Fortune and Hindsight: Gene Patents' Muted Effect on Medical Practice

Jacob S. Sherkow & Ryan Abbott

JSS (corresponding author)
Associate Professor, Innovation Center for Law and Technology, New York Law School;
Visiting Assistant Professor of Health Policy and Management, Columbia University Mailman School of Public Health
Permanent Visiting Professor, Center for Advanced Studies in Biomedical Innovation Law, University of Copenhagen Faculty of Law

e-mail: jacob.sherkow@nyls.edu

tel.: +1.212.431.2355

address: 185 West Broadway, New York, NY 10013 USA

RA
Professor of Law and Health Sciences, University of Surrey School of Law;
Adjunct Assistant Professor of Medicine, David Geffen School of Medicine at University of California, Los Angeles

e-mail: r.abbott@surrey.ac.uk

tel.: +44 (0) 1483.68.2851

address: University of Surrey, Guildford, Surrey, GU2 7XH UK

running title: Gene Patents' Muted Effect on Medical Practice

keywords: patents, genetics, medicine, policy, law

Authorship Confirmation Statement

JSS and RA both contributed substantially in the preparation and writing of this manuscript. The order of authors reflects the quantity of respective contributions. This manuscript has been submitted solely to this journal and is not published, in press, or submitted elsewhere.

Structured Abstract

Introduction

Physicians have long worried about gene patents' potential to restrict their medical practices. Fortune and hindsight have proven these worries exaggerated both in the U.K. and elsewhere. Neither current nor future medical practices appear to be impinged by gene patents, although they may be subject to future intellectual property disputes.

Sources of Data

Qualitative and quantitative (survey) studies of gene patents' effects on medical practice; recent developments in patent law.

Areas of Agreement

Traditional gene patents do not appear to have restricted medical practice in the U.K., although their effect elsewhere has been more nuanced.

Areas of Controversy

Whether patents will restrict the spread of newer medical technologies is unresolved.

Areas Timely for Developing Research

Continuing survey data on practitioners' views concerning patents' role in the distribution of newer technologies would be beneficial.

Authors Disclosure Statement

The authors have no conflicts to disclose.

Review:

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Jacob S. Sherkow[1,2,3] & Ryan Abbott[4,5]

[1] Associate Professor, Innovation Center for Law and Technology, New York Law School; [2] Visiting Assistant Professor of Health Policy and Management, Columbia University Mailman School of Public Health; [3] Permanent Visiting Professor, Center for Advanced Studies in Biomedical Innovation Law, University of Copenhagen Faculty of Law. e-mail: jacob.sherkow@nyls.edu.

[4] Professor of Law and Health Sciences, University of Surrey School of Law; [5] Adjunct Assistant Professor of Medicine, David Geffen School of Medicine at University of California, Los Angeles. e-mail: r.abbott@surrey.ac.uk.

Introduction

The specter of "gene patents" interfering with medical practice has long haunted clinicians.[1] For over a decade, physicians have fretted over the possibility that corporate ownership of human genes, through patents, would restrict doctors' ability to diagnose and treat their patients.[2] In 2013, these fears were heightened in the run-up to the *Myriad Genetics* case before the Supreme Court of the United States, a case concerning the patenting of *BRCA1* and 2, genes of critical importance in assessing early-onset breast and ovarian cancer risk.[3]

Today—with both fortune and hindsight—such seem exaggerated. The weight of evidence, both empirical and qualitative, have found that "gene patents"—an amorphous term, not readily subject to definition—have not affected the practice of medicine in the U.K.[1-2,4] Gene patents covering medically important tests have frequently been licensed cheaply and easily.[5] In other instances, gene patents have been invalidated by courts or patent offices; genetic technology has advanced to the point where it is no longer covered by traditional gene patents; or clinicians have simply ignored patents in their field.[2-3,6] In addition, many jurisdictions—such as the United States and Australia—have placed restrictions on patentable genetic subject matter.[3,7] At the same time, genetic diagnostics appear to be developing and rapidly integrated into in the medical landscape, despite patent protection—or, in some cases, the lack thereof.[6]

Gene patents' muted effect on medical practice is a complex function of law, history, technological development, and medical mores. Whether such an effect will remain muted is uncertain. New, medically significant genetic technologies, like whole genome sequencing, precision medicine, and genetic engineering are similarly being integrated into medical practice while being covered by patent protection. This review examines what constitutes a "gene patent," gene patents' current legal status in the U.K. and the rest of the world, and their present—and potential future—effects on medical practice.

Defining "Gene Patent"

Despite common use of the term, it is difficult to clearly define what constitutes a "gene patent." Many patents describe or lay claim to genetic sequences, but often do so in relation to other technical inventions having little to do with the underlying sequences themselves.[8] Others claim genetic material that is either synthetic—that is, recombinant—or significantly modified from the natural products from which they derives.[5] Further, neither the Intellectual Property Office nor the European Patent Office labels patents as "gene patents." Referring to a patent as a "gene patent" is more of a lay term—or, frequently, an anti-normative sentiment—than it is a well understood term to patent attorneys.

Nonetheless, when the public refers to "gene patents," it is likely circumscribing a population of patents that claim, as their principal invention, a naturally occurring or insignificantly modified nucleic acid.[1,5] That is, the likely best definition of a "gene patent" is one that claims a naturally occurring gene or allele or some significant portion thereof. This understanding of "gene patent" has some basis in patent law. Today, patent offices throughout the world have established a set of international protocols for submitting sequences of nucleic acids, known as "sequence listings." For example, the most recent version of The Patents Rules, the secondary legislation that complements the U.K.'s 1977 Patents Act, require a sequence listing for any patent "[w]here the specification of an application discloses a sequence."[9] Similarly, Rule 30 of the European Patent Convention requires sequence listings "conforming to the rules laid down by the President of the European Patent Office for the standardised representation of nucleotide and amino acid sequences."[10] At a minimum, gene patents are likely those that come with sequence listings.

These efforts at standardization aside, defining gene patents by reference to their inclusion of naturally occurring sequences belies greater complexities about the genetic code. How *much* of a naturally occurring gene is required for a patent to become a gene patent? How should unintentional redundancy—a synthetic sequence's overlap with a natural one—be treated? And, like the ship of Theseus—rebuilt plank by plank until none of its original boards remained—how much alteration of a naturally occurring sequence is required for a gene patent to become, simply, a patent claiming a man-made genetic sequence? Different jurisdictions have answered these questions differently, and however "gene patent" is to be defined, the term will always be fraught will some degree of ambiguity.

The Patentability of Genes

Many physicians think of gene patents as a relative recent phenomena, which is understandable given the attention gene patents received in the late 1990s and the early 2000s together with the Human Genome Project.[2] But genetic material has been the subject of patents since at least the 1960s when researchers began to receive U.S. patents on naturally occurring RNA sequences. With the advent of recombinant DNA in the 1970s and 1980s, researchers also began to receive patents covering recombinant DNA—most famously, Herbert W. Boyer and Stanley Cohen's 1980 patent, widely seen as a watershed moment in biotechnology. In 1981, the first patent claiming a naturally occurring genetic sequence was awarded in the United States: a patent covering a naturally occurring yeast plasmid.[5]

In tandem with the advent of large scale sequencing of the human genome, researchers—both at public and private institutions—began to obtain patents on isolated human genes by the thousands. Such patents famously included clinically significant genes, like *HFE*, a gene implicated in hereditary haemochromatosis; *CFTR*, the cystic fibrosis gene; and, of course, *BRCA1* and *BRCA2*, the breast- and ovarian-cancer risk genes.[11] Patents at the time also included fragments of expressed mRNA, also known as "expressed sequence tags"—a strategy finally outlawed in the United States in 2005. Since that time, there has been disagreement as to how much of the human genome was ultimately the subject of patent protection, although early upper estimates that, for example, 90% of the human genome was patented, are almost certainly incorrect.[8]

Despite the widespread nature of gene patents in the early 2000s, there were few reported instances of these patents impinging on physicians' autonomy to test, diagnose, and treat their patients. An influential 2002 report from the Nuffield Council on Bioethics found that patents covering genes related to HIV, hepatitis B and C, and the MSP-1 malaria protein were mostly

unobjectionable because they were used to broadly license diagnostic tests in aid of diagnoses and treatment. The Council ultimately concluded that gene patents were, "in the main, defensible . . . [but] that in the particular case of patents that assert property rights over DNA, consideration should be given to whether the balance between public and private interests has been fairly struck."[1] Other, later empirical studies came to similar conclusions.[2,4]

While gene patents did not appear to interfere with physician autonomy, they did—at least initially—dampen patient choice and access to tests outside Britain. A 2003 empirical study found that while specific patent demands were rare, U.S. clinicians were nonetheless fearful that gene patents would stymie their work.[12] This was followed, in 2010, by an influential report in the United States concluding that, in several, isolated incidences, "patents have been used to narrow or clear the market of existing tests, thereby limiting, rather than promoting availability of testing." Further, because the prices of genetic tests in the United States are driven by market forces, rather than rate-setting, U.S. patients were unable to pay for patented tests their insurance providers would not cover.[13] This link between patents and prices was similarly raised in a recent dispute in Canada concerning genetic testing for familial long QT syndrome.[14]

This disconnect between gene patents' effects in the U.K. and elsewhere may have been partially tied to the patenting and licensing activities of a single company: Myriad Genetics and its patents covering *BRCA1* and *BRCA2*, genes strongly implicated in early-onset breast and ovarian cancer. Unlike most other gene patent holders, Myriad Genetics both refused to outlicense its patents to other clinical laboratories and—shockingly—threatened to sue U.S. clinicians in the who were performing *BRCA1* and *BRCA2* sequencing at their own laboratories.[5,15] This culminated in an advocacy suit against the company, seeking to invalidate gene patents on a large scale. In 2013, the Supreme Court of the United States decided an appeal from the case—*Association for Molecular Pathology v. Myriad Genetics, Inc.*—and ruled that gene patents covering "isolated human genomic DNA" were no longer eligible for patent protection.[3] Parallel litigation concerning Myriad in Australia produced similar results against gene patenting. In 2015, the Australian High Court also ruled against Myriad, concluding that the company's invention was "not 'made' by human action" but "discerned," and therefore unpatentable.[7]

The recent turn against patent eligibility for genes in the United States and Australia stands in contrast to the rest of the world. The 1998 European Council's Biotech Directive affirmatively allowed the patenting of DNA sequences, so long as their patents disclosed their respective genes' functions.[16] This directive was later embodied in the European Patent Convention—to which the United Kingdom belongs independently of her association with the European Union. Rule 29 of the Implementing Regulations to the EPC reads that "the sequence or partial sequence of a gene, may constitute a patentable invention."[10] In addition, a 2005 House of Lords decision interpreting the regulation, *Kirin-Amgen v. Hoechst Marion Roussel*, concluded that isolated and extracted DNA sequences were patentable inventions of their own.[17] Much of the Commonwealth has decided similarly. Gene patents—again, in their isolated form—are still valid in Canada, where they were recently subject to litigation between Transgenomic, Inc. and the Children's Hospital of Eastern Ontario.[18,19] Today, gene patents remain alive and well in the U.K. and most of the world, but largely without the sort of exclusionary behavior propounded by Myriad Genetics rarer ever still.[20]

Gene Patents in Current Medicine

Much of the early fear of gene patents stemmed from genetic sequencing's nascency in medical practice. In the 1990s and early 2000s, diagnostic sequencing was generally ordered only for single-gene, Mendelian traits, and performed using DNA amplification and Sanger sequencing, technologies that required the creation of multiple, isolated copies of individual genes or gene fragments.[20] This made diagnostic sequencing all the more likely to infringe on patents covering individual, isolated genes.[6,8] Today, medical practice has adopted new forms of genetic sequencing and for a greater number of applications, including next-generation sequencing, therapeutic companion diagnostics, and prenatal genetic diagnosis. Like their predecessor technologies, the impact of traditional gene patents on these applications are likely to be muted.

Next-Generation Sequencing

Traditional diagnostic genetic sequencing was both burdensome and time intensive. The particular gene of interest was amplified using PCR, using gene-specific or, in some cases, allele specific primers. The resulting, amplified product, with radiolabeled terminal nucleotides evenly spread throughout the target gene, was then sorted by size via gel electrophoresis, and read either manually or by computer. This process, named Sanger sequencing after Frederick Sanger, who won the Nobel Prize in Chemistry for the technique in 1980, took hours if not days to complete and was prone to human error. In addition, because the process required the creation of isolated copies of the target gene, it put clinicians at risk for infringing gene patents: they were, in effect, "making" the patented gene without permission from the patent holder.[6]

To date, Sanger sequencing has been largely replaced by "next-generation sequencing" technologies (NGS), a catch-all term describing a variety of automated, robust, multigene sequencing platforms. One of the more popular NGS platforms, Illumina sequencing, uses DNA randomly broken up into short segments, that are then "tagged" with adaptors and amplified. The resulting amplification products are then passed through a flow-cell, labeled with nucleotide specific fluorescent dyes, and read by machine. At the end, these reads are then reassembled into gene sequences using specialized software. Importantly, it is unlikely that a complete copy of an isolated gene is ever created. As a consequence, users of Illumina's platforms are unlikely to infringe on traditional gene patents. Another NGS platform, nanopore sequencing, does not even require amplification, and simply "reads" long stretches of DNA through an electrically sensitive molecular channel, i.e., a "nanopore." Here, too, NGS technology is unlikely to infringe traditional gene patents.[6]

While Sanger sequencing is still important for some applications, NGS technologies have largely supplanted them. Oxford University Hospitals NHS Foundation Trust, for example, now offers a suite of gene panel screens—multiple genes sequenced at once—all using NGS technologies.[21] To date, the Trust offers at least 20 such panels—and there is no evidence, to date, that the development or use of any of these panels have been restricted or hampered by patents. In the U.S., several private companies—such as Exact Sciences and Foundation Medicine—each offer their own gene panel screens for different indications, and none of which appear to be embroiled in gene patent disputes.

This is not to say that patents will not play a role in the development, pricing, and licensing of NGS. Indeed, Oxford Nanopore and Pacific Biosciences are currently embroiled in patent litigation in the United States over nanopore sequencing technology.[22] Rather, gene

patents—patents covering specific nucleotide sequences—do not appear to have had a particularly significant on the medical establishment's adoption or dissemination of these technologies.

Therapeutic Companion Diagnostics

Aside from traditional diagnostic testing, genetic diagnostics are also increasingly taking the form companion diagnostics, *in vitro* diagnostics (IVDs) to guide pharmaceutical treatment. The breast cancer antibody-drug conjugate Kadcyla (trastuzumab emtansine), for example, is indicated for patients with *HER2*-positive tumors. Physicians wishing to treat their patients with Kadcyla must screen biopsies for *HER2* overexpression; a variety of tests are available from a number of UK testing centres as well as commercial providers.[23,24]

Although the genetic sequencing of single genes to guide a course of treatment would seem to implicate gene patents, there is little evidence that gene patents have hindered companion sequencing. To the contrary, commercial developers of therapeutics that require companion sequencing tend to co-develop and then outsource sequencing to other providers, gene patents notwithstanding.[25] This means that, frequently, after approval of the therapeutic product itself, related companion diagnostics tend to be offered by multiple providers. In Kadcyla's case, *HER2* testing has been offered by at least six commercial providers, none of which have attempted to enforce gene patents against the other.[24] Depending on the therapeutic, doctors wishing to order companion diagnostics to guide treatment may have choices surrounding speed, accuracy, and cost.

To be sure, patents still play an important role regarding IVDs. Many IVD providers have substantial patent portfolios and, in some instances, have not been shy about enforcing their patents against competitors. In the United States, Caris MPI recently sued Foundation Medicine on five patents covering the molecular profiling of certain tumors for chemotherapy.[26] But such patents are typically directed not toward specific genetic sequences as much as methods of treatment conditioned on a collection of results derived from patients' genetic profiling. As such, patents concerning companion diagnostics tend not to raise some of the more troubling issues concerning gene patents: they do not restrict research or diagnosis concerning all aspects of a given gene; they are often relatively narrow to specific gene panels and testing regimes, for which there may be alternatives; and they are frequently "industrial" enough to avoid ethical concerns surrounding the patenting of natural products. Here, too, gene patents—even where broadly applicable—do not appear restrict physician autonomy or patient access to treatment regimens.

Prenatal Genetic Diagnostics

Recently, medical practice has also widely adopted the use of prenatal genetic diagnostics, especially concerning the sequencing of maternal blood to detect fetal aneuploidies. Although several methods have been described, one popular method involves using NGS sequencing to sequence millions of short DNA tags extracted from maternal blood. The sequences of these tags are then aligned to various chromosomes along the human genome and quantified relative to a healthy, male reference sample. Overrepresentation of a particular chromosome, relative to other the chromosome's "sequence tag density" in the control, suggests the presence of a fetal aneuploidy, such as those giving rise to Down, Edward, and Patau syndrome.[27]

Significantly, the technique does not rely on the sequencing of any genes in particular. Rather, "it can be applied to arbitrarily small fractions of fetal DNA," as small as 25 base pairs in length—well short of the length of any human gene.[27] As a consequence, the technique is unlikely to infringe on, or make use of, traditional gene patents. To that end, medical providers have seen substantial market evolution for such tests following their commercial introduction around 2012. By that time, four commercial providers were providing the test to practitioners—Sequenom, Verinata Health, Ariosa Diagnsotics, and Natera—prior to some recent market consolidation.[28]

While gene patents have not stymied the introduction and development of prenatal genetic diagnostics, basic aspects of the technique itself was the subject of several foundational patents, held among competing entities. This has a triggered a hard-fought, costly, and still-litigated patent suit between Sequenom, now held by LabCorp, and Verinata, since acquired by Illumina.[28] In addition, "[e]ven in the absence of market monopolies, IP-related issues…could affect how tests are priced," a potentially significant concern for NHS.[29]

The patent situation concerning prenatal genetic diagnostics is therefore particularly nuanced. Foundational patents in this area do have the ability to control prices and access to a broad landscape of medically significant technology, much in the same way gene patents originally threatened to do. But unlike gene patents—which restrict physicians' use of sequence information from a particular gene for any purpose—broad patents covering prenatal genetic diagnostics lock up only a particular technique that may, eventually, be supplanted, albeit with newly patented technologies.

Patents and The Future of Genetic Medicine

While gene patents appear to have only a muted effect on current medical practices, they seem similarly quiet on future practices—namely, whole genome sequencing, precision medicine, and genetic engineering. Like current genetic diagnostics, these technologies do not depend on the isolation and amplification of individual human genes, the fulcrum to gene patents' force. Instead, they typically rely on large-scale, gene-independent sequencing, and, in the case of genetic engineering, the creation of synthetic sequences unlikely to be covered by traditional gene patents.

These future technologies, however, are not free from patent controversies. Each has been the subject of broad patents covering important implementations of the technology; some of these have been litigated vigorously between competitors. Thus, while gene patents may have a muted effect on the next generation of genetic medicine, the future adoption of these technologies in medical practice may depend on more technologically focused patents.

Whole Genome Sequencing

Since the completion of the Human Genome Project in 2003, commentators have advocated for whole genome sequencing (WGS) to become part of the medical canon.[30] First viewed as an impractical, quixotic luxury, the cost of WGS has now dropped to about £750, and is continuing to fall.[31] In addition, WGS—even with some significant technical limitations—has been demonstrated to be clinically useful in detecting some cardiac pathologies, as well as diabetes and cancer risk.[30] Today, companies such as Ambry, Counsyl and InVitae now offer competitively priced WGS, and no patent holder appears to have tried to obstruct WGS on the basis of single gene patents.[32]

But, like many revolutionary technologies, WGS is subject to what have essentially become standards wars—disputes over foundational, technological standards—mediated through patent litigation among NGS companies. In addition to the dispute between PacBio and Oxford Nanopore,[22] there are also lawsuits among Illumina, Complete Genomics, Helicos, Intelligent Bio-Systems, Ion Torrent, and Roche.[33] Cost and access to WGS may be affected by the outcome of these disputes.[33] And, because each WGS technology operates slightly differently—with different limitations concerning what it can and cannot detect[30]—these patent disputes may ultimately drive how far WGS is clinically available.

Precision Medicine

Precision medicine can be defined as "precisely tailored therapies to subcategories of disease, often defined by genomics."[34] That is, rather than diagnosing and treating patients from constellation of symptoms—as physicians have done for millennia—doctors may utilize precision medicine to prescribe therapies on the basis of genetic diagnostics.[35] These include treatments that are, themselves, indicated and approved for genetic markers rather than diagnoses of disease. Recent therapeutic advances in precision medicine include, Keytruda (pembrolizumab), Kymriah (tisagenlecleucel), and Alnylam's forthcoming patisiran RNA therapy product.[36]

These therapeutic products seem neither to rely on nor are stymied by individual gene patents. While each does require the sequencing of individual genes, like companion diagnostics, to date, no precision therapy appears to have been held back from clinical investigation or regulatory approval due to the assertion of patents covering individual genes.

Nonetheless, patents appear to have had a significant effect on the development of precision therapies. Precision medicine often derives from fundamental research originally sited at universities, many of which seek patent protection on their contributions and then later engage in restrictive licensing practices. These have the capacity to bottleneck further research, as well as increase cost, shape development, and limit patient access.[37-38] Thus, while it is unlikely that gene patents will guide the future course of precision therapies, they may very well turn on how their related patents are licensed and enforced.[36]

Genetic Engineering

Lastly, genetic engineering holds substantial promise for the future of medical practice, with the potential to treat patients by permanently repairing their underlying genetic etiologies. Recent advances, such as the much-hyped gene-editing system, CRISPR, as well as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), have shown strong potential in both laboratories and preclinical trials.[39] Even older technologies, such as permanently stable DNA delivered through adeno-associated viruses (AAVs), have demonstrated recent successes, as with Spark Therapeutics' recent U.S. approval of Luxturna (voretigene neparvovec-rzyl).

Because most of these technologies rely on the creation of synthetic nucleotide sequences, they, too, do not seem to be affected by traditional gene patents. But they are often the subject of broad, foundational patents in the area that may squelch competition much as gene patents were once feared to do. Famously, basic forms of using CRISPR are the subject of a particularly contentious patent dispute between the University of California, Berkeley and the Broad Institute, that has yet to be resolved. The resolution of that dispute is likely to affect the ownership over vast swaths of clinically useful applications of CRISPR, and may ultimately

impede on physician and patient choice by modulating pricing, coverage, and regulation of the technique.[40]

Conclusion

Although gene patents—however defined—have captured the medical profession's collective imagination, recent developments in law, medicine, and technology have muted their effects. While gene patents remain valid in the United Kingdom, they do not appear to have had a strong effect on medical decision-making or access to genetic tests. Elsewhere, earlier attempts to stringently enforce single-gene patents against clinicians have either been rare or effectively hobbled. Additionally, medicine's current use of genetic testing—through next-generation sequencing, therapeutic companion sequencing, or prenatal genetic diagnostics—does not appear to come within the scope of traditional gene patents. Nor do newer genetic technologies and applications, such as whole genome sequencing, precision medicine, and genetic engineering. This is not to say that genetics, writ large, has moved beyond patent protection. To the contrary, some of these technologies lay as spoils in particularly fevered patent disputes between rivals. And the outcome of these disputes will likely have significant effects on patient access and physicians' choice of diagnostics and treatments. Patents may still significantly shape medical practice. But those patents will not be on isolated genes.

Acknowledgments

Special thanks to Hank Greely for the opportunity and encouragement to write about this topic.

References

[1] *The ethics of patenting DNA.* London: Nuffield Council on Bioethics, 2002.

[2] Hawkins N. The impact of human gene patents on genetic testing in the United Kingdom. *Genet Med* 2011; **13**: 320-324.

[3] Association for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013) (U.S.).

[4] Liddicoat J, Whitton T, Nicol D. Are the gene-patent storm clouds dissipating? A global snapshot. *Nat Biotech* 2015; **33**: 347-352.

[5] Sherkow JS, Greely HT. The history of patenting genetic material. *Ann Rev Genet* 2015; **49**: 161-182

[6] Price II, WN. Unblocked future: why gene patents won't hinder whole genome sequencing and personalized medicine. *Cardozo Law Rev* 2012; **33**: 1601-1631.

[7] D'Arcy v. Myriad Genetics Inc. [2015] HCA 34 (Austl.).

[8] Tu S, *et al*. Response to 'pervasive sequence patents cover the entire human genome.' *Genome Med* 2014; **6**: 14.

[9] *The patents rules 2007 (as amended)*. London: Intellectual Property Office, 2017.

[10] *Implementing regulations – to the Convention on the Grant of European Patents*. Munich: European Patent Office, 2015.

[11] van Overwalle G, van Zimmeren E, Verbeure B, Matthijs G. Models for facilitating access to patents on genetic inventions. *Nat Rev Genet* 2006; **7**: 143-148.

[12] Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *J Mol Diagn.* 2003; **5**: 3-8.

[13] *Gene patents and licensing practices and their impact on patient access to genetic tests*. Bethesda, Md., USA: Secretary's Advisory Committee on Genetics, Health, and Society, 2010.

[14] Ali-Khan SE, Gold ER. Gene patents still alive and kicking: their impact on provision of genetic testing for long QT syndrome in the Canadian public health-care system. *Genet Med* 2017; **19**: 1253-1259.

[15] Sherkow JS, Greely HT. The future of gene patents and the implications for medicine. *JAMA Int Med* 2013; **173**: 1569-1570.

[16] Council Directive 98/44, On the Legal Protection of Biotechnological Inventions, 6 July 1998.

[17] Kirin-Amgen v. Hoechst Marion Roussel [2005] RPC 9.

[18] Monsanto Canada Inc. v. Schmeiser [2004] 1 SCR 902 (Can.).

[19] Children's Hospital of Eastern Ontario v. Transgenomic, Inc. (14 May 2015) T-2249-14 (Can.).

[20] Sherkow JS, Scott C. Myriad stands alone. *Nat Biotech* 2014; **32**: 620.

[21] Molecular genetics laboratory. Oxford University Hospitals NHS Foundation Trust. http://www.ouh.nhs.uk/services/referrals/genetics/genetics-laboratories/molecular-genetics-laboratory/default.aspx.

[22] Pacific Biosciences of California, Inc. v. Oxford Nanopore Technologies, Inc., Case No. 1:17-cv-1353 (D. Del. Sept. 25, 2017) (U.S.).

[23] Rakha EA, *et al.* Updated UK Recommendations for *HER2* assessment in breast cancer. *J Clin Path* 2014; 1-7.

[24] Perez EA, Cortés J, Gonzalez-Angula AM, Bartlett JMS. *HER2* testing: Current status and future directions. *Cancer Treat Rev* 2014; **40**: 276-284.

[25] Cheng S, Koch WH, Wu L. Co-development of a companion diagnostic for targeted cancer therapy. *New Biotech* 2012; **29**: 682-688.

[26] Caris MPI, Inc. v. Foundation Medicine, Inc., Case No. 1:17-cv-12194 (D. Mass. Nov. 7, 2017) (U.S.).

[27] Fan HC, Blumenfeld YJ, Chitkara U, Hudgins L, Quake SR. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc Nat'l Acad Sci USA* 2008; **105**: 16266-16271.

[28] Agarwal, A, Sayres, LC, Cho, MK, Cook-Deegan R, & Chandrasekharan, S. Commercial landscape of noninvasive prenatal testing in the united states. prenatal diagnosis. *Prenatal Diag* 2013; **33**: 521-531.

[29] Chitty LS, *et al.* Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. *BMJ* 2016; **354**: i3426.

[30] Ashley EA, *et al.* Clinical assessment incorporating a personal genome. *Lancet* 2010; **375**: 1525-1535.

[31] Herper M. Illumina promises to sequence human genome for $100—but not quite yet. *Forbes* 9 Jan 2017; https://www.forbes.com/sites/matthewherper/2017/01/09/illumina-promises-to-sequence-human-genome-for-100-but-not-quite-yet/.

[32] Cook-Deegan R, Chandrasekharan S. Patents and genome-wide DNA sequence analysis: is it safe to go into the human genome? *J Law Med Ethics* 2014; **42**: 42-50.

[33] Holman CM. Advances in DNA sequencing lead to patent disputes. *Nat Biotech* 2012; **30**: 1054-1058.

[34] Ashley EA. The precision medicine initiative: a new national effort. *JAMA* 2015; 313: 2119-2120.

[35] Abbott R, Chang DD, Eyre HA, Bousman CA, Merrill D, Lavretsky, H. Pharmacogenetic decision support tools: a new paradigm for late-life depression? *Am J Geriat Psych* 2018; https://doi.org/10.1016/j.jagp.2017.05.012

[36] Sherkow JS, Contreras JL. Intellectual property, surrogate licensing, and precision medicine. *IP Theory* 2018 (forthcoming); https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3106340.

[37] Abbott R. Balancing access and innovation in India's shifting IP regime, remarks. *Whittier Law Rev* 2014; **35**: 341-348.

[38] Abbott R, *et al.* The price of medicines in Jordan: the cost of trade-based intellectual property. *J Generic Med* 2012; **9**: 75-85.

[39] Cai L, Fisher AL, Huang H, Xie Z. CRISPR-mediated genome editing and human diseases. *Genes & Diseases* 2016; **3**: 244-251.

[40] Sherkow JS. *CRISPR*, patents, and the public health. *Yale J Biol Med* 2017; **90**: 667-672.