Contemporary Issues

Report

Patent Policy in Genomics and Human Genetics: A Public Health Perspective

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Executive Summary

The patentability of DNA sequences has stirred a debate on both sides of the Atlantic, and views are mixed with regard to the impact of patents on research and development (R&D) and the degree to which they bring benefit to present and future patients of public health systems. One aspect of the problem concerns the licensing of technologies generated by universities and other public institutions to private companies. For instance, in the UK the 100,000 Genomes Project, which aspires to put to commercial use whole genome sequences, raises important questions: How should we think about licensing, so that commercialization brings benefit to present and future patients by guaranteed access to diagnostic services in the National Health Service? Even if we allow commercialization of research funded by public money, how can we ensure that society gets back its fair share?

Another important aspect of the problem concerns the viability of models of open data and open source licensing. In the past, on certain occasions governments have forced companies to share intellectual property (IP) rights in the public interest, and nowadays various public–private partnerships have been created to address the same need. We need to ask: How successful are public–private partnerships operating in the spirit of open science, advancing sharing and collaboration? Is the open source model of licensing a viable tool?

Introduction

A workshop held at Wolfson College, Oxford on 11 February 2015 brought together policymakers and academic experts in the field of genetics and bioethics to discuss the governance of biomedical patents in the public interest. The workshop considered the broader context of DNA patentability, but the focus was on the post-(patent) grant stage. The aim was to propose policies that can accommodate both public health needs and the policy drive towards competitiveness in local and global markets.

The workshop reflected on the following questions:

1. Patents on DNA Sequences in Europe and the USA;
2. Biomarker Patenting, Monopolies, and Public Health;
3. The 100,000 Genomes Project and IP Licensing;
4. University Licensing;
5. Collaborative R&D, Open Science, and Open Source.

Session I: Patenting DNA Sequences and Stem Cells. Law and Politics in Comparative Perspective

Dr Julian Cockbain explained that the United States Patent and Trademark Office (USPTO) in 2014 rejected a patent application by the pharmaceutical company Novobiotic for an antibiotic compound called teixobactin, on the basis that it is not patent-eligible subject matter. Teixobactin was discovered using a new method of culturing bacteria in soil, allowing researchers to grow previously unculturable bacteria that produce the antibiotic. The USPTO decided that the compound and methods of treatment involving the compound were not different from a naturally occurring product. The decision clearly follows the spirit of *AMP v. Myriad* (in that the combination of the natural with the conventional was not deemed to confer patent-eligibility in the absence of an inventive concept), *Mayo v. Prometheus*, and *Alice v. CLS* (simply combining the excluded natural component with a conventional component would eviscerate the exclusion of the natural, making patent-eligibility dependent on the patent attorney's drafting skill). Dr Cockbain explained that Article 5 of the European Commission's Biotech Directive states that elements isolated from the human body are patent-eligible even if they are identical to the elements as they existed in the body. This means the teixobactin claims mentioned earlier are acceptable, and the European Patent Office (EPO) practice follows this approach. Europe should learn from the US jurisprudence on the question of patent eligibility, and the distinction between the natural and technical in biotech needs to be revisited.

Professor Ingrid Schneider focused in her presentation on stem cells and the democratic shaping of patent law, arguing that the patent system is striking in how closed it remains, and it is only those involved in the practice of law (judges, attorneys, applicants, examiners) who interpret, redefine, and reconstitute the meaning of the law. She expressed concern that the EPO's Granting Practice is to allow patents on methods and products derived from human embryonic stem cell (hESC) lines which were filed after 10 January 2008. According to the Technical Board of Appeals T 1441/13, hESC patents can once again be granted, despite the Court of Justice of the European Union (CJEU) judgment C-34/10 (*Bruestle v. Greenpeace*) which refused such patents on the grounds that they involve the destruction of the embryo, which the court found to be immoral. Specifically, the Technical Board of Appeals decided to allow patents on methods and products derived from hESC lines, as long as these are based upon the derivation method disclosed by Chung et al. in 'Human Embryonic Stem Cells Lines Generated without Embryo Destruction', *Cell Stem Cell* 2(2) 2008: 113–17. This article claims to have allowed for the first time the provision of hESC cultures (cell lines) without destroying a human embryo in any production step. Has Chung's method indeed changed the field of human embryonic stem cell research? This is debatable, as the existence of the cell line in question (No. 5 in Chung et al. 2008) is contested, as it is not registered in any international stem cell registry. The method has no real-world applicability with respect to transfer of the remaining, biopsied embryo to a woman's uterus. The method applied in practice — taking a blastomere from a human embryo without destroying it — could cause harm to the embryo, without any indication and medical benefit for the embryo itself (Recital 42 of Dir. 98/44 does not apply). Therefore, the EPO appears to be using this method as a legal construct without sufficient technical basis, and no stem cell lines produced by this method are currently used in hESC research.

Professor Schneider concluded her presentation by noting that patent attorneys, patent examiners, and boards of appeal undermine legislatively fixed exclusions from patentability. Decisions on patentability of hESC for patents (applied for after 10 January 2008) at the EPO are not documented in its Guidelines for Examination. The problem of lack of accountability to the EU legislator needs to be addressed.

Session II: Biomarker Patenting, Monopolies, and Public Health

Dr Michael Hopkins opened his presentation by outlining the different innovation pathways in the health sector, such as the development of pharmaceuticals, which currently relies on the maximization of profit through intellectual property rights. However, as Dr Hopkins explained, the NHS in the UK presents a different model, one which facilitates innovation in the public sector without industry involvement or patents, even though such innovation may remain hidden, or go unmeasured. Policymakers rarely acknowledge the different characteristics of diverse innovation pathways, and mistakenly seek to apply uniform policies to the industry and public health sector. An important first step in addressing this problem is to measure how much innovation is produced in the public health sector.

In the ensuing discussion, the idea was raised that DNA patents are in fact 'a phantom menace', in that few public sector labs report actually withdrawing a service due to IP (4% in the EU vs. 25% in the US). Hospital staff are hostile to industry attempts to use IP (especially on genes), and there is a lack of Department of Health/NHS guidance on in-licensing IP.

Dr Hopkins concluded his presentation with questions for future research: How do diagnostic patent owners utilize European IP? What is the consequence of biomarker IP not being upheld? Is there sufficient motivation for industry to develop evidence for biomarker validation/utility in the UK market? (or will government fund it?) On balance, which innovation pathways does the de facto UK policy environment favour?

Dr Stuart Hogarth discussed the Human Papilloma virus genetic test (HPV, a viral model of cancer). He noted the uneasy relationship between the HPV test and the Papanicolaou (Pap) smear test and the aggressive business tactics employed by Digene (the only manufacturer of the test in the US with Food and Drug Administration [FDA] approval) in its attempts to replace Pap smear testing in certain groups of the population. The idea of introducing co-testing has also been discussed in the UK. In 2011 the National Institute for Health and Care Excellence (NICE) established a Diagnostics Advisory Committee, which begun evaluation of genomic diagnostics to guide adjuvant chemotherapy in early breast cancer management. There were three commercial tests — Mammostrat, Mammaprint, OncotypeDX (costing £2580) — and one in-house NHS test, IHC4 (costing £150). The NICE draft decision was to recommend Oncotype DX, based on a narrowing of the population for which the test would be used, but the Directly Commissioned Services Committee (DCSC) ultimately decided to ratify the recommendation of the Clinical Priorities Advisory Group (CPAG) to not currently commission OncotypeDX on the grounds that 'the cost of the test to NHS England is significant, even when the additional savings in chemotherapy costs are factored in.'

Although co-testing was not endorsed by the DCSC, it is worth explaining the reasons why NICE initially recommended Oncotype DX for certain groups of the population and not the cheaper alternative, IHC4. The key advantage which OncotypeDX enjoys over IHC4 concerns the supporting evidence for the efficacy of each test. The IHC4 has been in development for a relatively short time, and although NICE deems it promising, it lacks the cumulative weight of evidence from multiple studies which support use of OncotypeDX. What this suggests is that in the era of proprietary combinations of biomarkers, significant first-mover advantage is gained by building a clinical evidence base at an early stage. The two leading tests — Mammaprint and OncotypeDX — are now benefiting from large publicly funded trials to test their utility (MINDAct and TailorRx respectively). This is set to change with the launch in the UK of the OPTIMA trial, a study which may give IHC4 the chance to prove its worth against its commercial counterparts.

Session III: The 100,000 Genomes Project and IP Licensing

Professor Sigrid Sterckx detailed in her presentation the Health and Social Care Act 2012 in the UK, which gives the power to the Health and Social Care Information Centre to collect, collate, and provide access to the medical information for all patients treated by the NHS in England, whether in hospitals or by general practitioners (GPs). Leaving aside questions with respect to informed consent, a different set of questions concern the commercialization process and the ways the Information Centre would be used as a source of profit by the UK government. The Information Centre reassures people that it will not make a profit from providing data to other organizations, but will only charge an access fee to cover its costs. However, according to Professor Sterckx, this means that commercial companies have access to assets they have not themselves bought/created, effectively receiving a quasi-free commercial boost by the UK government. To put NHS databases at the disposal of industry, without requiring a 'kick-back' to help enhance the service that the NHS provides, is inappropriate at best.

Professor Sterckx suggested that some form of benefit-sharing is needed, with benefit effectively passing back to UK citizens whose data will be used to commercial advantage; the mere fact that new drugs might reach the market is not sufficient. One possible improvement would be for the companies seeking access to be required to provide the NHS with reduced access costs for the resulting drugs or other health-related products.

Dr Mark Bale explained that the UK 100,000 Genomes Project is a hybrid research/service project aiming at developing key elements of UK research and clinical infrastructure to sequence 100,000 genomes by 2017, focusing on cancer, rare diseases, and infectious diseases. Genomics England was set up by the Department of Health to deliver the project, which raises a number of challenges concerning patents, copyright and database rights, and licensing strategies.

Dr Bale explained that the Ethics Working Group established by the Chief Medical Officer recommended the adoption of a balanced approach to IP to ensure that any commercialization is in the public interest and brings benefits to the NHS. One aspect of the problem concerns future lincensing strategies. In this respect there is a need to reach agreement on IP across the Department of Health, Genomics England, NHS England, NHS Genomic Medicine Centres, universities, and commercial users. A good starting point is the OECD *Guidelines for the Licensing of Genetic Inventions* published in 2006 which state that 'Licensing practices should seek to strike a balance between the delivery of new products and services, healthcare needs, and economic returns'. Beyond the 100,000 Genomes Project there remain some challenges to the appropriate licensing of diagnostic patents for NHS laboratory use, such as a lack of awareness of existing IP rights by NHS diagnostic labs. The Department of Health is still exploring practical approaches that respect IP rights while striking the right balance regarding the diagnostic uses of genomics with the growth of a vibrant genomics industry in the UK.

Session IV: University Licensing

Dr Harry Thangaraj outlined the current picture of university licensing of patents, explaining that 57 percent of the research origin of biopharmaceutical patents can be found in universities and 6 percent in industry–academia collaborations (data published in 2009 in *Nature Biotechnology*). Dr Thangaraj discussed the non-profit organization Universities Allied for Essential Medicines (UAEM), established as part of a global movement of university students to promote socially responsible licensing (SRL). According to UAEM, academic licensing contracts can be structured in a flexible manner to improve access to essential technologies for the poor in developing countries. Before licensing academic inventions, consideration should be given to market segmentation, tiered or differential pricing (territorial), field of use (suited for platform technologies), humanitarian use, reservation of rights, and inserting a non-assert clause (not to seek to enforce patents or other intellectual property rights in certain countries).

Nowadays, various funders (Wellcome, Gates etc.) make funding conditional on the mandatory development of fair access policies, and, in certain cases, on early release of data. However, access to essential medicines, particularly antiretrovirals (ARVs), has been a long and difficult battle, which has only partly been won. Dr Thangaraj concluded with the recommendation that funders of public research should insist on social responsibility, and that responsible licensing policies for all diseases, rather than a selection of diseases, should be considered.

Dr Adam Stoten introduced Isis Innovation, the University of Oxford's technology transfer company, which translates research into innovation and impact through technology transfer. Impact is an increasingly important factor in the UK government's mechanism for assessing University performance (REF) and subsequent allocation of block funding from Research Councils UK. Impact accounts for 20 percent of the evaluation of research under the REF 2014, and is defined as 'an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.' It is also of increasing importance to other funders of academic research, such as charities and the European Commission. The focus on wider impact differentiates universities from commercial technology developers, who by necessity must prioritize financial return for their shareholders.

Dr Stoten emphasized the importance attached to the delivery of technologies at affordable cost and in suitable quantity to developing countries and least developed countries (LDCs), and acknowledged that a high level of social responsibility is appropriate given the fact that the majority of funding comes from public sources. He also highlighted the commercial pressures on technology developers, and argued that suitable private partners are difficult to find for most early stage university technologies. Oxford's access to medicines policy follows the responsible licensing model as explained by Harry Thangaraj. However, one size does not fit all — each licensing opportunity needs to be considered separately and within its particular context. The terms of a licence cannot be so restrictive that companies will not sign up, since if there is no commercial partner and ultimately no product ensues, then no one will benefit, so a balance needs to be found, for which the early appraisal of the likely applications of a new technology and the pathway to its commercialization is essential.

Session V: Open Science and Open Source

Dr Javier Lezaun began his presentation by asking: Why does a pharma company decide to create a public resource, employing open source ideas and models? Looking in particular into antimalaria drug discovery, and noting that market mechanisms have failed to incentivize the production of drugs, Dr Lezaun explained that GlaxoSmithKline (GSK) used phenotypic (whole-cell) screening to create a compound library (two million compounds) at Tres Cantos Malaria (TCAMs) Drug Performance Unit (DPU). Realizing that there was need for new and structurally different drugs, but there was a lack of validated targets (functional information about the naturally existing cellular or molecular structure involved in the pathology of interest), the company decided to make the data public, but stipulated that, in exchange for their openness, users of its compound library should also share data. GSK's own lawyers revealed to Dr Lezaun, in the course of various interviews conducted at TCAMs DPU, that they opposed the opening up of a proprietary database on the grounds that it may jeopardize the company's intellectual property. Importantly, the release of data by TCAMs redefined the pre-competitive space, as chemical space became 'public', constraining the breadth of patent claims that could be pursued by other actors. This in turn forced IP lawyers to change their focus, since they could only pursue market exclusivity for any eventual treatment that might emerge from this research.

Dr Lezaun continued his presentation by presenting the details of the Open Access Malaria Box (MMV) a not for profit partnership based on the idea of reciprocity, and Open Source malaria drug discovery led by Matthew Todd's laboratory at the University of Sidney. In the latter case, by means of crowdsourcing the evaluation of compounds, the hope is to advance faster science (up to Phase I), raising a number of questions, such as how to ensure some form of market exclusivity and therefore financial reward in an open source project. Julian Cockbain intervened to point out that orphan drug protection may serve as a model of protection, as it states that for any drug designated for a rare disease or condition, the statute provides for seven years of marketing exclusivity.

Dr Wen Hwa Lee introduced the Structural Genomics Consortium (SGC) at the University of Oxford, explaining that it was established in 2004, with members drawn from three government agencies, the Wellcome Trust, and ten leading pharma companies. The SGC is involved in more than 550 international collaborations, an example being the SGC–CHDI alliance, to rapidly discover and develop drugs that delay or slow Huntington's disease. The SGC advocates a new model for biomedical research based on open innovation drug discovery (patent-free). Funding sources are $100m funding from global pharma and $200m from public sources and foundations. The SGC has contributed 15 percent of all human protein structures in the public domain, and produced 776 peer-reviewed articles (20% of which in high-impact journals).

Focusing on the crisis in drug discovery, Dr Lee explained why neither academia nor pharmas offered innovative solutions, in an example of the phenomenon dubbed the Harlow–Knapp effect. The vast majority of the cancer research conducted on kinases, the class of proteins implicated in several cancers, covers only between forty and fifty types, which represents less than 10 percent of the total number. In the pharma industry, similar gaps can be observed: patents cover only 10 percent of kinase types. As a result, despite massive investment, insufficient novel medicines are being delivered, and over 90 percent of early activity is destined for failure, since no single organization has the range of capabilities necessary to deliver success. The current model requires the patenting of early-stage research, and the resultant secrecy prevents collaboration, resulting in unneccessary duplication of research

and suboptimal use of public (and industrial) resources. The solution can only be open innovation. The pre-competitive space requires redefinition to include research tools and basic knowledge (for example, on the structure of novel proteins) and then the proprietary phase will include drug discovery and development, facilitated by access to increased amounts of information in the public domain. This approach is endorsed in economic analysis produced in 2014 by the New York Academy of Sciences, which focused on opportunities to accelerate R&D for Alzheimer's disease. Dr Lee concluded that translational research in a pre-competitive commons through public–private partnerships will bring the best possibility of success.

Professor Graham Dutfield discussed the management of intellectual property in the emerging technologies of synthetic biology and assessed the recent ascendance of open source-type licensing models. Questioning whether synbio products are best characterized as drugs (discrete technologies) or as something more akin to mobile phones or microprocessors (complex technologies), or even as hybrids comprising characteristics of both, he reviewed the implications of such categorizations for IP policy and business models. Synbio is a complex technology; hence, the smartphone comparison is a useful one, since it illustrates the complex patent issues that are likely to emerge in the future. Assessing the alternatives, Professor Dutfield questioned whether open innovation provides a real opportunity for a better balance between IP and the public domain, arguing that how we address this question depends largely on our categorizations of synbio, as a hybrid comprising characteristics of diverse technologies, at the intersection between true engineering systems and biology.

Key Findings

1. Patents may protect technologies, but products of nature fall outside the realm of patent protection. Europe should learn from the current turn in the US jurisprudence on the question of patentability of products of nature, which reflects the concern that the drafting skills of patent attorneys render meaningless the distinction between the natural and the technical in patent law.

2. The European Patent Office (EPO) Granting Practice is to allow patents on methods and products derived from human embryonic stem cell lines which were filed after January 2008 if the invention uses the derivation method disclosed by Chung et al. in 2008, which for the first time has allowed the provision of hES cultures (cell lines) without destroying a human embryo in any production step. However, the grounds of this decision should be scrutinized, and the problem of lack of accountability of an administrative agency such as the EPO to the EU legislator needs to be addressed.

3. Public institutions such as the NHS participate in 'hidden' innovation, which escapes measures of quantity and impact applied to the private sector. We need to understand better the amount and quality of this type of innovation and devise policies that accommodate the characteristics of different innovation paths, both public and private.

4. Human Papillomavirus testing illustrates recent attempts by private companies to monopolize the market for genetic testing. In the UK, a decision was made on whether to endorse co-testing with the Pap smear test or not, and whether proprietary technology should be used instead of much cheaper tests developed in-house by the NHS. In these cases, policymakers should take into account that significant first-mover advantage is gained by building a clinical evidence base at an early stage.

5. The Health and Social Care Act 2012 in the UK allows the Health and Social Care Information Centre (HSCIC) to collect and share confidential information from medical records. The subsequent Care Act 2014 means that the public's data can only be shared and analysed when there is a clear healthcare benefit. Beyond well-rehearsed arguments with respect to informed consent, the lack of public trust resulting from the commercialization of personal information needs to be addressed. In this respect, the idea of reciprocal benefit-sharing becomes salient: if a public resource such as the databases held by the National Health Service are shared with industry, a reciprocal benefit must be secured to enhance the healthcare services that the NHS provides.

6. The 100,000 Genomes Project requires the adoption of a balanced approach to IP to ensure that any commercialization is in the public interest and brings benefits to the NHS. OECD guidelines for the licensing of genetic inventions may serve as a useful model.

7. University technology transfer offices should determine the correct balance between commercial considerations and the translation of technologies to products that serve the needs of the public. On the assumption that social impact should be of primary importance, academic licensing contracts should be structured in a flexible manner to improve access to important technologies.

8. Given the current drive to translate university research into valuable commercial products, it is argued that public institutions lead private companies in the discovery of novel drug targets. The question is whether there is value in filing for patents in early research, or whether to adopt open access policies. Given the declining levels of pharma innovation, serious consideration should be given to the adoption of open science and open source initiatives that redefine the pre-competitive (tools and basic knowledge) and competitive

space/proprietary (drug discovery and development) phases, facilitated by access to increased amount of information in the public domain. The management of intellectual property in synthetic biology and other emerging technologies and the ascendancy of open source licensing models present interesting questions for the best way to incentivize future innovation, and should be subject to further research.

Participants

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