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Workshop Report

Realising Genomic Medicine: Intellectual Property Issues

1 May 2015

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Introduction

On 1 May 2015 the University's Centre for Law, Medicine and Life Sciences (LML) and the Centre for Science and Policy (CSaP) hosted a workshop to discuss the intellectual property (IP) issues surrounding the realisation of genomic medicine. The event was chaired by Sir John Chisholm (Executive Chair, Genomics England) and took place at Trinity Hall, University of Cambridge.

> *"Genomic medicine will transform humanity in the 21st century. But quite where it is going, and how it will get there, is relatively unimaginable. For today's meeting we must attempt to imagine the unimaginable, and articulate the profound. It will be no easy task."*[1]

Prior to the workshop a document prepared by Dr Kathy Liddell on the background issues was circulated to participants.[2] A copy of this document is appended to this report.

Since the sequencing of the human genome, a key goal has been to make personalised medicine an everyday reality. Research that recognises a *correlation* between genetic make-up and a future health outcome is not enough. Considerably more research is necessary to understand how genes, drugs and other environmental factors work together, and how they work in *particular* individuals. Only then will we have enough knowledge for genomic medicine to be useful in a clinical setting. An important and complex policy issue is whether intellectual property policies are working effectively to support the achievement of this bold objective.

1. Aims

- To discuss IP policies, strategies and licensing practices to help improve the translation of basic genomic science into affordable and widely adopted new treatments;
- To address IP and access policies applicable to academic and commercial involvement in major publicly-funded biobanks (e.g. 100,000 Genomes Project);
- To identify crucial IP trends within the public and commercial genomic medicine sectors—including patents and non-patent based incentives;
- To discuss the future significance of DNA-related patents for genomic medicine in Europe and the US, following the US Supreme Court decisions in *AMP v Myriad,*[3] *Mayo v Prometheus Laboratories*[4] and *Alice Corp v CLS Bank*[5];
- To discuss the relationship between IP and the financial and regulatory environment for genomic medicine (e.g. EMEA/FDA standards; health technology assessment; reimbursement).

2. Discussion

2.1 General Considerations

2.1.1 How does IP help or hinder the development of genomic medicine?

The discussion began with several perspectives on how IP helps or hinders the realisation of genomic medicine. These views echoed throughout the afternoon's debate, demonstrating the enduring importance, even in policy development, of theoretical debates.

Importance of IP protection for industry

The past decade of experience was said to indicate that patenting of single gene sequences and other biomarkers is of limited usefulness—however, patent protection for combinations of biomarkers, associated therapeutics and platforms for delivering assays is increasingly important. Explaining this view, it was said that single gene patents were costly, not obviously productive of new health benefits, and problematic in creating uncertainties about freedom-to-operate and patent-thickets. The benefits of this sort of genetic data (gene location and sequence) were generally better served by publishing it in academic literature and publicly available databases. More useful IP portfolios and business models can then be built on top of this information.

A contrasting view was that IP rights *could* usefully protect 'early' 'upstream' developments, if the IP is used as a 'shield' for open innovation. For example the IP owner can liberally license the invention, including a term that rescinds the licence if the licensee uses the DNA sequence in a way not conducive to public health. Query though whether these 'march in' clauses are genuinely enforceable and, if so, whether they in fact discourage potential licensees from entering into a licence and exploiting the innovation for fear that the licence may be fundamentally altered. 'March in' clauses may have social, rather than legal, effect. For instance, members of the public may be more inclined to donate to a biobank if they believe that commercial users can be stopped from using derivative innovations contrary to public health needs.

Even more contentious was the relative importance of IP, and its implications, for downstream innovation. It was reasoned that, although it is just one of many factors, companies need IP in order to obtain venture capital financing, to take on the challenge of refining the initial discovery and securing clinical uptake, and to protect a reasonable return in the marketplace. However, there is continuing concern for gene panels, aggregate tests and whole genome sequencing, that royalty stacking or work-arounds to avoid infringement are difficult (although it is difficult to find clear evidence of this being a major problem). Doubts were also expressed about the real level of need for IP protection given that the costs of diagnostic innovation are significantly less than pharmaceutical innovation, and the fact that some large multinationals support the idea of open science. In reply, it was pointed out that the pattern of diagnostic innovation is evolving (with increasing costs associated with proving clinical reliability ('validity') and utility). Additionally, the acceptance of open science by *some* multinationals in *some* circumstances could not be presumed to mean it was routinely viable. Open access to genetic data might play to the strengths of a multinational, for example a multinational with powerful (private) algorithms; and be more problematic for SMEs.

Impact of IP protection on NHS service delivery

Concerns were also raised about the impact of downstream IP on NHS service delivery. *FLT3* mutation testing for acute myeloid leukaemia and non-invasive prenatal diagnosis were offered as examples. In the case of FLT3, at least four labs have ceased *FLT3* testing since LabPMM asserted an

exclusive licence that requires tests to be completed at LabPMM in Germany. Exclusive licensing of DNA-related patents continues to elicit strong and divergent opinions. Some see it as highly problematic, particularly where it means a genetic test is offered by one lab only, and in contravention of international good practice (e.g. OECD guidelines[6]), whereas others are of the view that flexible, case-specific approaches will always be necessary.

There was particular scepticism about the appropriateness of high costs for the NHS and publicly-funded patients in future situations where innovation is based on public research moneys and data freely donated by NHS patients to accessible biobanks. In reply, though, it was pointed out that a donation of public funds and personal data does not cover all the costs of innovation. Furthermore it could be argued that the limitations in NHS could be due to many other factors in NHS organisation. NHS policy and practice on IP in-licensing needed further examination.

In this context, some participants noted that a significant number of NHS labs appear to be 'wilfully blind' to the potential patent implications of their work.[7] This attitude has been possible to date as there has been relatively little patent enforcement in Europe against publicly-funded health services. These participants questioned the appropriateness of this stance, and queried whether the situation could continue. The European medical genomics industry may become more litigious as it matures and when the Unitary Patent takes effect and patent owners can, for the first time, enforce their rights throughout Europe with a single legal action. (To date, patent infringement actions must be brought in individual European member states). An issue to consider if the landscape changes is that NHS labs may not be able to afford to carry out freedom-to-operate patent searches every time they introduce a new lab-based test. However, there are obvious downsides to negotiating a license fee, paying damages or being asked to cease testing after a test has been introduced.

Alongside the issue of NHS in-licensing, the existence of considerable 'hidden' innovation in the NHS was mentioned (ie. innovation which is unrecognised, or not captured by standard indicators), raising the question whether more strategic innovation management within the NHS is needed to maximise public benefit.

Diverging views on the role of IP

Underpinning these views were questions about the nature and purpose of IP in the health sector. Is it the promotion of health or wealth? Is it for individuals, or society collectively? To what extent should *national UK* health or economic concerns be privileged over those of other countries (such as the US) and international trade objectives? Are these various dichotomies mutually exclusive, or overlapping in some way? What sorts of outcomes do various IP arrangements really achieve? To what extent can the health sector learn from IP experiences in software, engineering, and semi-conductor industries? To what extent are answers to all these various questions ultimately 'faith-based', rather than grounded in empirical evidence? And is a 'faith-based' perspective on IP a problematic retreat from evidence-based opinion (as argued by Lemley[8]), or is it inevitable in a pluralist society faced with extensive, but reasonable, moral and empirical uncertainty?[9]

2.1.2 Types of IP beyond patent incentives

The discussion also considered the relative importance of non-patent incentives. A repeated view was that patents are likely to remain the backbone of pharmaceutical innovation, but that complementary protection (such as data exclusivity, trade secrets, database rights, algorithm protection, copyright, trademarks, and regulatory data protection) were becoming increasingly important to the diagnostics and genomics industries. A key challenge in genomic medicine is to move beyond a basic gene-disease or gene-drug association to clear proof of clinical validity, and

then beyond that to clinical utility. This requires research into combinations of genetic biomarkers, and accordingly very large and extensively curated collections of data, complex algorithms, and sophisticated clinical trials.

Significantly more research is needed on non-patent incentives. How are non-patent IP protections used within the public and private genomics sectors, and how successful are these strategies? How might they be developed? How does this vary in different jurisdictions, bearing in mind that there is considerably less international harmonisation (compared with patent law) of database rights, algorithm protection, and regulatory data protection?

2.1.3 The significance of IP for the diagnostics/biomarker Industry

More research is also needed on the differences between the diagnostics/biomarker and pharmaceutical industries, and SMEs and large corporations, in terms of the importance of IP protection and the IP strategies that are used. There are many different ways to capture value – generalised views of large pharma are important, but cannot be taken to represent large diagnostics, nor SMEs in biopharma and diagnostics. There are indications, albeit mixed, that IP protection is in fact particularly important for smaller firms. The significance of patent thickets for the diagnostics/biomarker industry remains an on-going issue.

2.2 Understanding the IP landscape

2.2.1 Reaction to recent US Supreme Court rulings

Recent landmark rulings by the US Supreme Court have invalidated patent protection for natural DNA sequences and patents that claim a natural correlation between biomarkers and disease. This presents a number of challenges for the genetic diagnostics market in the US (particularly the *Prometheus* decision), and it is too early to predict their full implications for genomics medicine. Several participants questioned the significance of the *Myriad*[3] decision pointing out that it confirmed the patentability of cDNA. *Prometheus*[4] was a more important case in their opinion. Whatever the relative significance of the rulings, it is clear that the patent refusal rate for DNA-related patents before the US IPO is now much higher. Going forward, one issue is that the rulings are difficult to interpret, leaving considerable legal uncertainty for small molecules as well as DNA-related inventions.

There is, however, no reason to think that the US genomics industry will not survive. The rulings may lead to more innovative approaches to IP protection, and greater freedom may assist lab-developed tests. Indeed, lack of patent protection for gDNA may not be an issue for clinical diagnostics, algorithms, probes, kits and platforms. And some participants were of the view that the Myriad and Prometheus technologies were 'old' or 'simple' technology and not directly analogous to modern developments. In time, the major impact of the Supreme Court rulings could be to limit the scope of 'upstream' protection in the US and force patent applicants to narrow their claims; arguably a positive development for the industry.

There was some discussion about whether recent US rulings would make the European market more significant, given that isolated DNA is patentable under the EU Biotech Directive 98/44. Due to US market size, substantially higher prices paid for US healthcare services and much greater venture capital spending (including the specialist biotech VC funds), the US is likely to continue to be the primary and most lucrative market for the genomics industry. Furthermore, Europe restricts the

scope of DNA-related patents in its own ways (eg. the CJEU decision in *Monsanto*[10]) so it is not seen as offering dramatically more favourable IP protection.

2.2.2 Recent trends

Genomic IP trends in Europe warrant further research. Preliminary findings indicate a steep increase in the rate of filings, but a decreasing emphasis on broad DNA molecule *per se* claims. Most patents are apparently driven by therapeutic concerns (eg claims related to peptides, antibodies etc), with diagnostics as an 'along with' claim. Very few of the top 20 patent applicants are companies with UK-based headquarters. And very few patent applicants are UK universities or hospitals, although there are a significant number of foreign applicants from these sectors. This raises important questions about the success to date of the UK genomics industry, despite years of activities to build a strong UK life sciences sector. Why is there significantly less patent activity in the genomics sector from companies, hospitals and universities in the UK? And what does the future hold?

A tendency for larger multinational companies to dominate smaller companies was also described; with non-invasive prenatal testing (NIPT) using cell free DNA, and the Illumina/Sequenom patents mentioned as examples. An increase in funding for organisations, such as Innovate UK, to support the development of new healthcare technologies has been observed in recent years. There have also been notable developments in the evaluation of high-value diagnostics (eg. NICE's approval of Oncotype Dx). However, these developments are in tension with concerns about financial encumbrances for the NHS.

2.3 Promoting collaboration with biobanks and bioresources

Due to the complex interactions between genes and their environment, large amounts of human data are necessary to understand the causal relations in the genetics of complex and common diseases. Large biobanks and bioresources will be critical to the future of genomic medicine.

The UK Biobank and the 100,000 Genomes Project are two leading examples, set up by public sector funds. In order to realise the full potential of these collections, collaborations with volunteers, clinicians, academic researchers and industry (both pharma and diagnostics; large and small companies) are required to interpret and exploit the data. There was general consensus that one of the main challenges is to develop fair and effective policies for the involvement of public and private sector organisations, smaller and larger organisations, and a variety of –omic sciences. Different concepts and approaches to value capture (including both economic and social values) will be issues to consider.

2.3.1 IP and Access strategies

There are a variety of permutations and combinations in biobanks' Access and IP policies, but these can be organised into several general approaches. One general approach, represented by UK Biobank's policy, provides:

> 'UK Biobank…will have no claim over any inventions that are developed by researchers using the Resource (unless they are used to restrict health-related research or access to health-care unreasonably)'.[11]

In contrast, Genomics England, which is tasked with delivering the 100,000 Genomes Project, is developing a different style of Access and IP policy which it hopes will enable the achievement of the project's four aims, which are to:

- bring benefit to patients
- create an ethical and transparent programme based on consent
- enable new scientific discovery and medical insights; and
- kick start the development of a UK genomics industry.

In terms of ownership of the data collection, Genomics England's policy is that:

> 'Genomics England owns the combination of the whole genome sequence and the clinical data for the entire dataset from the 100,000 Genomes Project.'[12]

In terms of *access* to the data, and ownership of IP *generated* from the data, Genomics England's current approach draws a distinction between academic/public sector researchers, large private companies, and small private companies.

For academic/public sector researchers, Genomics England's policy is:

> IGenomics England owns any new intellectual property generated from the data but we will license this to third parties [such as an academic institution] the opportunity to commercialise opportunities on favourable terms.'[12]

For private companies, Genomics England has established the GENE consortium to manage an industry trial during 2015. As part of the trial, small private companies (i.e. companies with a market capitalization less than one billion dollars) that wish to access the 100,000 Genomes Project data will need to pay approximately £25,000 as a fee for services for 2015, while large private companies pay £250,000. In both cases, any future products developed by a company in collaboration with Genomics England will be owned by Genomics England. Any future products developed *solely* by the company from information gained from access to Genomics England data will be owned by the company. In the case of smaller companies, the commercialisation of such products will subject to a royalty fee, in return for the lower access fee. (No royalty is payable by larger companies).[13] The outcomes of the 2015 trial will help to inform future Access and IP policies for the project. Consultation with diagnostics companies is also planned.

The decision to establish an industry consortium was viewed as a positive idea by workshop participants; likewise the decision to operate a tiered fee-for-access system, although there was also debate about whether a more open model with fewer restrictions on downstream commercialisation would provide a greater incentive for industry involvement in the future. There were mixed opinions about the concept of reach-through royalty rights that claim a share of the benefits from future developments (as presently proposed for smaller companies), and Access and IP policies that emphasise the idea that biobanks should generate a commercial return or be self-sustainable. Some participants held the view that biobanks are critical scientific infrastructure, which should be funded by the public purse without expecting a return or self-sufficiency (similar to public roads, buildings and parks). There was general support for the NHS having special access to IP generated through the data, but mixed opinions and doubts about how this might be implemented. Questions were also raised about the definition of key terms and concepts, for example, 'any new intellectual property', 'inventions', 'products developed from information gained from access to Genomics England data', 'licensing on favourable terms', and 'fair and reasonable'. It was acknowledged that an industry view on fair and reasonable licencing terms may differ significantly from a public sector view. For instance, industry might readily consider it fair and reasonable to seek

'super profits' when commercialising inventions to recoup costs invested in products that do not succeed; whereas a public view might consider the high price to represent over-inflated monopoly pricing.

2.3.2 Related issues

The security of patient information, the terms of volunteers' consent, and subsequent access by commercial companies, are contentious issues that are likely to have a substantial bearing on public support for biobanks (including by clinicians and patients). The potential for relatives to raise future objections to the inclusion of familial data was also discussed. Patients participating in the 100,000 Genomes Project are made aware that companies can access data within a secure infrastructure, but that commercial researchers cannot 'take away' the raw data. Query how much more participants understand (or would like to know) about the terms and conditions of commercial engagement. The Personal Genome Project (PGP) has adopted an unusual consent protocol drawing volunteers' attention to the fact that data is publicly shared with organisations of all types, and that privacy, confidentiality and anonymity of volunteers cannot be guaranteed. Interestingly, this project currently has more participants than the 100,000 Genomes Project. However, in contrast to the 100,000 Genomes Project, it does not have strict eligibility criteria (the 100,000 Genomes Project is focussing specifically on rare disease and cancer patients and their families) and it may ultimately be a smaller cohort.

3. Conclusions and Recommendations

Genomic medicine has the potential to revolutionise healthcare and contribute to economic growth, but success will require substantial public and commercial support, innovative science and thoughtful policy development. From the discussions it was clear that IP issues are highly complex and integral to the achievement of this goal. It is difficult to articulate accurately and profoundly the best avenues by which to proceed. Research and debate will help shape and guide developments, but ultimately there will not be any single 'holy grail'.

Moving forwards, the following ideas were proposed:

1) The preparation of a report or reports drawing attention to literature already available on key themes (to avoid re-inventing the proverbial wheel) such as upstream and downstream patent protection, licensing models and typical licensing terms and conditions, pros and cons of open science and open innovation, translational innovation business models, database rights, and public understanding of IP in the biomedical sector. This paper should also seek to identify the key research gaps.

2) The provision of further support for the exploitation of bioresources by the public sector, and research into how best to provide this support.

3) Research to understand better:

    a) how, in the genomics sector, firms are capturing value, and in what ways they are using IP to assist them. In what ways does this differ between SMEs and multinationals, and between companies based in Europe and the US?

    b) the political economy of the diagnostics/biomarker industry (which differs significantly from the more widely studied pharmaceutical industry);

c) trends in the evaluation and reimbursement of high-value diagnostics, and the role played by intellectual property rights in pricing;

d) the implications, over time, of the US Supreme Court rulings in *Myriad* and *Prometheus*;

e) European legal developments affecting genomic IP, including German court rulings on the FLT3 patent, and the doctrinal developments by the (future) Unified Patent Court.

f) non-patent incentives in the medical genomics sector. For example, how are non-patent IP protections used currently within the public and private genomics sectors? How might they be used? How does this vary in different jurisdictions, bearing in mind that there is considerably less international harmonisation (compared with patent law) of database rights, algorithm protection, and regulatory data protection;

g) the intellectual property protections available for algorithm development;

h) NHS in-licensing policy for genomic-related technology;

i) whether there is evidence of a problem of 'patent hold ups' in and around gene panels, aggregate tests and whole genome sequencing;

j) why there is relatively little patent activity in the genomic sector by UK-based companies, hospitals and universities.

4) An evaluation, in due course, of the IP and Access policies developed by Genomics England, and consideration of their utility for other large scale bioresources;

5) Monitoring of public support for large scale bioresources, including an assessment of how much participants understand (or would like to know) about the terms and conditions of commercial engagement.

Endnotes

[1] Sir John Chisholm, Chair's Opening Remarks (01/05/2015)
[2] K Liddell, 'Realising Genomics: Some Background on the Intellectual Property Issues" (April 2015)
[3] *Association for Molecular Pathology v Myriad* 133 S.Ct. 2107 (2013)
[4] *Mayo Collaborative Services v Prometheus Laboratories Inc* 132 S. Ct. 1289 (2012)
[5] Alice Corporation v CLS Bank 134 S. Ct. 2347 (2014)
[6] OECD, Guidelines for the Licensing of Genetic Inventions (2003). See: http://www.oecd.org/science/biotech/guidelinesforthelicensingofgeneticinventions.htm . See also, OECD, Valuation and Exploitation of Intellectual Property (2006) http://www.oecd.org/sti/sci-tech/37031481.pdf .
[7] N Hawkins, The Impact of Human Gene Patents on Genetic Testing in the UK (2011) 13(4) Genetic Medicine 320-4; S Gaisser, M Hopkins, K Liddell, E Zika, D Ibarreta, The phantom menace of gene patents (2009) 458 Nature 407-8.
[8] M. Lemley, Faith-Based Intellectual Property (2015) 62 UCLA Law Review 1328
[9] R.P. Merges, Justifying Intellectual Property (Harvard University Press, 2011); K Liddell, 'Biolaw and Deliberative Democracy: Regulating Human Genetic Technology in a Morally Pluralist Society' (D.Phil thesis, Faculty of Law, University of Oxford, 2003)
[10] *Monsanto v Cefetra* (06/07/2010, CJEU)
[11] UK Biobank, Access Policy (Nov 2011), Summary, B8.5 and B8.6
[12] Genomics England, Clinical Interpretation Partnership Guidance (Nov 2014) p 20; (July 2015) p 19.
[13] Genomics England, A Framework for Industry Engagement (Mar 2015) p 5 & 6

Appendix I: Participants

- CHAIR: Sir John Chisholm, Executive Chair, Genomics England
- Dr Mark Bale, Deputy Director, Health Science & Bioethics Division Public and International Health Directorate, Department of Health
- Dr Kathy Liddell, Director of the Centre for Law, Medicine and Life Sciences, University of Cambridge
- Dr Robert Doubleday, Executive Director, Centre for Science and Policy

- Dr Rolf Apweiler, Joint Associate Director and Senior Scientist, European Bioinformatics Institute
- Dr Emmanuelle Astoul, Business Development Manager, Wellcome Trust Sanger Institute
- Dr Rachel Atfield, Technology Manager, Cambridge Enterprise
- Professor Michael Barrett, Professor of Information Technology and Innovation, University of Cambridge
- Professor Lionel Bently, Director, Centre for Intellectual Property and Information Law, University of Cambridge
- Dr Eddie Blair, Managing Director, Integrated Medicine Ltd
- Dr John Bradley, Director, NIHR Cambridge Biomedical Research Centre
- Professor Dan Burk, Chancellor's Professor of Law, University of California, Irvine School of Law
- Dr Hilary Burton, Director (CEO), Public Health Genomics Foundation
- Thomas Finnegan, Legal / Regulatory Policy Analyst, Public Health Genomics Foundation
- Professor Michael Griffiths, School of Cancer Sciences, University of Birmingham; Director of the West Midlands Regional Genetics Laboratory, Birmingham Women's NHS Foundation Hospital
- Dr Stuart Hogarth, Senior Research Fellow, Social Science, Health and Medicine, King's College London
- Dr Michael Hopkins, Senior Lecturer, Science Policy Research Unit, Business and Management, University of Sussex
- Paul Jones, Chief Executive Officer, Genomics Enterprises
- Dr Loic Lhuillier, Programme Manager – Stratified Medicine, Innovate UK
- John McKinley, Spokesperson, Precision Medicine Catapult
- Nick Maltby, General Counsel and Company Secretary, Genomics England
- Natalie Miazga, Policy Intern, Centre for Science and Policy
- Timo Minssen, Associate Professor, Faculty of Law, University of Copenhagen
- Catherine Page, Senior Policy Advisor, Office for Life Sciences, Department for Business, Innovation & Skills / Department of Health
- Julia Powles, PhD Student, University of Cambridge
- Jacqui Real, Policy Manager, Health Science & Bioethics Division, Department of Health
- Dr Nigel Skinner, Thomson Reuters
- Matthew Warren, Partner, Bristows LLP
- Dr Peter Weinstein, Chief Executive Officer, One3 IP Management
- Dr Glenn Wells, Director of Research Programmes & Deputy Centre Director, NIHR Central Commissioning Facility
- Gareth Williams, Partner, Marks & Clerk

Thousands of papers have identified research-grade genetic biomarkers. Many more will be found in the coming years. However, relatively few biomarkers have been successfully validated for routine clinical practice.[i] This is because biomarker discoveries typically lack sufficient sensitivity and specificity—in a clinical setting they would give rise to too many false positives and negatives.

To reach the clinic, one approach is to improve the predictive, prognostic and diagnostic power by combining a number of different biomarkers.[ii] This involves considerable effort and risk, and clinical utility is standardly required for reimbursement. R&D of this kind raises a number of questions for intellectual property policies and strategies, requiring concerted and collaborative input from many disciplines, as well as business and public policy experts. Below we describe two such challenges.

I

One of the policy challenges concerns large-scale longitudinal biobanks. Due to the complex interactions between genes and their environment, large amounts of human data are necessary to understand the causal relations in the genetics of complex and common diseases. The UK Biobank, and the more recent 100K Genome Project, are primary examples of these collections. As these collections approach and reach the stage where public and private organisations can seek access to the amassed tissue, data and genetic data, consideration is being given to the governance of intellectual property rights, particularly in relation to publicly funded biobanks. Awareness of these issues is growing[iii] but it is still in at early stage. It is markedly influenced by views about public benefit, given the reliance of public biobanks on altruistic volunteers. The available literature is less knowledgeable of the pressures faced by the diagnostic and stratified medicine industries. To date there has been relatively little work that investigates the role that different *types* of intellectual property and licensing practices may play (for example, trade secrets, private contract law, database rights, orphan drug regulation, unfair competition laws, as well as patents), or that compares the different sorts of policies that important biobanks are adopting.[iv] The way in which research organisations (particularly from the commercial sector) respond to the IP governance arrangements, which are often quite stringent, is also yet to be seen.

An interesting and stark contrast that has emerged in the current approach of the UK's two largest biobanks, warranting further investigation, concerns 'reach through' rights. For example Genomics England, tasked with guiding the establishment of the government's flagship 100K Genome Project has published a preliminary IP and Access proposal. It states that Genome England:

> 'owns any new intellectual property generated from the data but …will license this to third parties the opportunity to commercialise opportunities on favourable terms.'[v]

Meanwhile Biobank UK, a public sector database initiated several years ago, has just entered a stage where private companies can now seek access to the tissue, data and genetic data they have amassed. Its Access Policy states that:

> 'UK Biobank…will have *no claim* over any inventions that are developed by researchers using the Resource (unless they are used to restrict health-related research or access to health-care unreasonably).'[vi]

The issues emerging here are competing views about 'reach-through' right; e.g. their importance

for recovering the cost of establishing large bioresources, how to draft, manage and enforce derivative rights, and how such encumbrances could affect research organisations' willingness to analyse the biobank data. More extensive comparative research across international bioresources is likely to reveal a range of other important differences.

II

A second policy challenge relevant to the development of genomic medicine concerns the business models of genetic diagnostic companies and laboratories, and the way in which IP law interacts with those strategies. In contrast to *pharmaceutical innovation*, relatively little is known about *diagnostic markets* and *diagnostic innovation* despite the high expectations surrounding personalized/genomic medicine. A few authors have made inroads to redress this balance, but the field is changing and warrants considerably more attention [vii] As with pharmaceutical innovation, there is a link in diagnostic innovation between the costs of meeting regulatory burdens for market access, the costs of R&D, the prospect of competitors meeting these costs far more cheaply, and intellectual property rights. There is also a link with the ways in which diagnostics are priced and reimbursed. But while the 'headline' issues are similar, the details of diagnostic innovation are significantly different from pharma innovation and undergoing considerable change.

Four core differences include: (i) market authorization: regulatory standards for marketing *in vitro* diagnostics are different from medicinal products and becoming more demanding in some jurisdictions; (ii) pricing: stratified products do not fit comfortably in traditional pricing arrangements. Stratification offers greater precision and is thus valuable for patients, but it reduces a manufacturer's market—shifting medicines away from a one-size-fits-all, to more of an orphan-drug model; (iii) creation: the demands of R&D (principally robust clinical interpretation) differ from the creation or discovery of new molecules; (iv) ethical attitudes: complex ethical attitudes have swayed opinions about acceptable business models in the diagnostic industry. An illustrative example of the latter point is that Myriad's European patents on breast cancer diagnosis are valid but widely disregarded by clinical laboratories, and its business model has been heavily criticised by clinicians. In contrast Digene's patents on HPV testing for cervical cancer have not been the subject of outrage (despite also relating to cancer in young women of child-bearing age) and were a key part of its successful business model.[viii]

The second policy issue is all the more complex because the diagnostics industry's intellectual property strategies are in a state of flux. Several years ago, diagnostics companies were in the process of moving towards a model where they relied on biomarker patents. In the last two years, however, following several landmark rulings by the US Supreme Court (for example, *Association for Molecular Pathology v Myriad* [ix] and *Mayo Collaborative Services v Prometheus Laboratories Inc*[x]) this is under unprecedented pressure in the US, and faces an uncertain future in Europe. By way of example, many of Myriad's US patents (and similar patents owned by other companies) have now been effectively invalidated by the US Supreme Court for covering ineligible subject-matter (isolated DNA sequences). Patents covering 'natural' correlations between biomarkers and phenotype have also been invalidated. This has serious implications for patents with diagnostic claims based on DNA and similar sorts of biomarkers. It is thought that companies are thus

focusing on other intellectual property rights that may exist in data they have collected to improve the power of DNA biomarkers.[xi] But in fact, very little is known about how diagnostic innovators are responding to the legal changes, the differences emerging between the US and Europe, and how this is effecting diagnostic innovation.

Endnotes

[i] E Drucker and K Krapfenbauer, 'Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalised medicine' (2013) 4 *EPMA Journal* 7.

[ii] C Wright, H Burton, A Hall, S Moorthie, A Pokorska-Bocci, G Sagoo, S Sanderson, R Skinner, PHG Foundation, *Next steps in the sequence. The implications of whole genome sequencing for health in the UK* (2011); Academy of Medical Sciences, *Realising the Potential of Stratified Medicines* (2013); A Hall, T Finnegan, C Alberg, PHG Foundation, *Realising Clinical Genomics in Practice* (2014).

[iii] This issue has been addressed to a limited degree in academic literature: e.g. A De Robbio, A Corradi, 'Biobanks on Balance between Private Property and Commons: Patents or Open Data Sharing?' (2010) 1(2) *Journal of Library and Information Science* 305-329; D Gitter, 'The challenges of achieving open-source sharing of biobank data' (2010) 29(6) *Biotechnology Law Report* 623-35; D Nicol, R Gold, 'Standards for Biobank Access and Intellectual Property' in M Rimmer, A McLennan (eds) *Intellectual Property and Emerging Technologies: The New Biology* (2012) 133-157; S Pthmasiri, M Deschenes, Y Joly, T Mrejen, F Hemmings, B Knoppers, 'Intellectual Property Rights in publicly funded biobanks: much ado about nothing?' (2011) 29(4) *Nature Biotechnology* 319-323; R Pigott, R Barker, T Kaan, M Roberts, *Shaping the Future of Open Innovation: A practical guide for life sciences organisations* (Sept 2014); G Pascuzzi, U Izzo, M Macilotti (eds), *Comparative Issues in the Governance of Research Biobanks: Property, Privacy, IP and the Role of Technology* (2013); R Sachs, 'Innovation Law and Policy: Preserving the Future of Personalised Medicine' (2016) 49 UC Davis Law Review, forthcoming.

[iv] A comparative study of modest breadth (approximately 7 biobanks) was undertaken by the Public Population Project in Genomics and Society (P3G). The generic access agreement it recommended as an international norm is different from both the UK Biobank and Genomics England policies. Knoppers et al, 'A P3G generic access agreement for population genomic studies' (2013) 31(5) *Nature Biotechnology* 384–5.

[v] Genomics England, Clinical Interpretation Partnership Guidance (Nov 2014) p 20; (July 2015) p 19.

[vi] UK Biobank, Access Policy (Nov 2011), Summary, B8.5 and B8.6

[vii] K Liddell, S Hogarth, D Melzer, R. Zimmern, 'Patents as incentives for translational and evaluative research: the case of genetic tests and their improved clinical performance' (2008) Intellectual Property Quarterly 286-327; Human Genetics Commission, S Hogarth, M Hopkins, *Intellectual Property and DNA Diagnostics* (Oct 2010); S Hogarth, *From the ethics of biomarker patenting to the political economy of diagnostic innovation: a Workshop* (2014).

[viii] Hogarth 2014, confidential pre-publication draft. Hogarth suggests several possible explanations for the different attitudes. His analysis reinforces the idea that the diagnostics industry has a complex and dynamic political economy, and warrants considerably more investigation.

[ix] 133 S.Ct. 2107 (2013)

[x] 132 S. Ct. 1289 (2012)

[xi] R Cook-Deegan, J Conley, J Evans, D Vorhaus, 'The next controversy in genetic testing: clinical data as trade secrets' (2013) 21(6) *European Journal of Human Genetics* 585-8; Cf J Strauss, 'Pharma embraces open source models' (2010) 28 *Nature Biotechnology* 631-4.