



Human
Genetics
Commission

Intellectual Property and DNA Diagnostics

A report of a seminar on the impact of DNA
patents on diagnostic innovation

by the Human Genetics Commission, October 2010



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This report has been prepared by Stuart Hogarth and Michael Hopkins on behalf of the HGC. The content is based solely on presentations and discussions that took place at the seminar of 25th October 2010.



Executive Summary

This report is a synthesis of a seminar convened by the Human Genetics Commission in October 2010 on the impact of DNA patents on diagnostic innovation. The seminar brought together a wide range of stakeholders, and discussion was facilitated under the Chatham House Rule in order to encourage an open exchange of views. The main aim of the seminar was to inform policy deliberation in the UK by collecting evidence and views on the impact of DNA patenting on innovation in diagnostics, and by eliciting views on what might constitute fair and equitable frameworks for intellectual property (IP) in the field of diagnostic testing.

Since the early 1980s the United States Patent and Trademark Office (USPTO), European Patent Office (EPO) and Japanese Patent Office (JPO), have granted thousands of patents with claims to sequences of human DNA. The proliferation of such 'DNA patents' has given rise to a number of concerns. There has been much discussion about whether genetic discoveries meet the legal requirements for patentability, and whether it is ethical to patent what some see as the common heritage of humanity. However, given the legal provision for the patentability of inventions related to DNA sequences in Europe, the seminar focused on another set of commonly aired concerns, as follows:

1. Research and development (R&D) costs for genetic tests are relatively small and do not justify patent rights;
2. The proliferation of patents may hinder test development;
3. Research may be prevented by inadequate exemptions from patent infringement for researchers;
4. Monopoly service provision may drive up the price of tests, increasing healthcare costs and/or hindering patient access to tests;
5. The quality of testing (and thus patient care) may be affected when only one company is conducting testing.

Empirical research has shown that the enforcement of DNA patents has led clinical genetics laboratories to withdraw some tests, although the problem would appear to be far more common in the USA than Europe. Genetics laboratories play an important role in diagnostic innovation, as well as test delivery, and there is concern that DNA patents distort the open and informal innovation process that has allowed public sector laboratories to provide such a diverse range of testing services. It would appear that, at present, genetics laboratories in the UK are largely unaffected by DNA patents and so on many occasions have not had to negotiate licensing agreements or other IP arrangements. However, licensing and royalty payments have been necessary for platform technologies such as Polymerase Chain Reaction (PCR), and there are currently discussions about whether the adoption of new technologies, such as free-fetal DNA testing, will require licensing.

DNA sequences are only one type of patentable biomarker, and the patenting of DNA affects areas of medicine other than clinical genetics, in particular oncology and infectious diseases. Recent research has confirmed that there is a strong trend for diagnostics companies to hold patents on biomarkers as well as on platform technologies. Furthermore, the rise in biomarker patents is being fuelled by academic researchers seeking to protect their discoveries. Industry representatives suggest that this may be a positive development, allowing companies in some cases to demand higher prices for their tests at a time when they believe the R&D process is becoming more expensive as a result of higher evidence requirements from regulators and healthcare payors. In the past, the diagnostics industry



has lacked a sustainable R&D infrastructure that is able to deliver high-quality clinical evidence for new tests in a timely fashion. The incremental accretion of data has occurred over decades and the reimbursement rates for diagnostics have not provided sufficient incentive for an efficient and effective R&D process. Whilst industry participants saw biomarker IP as an essential component of their business models, they also cautioned that it could have a negative impact on test development.

Thus the seminar revealed a profound tension between the industry's desire to exploit the financial value of biomarker patents and the routine infringement of such IP in NHS laboratories. This tension between public and private interest is reflected in the academic research community which, supported by public policy, continues to patent publicly-funded biomarker discoveries in the hope of capturing their commercial value. These issues are not new, having been raised at various times over recent years. Given the growing use of biomarker IP in applications with a far larger potential market than monogenic disorders (e.g. companion diagnostics and population screening programmes), it is necessary for policymakers to begin to address these tensions.

Recommendations

Recommendation 1: Given the reported growth in patenting by academic researchers, the UK research councils and other major biomedical research funders, such as the Wellcome Trust, Cancer Research UK and the British Heart Foundation, should review their guidelines on licensing.

Recommendation 2: To establish a biomarker IP monitoring function within the Department of Health (DH) or in an appropriate cross-departmental office. Duties should include: a) evidence gathering and analysis and reporting on the impact of current policies on the incentives for public sector and private sector biomarker-based innovation in diagnostics, b) encouraging private sector IP biomarker holders to contribute genetic data arising from diagnostic tests to public databases which aim to develop libraries of the relevant DNA sequences which are as comprehensive as possible, yet ensure confidentiality of individuals' data, and reporting on any problems encountered in this area, and c) developing guidelines for out-licensing and in-licensing of IP by public sector funded staff.

Recommendation 3: At present it is unclear who within the NHS might be responsible for dealing with the practical implementation of policy in this area. Support should be given to senior management at a national level to help develop the capacity to manage biomarker IP issues.

Recommendation 4: More independent evidence needs to be generated on the impact of biomarker IP on diagnostic innovation. A starting point would be research to address the questions that were raised and evidence gaps identified by this seminar. An appropriate forum and process will be required that provides time for detailed deliberation and an assessment of the divergent needs and preferences of a range of stakeholders.



Introduction

This report is a synthesis of a seminar convened by the Human Genetics Commission in October 2010 on the impact of DNA patents and diagnostic innovation. The seminar brought together a wide range of stakeholders, and discussion was facilitated under the Chatham House Rule in order to encourage an open exchange of views. The main aim of the seminar was to inform policy deliberation in the UK by collecting evidence and views on the impact of DNA patenting on innovation in diagnostics, and by eliciting views on what might constitute fair and equitable frameworks for IP in the field of diagnostic testing.

Chair's opening remarks

Graeme Laurie (Chair) introduced the seminar, and set out three objectives:

1. To collect evidence and views on how DNA patenting might be inhibiting or benefiting research and innovations in DNA diagnostics.

Several decades of DNA patenting have resulted in an emerging evidence base regarding its impacts, and this needs to be considered for the UK, Europe and beyond. A recent US report by the Health Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) suggests that there is no convincing evidence that diagnostic patents facilitate or accelerate diagnostic innovation, nor that exclusive licensing is required to bring testing services to market (SACGHS 2010). Litigation around gene patents rarely appears to involve genetic tests (Holman 2008). Some cases are well known, in particular that of the US biotechnology firm Myriad Genetics, whose intellectual property on breast and ovarian cancer (BRCA) genes has given it a monopoly over genetic testing for certain forms of breast and ovarian cancer. But what is the situation regarding other diseases, such as Long QT or Alzheimer's?

2. Is there a common consensus on what might constitute fair and equitable frameworks for IP in the field of diagnostic testing?

There have been a number of recommendations, by the Organisation for Economic Co-operation and Development (OECD), the Nuffield Council on Bioethics, and others. How can we move forward in a concrete and pragmatic fashion? It is clear that the role the law plays should only form part of the debate. Gene sequences are patentable lawfully, *Ordre Public* exceptions are possible, but interpretation is narrow. We need to consider the post-patent grant context, which means the licensing practices of those who own the patents. If patent owners do not license on fair and equitable terms, when is compulsory licensing desirable? There is a research exemption that protects researchers from patent infringement suits, but should there be such an exemption for diagnostics?

3. What pragmatic developments are planned for the future?

A report by Cornish et al. (2003) recommended that the DH monitor developments in IP, and establish horizon-scanning activities, perhaps with the help of other organisations. The report stressed that the DH could be more proactive, for example intervening at the EPO via opposition proceedings against particular patent applications. Should the public mission of the NHS and universities influence IP policies and practices?

The importance of avoiding polarisation, which is a feature of the US debate, was stressed.



Presentations

Michael Hopkins and **Stuart Hogarth** presented an overview of recent empirical research on the impact of DNA patenting in relation to diagnostics. Michael Hopkins focused on reviewing published academic research.

Since the early 1980s the USPTO, EPO and JPO have granted thousands of patents with claims to nucleotide sequences (colloquially termed ‘gene patents’ or ‘DNA patents’, which are technically less inclusive terms. We focus here on the broader usage generally implied, i.e. all patents and patent applications seeking to claim nucleotide sequence when using the term DNA patents). Overall, around 30% of these patents originate in the public sector, although in diagnostics for rare disease genetics it seems a disproportionately high number involve patents generated by technology transfer offices, which tend to license these inventions, often on exclusive terms (Hopkins et al. 2006, Huys et al. 2009).

The proliferation of DNA patents has given rise to a number of concerns, and some empirical research has been undertaken to investigate these, particularly in the USA. One longstanding concern is that patents will disrupt or slow knowledge flows to researchers, particularly in the public sector, and this has now been demonstrated through bibliometric analysis of citation patterns of publications associated with patented research. Huang and Murray (2009) report that the granting of a patent reduces citations to published scientific papers based on the same work by 5-10%, and that as the number of patents on a gene increase, citations decrease, demonstrating a moderate ‘anti-commons’ effect.

A common concern, especially amongst the community of practitioners involved in providing clinical genetic services, is that patents on DNA sequences cannot be invented around, thus limiting the options of laboratories providing genetic testing services when broad patents are granted. However, it is often possible to invent around sequence claims, although this is possibly time-consuming and expensive. In fact, patent claims on diagnostic methods are more commonly considered insurmountable, according to Huys et al. (2009) who have conducted a detailed study of claims for 22 commonly used genetic tests.

The SACGHS (2010) report shows that where patents cannot be invented around and monopoly provision of a genetic testing service results (e.g. Myriad Genetics’ testing services for breast and ovarian cancer in the USA over recent years), the opportunities for innovation are constrained, with other providers and alternative testing methodologies being cleared from the market. This may also mean that the quality assurance for the testing services provided is limited or less transparent, or that second opinions on test results are not available for patients. There has also been concern that monopoly service provision leads to increased pricing of tests. However, there is no consistent evidence of this, and many other factors affect test price (including economies of scale in service providers, and the reimbursement levels set by health insurers).

Hopkins emphasised that there have been great variations in the patenting of human DNA sequences across countries and over time (Hopkins et al. 2007). Comparative analysis of patent applications filed and patents granted by the EPO and JPO shows many fewer DNA patents have been filed and fewer still granted outside the USA. The rate of filing of such patents also declined after 2001, partly due to the publication of much of the human genetic code following the Human Genome Project, but also because patent examination guidelines have tightened and the perceived value of DNA patents in industry has reduced.

How have diagnostic laboratories been affected when patents have been granted? In the USA, the relatively large number of patents on diagnostics has reportedly led to around 25% of interviewed



laboratories withdrawing a testing service for rare genetic diseases due to patent enforcement activities (Cho et al. 2003). Many of these tests subsequently became case studies for the SACGHS report. By comparison, only 7% of surveyed European laboratories reported that patent enforcement had hindered their provision of testing, and for public sector laboratories this fell to 4% (Gaisser et al. 2009). Less evidence of enforcement in Europe could be due to a number of factors, including the presence of fewer patents in the EU and the smaller size of EU laboratory workloads (making litigation less lucrative). Other factors may relate to timing. EPO patents grant more slowly than in the USA, and US patent owners may have not yet begun to focus on overseas litigations while they concentrate on their domestic markets. While there is little evidence of a negative impact in diagnostics provision in European laboratories at present due to patent enforcement, there is no room for complacency. The survey revealed that European laboratories are ill-prepared to deal with licensing issues and they will require greater support to identify and negotiate with holders of IP, or to work to invent around or challenge patents (Gaisser et al. 2009).

The role of the public sector laboratories in generating innovation was explored. Since the emergence of molecular genetic testing, NHS laboratories have been responsible for making hundreds of new services available, with substantial innovations occurring in hospitals, often with little or no commercial involvement - so called 'hidden innovation' because it is often excluded by standard metrics of innovative activity (NESTA 2006). Such diagnostic innovation is associated with informal processes of regulation, rapid translation, and low costs of development. While this has been an extremely productive 'hidden research system' (Hopkins 2006), in the UK and elsewhere, this mode of innovation is only one of the possible ways in which diagnostics can be developed. Little of the empirical research has looked beyond the associated framing of genetic tests resulting from 'hidden innovation' as low cost and straightforward to develop. Much of the present debate in the USA takes these tests, which mainly relate to the diagnosis of rare genetic disorders, and associated commercial competition, as the frame of reference. It was noted that the second presentation of the seminar would be moving beyond this framing, to explore other spheres of genetic testing.

The second half of the opening presentation was given by Stuart Hogarth and was focused on industry perspectives on biomarker patenting, based on new, unpublished research from a European Commission funded research project (commissioned by the Institute for Prospective Technological Studies - IPTS). Hogarth began by suggesting that opponents of DNA patents and exclusive licensing frequently argue that the cost of bringing diagnostic tests to market is too low to justify a period of market exclusivity. This view was expressed in the Nuffield Council's report on the ethics of DNA patents, although the report also said that in some cases the complexity and cost of developing a genomic test might justify an exclusive licence. However, this scenario was not something the Council explored in any detail, a lacuna that is reflected in the broader policy discussion about DNA patents. For instance, it was one of the primary criticisms levelled at the recent SACGHS report on DNA patenting. A minority of SACGHS members issued a dissenting statement in which they argued that test development is becoming more complex and costly as regulators and healthcare payors demand higher levels of evidence.

Hogarth suggested that this greater demand for clinical evidence is in some ways incompatible with the *In Vitro* Diagnostic (IVD) industry's traditional business model, which is based on companies holding platform IP rather than biomarker IP. He illustrated the tensions using the example of the Roche Amplichip CYP450 Array, the first DNA microarray-based test to gain Food and Drug Administration (FDA) approval for clinical use. The test distinguishes 29 known polymorphisms in the CYP450 genes whose role in the metabolism of many commonly used drugs is well established. The purpose of the test was to inform optimal levels of drug dosing for patients according to their genetic profile. There is a large amount of literature documenting the clinical validity (albeit generally



insufficient to give very clear guidelines on drug dosing). Although approved by FDA in 2004 the test has not been widely adopted, and has been the subject of a series of negative Health Technology Assessments (HTA) by North American health payors, which state that the utility of CYP450 testing remains unproven. The absence of such evidence in part results from Roche not having an incentive to invest in the type of clinical studies being demanded. They hold no patents or exclusive licences on the CYP450 genes, and therefore any investment they make in building the clinical evidence base would also benefit rival companies who have either entered the CYP450 market or are preparing to do so. This tension between rising regulatory hurdles in the form of demands for greater evidence of clinical utility, and the lack of incentive to make the necessary investment in clinical research, provides an important context for understanding industry attitudes to biomarker patents.

Representatives from 17 companies were interviewed as part of the IPTS study. The companies ranged from industry leaders to small start-ups, working in a range of clinical areas including oncology, infectious diseases and clinical genetics. Some companies were kit manufacturers, others were reference laboratories and some were both. The interviewees confirmed the view that there is a clear trend towards IVD companies holding biomarker IP, either as an alternative to platform IP or as a complementary asset, and that biomarker IP is a fundamental issue at the initial stage of the test development process, requiring companies to map the existing patent landscape, devise work-round strategies or negotiate licences where necessary. There were mixed views regarding the impact of biomarker IP: benefits include access to venture capital for new companies, increased revenue, and a greater incentive to invest in clinical research; the disadvantages include the possibility that companies are prevented from developing tests, thus hindering patient access and incremental innovation, which complicates the innovation process and increases associated legal costs. More fundamentally perhaps, there was a view that the value of biomarker IP could be over-estimated, and that it is often too early to be certain of the value of biomarker IP, because of a range of uncertainties concerning patentability, defensibility and the willingness of purchasers to pay higher prices. Thus patents on platform technologies remain crucial to most of the IVD industry, as intellectual assets that are easier to patent and protect and whose commercial value is well understood.

Hogarth then concluded with a case study, also drawn from the IPTS project, concerning the use of Human Papilloma Virus (HPV) tests in cervical cancer screening. Since the discovery of the role of HPV in cervical cancer in 1983, there has been growing clinical and commercial interest in the use of HPV tests in cervical cancer screening programmes based on detection of HPV DNA sequences in patient smear samples. One US diagnostics company, Digene (recently acquired by the European company Qiagen) has dominated this field, in large part because it acquired patents or exclusive licences for the high-risk HPV strains associated with cervical cancer. Following FDA approval in 1999, its test was in widespread use in the USA by 2003. Clinical acceptance of the test was driven in part by the development of a large body of evidence demonstrating the utility of Digene's test as either an alternative or supplement to the traditional Pap smear test. Digene played a major role in the development of this evidence base, investing millions of dollars in a series of clinical studies which involved over ninety thousand women on four continents. However, it should be noted that much of the money for these studies came from the public sector. The crucial trial in the USA, for instance, was the ASCUS/LSIL Triage Study (ALTS) funded by the country's National Cancer Institute, which is supported federally. Digene was involved in patent litigation with a number of rival test makers to defend its US monopoly, although it did not litigate against infringing parties in Europe (where a broader range of rival tests are available) or against HPV tests produced as laboratory-developed tests (LDTs), generally associated with the 'hidden innovation' processes in public sector laboratories, as described by Hopkins in the first part of the presentation. The HPV story differs from the more familiar case of Myriad and BRCA testing in that the monopoly was in the form of a kit rather than an LDT. The two US laboratory directors interviewed for the case study felt that Digene had played



a leading role in driving acceptance of HPV testing and that its test was a significant advance on the LDTs which had been available until then. However, they expressed some concerns regarding cost and patient access (although no evidence of harm) and were of the view that competition is desirable and that alternatives to the Digene test were now needed, and indeed beginning to come to the market. Finally, they noted that other factors might be affecting the availability of rival tests, including the need for FDA approval. Hogarth suggested that this illustrates the trade-offs between different policy imperatives – the desire for robust clinical evidence comes at a price, whether it is paid for through publicly-funded trials or by private R&D investments which companies recoup through securing temporary monopolies and higher prices for their tests.

Gail Norbury

Gail Norbury was invited to present a perspective from the NHS genetic testing laboratories. She emphasised that genetic testing in the NHS is part of a complex, varied and changing pathology landscape. The presentation focused on the experiences of laboratories working in the Regional Molecular Genetics Laboratory (RMG) network (whose staff are represented by the Clinical Molecular Genetics Society). The RMG laboratories are specialists in testing for around 400 rare inherited diseases, issuing around 100,000 reports for patients per year. However, molecular genetic testing is used more widely, and at much higher volumes in diverse applications beyond the RMG network, particularly in haematology, virology and oncology laboratories. It is also widely expected that the use of genetic testing will support more precise use of therapeutics in the future. More diverse providers of testing services are emerging, such as private sector groups. This trend was encouraged in Lord Carter's review of pathology services, which also discussed the need for wide-ranging change in delivery of pathology services, noted to be of growing importance in the NHS (Lord Carter 2006). The Carter review is unclear on the role of intellectual property or how to manage these issues.

A number of factors have implications for how gene patents affect diagnostic services, meaning that varied outcomes can be expected for different tests. This is illustrated by the US case studies produced to support the SACGHS report.¹

Some testing, for example, is conducted at very high volumes, perhaps with the same test available in a large number of laboratories. In other cases, a test may only be available in unaccredited laboratories that mainly focus on research rather than clinical testing. For certain tests, laboratories may conduct analysis on many genes, and consequently their work could be related to many patents. Laboratories may also supply testing services to patients locally or internationally. The rapid changes in available science and technology mean that it is a challenge to stay up-to-date with the intellectual property rights relevant to the services that are offered.

The responses to intellectual property differ between the private and public sector providers – in the case of the latter, the view has sometimes been to 'look the other way'. In 1997, for example, NHS test providers in the UK received a letter from the Canadian patent holder inviting laboratories to take out a licence to conduct testing for cystic fibrosis testing. This invitation was ignored, partly because it was felt by clinical scientists that the request was audacious, and partly because the request came from a hospital in Canada, which seemed to make it less relevant. While NHS laboratories have not paid direct licensing fees for use of the cystic fibrosis gene patent, some laboratories do use commercial testing kits, the price of which includes a royalty fee for use of the patent.

Another gene patenting concern has been the BRCA patents, initially licensed by Myriad Genetics to Rosgen for the UK, and later to Lab21. There was a great deal of concern in the NHS laboratories that

1 These cases are available as a series of papers in a special issue of *Genetics in Medicine*, April 2010.



these patents would impact on their ability to provide testing services relating to breast and ovarian cancer. Efforts to deal with clinical workload backlogs by involving private sector providers were hampered, as these laboratories felt they would be infringing the patent. The case also drew attention to the need for greater investment in the NHS laboratories at the time of the UK government's genetics white paper in 2003. Norbury suggested that the quality of NHS genetic testing services for BRCA improved as a result of Myriad's intervention in the UK market, since the standard of testing Myriad provided led to the NHS laboratories improving their services.

While NHS laboratories have often ignored gene patents, licensing agreements have been signed for technologies such as PCR. The PCR licence required that laboratories pay a small fee per PCR reaction conducted, or a larger fee for tests that required multiple PCR reactions. In practice, this was complicated to implement. Laboratories were responsible for self-reporting PCR usage, and there was concern in some laboratories that differences in the extent to which others declare their PCR usage affected the prices they charged for services, leading to price differentials between laboratories offering the same tests. Real-time PCR is another technology around which complex licensing issues needed to be resolved. Laboratories in different parts of the UK were not all covered by a single agreement and were uncertain of the licensing situation for several years in some cases.

Most recently, the detection of free-foetal DNA in maternal blood is an application that the NHS laboratories have been considering licensing. However, the patent has been licensed to a series of companies, causing confusion about who to approach to discuss use of the technology. The uncertainty created by not being able to access details on licensing fees has implications for costings in grants and planning for service contracts, while the possibility of patents excluding laboratories from using the technology is much less acceptable than non-exclusive licensing.

In conclusion, Norbury identified a number of important questions that need to be addressed: Where can laboratories get a fair and accurate view of the IP situation that is up-to-date for a particular test? Who is responsible or accountable for addressing IP issues within the NHS? Is it the laboratory director, the hospital chief executive, or (where public private partnerships are in place) the chief executive of the company? Where are the boundaries of what might be considered research (and therefore exempted from patenting concerns)? What are the implications of IP for the free exchange of genetic testing services between laboratories that are currently conducted on an informal no-fee reciprocal basis? Should IP issues be explored when a new test is being evaluated for approval within the NHS?

Berwyn Clarke

Berwyn Clarke provided a perspective from Lab21, a small UK diagnostic company backed by venture capital. Lab21 has the capabilities to develop diagnostics for novel biomarkers, meeting an increasing demand for 'companion diagnostics', generally for pharmaceutical partners. These tests are increasingly being demanded by regulators such as the FDA because biomarkers can be used to stratify patient populations. Tests are used to target the use of therapeutics, during trials, and once drugs are approved for the market, ensuring that the patients most likely to benefit from the drug are prescribed it, and non-responders (or those that may be more likely to have adverse drug reactions) are not. A number of existing drugs that are used in conjunction with these tests were mentioned, including Herceptin (cancer), Maraviroc (HIV) and Iressa (cancer). So called 'companion' diagnostics have to be fully regulated, given the risks raised for patients if results are unreliable. Poorly validated 'home-brew' tests (another name for LDTs), for example, have been associated with incorrect reporting of results in some cases. Targeting the wrong patients dilutes drug efficacy and may cause unnecessary toxicity, which is bad for the reputation of the pharmaceutical product and has profound pharmacoeconomic



implications. Lab21 also operates diagnostic testing service laboratories and, as a commercial services provider, is required to use only tests with full regulatory approval in the local environment.

Lab21 has obtained regulatory approval for multiple diagnostic products that it has developed and brought to market. So far it has done so without always relying on biomarker IP. However, many of the products it now has in development do have IP protection and this is seen as vital, since it creates a unique selling point for the company and creates a barrier-to-entry for competitors. IP is a core component of any business plan drawn up by a diagnostic company seeking investment. Echoing Hogarth's presentation, Clarke noted that companies with biomarker IP are more likely to invest in obtaining full regulatory approval. However, the IP often covers only the US and European markets, where patents are generally upheld. The situation is different in markets such as India and China, where IP is often infringed.

Hepatitis C virus (HCV) was presented as an example of how commercial investment, incentivised by a strong IP protection, had allowed the US biotechnology firm Chiron to invest heavily in research into this infectious disease that affects millions of people worldwide, of which several hundred thousand may be expected to develop serious health problems such as cirrhosis. Chiron's research has helped the development of diagnostics and therapeutics, and Chiron was bought out for more than \$5 billion in 2005 by Swiss pharmaceutical company Novartis. Such profitable innovation has to be regarded as a win-win situation. More recently, a biomarker related to a form of interleukin 28 associated with patients that can clear HCV has been patented by Merck-Schering-Plough, who are sub-licensing it to a small number of laboratories to ensure high-quality diagnostic testing. Clarke suggested that in cases where testing is centralised some benefits do result. Myriad, for example, has the best database of BRCA mutations as a result of its activities, which supports the reporting of accurate results. Pharmaceutical firms also want to ensure that diagnostics laboratories can undertake testing to support their products with a rapid turnaround service (i.e. 48 hours), and this has been a problem before in the USA and the UK. The BRCA testing conducted by the NHS is an example of a slow turnaround service, although the situation has now improved.

At several points in Clarke's presentation, IP infringement in the UK was noted as problematic. It was suggested that commercially, Lab21's Myriad licence wasn't worth the paper it was written on, as the NHS laboratories are infringing the patents in this and other areas. The situation with BRCA IP is complicated by conflicting claims by UK entities, but infringement of patents is generally only recognised when the company that owns the patent actually prosecutes the infringement. Until now patent enforcement against the NHS has not been widely respected but this situation is likely to change. A recent, potentially promising study by CRUK to profile the tumours from 9,000 cancer patients may infringe some gene patents, and there is a wider concern that whole human genome sequencing will lead to problems of infringement that will present challenges in the future. In conclusion, it was noted again that personalised medicine has become an area of major interest in recent years and that respect and recognition for IP is critical in supporting investment in order to encourage the development of high-quality diagnostics.

M J Finley Austin

M J Finley Austin presented a perspective from the pharmaceutical industry. She focused on drug response biomarkers and the need for better incentives for the development of high-quality, robust companion diagnostics with drugs through the appropriate management of IP. Strong IP protection has been a cornerstone of the pharmaceutical industry's business models and is needed to preserve incentives for R&D investment. Companion drug/diagnostics can provide benefits to patients, healthcare systems and industry by reducing the uncertainty surrounding the development and



clinical use of new drugs. However, the benefits are not easily achieved; the variation in response to a new molecule can only be detected after it is introduced into a significant number of people and therefore estimates emerge late in the development process. Thus discovery and validation of response biomarkers often requires more R&D expenditure.

The additional expense is only one of the complications that companion diagnostics add to the development process for new drugs. There are also questions about who makes the investment in a companion diagnostic – the drug company or the diagnostics company? This tends to vary according to whether the diagnostic has some utility independent of the specific drug. If not, then the pharmaceutical company is expected to take the risk and pay for development. Then there are a number of issues arising from the different regulatory and business environments in which the products exist. Diagnostics reimbursement is rarely value-based so there is little incentive to invest in trials to demonstrate clinical utility. Without exclusivity, diagnostics companies with innovative products are competing with ‘fast followers’, which may raise issues about quality if the test was not validated with the drug. This is a problem with rival kit manufacturers, but where the competition is with laboratory-developed tests there is added concern about the lack of regulatory constraints on the claims laboratories can make for their tests. These issues apply both for simultaneous co-development, and where a test is developed once a drug is on the market. However, in the latter case there is a lack of recognition that whilst it is relatively easy to discover potentially useful response biomarkers, the cost of validating them and demonstrating cost-effectiveness is very high. Prospective trials are required and biomarkers will fail, just as many drugs fail to prove safe and effective in clinical trials. Again, this demonstrates that whilst the benefits of companion diagnostics are considerable [to avoid repetition], so are the commercial risks; patients, industry and society will suffer if bad tests lead to mistakes in drug treatment and selection.

In the past, the diagnostics industry has lacked a sustainable R&D infrastructure, able to deliver high-quality clinical evidence for new tests in a timely fashion. The incremental accretion of data has occurred over decades and society has not demonstrated a willingness to pay for a more efficient and effective R&D process for diagnostics. Such a system will require value-based reimbursement and market exclusivity, either in the form of patents or perhaps tied to the regulatory process. For example drug regulators grant periods of monopoly to companies developing medicines with commercially less attractive markets (so called orphan drugs).

Hadleigh Stollar

Hadleigh Stollar of NTAC was invited to present NHS perspectives on the adoption of new diagnostic devices. NTAC was launched in 2007 to address problems in the adoption of new healthcare technologies within the NHS. Many new technologies enter the market without evidence of clinical utility, as Hogarth pointed out in his earlier presentation. Furthermore, healthcare technologies are seldom subject to evaluation by the National Institute for Health and Clinical Excellence (NICE), and even where NICE recommends adoption, clinical uptake is often limited.

NTAC was established with a remit to develop a clearer understanding of the barriers to technology adoption; to help organisations navigate the complex process of technology adoption; to ensure that implementation takes account of how new technologies will impact on clinical pathways and that the adoption process is integrated within services and system change. NTAC is creating tools for the clinical adoption of a number of technologies whose utility has already been demonstrated, the main tool being their online ‘How to, Why to’ guides, which work through the case for adoption and all the issues relating to implementation in a stage-by-stage process, including the decommissioning of



outdated practices/services. One of the challenging issues to be addressed is silo budgeting: instances in which cost benefits are realised in budgets other than the one that must pay for the technology.

Stollar then described a project involving a novel molecular diagnostic - the breast lymph node assay (BLNA) - a test that provides immediate analysis of a patient's tumour whilst surgery is taking place, thus avoiding the need for a second operation and allowing chemotherapy to start sooner. The example illustrated the challenges facing companies with innovative new diagnostic tests. Within the current NHS payments-by-results system, for instance, financial incentives may not favour technologies which reduce the number of chargeable procedures. As a result of under-adoption in Europe and North America, the producer of one of the BLNA kits withdrew its product from the market during the NTAC implementation process. In order to continue to use the technology it was necessary to negotiate an agreement to access the necessary IP. IP rights can therefore intersect with the broader innovation process and the multiple challenges facing test developers and test users.



Discussion

The main part of the discussion was framed by the following question: What evidence is there that IP is inhibiting or benefiting research in DNA diagnostic innovations and patient access to tests? The following part of the discussion was scheduled to explore whether there was a common consensus on what would constitute the elements of a fair and equitable framework for IP in the field of diagnostic genetic testing and to try and identify pragmatic developments for the future. Unfortunately, time constraints meant that the latter questions were only touched upon rather than explored in any depth.

Biomarker IP was seen as essential by participants from the diagnostics industry – as a means for start-up companies to gain venture capital, as a way for small companies to compete with their larger rivals, and as a justification for investment in R&D, which brings products to the market more quickly than might otherwise occur. Taken together, these views reflect the broader industry views (reported in the opening presentation) on how biomarker IP has become an important mechanism for increasing the number of innovative companies in the sector developing novel diagnostic tools and making greater investments in the clinical evidence for their products. Furthermore, this is not simply being driven by industry; patent lawyers have stated that they are seeing an increase in the number of patents being sought by UK academic researchers seeking to protect their genomic discoveries.

One industry figure raised concerns, suggesting that biomarker IP is inhibiting the commercial development of diagnostics. However, he also suggested that evidence of this is difficult to collect; whilst litigation provides a visible sign of the impact of biomarker IP, much of the legal activity between companies – whether warning letters or licensing agreements – is treated as commercially confidential. There were additional concerns about the impact of diagnostic monopolies on the traditional process of incremental innovation, with further discussion of the HPV case and the desire for alternatives to the Digene test. Again, the case of the Myriad/BRCA testing was raised in relation to the company's unwillingness to share their data on BRCA variations with the research and clinical communities, leading one participant to conclude that 'defending IP on [gene] sequences is not in the public interest'. Whilst the discussion of IP focused largely on the commercial/clinical interplay, one of the patent lawyers also noted that much of the current push for gene patents is actually coming from academic institutions wanting to realise the commercial value of their discoveries.

There was much discussion concerning the importance of context and the idea that a one-size-fits-all approach to policy was inappropriate given the variety of outcomes contingent on the specific context. A recurring theme was the differences between national and regional markets, in particular differences between the USA and the UK or EU. In a number of respects, the USA was deemed a more attractive market for diagnostics companies, in part because of the market size and its healthcare system, which is quicker to adopt new technologies. It is easier and less expensive to run clinical trials in the USA and routine testing services are dominated by large commercial laboratories, which are more willing to respect IP than public sector laboratories in Europe. US patent procedures are also far less complicated than they are in Europe. Patent lawyers at the meeting described a recent procedural change at the EPO, which requires companies seeking to patent a large number of biomarkers at the same time to file separate 'divisional' applications for each one within two years of first filing. In the USA the system is far more flexible, and much more time is allowed for this process, enabling companies to do further research to establish which biomarkers are most worth protecting. It was suggested that this new development, coupled with the apparent difficulty of trying to prevent widespread public sector infringement of biomarker IP in Europe, was beginning to make the EU an unattractive market for diagnostics companies. In the words of one industry representative: 'If you are developing a new biomarker there is absolutely no incentive to filing IP in the UK because you know



good and well that the public sector is just going to walk all over it and do what they like anyway ... We focus on other markets.'

For those who oppose the creation of diagnostic monopolies through DNA patents and exclusive licensing, these problems can of course be seen in a positive light, presenting a clear advantage over the USA where litigation, or the threat of it, has, thus far, had far greater impact. It was suggested that not only is infringement more common in Europe but that hostility to gene patents is more intense. One participant suggested that amongst the European genetics community Myriad Genetics was as unpopular as 'tobacco companies and estate agents'.

National or regional differences were only one of the sources of heterogeneity discussed at the meeting. Regarded as equally important was the variety of clinical applications - pharmacogenetics, susceptibility testing for common diseases, rare monogenic disorders - and types of marker. One participant made a fundamental distinction between genetics and genomics in terms of the complexity of testing, the capacity for laboratories to deliver such testing and innovation pathways. Even within one area, such as pharmacogenetics, there might be different approaches depending on whether a test is co-developed with the drug or retro-fitted to an approved drug. Another variable that can affect outcomes is the business model of the company and its delivery mechanism - producing a test kit, as was the case with Digene and the HPV test, or a laboratory-developed test, as in the Myriad BRCA case. Another recurring theme was the collaborative nature of test development and the varieties of form such collaboration might take - pharma/IVD collaboration in the case of pharmacogenetics, public/private collaborations in other types of test development, or purely public sector efforts in the case of rare diseases.

There was some discussion about alternative forms of exclusivity, for instance tied-to-market approval. It was noted that such arrangements are in place for pharmaceutical products in Europe but not for medical devices.



Conclusions

Four underlying themes emerge from the issues and evidence raised in the discussion and presentations:

Heterogeneity of scenarios – the variety of commercial, clinical, technological and organisational contexts which make generalisation about the significance and impact of biomarker IP difficult, and which point to the need to move beyond reliance on discussing BRCA and Myriad as the paradigmatic exemplar;

Uncertainty – the extent to which the impact of biomarker IP on diagnostic innovation is not yet clear. The commercial value of IP, its defensibility, and impact on costs and quality of tests for patients remain underexplored;

Interconnections – the relationship between biomarker IP and other important issues such as investment, regulation and reimbursement;

Trade-offs – different policy approaches to biomarker IP will have multiple knock-on effects on other policy priorities, and balancing the need to support commercial innovation in the molecular diagnostics sector whilst ensuring patient access and improved types of test will require attention to the complex interaction of factors that affect diagnostic innovation.

Whilst the seminar had set out to avoid a discussion that became entrenched in polarised positions, it revealed a profound divergence between a commercial diagnostics sector intent on exploiting the financial value of biomarker patents and a public sector laboratory community that routinely infringes such property rights. Straddling this public-private divide is the academic research community who continue to patent publicly-funded biomarker discoveries in the hope of capturing their commercial value.

Recommendation 1: Given the reported growth in patenting by academic researchers, the UK research councils and other major biomedical research funders, such as the Wellcome Trust, CRUK and the British Heart Foundation, should review their guidelines on licensing.

Whatever the outcome of the current legal case in the USA, where Myriad are appealing the decision to declare many of their gene patents invalid, in Europe the legality of DNA patents (and other forms of biomarker IP) is set out in the Biotech Directive. Given the growing use of biomarker IP in applications with a far larger potential market than monogenic disorders (e.g. companion diagnostics and population screening programmes) it would seem prudent for policymakers to begin to address this tension.

Recommendation 2: To establish a biomarker IP monitoring function within the Department of Health (DH) or in an appropriate cross-departmental office. Duties should include: a) evidence gathering and analysis and reporting on the impact of current policies on the incentives for public sector and private sector biomarker-based innovation in diagnostics, b) encouraging private sector IP biomarker holders to contribute genetic data arising from diagnostic tests to public databases which aim to develop libraries of the relevant DNA sequences which are as comprehensive as possible, yet ensure confidentiality of individuals' data, and reporting on any problems encountered in this area, and c) developing guidelines for out-licensing and in-licensing of IP by public sector funded staff.



Recommendation 3: At present it is unclear who within the NHS might be responsible for dealing with the practical implementation of policy in this area. Support should be given to senior management at a national level to help develop the capacity to manage biomarker IP issues.

Although the meeting explored the complexity of the IP landscape as it relates to diagnostic innovation there was insufficient time to begin to map alternative policy approaches on to the various innovation pathways and business models. The discussion of harms and benefits did not raise any new issues but it did highlight the need for more evidence, reflecting the degree to which there are still many unknowns in this area. As the discussion of companion diagnostics and the case of Digene's HPV test illustrated, DNA patents are affecting many areas of medicine beyond clinical genetics, yet the current evidence base is focused on this domain. Given that an increasing number of companies are developing polygenic tests for applications such as measuring heritable susceptibility to common diseases or molecular profiling of tumours for prognosis and treatment selection in post-operative cancer patients, there is an urgent need to broaden the discussion and the evidence base. Polygenic applications have considerable potential for problems arising from royalty stacking. The advent of more affordable whole genome sequencing seems likely to amplify this problem. There is a need for more evidence concerning the development and adoption of tests in areas outside clinical genetics. Whilst the commercial sensitivity of some IP issues presents challenges for those wishing to research the impact of gene patents, there are many areas where more research could be done. The Technology Strategy Board's current call for research on business models for stratified medicine is one place where the government could begin to address these issues.

Recommendation 4: More independent evidence needs to be generated on the impact of biomarker IP on diagnostic innovation. A starting point would be research to address the questions that were raised and evidence gaps identified by this seminar. An appropriate forum and process will be required that provides time for detailed deliberation and an assessment of the divergent needs and preferences of a range of stakeholders.



Acronyms

ALTS	ASCUS/LSIL Triage Study
BLNA	Breast Lymph Node Assay
BRCA	Breast and Ovarian Cancer
CRUK	Cancer Research UK
DH	Department of Health
DNA	Deoxyribosnucleic Acid
EPO	European Patent Office
FDA	Food and Drug Administration (USA)
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HTA	Health Technology Assessment
IP	Intellectual Property
IPTS	Institute for Prospective Technological Studies
IVD	In Vitro Diagnostic
JPO	Japanese Patent Office
LDT	Laboratory Developed Test
NHS	National Health Service
NTAC	National Technology Adoption Centre
NICE	National Institute for Health and Clinical Excellence
OECD	Organisation for Economic Co-operation and Development
PCR	Polymerase Chain Reaction
R&D	Research and Development
RMGL	Regional Molecular Genetics Laboratory
SACGHS	Secretary's Advisory Committee on Genetics Health and Society (USA)
USPTO	United States Patent and Trademark Office



Glossary

Anti-commons effect

An effect whereby competing intellectual property rights prevent innovation (derived from the work of Michael Heller and Rebecca Eisenberg).

Array

See *Microarray*

Biomarker

A biological indicator (such as a gene, protein or metabolite) of a process, event or state useful for identifying or tracking the progression of a disease or response to treatment.

Companion diagnostic

A diagnostic test used to guide the process of prescribing medical treatments as a decision-making aid, whereby the diagnostic test was developed along with the treatment.

DNA (DeoxyriboNucleic Acid)

A chemical substance that provides the primary means of encoding genetic information in long molecular structures or genes.

Free foetal DNA detection

A technique for detecting the presence of foetal DNA in maternal blood, useful for prenatal genetic testing.

Long QT syndrome

A rare, heritable heart condition characterised by an elongated echocardiogram signature.

Microarray

A two-dimensional arrangement of molecular probes usually fixed to a glass or silicon wafer used for assaying large numbers of biological molecules, for example of DNA.

Ordre Public

In the context of patent law, ordre public relates to the exemption from patentability of subject matter judged to be controversial, to the extent that allowing a patent would be detrimental to civil society.

Polygenic

A disease or characteristic that is determined by more than one gene.

Polymorphism

A variation across a population of individuals in the sequence of a gene that is found to occur more commonly in 1% of that population.



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