). For many, disobedience of a law involves a high personal moral cost which outweighs other factors such as the low possibility of being caught (Ayres & Braithwaite 1992). However, this view of the costs of disobedience may vary for different types of law. Some laws are perceived as being more legitimate than others and

these laws tend to be more widely obeyed (Tyler 1997, 2006). For some types of laws, there may also be moral aspects as to how a person views the costs of compliance or non-compliance. For example, where a law is seen as immoral in and of itself, there may be an impetus to disobey it, which may overcome other natural inclinations to obey the law (Murphy et al. 2009). Similarly, where obedience to the law is perceived to result in an immoral outcome then this factor may be balanced against others and result in a decision to disobey. Certainty of punishment is also an important factor. People tend to be more inclined to disobey a law when they believe there to be a low risk that they will 'get caught' (Tyler 2006). Although patents are not 'laws' in the sense of criminal law or state imposed regulatory obligations, but are instead state granted private rights, compliance in this sense connotes respect for those state granted private rights. In this sense, there are parallels between punishment and patent enforcement and there may similarly be a perceived moral obligation to respect private property rights and on the other hand, perceived moral or ethical reasons why those private property rights should be ignored.

This framework for analysis focuses very much on the behaviour of those whose actions may or may not infringe a right, rather than on the actions of the rights holders. Obviously, the actions of the rights holders are important and cannot be ignored. In this framework, the actions of the rights holders (such as, for example, whether they tend to enforce their rights, with what vigour, and the sanctions they pursue) are factored into the analysis through their influence on the perceived costs of non-compliance.

There will be a multitude of factors which influence the balancing process in the case of particular laws, particular situations and particular individuals. The socio-legal approach taken in this study allows the exposure of some of these factors, together with a sense of the likely result of the balancing exercise.

Awareness

Awareness is an important pre-condition to compliance with a legal framework. If someone is unaware that the law might impose particular obligations or restraints on their conduct then they will not take action to ensure that their conduct is compliant with those obligations or restraints. This paper distinguishes between two different levels of interviewees' awareness of legal obligations: firstly, their knowledge of patent law in general; and secondly, knowledge of specific patents as they might impinge on specific tests, gained through freedom to operate searches.

General Awareness

Many interviewees framed their awareness of patents in NIPT in terms of being aware of a large number of patents in the field of NIPT.

> *Well, I know that there are lots of patents and that pretty much everybody is in some sort of litigation fight with everybody else. (Int 10)*

Patents are always an issue but that field seems to be like a minefield. So if you look at GenomeWeb … every other day there is some juice on patent issues in that field that is published. I haven't seen that before actually. (Int 27)

The gene patent debates of the late 1990s, particularly in relation to the policy of Myriad genetics to engage in restrictive licensing practices (Parthasarathy 2007) were influential for interviewees in framing their awareness in relation to NIPT patents. This translated into certain background beliefs which shaped their general awareness of patents. First, in the early stages of the study, many were of the view that patents in the field of genomic medicine would be unlikely to be enforced, drawing on the background that the Myriad patents, and other patents relevant to SGT, were not widely enforced in Europe. Significantly, this view became much less prevalent over the course of the study, as the US litigation between Ariosa and Illumina proceeded, Sequenom and Illumina settled their litigation, and Illumina began litigation against various parties outside the USA. Secondly, some interviewees expressed the view that, as the Myriad case in the USA resulted in the overturning of the breast cancer gene patents, there would be protection against infringement of NIPT patents in Europe. Whilst legally dubious, this belief was more influential in early interviews, and again was largely overcome by later events.

The background of lack of enforcement of single gene patents was highly relevant to initial awareness of patenting. As with single gene patents (Hawkins 2011), some interviewees expressed an attitude of wilful blindness to NIPT patents.

I was advised by people who know a little bit more about IP and genetic testing that it might be wise not to know too much about it. (Int 3)

I must say I'm not really very well aware… I know that there are patents and I know there is IP, but we didn't really investigate this in much detail. So we didn't really go out to look - what can we do, what can't we do? What we did, and we are, kind of, saying, 'Well this is a very good test that should be offered to pregnant women,' and that's, kind of, the thing that we have in our minds. (Int 6)

I can remember asking about it and saying, 'What are you going to do about the IP?' and [name] saying, 'Well, I'm very much burying my head in the sand at the moment'. (Int 21)

The wilful blindness is more evident in the early interviews however, and active litigation and approaches from patent holders changed those attitudes.

Nobody seems too worried about something until it actually hits. … it's just more an attitude 'deal with it when it happens'. (Int 21)

Well, because they say we had the same with the breast cancer genes. Actually, no one ever paid for that, or not really, especially not in [European country]. So that was also a patent. We're now how many years later? … The patent now is no longer there. So they all think, 'Well, if that one turns out to be not patentable, then the NIPT patents are also not valid.' So they say, 'Just wait and see.' Furthermore, they also think that the companies they are very big, and we are only very small compared to them, so why should they bother?... They

have to sue each [lab performing NIPT] separately. They say, 'Well, they're probably not going to do that.' (Int 5)

When re-contacted later in the study, some interviewees who initially engaged in wilful blindness discussed their plans for negotiating with the patent holder and attempting to license the patent, following the developments in the patent enforcement landscape.

Many interviewees mentioned their knowledge of ongoing litigation between NIPT providers when asked about their awareness of patents in NIPT. This was generally in fairly non-specific terms; that is, they were aware of on-going litigation, but usually not the detailed subject matter, or sometimes even the parties in question.

Well, I know that there are lots of patents and that pretty much everybody is in some sort of litigation fight with everybody else. (Int 10)

I know that everybody was suing everyone [laughter], but I don't know who that involved. I can't even remember the company… (Int 15)

We know there are patent wars going on. I just haven't really gone there in terms of trying to keep up with who's suing who and over what… (Int 17)

Well, we're well aware that Illumina are suing a number of people for use of sequencing technology around NIPT. (Int 33)

Their sources of awareness of the patents, and the patent litigation, included discussion with colleagues, both in local meetings and at national and international conferences.

It is certainly discussed and it's a big issue. It's a big issue in the literature and a big issue at scientific meetings. (Int 14)

Many interviewees also mentioned gaining awareness from the academic literature and scientific and industry press, particularly the Genomeweb news service, which regularly reports business and legal developments in genomic medicine.

I think when you're in the prenatal genetics environment you hear about all the patents all the time and it's in editorials here and there and review papers…. It's almost impossible not to be aware of. (Int 10)

Probably the most I get GenomeWeb daily, …so it's mostly the news media. (Int 12)

I: Where does that knowledge come from? *R: GenomeWeb. [Laughter] I tend to subscribe to that … And word of mouth, just talking to the various companies. (Int 23)*

Finally, and importantly, many interviewees disclosed that they were generally aware of the existence of patents in the field through direct contact with companies, including patent holders. Few disclosed that they had received formal warnings or requests to licence, but many had been involved in more informal discussions or negotiations about the nature of their in-house testing programmes, and the existence of relevant patents. Such discussions then tended to lead towards more specific awareness of particular patents.

Specific Awareness

The term specific awareness is used to connote knowledge of specific patents that are relevant to the work of interviewees. The means of gaining specific awareness is through due diligence and conducting freedom to operate searches. Alternatively, specific awareness could arise from direct contact from patent holders.

In marked contrast to previous studies in relation to patents in SGT, where those in public sector laboratories engaged in wilful blindness and did not consider freedom to operate (Hawkins 2011), in this study, freedom to operate was a concern for the majority of interviewees in the public sector also.

The 540 patent was particularly central in discussions of freedom to operate. Most interviewees had some knowledge of the patent, what it covered and whether or not their testing methods might fall within its scope. When discussing this patent, many interviewees expressed their concern about its breadth and its potential to be a block on further research and on development of the field of NIPT. In this respect, their views mirrored the emblematic objections to gene patents heard in the 1990s, and which were often cited in press reports surrounding the recent *Myriad* decisions.[19] They expressed the view that the subject matter of the patent was a discovery rather than an invention, and should not be amenable to patent protection. However, this discussion did not link to any intention to ignore the patent or refusal to license.

Freedom to operate analysis was generally perceived to be expensive, time consuming, and often unhelpful by virtue of being too complex, providing advice that was general and which lacked the necessary specificity. Others felt that the advice contained too many grey areas to be useful as a basis for taking action. However, on the other hand, it was also seen as necessary in the particular environment of NIPT research and delivery.

> I: Did you have an IP advisor? *R: Well, we have this company, [name] …So they give IP advice. But as far as I can see, they are not patent attorneys. So basically they give you not very in-depth advice but a bit of advice. But if you need to do a thorough freedom-to-operate search, you have to pay a separate patent attorney, which can be quite expensive. (Int 21)*
>
> *There was no interpretation and summary of what I should do. (Int 3)*

Some reported carrying out freedom to operate searches.

> *So we had to do some investigation, and actually we are going to end up having to pay a patent attorney to do a thorough IP freedom-to-operate search. (Int 21)*

For others, their concerns over freedom to operate did not necessarily translate into full due diligence searches or appropriate advice. Often, they said that they were considering obtaining formal advice in the future. In other cases, they were relying on information about the patents

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[19] *D'Arcy v Myriad Genetics Inc* [2015] HCA 35; *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013).

gained from colleagues or at meetings as sufficient to indicate that patents would restrict their freedom to operate. In some cases, such as where the decision had been made to licence technology from the primary patent holder, the formal freedom to operate analysis was often skipped, and reliance on minimal information, press reports of patents, rumours, or contact from companies was the source of awareness in place of formal advice. The ways that such awareness interacted with the balancing of factors in making a decision to license will be explored in more detail below. At this point, it is relevant to note that all interviewees engaged with the concept of freedom to operate on some level. Interviewees understood the concept, and had generally turned their mind to it in some way previously.

Interviewees therefore have a greater level of awareness than has previously been found in relation to SGT. The increased awareness relates to both general awareness, where interviewees are more conscious of patents as a potential issue, and specific awareness, where there is greater attention to issues of freedom to operate in relation to particular patents. Much of this awareness has been raised through reporting of litigation over NIPT testing technologies in the USA, and more recently Europe. However, the depth of specific awareness is still in many cases quite superficial. Whilst particular patents, in this case the 540 patent, are on the radar of interviewees, detailed knowledge of the terms of this and other relevant patents, and analysis of claims, scope and potential infringement is rarely present in public sector interviewees. Such interviewees rarely report carrying out detailed due diligence, or commissioning professional due diligence searches, and if they are conducted, they tend not to be conducted by legally qualified individuals. Moreover, in some cases, interviewees discuss rumours or erroneous understandings about patents (such as beliefs about US law being applicable in Europe). In such cases, they usually disclaim these beliefs as being the only reason for taking a particular course of action, but they may be one of many factors that influence a decision, for example to not develop in house testing and to send samples to a commercial provider.

Nonetheless, the interviewees use the level of awareness that they possess to then carry out a balancing exercise, to determine the costs and benefits of compliance. On the whole, the balancing exercise is informed by much greater general and specific awareness than in relation to SGT.

Balancing compliance

In previous studies exploring patent compliance in SGT, it was evident that those involved in developing and delivering SGTs carried out a rudimentary balancing of the costs and benefit of compliance as against non-compliance. They weighed factors such as the risk of being sued (perceived to be low) as against the costs of licensing (perceived to be high) and the harm to patients (perceived to be high) and came to the view that the balance was in favour of wilful blindness in relation to patents (Hawkins 2011). Here, I report the results of a similar balancing exercise which is conducted by interviewees in relation to NIPT.

Again, what is characterised as being a ‘cost’ or a ‘benefit’ is very broad, and encompasses not only monetary costs, but also time and effort, as well as moral and ethical values. Moreover, it is the perceived, rather than actual, costs that are most relevant to this analysis. Compliance

connotes engagement with the patent law system; in this context, most commonly due diligence and licensing or forbearance from testing in the absence of a licence. In the majority of cases, discussion about due diligence and licensing focused on licensing of the portfolio of patents held by the Illumina/Sequenom 'partnership', built around the 540 patent. There was almost no discussion of other patents which might be relevant.

In general, interviewees focused much more around the risks of non-compliance than any perceived benefits of non-compliance in this study. Interviewees also discuss how licensing brings other benefits, such that the question of patent law compliance is almost incidental in their decision making. The compliance choices in NIPT are more informed generally than in SGT, as discussed above with respect to awareness. It appears that interviewees engage in behaviour that a lawyer would characterise as rational; an awareness of relevant patents, an assessment of the scope of patent claims and a calculated choice as to whether to invent around, negotiate a licence, forebear from testing or continue and take the risk of being sued. However, on closer analysis, in many cases it appears that a decision has been made about compliance before conducting a detailed freedom to operate analysis, which will be explored further below.

Balancing - in favour of compliance

Many interviewees were highly influenced by factors which they saw as weighing in favour of compliance – in this case, licensing from the patent holder, or forbearance from testing in the absence of a licence. The two most influential themes which emerged from the interviews are litigation, and other benefits of licensing from the patent holder.

Litigation

Litigation is a theme which emerges in virtually all interviews. Most interviewees express concern about the risk of being sued for patent infringement. They characterise being involved in patent litigation as expensive, troublesome and time-consuming. They see litigation as overwhelming negative, and this is the case whether or not they consider themselves to be infringing a patent or not – interviewees are reluctant to be embroiled in litigation regardless of their views about the likelihood of a successful outcome.

> *I think they were majorly afraid of suing, and costs. (Int 26)*

Moreover, interviewees weigh the perceived unpleasantness of patent litigation together with their assessment of the risk of being sued. In early interviews, a number of interviewees expressed the view that the chances of being sued were low, drawing on past experiences with SGT. However, in later interviews, and follow-up interviews in some cases with the same interviewees, most saw the risk of being sued for patent infringement as a real and appreciable risk. In making this assessment, interviewees referred to the US litigation between Sequenom and Ariosa and the litigation in various European jurisdictions, as well as regular approaches from the patent holders to laboratories developing and conducting NIPT. As more parties became involved in litigation and it was more widely publicised, this assessment of the real and appreciable risk became more prevalent.

Well, I know that there has been litigation in the United States, hasn't there, … They are actively suing a number of people in [country] for carrying out NIPT using their sequencing technology. And so, yes, we have concerns that they will approach us for exactly the same reasons…. We've not gone any further because of concerns around that. (Int 33)

There's always the risk of being sued by Illumina. This is perceived as a huge risk. (Int 27)

Interviewees noted that most laboratories already have contact with Illumina for the purchase of sequencing machines and reagents for other areas of genetic and genomic testing and that Illumina representatives are regularly visiting and negotiating with them. As a result, conversations about NIPT and licensing can be initiated in these regular meetings, and are therefore harder to avoid than contact with other patent holders in the past.

Where samples were being sent out on a short term or one off basis to external providers, there was less concern about litigation.

People don't make decisions on what company to send a test to based on the fact that somebody has a patent or somebody doesn't have a patent. (Int 4)

However, concern about litigation was more relevant when licensing in technology or implementing an in-house test based on commercially licensed systems. Then, the fact that a small company was either being sued, or at risk of being sued, was seen as key to whether they would be a reliable long-term partner.

Illumina and Natera are big US companies with lots of IP. They are the ones who have been involved in the big battles, and so there is a lot more out there regarding their IP. Premaitha are a new company and I'm not sure that I feel as comfortable with what they state they've got as IP and how that would hold up. (Int 21)

Similarly, competitors of the major patent holder Illumina/Sequenom, particularly those either currently or likely to become involved in litigation were often not perceived to be a reliable or viable partner for a long term contract. The patent holder was seen to be a safe option as a testing technology provider.

But I think that that to me is so uncertain, that there is an element of safety going with one of the much bigger companies. (Int 21)

Other reasons for licensing

A number of interviewees had decided to partner with a patent holder for technology transfer into their laboratory, or to rely on sending samples to another provider of testing, and therefore avoid potentially infringing patents. These interviewees expressed that there were other reasons for making this decision, and generally denied that intellectual property concerns had any major influence on the decision.

First, commercial providers were perceived to have a good product, with high standards. NIPT technology was recognised by interviewees to be a genuinely important advance over

previously available testing technologies, and valuable and important for laboratories to offer to patients.

> *Well, I give credit to the companies also because they've pumped in a huge amount of money into this thing, and they've brought it up faster than anybody could ever have imagined. And they have a good product, most of them, all of them, and they're trying to make it as good as possible. (Int 1)*

Moreover, at least in the later interviewees, the price of the tests offered were seen as competitive with what interviewees could do in their own laboratories. A number of interviewees expressed the view that as NIPT is a complex technology, it made more sense to outsource than to develop the necessary expertise in their own laboratory.

> *And when we did the health economics on it, I think it was break-even with sending them away. And you think, well, if we are running the machine flat-out all the time, it's not like we can use it for anything else, so what is the benefit really? You've got all the legal stress and all the rest of it, and the quality control and the validation, and the validation's an extra cost. You've then got to ensure quality over time. So for us it just seemed… (Int 23)*

Moreover, because of the nature of the technology, as a higher volume screening test, it makes sense to concentrate expertise in a smaller number of providers to carry out testing, rather than to have small testing done by many providers. This also provides economies of scale.

The choice of external partner, particularly when licensing-in through technology transfer of the whole testing system (as a 'black box', with little to no capacity to modify the protocol) can be influenced by patents, but also by other factors. The quality of the test is highly influential; some providers have stronger clinical evidence for their test, such as larger clinical validation studies. The size and stability of the company was also important. This was not explicitly tied to patent position, but a number of interviewees expressed concerns about the lack of stability of companies that were currently, or might in the future, be sued for patent infringement. Although the patents were expressed to be largely irrelevant by many interviewees, they do seem to have had this incidental influence on decision making.

These factors all tend to push toward compliance, unlike in the case of SGT, where the other factors pulled away from compliance.

Considerations against patent licensing

Interviewees also discussed a number of factors which they considered weighed against compliance. The two most prevalent and influential were the costs involved, as well as a calculation of the risks of being sued and losing patent litigation.

Costs

Interviewees often expressed concern about the increased costs associated with patent licensing. Their concerns were mostly focused on royalties, although some mentioned the transactional costs associated with negotiation of licences. Many discussed the high level of

royalties per test as increasing the costs of testing for the payor and as making the tests uneconomic in a public healthcare system, increasing test margins.

> *They charge a fee of USD75 per test, which is a lot of money. That's basically one-third of the cost customers have for those tests. (Int 27)*

> *They want us to pay a licensing fee of USD75 per sample… And for that reason, we are probably going to withdraw the service completely. (Int 33)*

> *I don't object to paying a reasonable amount, say, 1 or 2, [laughs] but not 75. (Int 32)*

Although the level of the royalty set at USD75 might arguably be objectively reasonable given the investment in development of the technology, interviewees strongly expressed the view that it was far higher than they considered reasonable in the circumstances. This is perhaps unsurprising given that there are few situations where genetics laboratories are paying unbundled royalties in relation to patents.

Many interviewees expressed a perceived lack of value for money of the royalty fee.

> *They are buying already this sequencing instrument from Illumina. They buy also their reagents from Illumina. …So they don't understand why on top of that they would have to pay additionally a fee for some patents, because people understand that those patents are already paid for with what they pay as instrument and as reagents. (Int 27)*

Moreover, there is a lack of bargaining power to negotiate the level of royalty.

> *There's not much discussion going on, it's just, 'This is it.' (Int 32)*

> *They said that it would be USD75 a go … I didn't get the impression there was any room for negotiation on that. (Int 33)*

Licensing problems

The process of negotiating a licence was seen as difficult in theory, and in practice.

Some interviewees reported that they encountered willingness to grant a licence, but unwillingness to negotiate the terms. Many interviewees felt they lacked sufficient bargaining power. They wished for flexibility, not only in terms of royalty levels, but also with respect to other matters, such as their insight into the algorithms, which some referred to as a black box, and ability to obtain more detailed information about non-routine cases or borderline results. Other interviewees expressed that they had a lack of experience in negotiation. The process of negotiating terms following a formal tender process according to EU rules was interestingly seen as a means of rebalancing the inequalities in bargaining power.

> I: The process of agreeing the terms and conditions, how difficult was that? *R:It was actually made easier by the tender process, because prior to us going out to tender when we thought there was only one company available, there was an awful lot of toing and froing because the company we were going to go with were an American company … their*

contract was horrendous. And that would have been a major stalling point. By going out to tender, we've managed to avoid that… I think because you are putting them through a competitive process there's more pressure for them to agree some of those terms and conditions. So it was very helpful. (Int 21)

A number of interviewees expressed the desire for collective negotiation at the national level in their jurisdiction. They felt that the relevant department of health, or the body responsible for the regulation of genetic diagnostic testing provision in their country would be better placed to negotiate an agreement on behalf of laboratories for the national provision of testing. They felt that this would both re-balance inequalities in bargaining power, and also draw on the necessary experience in negotiation that they felt they lacked.

I think we felt that it was such a big area and potentially such a large number of women, that really we needed guidance from [national department of health] about how best to proceed with that… that really was best negotiated at a national level than a specific lab level. (Int 23)

Risks of infringing

Some interviewees were reluctant to negotiate a licence of patents because they considered that they were not infringing - because they argued that the patent was invalid, and/or that their conduct did not fall within its scope. In some cases, this appeared to be a reasonably well informed analysis, based on professional advice. Such interviewees were prepared to take the risk of being sued, and reported that they would continue to reassess their decision based on developments in the law, and if contacted by patent holders would consider licensing at that point. Such conduct appears to be entirely consistent with the law.

Others expressed an attitude more consistent with wilful blindness. Those interviewees claimed that the risk of being sued in genetic and genomic medicine is low, drawing on experiences with Myriad genetics and SGT in Europe in the 1990s and 2000s. In this respect, they claimed that, whatever their conduct and whether it fell within the scope of valid patents, they need not consider licensing. This attitude was not universal, and became much less prevalent in later interviews, where the risk of litigation was evaluated as more real and with possible significant negative consequences.

In a third subset of interviews, interviewees were engaging in what might be termed uninformed compliance. They had general awareness of patents and some specific awareness, but this awareness was not informed by freedom to operate analysis. Instead, they gleaned awareness of patents from industry press reports and anecdotal discussions with colleagues from different institutions, often in different jurisdictions. They formed the view that patents existed, and therefore concluded that they should not offer testing as a result, or that they should send samples to a commercial partner or otherwise negotiate with a commercial party. While the patent situation was unlikely in such a case to be the only reason for the action taken, it played some part.

Discussion

The study demonstrates that in NIPT as compared to SGT, there is a move towards compliance with patent law. The field appears to be moving from a position of wilful blindness, to greater engagement with patent law, including openness to negotiation and licensing. Law and law-in-practice are more congruent.

However, compliance can take different forms; whilst a patent licence represents one form of compliance, forbearance from offering a test in the absence of a patent licence is equally a form of compliance, and one which will reduce the testing options available to patients. Similarly, where it is not possible to negotiate a licence on appropriate monetary or other terms, then a move towards compliance seems likely to result in a reduction in testing providers. Although NIPT is available from commercial providers on a pay for service basis in most of the world, as yet, it has not proved possible in many jurisdictions for the public sector to provide testing. Although there are many factors associated with this delay, including allocating funding for a new type of testing and deciding its appropriate place in the prenatal care pathway, the negotiation of IP rights adds an extra layer of complexity to an already complex problem. In many public health systems, there is little experience in the negotiation of these types of patent licenses in the laboratories which conduct this type of testing, and experience in drug pricing negotiations for example is usually centralised, and is not easily transferrable to other contexts. Moreover, while commercial providers who provide testing to patients on a private, pay-for-service basis, can pass on increased costs to the consumer, where testing is to be provided in the public sector, when multiplying those costs across the population, those increased margins can make a test uneconomic.

There are some key differences between the fields of SGT and NIPT, which arguably explain the different approach to compliance. Because pregnancy is common, and because this is a screening test, there is a large patient population for whom it will be relevant. As a result, there is a commercial incentive to engage in R&D in this area, with parallels to block-buster vs orphan drugs. Therefore, commercial entities were incentivised both to obtain patents (through licensing and assignment, as well as through filing) and to enforce them, through informal and formal means.

The litigation of the NIPT patents has been highly publicised in the relevant scientific literature and press, and is well known amongst those developing and conducting NIPT. They have weighed their risk of being sued for patent infringement as real and appreciable, and therefore have been less inclined towards wilful blindness. The fact that the major patent holder, Illumina, is also a provider of sequencing machines and reagents also means that avoiding discussions about licensing is more difficult for most laboratories, and the risks of endangering other aspects of core laboratory business by a dispute with the patent holder were at least potentially a factor in considerations of compliance. However, it is notable that levels of specific awareness informed by either laboratory or professional freedom to operate searching remains very low, and as a result compliance is frequently relatively uninformed.

Other factors also seem likely to have influenced the willingness for interviewees to comply, rather than to resist. A key factor that influenced the resistance to single gene patents was the

concern about lack of patient access, and the perceived harm to that access that compliance caused – this was a consistent theme expressed by all interviewees in the author's previous work on SGT (Hawkins 2011). In the case of NIPT, there was, from the early stages of clinical NIPT testing, a thriving market for private testing outside of the public healthcare system. The cost of commercial testing has continued to drop, such that a number of interviewees claimed that it was comparable to what could be provided in a public sector laboratory. Commercial testing was not perceived, by at least some interviewees, to be unreasonably expensive, and therefore not an insurmountable bar to patient access through a public system. Secondly, patent holders seemed to have learnt from the Myriad example, and were providing solutions which were more acceptable to public sector laboratory staff, such as enabling the licensing-in of technology, rather than requiring all samples to be sent away to a central laboratory for testing. There were also multiple commercial providers of testing, such that there has never been a single monopoly provider of testing – something which provoked a great deal of resistance to the breast cancer patents. Moreover, academic research has been allowed to continue without threat of patent litigation, and has even been tacitly encouraged by patent holders, for whom it provides advantages in strengthening the evidence for NIPT as an alternative to existing screening tests. Therefore, in contrast to SGT, interviewees did not express the same ethical concern about patient interests as a justification for wilful blindness to patents.

All of these factors together may be reasons why compliance has been the predominant outcome in NIPT, compared to the widespread non-compliance in SGT. If some of these factors had been different, the balance might have been struck differently. For example, if the outcome of the litigation had been different, and a single monopoly provider had emerged as being able to wield greater market power, then it seems likely that there would have been greater resistance amongst public sector staff. However, at the same time, it might have also increased the risk of being sued, which would have weighed in the opposite direction, in favour of compliance through licensing.

Implications for personalised medicine

Both NIPT and SGT can serve as a useful case study to understand the way that patents may influence the development and delivery of innovations in personalised medicine. The ways in which the factors discussed above may be balanced by the relevant parties will likely differ depending on the nature of the innovation in question. Although it is difficult to generalise, it seems likely that patents will play a more important role, and there will be more convergence between law and law-in-practice in situations where there is a broad 'platform' technology, or where there is a personalised medicine innovation which has wider population relevance and therefore a large market. In such a case, there will be greater incentives for the filing, ownership and enforcement of patents, with more similarities to NIPT than SGT. In contrast, where a personalised medicine innovation involves the generation of innovations relevant to a very small and specific patient group, it seems that a situation akin to SGT, with its widespread wilful blindness to patent law compliance, is more likely to develop.

Of course, whether or not there is compliance with law is not particularly relevant in the abstract – of much more interest to patients and the wider public is whether or not innovative biomedical technologies are being developed in the first place, and secondly whether those patients who will benefit from them are able to access them. Whether patents appropriately

allocate incentives and costs to optimise innovation is contested, and with no consensus in the literature (see for example Plant 1934; Bently et al 2018). Patents are often justified as important to provide an incentive to technological development,[20] and it is possible that patents have helped to bring NIPT technology to the clinic faster, or improved the quality of the technology. In terms of patient access also, compliance with the law does not necessarily equate to optimal outcomes. In the case of SGT, patent law did not appear to pose problems for patient access, largely because patents were ignored and not enforced. In contrast, in the case of NIPT, compliance does not seem to be resulting in broader availability of testing. In fact, the evidence disclosed in the interviews for this study suggest that the royalty fees and transactional costs associated with the negotiation of licences, and the delays from due diligence and licensing have slowed adoption in the public sector and therefore likely decreased patient access. Adding the resolution of patent problems into an already complicated process of commissioning a new test into public healthcare services has further complicated an already complex problem. However, only time, and economic evidence, will demonstrate whether there are patient access problems in NIPT.

Concerns about the potential for patient access to medicine and medical care to be compromised by patents are often addressed by the proposal of solutions which are based on existing law, and which usually rely on licensing models. Indeed, models of open innovation are often predicated on strong intellectual property rights which are then licensed or pooled (van Overwalle 2009). There are significant flexibilities within the framework of existing patent law which could assist to resolve difficulties. Patent pools, clearing houses and open source models are all possible within traditional intellectual property frameworks, and depend to some extent on the grant of intellectual property rights, with ownership necessary to ensure openness. Moreover, compulsory licensing[21] or the Crown Use exemption in the UK[22] would be ideally suited to resolve intractable licensing negotiations, perhaps most usefully as a spur to encourage negotiation of licences on reasonable terms (Cornish et al. 2003). However, recourse to licensing models or compulsory licensing regimes rely on those working the relevant field of technology also recognising property rights and operating within the framework of the law. In a situation where there is widespread wilful blindness to patent rights, such solutions are unlikely to be adopted by those working in the field and thus be largely ineffective. Any proposal to ensure access to innovation will need to fit well with the existing institutional norms and culture and the current practice in the field. Greater attention to the law-in-practice is therefore essential; understanding whether patent rights are likely to be observed and widely enforced or more marginal will be important to enable smoother translation of innovative personalised medicine into clinical use.

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[20] *Asahi Kasei Kogyo* [1991] *RPC* 485 (HL).

[21] As regulated by Art 31 Agreement of Trade-related Aspects of Intellectual Property Rights 1994, translated into UK domestic law as ss48-53 of the Patents Act 1977 UK

[22] ss 55-59 Patents Act 1977 (UK)

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