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Persistent Confusion and Controversy Surrounding Gene Patents

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Abstract

There is persistent confusion and controversy surrounding basic issues of patent law relevant to the genomics industry. Uncertainty and conflict can lead to the adoption of inefficient practices and exposure to liability. The development of patent-specific educational resources for industry members, as well as the prompt resolution of patentability rules unsettled by recent U.S. Supreme Court decisions, are therefore urgently needed.

Introduction

Next-generation sequencing (NGS) technologies are evolving at a rapid pace. At the same time, the legal landscape in which these technologies are developed and used is also changing. Many of these changes are small regulatory adjustments, while others represent seismic shifts in the law. For example, in 2011, Congress enacted the America Invents Act (AIA), which changed the basic nature of the U.S. patent system from one that awarded patents to first inventors to one that awards patents to first applicants.¹ Two years later, the U.S. Supreme Court held that naturally occurring DNA is not patentable,² overturning decades of precedent and calling into question the validity of thousands of patent claims.

It is important to understand how NGS industry leaders are interpreting and responding to these events, as confusion and controversy could suggest a disconnect between law and practice that is promoting undesirable activities in the NGS industry. In particular, uncertainty may lead to the adoption of protocols, practices, and strategies that introduce inefficiencies into the NGS pipeline or expose participants in that pipeline to liability.

In 2013, we conducted semi-structured, in-depth interviews of 19 NGS industry leaders to identify organizational trends and policy concerns. Interviewees came from hardware and reagent manufacturers, clinical laboratories performing NGS, informatics companies, test manufacturers, and one professional association. Average interview length was 57 minutes. Each interview was audio recorded with permission, transcribed, de-identified, and analyzed for thematic content.

We have reported elsewhere our findings regarding interviewees' perceptions of the structure and future of the NGS industry.³ Here, we report our findings regarding interviewees' understanding of patent law's influence on NGS clinical care and research. We found that interviewees were confused or troubled by four important points of patent law. These

concepts, and the practical consequences of their continued misunderstanding and debate, are summarized in Table 1.

Genomics leaders have made a compelling case for improving the genomic literacy of health care professionals^{4,5} and the public.⁶ Our findings and analysis suggest that educational initiatives responding to these appeals should include relevant information about patent law. Our findings also support the prompt judicial or legislative resolution of the test of patent eligibility, which has been unsettled by recent case law.

The analysis set forth in this article is based on the laws in effect at the time of this writing. As noted, however, the legal landscape is evolving. Genomic service providers and researchers are therefore encouraged to seek professional advice before proceeding with activities that implicate patent concerns.

Issue 1: The End of Gene Patents

There is a perception among some NGS industry leaders that the 2013 U.S. Supreme Court decision in *AMP v. Myriad* severely limited the ability to patent gene-related innovations. One leader interviewed shortly after *Myriad* summarized his view of the patent landscape as follows: “Gene patents are terrible for everybody except the few people who have them, so I’m glad those things are gone.” While it is true that naturally occurring DNA sequences are no longer patentable, patent law may still impinge on the NGS pipeline in important ways.

Myriad concerned a threshold question of patentability of an invention: whether the invention covers eligible subject matter.⁷ According to patent doctrine, laws of nature, abstract ideas, and natural phenomena are not eligible for patenting.⁸ In *Myriad*, the Court held that isolated DNA—i.e., nucleotide sequences identical to those found in nature—is an ineligible product of nature, although cDNA and other non-naturally occurring biological compositions remain patentable.² The Court also determined in *Mayo v. Prometheus* that methods for calibrating drug dosage in response to metabolite levels cover a natural law and so are invalid.⁹ Most recently, in *Ariosa v. Sequenom*, the U.S. Court of Appeals for the Federal Circuit, the intermediate appellate court that resolves all patent cases, held that the process of diagnosing fetal characteristics based on amplified cfDNA covers an ineligible natural phenomenon.¹⁰ Some commentators believe the test for patentable subject matter has become too restrictive and that *Sequenom* may present an opportunity for the Court to relax that test (<http://www.patentdocs.org/2015/06/ariosa-diagnostics-inc-v-sequenom-inc-fed-cir-2015.html>).

In the meantime, though, it would be a mistake to assume that these decisions spell the end of patents in the NGS industry. The law on subject matter eligibility is far from settled, and the pendulum may soon swing in favor of broadened eligibility. In any event, there is much left to be patented in genomics. According to the courts and Patent Office, these include cDNA and other sequences markedly different from those occurring in nature, labeled DNA probes, host cells transformed by DNA, and associated bioinformatics tools and methods involving non-generic computers and directed at performing non-generic computer functions.^{11,12,13} Meanwhile, patent attorneys are developing strategies to “draft around”

Myriad and related cases to ensure that their clients' patents will withstand scrutiny going forward.¹⁴ Finally, it should be noted that neither the courts nor the Patent Office can “extinguish” categories of patents. The Patent Office can only issue, and the courts and the Patent Office can only invalidate, specific patents that are the subject of specific proceedings over which they preside. Even a so-called “gene patent” whose subject matter eligibility is doubtful in the wake of recent court decisions continues to be valid until held otherwise. If there is any room for a patent attorney to reframe a patent and effectively “argue around” the case law, one should think carefully before drawing negative conclusions about its validity.

In sum, reports of the death of patents in the NGS industry are exaggerated—or at least premature.

Issue 2: Mass Infringement

Another misunderstanding is that patentees cannot or do not sue multiple infringers as a legal or practical matter. One leader explained his view of the role of intellectual property in NGS diagnostics as follows: “I really don’t think [that patents will] be a deterrent, because if everyone starts to do it, I really don’t think there’s any way around that, to stop them.” The interviewee concluded that “companies won’t be able to sue every single lab that reports on their [patented] gene.” However, mass infringement does not make it less likely that a patentee will sue multiple defendants, and in fact it may make the patentee more likely to do so since it increases the potential recovery.

There is no legal limit to the number of defendants a patentee can sue for infringement, and before the enactment of the AIA, there were also few practical limits because patentees were allowed to sue multiple defendants in the same lawsuit. In 2011, the AIA made it more difficult to join unrelated defendants,¹⁵ but the law did not affect patentees’ right to request consolidation of multiple lawsuits to conduct pretrial proceedings. Consequently, patentees are increasingly taking advantage of this mechanism to reduce the cost of suing multiple defendants. For example, the Judicial Panel on Multi-District Litigation, the judicial body that determines whether cases filed in different districts may be consolidated for pretrial purposes, both considered and granted more requests for consolidation of patent cases in the two years following the AIA’s enactment than in the two years preceding it.¹⁶ In a lawsuit relevant to the NGS industry, following the U.S. Supreme Court’s decision, the Judicial Panel granted *Myriad*’s request to consolidate five lawsuits filed against five unrelated defendants in three different districts (<http://www.patentdocs.org/2014/03/panel-on-multidistrict-litigation-consolidates-myriad-cases-in-utah-district-court.html>).

Although patentees of genomic innovations may decline to file suit against certain defendants for political or other reasons,¹⁷ mass infringement does not impact their right to file suit. Patentees can and do sue multiple defendants, and they are sometimes able to do so at a reasonable cost by consolidating cases for pretrial procedures.

Issue 3: “Excusable” Infringement

The most common misperception of patent law voiced by our interviewees was that some infringement activities are excusable. For example, one interviewee defended patent

infringement in a context where “I’m not really stealing your business” and patients might “drop dead” without access to the patented technology. Another interviewee described a general view that infringement is justified where it is an unintended byproduct of other activities. In the case of the (since invalidated) patented BRCA sequences, for example, “[T]here’s some people that think, ‘Okay, if I do an exome and I happened to sequence through—for example, BRCA—that’s okay. I wasn’t targeting it. I just sorta’ found it along the way.’”

Because direct patent infringement is a strict liability tort, however, one’s intentions in infringing a patent, however virtuous, are simply irrelevant. That the infringement is for a non-commercial purpose is also irrelevant. (In this respect, patent law differs from copyright law, which excuses some non-commercial uses under the fair use doctrine.) Although there is an experimental use defense to infringement, it applies only where infringement is for non-commercial purposes such as satisfying a curiosity or for amusement.¹⁸ The Hatch-Waxman Act provides another narrow defense for experimental uses to obtain regulatory approval of a drug or medical device.¹⁹ It is unlikely that either defense will be relevant in the majority of circumstances involving infringement of patents in the NGS industry. Further, while patentees cannot obtain damages from medical practitioners whose medical activities constitute patent infringement, the universe of exempt activities is limited.²⁰ Practitioners remain liable for damages where, for instance, they use patented machines or biological compositions during medical procedures.

Not only are intent and financial impact irrelevant to a charge of infringement, but knowledge of the patent itself is also irrelevant. That is, one can be guilty of infringing a patent about which the person is completely ignorant. (This is, again, in contrast to copyright law, which excuses acts of independent creation.) Moreover, if one becomes aware that her actions likely infringe a patent and recklessly continues the infringement, she can become liable for up to three times the damages amount ultimately awarded to the patentee.²¹

Although some patent infringers in the NGS industry may feel morally justified in their actions, they will almost never be legally justified, and known and continued infringement will only increase their liability. It is therefore important that NGS professionals understand that when it comes to patent infringement, the general rule is: “no excuses.”

Issue 4: “Modest” Innovation

There is a notion among some NGS leaders that only pioneering innovations representing major advances over the existing technology are deserving of patent protection. One interviewee summarized this opinion as follows: “I think, when you really invent something, if there is a process that’s really unique and ... you can show that it’s different from anything else ... you know what? That’s okay. Not the [patent] cases that we are seeing. The case[s] that we are seeing, it’s really absurd.”

If a patent covers eligible subject matter, the next step in assessing its patentability is determining whether the invention is both new and not obvious as compared to the existing technology.²² Novelty and nonobviousness analyses involve an examination of the

innovation in light of the state of the technological art and industry knowledge. Despite the typically complicated nature of this examination, the Patent Office's and courts' application of the relevant standards tends to be more generous than some industry members might expect or prefer. Indeed, the following inventions are routinely held sufficiently novel and nonobvious to meet patenting requirements: a minor improvement over the state of the art; a new combination of known elements or steps; a new use for a known thing; and an invention that required minimal time, effort, skill, or resources to develop.

It may seem “absurd” to grant patents on such inventions, but precise identification of prior invention or knowledge will be necessary to convince the Patent Office and the courts that they are invalid.

Implications & Recommendations

Persistent confusion and controversy on these four issues of patent law have important implications for the NGS industry. Industry members may forego pursuing valuable patent protection of their innovations under the mistaken belief that these innovations are ineligible for patenting. Instead, they may choose to protect their innovations as trade secrets, thereby depriving other researchers of the opportunity to build on their discoveries. Legal misunderstanding can also expose participants in the NGS pipeline to liability. Those who assume that all gene-related patents are invalid, that their good intentions excuse patent infringement, that patentees cannot or do not file suit against multiple infringers, or that patents on modest innovations cannot be valid are vulnerable to potentially devastating legal action.

Genomics leaders have made a compelling case for improving the genomic literacy of health care professionals and the public, and their arguments have resulted in promising educational initiatives.^{23,24,25} In 2013, for example, the National Human Genome Research Institute (NHGRI), in collaboration with other NIH institutes, professional societies, and organizations interested in physician education, formed the Inter-Society Coordinating Committee for Physician Education in Genomics to identify basic genomic competencies for physicians.²⁶ The educational framework developed by ISCC is one of hundreds of learning resources that are now disseminated on the NHGRI's Genetics/Genomics Competency Center (G2C2) website (<http://g-2-c-2.org>).

There is a consensus that legal information should be included in these educational outreach efforts. The ISCC, for instance, identifies awareness of laws and regulations relevant to genomic testing as a core competency.²⁶ By and large, however, the resources developed to promote this competency are focused on issues of privacy, consent, and discrimination. A review of the G2C2 website and a query of educational events produced by relevant professional organizations suggest that resources devoted to patent issues, by contrast, are sparse.

Likewise, there is a consensus that intellectual property law information should be included in responsible conduct of research (RCR) educational programs. For example, a Delphi panel of research integrity experts strongly supported including instruction on “ownership of

data, patents, copyrights, and intellectual property” in such programs—more so even than instruction on privacy issues. 27 However, a review of RCR digital depositories, including CTSpedia (<http://www.ctspedia.org/do/view/ResearchEthics/WebHome>) and the resources section of the Office of Research Integrity’s website (<http://www.ori.dhhs.gov/general-resources-0>), suggests that patent law is, in fact, infrequently addressed by RCR educators, and when it is, such instruction is rarely tailored to the specific needs and experiences of genomics researchers.

Although there are many potential sources of patent law information, including educational and decisionmaking tools developed and disseminated within institutions, the confusion and uncertainty about patent law expressed by our interviewees suggest that reliance on these resources alone may be insufficient. Given the consequences of continued misunderstanding, we urge the development of learning modules, webinars, and conference sessions devoted to helping NGS professionals navigate the patent issues relevant to their work. Importantly, we recommend that these resources provide instruction not only on recent patent law developments, but also more doctrinally stable concepts like patent infringement that are of great practical significance. We also suggest that resources be developed for and made available to NGS researchers in addition to providers and students, who are the typical target audience.

We recognize, however, that some confusion about patent laws relevant to the NGS industry will persist even if instruction on the subject is fully integrated into primary and continuing education curricula for NGS providers and researchers. In particular, the test of subject matter eligibility is not yet settled, and until it is, NGS-related innovation and patenting will be hampered by uncertainty. Prompt judicial or legislative resolution of this controversy will promote clarity and efficiency in genomic investment, research, and application.

As NGS innovations are rapidly translated for clinical use, the universe of both patentees and potential infringers is expanding. At the same time, the U.S. patent laws are undergoing significant change. It is therefore increasingly important that those working in the NGS pipeline understand the basic patent rights and obligations that attach to their professional activities.

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Table 1

Patent Law Concepts Prone to Confusion and Controversy	Issue	Practical Consequences of Confusion and Controversy
What innovations can be patented?	1, 4	Misjudge the validity and enforceability of competitors' and one's own patents. Misjudge the patenting potential of innovations.
What actions constitute patent infringement?	2, 3	Misjudge competitors' and one's own legal liability.
Under what circumstances are patents enforced?	2	Miscalculate risk of patent being enforced.
What is the penalty for patent infringement?	3	Miscalculate potential damages award that can be assessed.