The Effects of *Myriad* and *Mayo* on Molecular-Test Development in the United States and Europe: Interviews from the Frontline

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**ABSTRACT**

US Supreme Court decisions in Mayo Collaborative Services v. Prometheus Laboratories and Association for Molecular Pathology v. Myriad Genetics Inc. caused US and European law on what is patentable subject matter to diverge significantly. Both cases related to molecular tests and changed decades of patent practice. Whether the decisions adversely affect the development of molecular tests in the United States and Europe has been a matter of much speculation but limited empirical investigation. This interview-based study has three main findings. First, Myriad and Mayo have negatively affected the development of some molecular tests. Notably, half of the US university technology-transfer offices interviewed decided not to develop tests, and many other organizations have found the legal uncertainty following the cases problematic. Second, small “patent-precarious” organizations—those that rely heavily on patents for competitive advantages, such as technology-transfer offices—have been the most affected because patent protection is now often weaker and more difficult...
to obtain. Third, US-headquartered organizations have been more affected by 35 U.S.C. § 101 case law developments than European organizations, even though both types of organizations file for US patents. This Article refrains from advising law reform, however, because this study only focused on the adverse effects of the decisions and the positive effects remain unexamined.

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I. INTRODUCTION

Patents, which provide inventors with rights to stop others from practicing their invention for twenty years, are commonly justified on the ground that they incentivize research, development, and disclosure of technological breakthroughs. However, two recent US Supreme Court decisions cast doubt on patents’ ability to fulfill these functions for molecular tests.

Molecular tests check for various chemical compounds, such as DNA or proteins, that are linked to diseases. Failure to incentivize new tests is a serious issue for medicine because much of the field pivots on results from these tests. It is also a serious issue for the emerging field of precision medicine, which is trying to better tailor medicine to individuals. A core component of precision medicine is providing new and better molecular tests that help prevent, detect, diagnose, provide prognoses, and treat diseases.

These two decisions restricted the subject matter that is eligible for patent protection, a topic commonly known as “patent eligibility,” “patentable subject matter,” or “35 U.S.C. § 101.” Association for Molecular Pathology v. Myriad Genetics, Inc. ended the US Patent and

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4. 35 U.S.C. § 101 (2018). Patentable subject matter is only one of several criteria that must be satisfied for a patent application to be granted. An invention must also be, for example, novel and nonobvious. See §§ 102, 103.

Trademark Office (USPTO) practice of granting patents on isolated genomic DNA, and Mayo Collaborative Services v. Prometheus Laboratories, Inc. ended the USPTO’s practice of granting patents on medical relationships between molecules and health outcomes when implemented using conventional scientific techniques.

The new patent-eligibility standards in the United States diverge significantly from those around the world. One prominent commentator argues the changes heralded by Myriad and Mayo are so significant that molecular tests are no longer patent eligible in the United States, and another asserts that the decisions threaten the next generation of tests. Indeed, in 2019, upon reviewing all relevant decisions, the US Court of Appeals for the Federal Circuit concluded that “[s]ince Mayo, we have held every single diagnostic claim in every case before us ineligible.”

Concerns surrounding the patentability of molecular tests in the United States have led several organizations to lobby for changes to 35 U.S.C. § 101. The current director of the USPTO and a previous acting

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8. See id. at 79–82.
10. Rebecca S. Eisenberg, Diagnostics Need Not Apply, 21 B.U. J. SCI. & TECH. L. 256, 286 (2015). Eisenberg actually states that “diagnostic technology is not patent-eligible.” Id. (emphasis added). One could argue that Eisenberg’s quote is inapt (to this Article) because molecular tests are different from diagnostic technology. However, since molecular tests are a subset of diagnostics, her reference is appropriate. One could also argue that this Article makes a broader claim than Eisenberg, as molecular tests is a broader category than diagnostics because it includes, among other things, prognostic tests—something Eisenberg did not specifically refer to. However, it is very common in the industry to use the term “diagnostic tests” when discussing prognostic tests, and, indeed, this is exactly what Eisenberg did. Id. at 260.
director are generally supportive of such efforts, and this reform is now on several senators’ agendas. That said, other commentators argue that Myriad and Mayo strengthen patent policy because they “[weed] out overly broad patents” by requiring that applicants claim a specific and inventive way of achieving a result, rather than just the result. Their position closely aligns with the rationale offered by the Supreme Court—namely, that patents on medical relationships and isolated DNA risk tying up the tools of future innovation due to their broad scope.

Myriad and Mayo have been the subject of much academic commentary, but researchers have yet to study if and how the cases affect the development of molecular tests. Scholars have analyzed the jurisprudence and history of the decisions, as well as how the judicial decisions interact with other US laws that affect the development of molecular tests. Likewise, other scholars have empirically evaluated how the decisions affect many aspects of patent practice, including

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These studies provide important macrolevel perspectives, but microlevel data on how the cases affect business decisions surrounding the development of tests are needed in order to see if and how the cases actually affect the development of new molecular tests.

This Article’s study conducted thirty-seven semistructured interviews with participants from the United States and Europe. The divergence in US and European patent law provides a natural experiment, enabling an examination of how different patent-eligibility criteria affect the development of molecular tests. Interviews were conducted with executives at molecular-test companies, managers in technology-transfer offices at research institutes, and patent practitioners. The interviews explored how patent prosecution has changed, whether the cases have created problematic levels of uncertainty, and whether development strategies have changed on either or both sides of the North Atlantic.

This Article is organized as follows. Part II provides a more detailed background to the study, including an overview of the relevant US and European law and the research questions pursued in this Article. Part III describes the methodological features of the study. Part IV reports the interview data. Part V distills the interview data to their most valuable components, drawing conclusions on the effects of the cases.


21. The exact title of the technology-transfer office interviewees differed, but all interviewees’ roles involved managing molecular-test technology and intellectual property. Not all research institution–based organizations involved in the transfer and commercialization of technology identify as “technology-transfer offices.” The term is, however, in wide use and serves as a useful label for the activities on which this study focuses.
II. LEGAL BACKGROUND

A. Myriad

The key holding in *Myriad* was that *isolated* genomic DNA from the human BRCA1 and BRCA2 genes are not patentable subject matter. The term “isolated” refers to DNA that has been removed from the rest of the genome. Naturally occurring variants in the BRCA1 and BRCA2 DNA sequences correlate with patients’ risk of developing cancers, and physicians can use the presence or absence of the variants during diagnosis and prognosis. The Supreme Court has long held that exceptions exist to what is patent eligible, and *Myriad* concerned the judicially created exception for “products of nature.” The Court’s justification for this exception is that products of nature are the “basic tools of scientific and technological work”; therefore, granting patents on them risks tying up the tools of future innovation.

To determine whether Myriad’s claims were patent-eligible products of nature, the Court applied the “markedly different characteristics” test. Pursuant to this test, which was derived from earlier cases including *Diamond v. Chakrabarty*, a nature-based product claim is patent eligible if it has characteristics that differ markedly from naturally occurring products. The Court found that isolated DNA molecules do not exist in nature per se (in the sense that they were man-made), but the Court held that merely separating the DNA from its surrounding genetic material did not make it markedly different from naturally occurring DNA. Consequently, Myriad’s claims to isolated forms of the BRCA gene were ineligible for patent protection.

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22. *Myriad* was decided after *Mayo*; however, this Article discusses *Myriad* first due to the issues it considered and its likely higher familiarity among readers.
24. *See id.* at 596.
25. *Id.* at 582–83.
26. *See id.*
27. *Id.* at 589–90 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)).
29. *Id.* at 590–91 (quoting *Diamond*, 447 U.S. at 310).
32. *See id.* at 593.
33. *Id.* at 591–93.
34. *Id.* at 596.
The Court reached a different conclusion in relation to complementary DNA (cDNA).\(^\text{35}\) Scientists produce cDNA artificially by working with an RNA template. RNA is an intermediary molecule between DNA and the protein it encodes.\(^\text{36}\) cDNA is thus an artificially synthesized DNA strand based on an RNA sequence of interest. The resulting cDNA is similar to genomic DNA, but cDNA lacks intervening sequences of DNA that punctuate long segments of genomic DNA and do not code for proteins.\(^\text{37}\) The Court held that cDNA claims were nature based but markedly different from naturally occurring DNA.

Immediately after Myriad, some commentators thought that the decision would apply to isolated DNA claims only.\(^\text{38}\) This would have meant that the decision affected a relatively small range of inventions on molecules derived from nature. However, it is now clear that the decision applies beyond isolated DNA. One study proved this by analyzing how frequently USPTO patent examiners cite the decision. They found that in 85 percent of the cases where USPTO examiners cite Myriad to reject patent claims, the examiners applied the case to subject matter other than isolated DNA.\(^\text{39}\) This subject matter included peptides, proteins, antibodies, cells, and pharmaceutical compositions.

**B. Mayo**

*Mayo* held that methods to optimize dosages of thiopurine drugs for treating autoimmune diseases such as Crohn’s disease were not patentable.\(^\text{40}\) Patients metabolize drugs at different rates. The idea underlying the patent for these methods was that medical professionals could tailor the dosage to the individual’s rate of metabolism by measuring a metabolite, a compound formed during metabolism of the drug.\(^\text{41}\) Tailoring the dosage of thiopurine drugs is important because a low dosage is ineffective and a high dosage can cause harmful side effects.\(^\text{42}\)

\(^{35}\) Id. at 576.

\(^{36}\) Id. at 581–82.

\(^{37}\) Id. at 582.


\(^{39}\) Surgical Strike, supra note 20, at 1147–48.


\(^{41}\) Id. at 73–74.

\(^{42}\) Id.
The Mayo decision concerned the judicially created exception that “laws of nature” and “natural phenomena” are patent ineligible.\textsuperscript{43} The justification for this exception is similar to the justification for the “products of nature” exception from Myriad: granting such patents may “preempt” future inventions due to their broad scope.\textsuperscript{44} However, all valid patent claims, to some degree, incorporate laws of nature;\textsuperscript{45} and the Court stated that claims applying natural laws can be patent eligible if they “contain other elements or a combination of elements . . . sufficient to ensure that the patent in practice amounts to \textit{significantly more} than a patent upon the natural law itself.”\textsuperscript{46} In the subsequent Supreme Court decision \textit{Alice Corp. v. CLS Bank International},\textsuperscript{47} which concerned a patent for computer-implemented business transactions,\textsuperscript{48} the Court helpfully distilled its reasoning in Mayo into a two-step test: (i) determine whether a claim is directed to a patent-ineligible concept (e.g., natural laws or natural phenomena); and (ii) if so, determine whether any additional features of the claim (either individually or in combination) transform it into eligible subject matter by claiming significantly more than ineligible subject matter.\textsuperscript{49}

In Mayo, the Court held that the dosage-optimizing claims were directed to a natural law, stating that the correlation “is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes.”\textsuperscript{50} The Court then considered whether the claims contained “significantly more.”\textsuperscript{51} The claims included the steps of administering the drug and determining metabolite levels;\textsuperscript{52} however, the Court found these steps were “not sufficient to transform unpatentable natural correlations”\textsuperscript{53} into patent-eligible claims because they were “well-understood, routine, conventional activit[ies] previously engaged in by scientists who work in the field.”\textsuperscript{54}

\textsuperscript{43} \textit{Id.} at 70–71. The Court reviewed the controlling precedents on this topic. \textit{See id.} at 80–87.
\textsuperscript{44} \textit{Id.} at 71–73.
\textsuperscript{45} \textit{Id.} at 71.
\textsuperscript{46} \textit{Id.} at 72–73 (emphasis added).
\textsuperscript{47} \textit{Alice Corp. Pty. v. CLS Bank Int'l}, 573 U.S. 208 (2014).
\textsuperscript{48} \textit{Id.} at 212.
\textsuperscript{49} \textit{Id.} at 217.
\textsuperscript{50} \textit{Mayo}, 566 U.S. at 77.
\textsuperscript{51} \textit{Id.} at 79.
\textsuperscript{52} \textit{Id.} at 78–79.
\textsuperscript{53} \textit{Id.} at 80.
\textsuperscript{54} \textit{Id.} at 73. For convenience, this Article refers to “well-understood, routine, conventional activities” as “conventional activities.”
Various courts have applied *Myriad* and *Mayo* to invalidate patent claims that protect specific molecular tests. In addition, courts have applied *Mayo* to invalidate molecular-test platform technology that detects DNA. Platform technology refers to technology that has multiple applications (e.g., can be used to perform multiple molecular tests). In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, the Federal Circuit found the foundational patent for noninvasive prenatal testing (NIPT) invalid. NIPT is a technique that allows medical professionals to genetically test fetuses by drawing blood from a pregnant woman. The technology relies on sequencing cell-free fetal DNA (cffDNA), which exists naturally in maternal blood. The claims in *Sequenom* included the steps of obtaining a blood sample from a pregnant woman and sequencing cffDNA, but the Federal Circuit held the patent invalid because it covered the natural phenomenon of cffDNA and did so using conventional techniques.

Although *Myriad* and *Mayo* cast doubt on the validity of patent claims protecting various types of molecular tests and platforms, they do not cast doubt on patents for “companion tests,” which are often but not always a subtype of molecular tests. These tests are, in short, necessary for the safe and effective use of a corresponding drug. They provide information such as dosage or whether a specific patient will respond to a drug. Since *Mayo*, the USPTO has treated claims for companion tests as patent eligible so long as the use of the drug is unconventional or if all the steps in the claim amount to more than merely “diagnosing a patient . . . and instructing a doctor to generically

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55. *See, e.g., Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC*, 927 F.3d 1333, 1350 (Fed. Cir. 2019); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 760 F. App’x 1013, 1016–18 (Fed. Cir. 2019); *Roche Molecular Sys., Inc. v. Cepheid*, 905 F.3d 1363, 1372 (Fed. Cir. 2018); *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1356, 1362 (Fed. Cir. 2017); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 762–65 (Fed. Cir. 2014); *PerkinElmer, Inc. v. Intema Ltd.*, 496 F. App’x 65, 69–73 (Fed. Cir. 2012). It should also be noted that in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test* and *PerkinElmer* the courts invoked the “abstract idea” or “abstract mental process” exceptions to patent eligibility, also described in *Mayo*. *See, e.g., Mayo*, 566 U.S. at 70–71, 82; *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*, 774 F.3d at 763–64; *PerkinElmer*, 496 F. App’x at 68. As reviewed by Rebecca Eisenberg, these exceptions operate in a similar manner for molecular tests as the “product of nature” and “natural laws” exceptions but may operate in different ways for drug-orientated claims. See Eisenberg, *supra* note 10, at 271–74.


57. Id. at 1373, 1376; *see also* Martin & Vines, *supra* note 11, at 438–39.

‘treat it.’” In 2018, the Federal Circuit in *Vanda Pharmaceuticals, Inc. v. West-Ward Pharmaceuticals International Ltd.* made the § 101 criteria of companion tests easier to meet. The Federal Circuit held that the particular method of treatment in *Vanda* was eligible. The reasoning in *Vanda* can be applied to companion tests. Briefly, a test is patent eligible if it is claimed as a method of treatment that incorporates a molecular test and administers a drug, even if the drug is already known to treat the medical indication. The court’s rationale was that a patent claim directed to a method of medical treatment is “not directed to” a natural law and therefore does not fail the first step of the *Mayo* two-step test.

This review of US case law shows how *Myriad* and *Mayo* altered US patent practice for molecular tests. Indeed, both *Myriad* and *Mayo* invalidated patent claims for molecular tests. On the other hand, *Vanda* shows that companion tests incorporating a molecular test are patentable subject matter. As a result, this Article’s study focused on molecular tests but excluded companion tests. The next Section contrasts US patent law against European law.

**C. European Law**

European law permits a broader range of subject matter to be patented than US law. This includes a wider variety of products derived from nature, such as isolated DNA, and methods of in vitro detection and diagnosis based on natural laws and phenomena (i.e., medical correlations). As such, US and European laws have diverged significantly.

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61. See Vanda Pharm., 887 F.3d at 1135–36; see also Memorandum from Robert W. Bahr, supra note 60, at 2.


63. See generally Nicol et al., supra note 6, at 532.

64. Id. at 533. For a detailed explanation of the differences between US and European law, see Mateo Aboy et al., *How Does Emerging Patent Case Law in the US and Europe Affect Precision Medicine?*, 37 *Nature Biotechnology* 1118 (2019) and Nicol et al., supra note 6, at 529–33. Nicol et al. show that, as a result of *Myriad* and *Mayo*, US patent law has diverged
The core requirement for patent eligibility under the European Patent Convention (EPC) is that the claim involves “technical character.” The European Patent Office (EPO) examines EPC patents and also decides “oppositions” that third parties raise against the grant of these patents, while domestic courts determine infringement and revocation disputes. The EPC’s implementing rules, which are consistent with the EU Directive on the Legal Protection of Biotechnological Inventions, state that “biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature” is patent eligible. The EPO has granted many isolated DNA patents on this basis, and the highest patent court in Germany, the Bundesgerichtshof, has confirmed their eligibility.

significant from European patent law, as well as from many other patent laws around the world. See Nicol et al., supra note 6, at 529–33. However, one notable difference to this divergence is Australian patent law, which excludes isolated DNA and cDNA. See D’Arcy v Myriad Genetics Inc. (2015) 258 CLR 334; Nicol et al., supra note 6, at 531. Aboy et al. confirm significant differences continue to exist between US and European law on the eligibility of biomarkers and medical correlations, despite guidance from the European Patent Office and USPTO at the end of 2018 and early 2019 that converged other areas of the law, including claims incorporating algorithms. See Aboy et al., supra, at 1125.


European Patent Convention, supra note 65, arts. 64, 94, 99, 138. For a brief overview, see Nicol et al., supra note 6, at 525.


See, e.g., Case T 0666/05, Univ. of Utah Research Found. v. Institut Curie, ¶¶ 74–76, at 43 (EPO Boards of Appeal, 2008); Case T 0272/95 Howard Florey Inst. Of Experimental Physiology and Medicine v. Aglietta, ¶¶ 6–9, at 10–11 (EPO Boards of Appeal, 2002).

European law is also generous with respect to natural correlations, methods of detection, and methods of in vitro diagnosis. All of these claims are patent eligible provided something in the claim confers technical character. On molecular-test methods and the application of natural correlations, the Bundesgerichtshof in Rezeptortyrosinkinase (Receptor Tyrosine Kinase) held that a method claim for detecting a genomic variant, which correlated with an acute form of leukemia, was patentable subject matter. The court reached this conclusion because the method included isolating DNA and other technical processes. In reaching its decision, the Bundesgerichtshof also noted that, unlike US law under Mayo, European and German patent law do not require an “inventive surplus” or significantly more for the application of a natural law to be patent eligible.

The UK High Court of Justice reached a similar outcome for broad method of detection (essentially a platform technology) patent claims in Illumina, Inc. v. Premaitha Health PLC. The case considered several NIPT patents, including the European equivalent of the patent litigated in Sequenom. The claims were patent eligible (although several were invalidated for other reasons) because they included creation of analytic samples and detection of cfDNA—steps that do not occur in the natural world and are technical in nature.


Id.

Id.


D. Predictions and Controversies

This Section describes the leading commentary, predictions, and empirical studies analyzing the differences between US and European law.

In the aftermath of *Myriad* and *Mayo*, a senior commentator stated that molecular tests are “not patent eligible” in the United States.78 This prediction remains untested, but empirical studies have evaluated other effects. For instance, several studies have assessed how *Myriad* and *Mayo* have affected general aspects of patent practice in the United States. With regard to patents granted before the decisions, researchers have found that tens of thousands of patents are now at risk of invalidation.79 And for patents prosecuted after the decisions, research indicates that the USPTO has issued thousands of office actions with 35 U.S.C. § 101 rejections, citing *Myriad* and *Mayo*.80 Applicants have opportunities to overcome rejections, and many do; the data indicate, though, that patent-eligibility rules in *Myriad* and *Mayo* result in claims with narrower scope.81

Studies of USPTO patent examination and prosecution also show that a high proportion of applicants are abandoning applications with *Myriad*-related claims82 and that applications that receive *Mayo*-based rejections spend much longer in prosecution (compared with claims that do not receive a *Mayo*-based rejection).83 Scholars suggest that high rates of abandonment and long prosecution times indicate there is a high level of uncertainty surrounding the cases—in particular, uncertainty regarding how to draft patent-eligible claims.84 A USPTO report, which elicited view from the public on § 101 law, reinforces this argument. The report details how practitioners have found the law “unworkable,” creating excessive “unpredictability in the [granting of] patents.”85

78. Eisenberg, *supra* note 10, at 286.
80. *Mayo’s Impact*, *supra* note 20, at 515; *Surgical Strike*, *supra* note 20, at 1147.
82. *After Myriad*, *supra* note 20, at 822; *Surgical Strike*, *supra* note 20, at 1147.
Several commentators argue that *Myriad* and *Mayo* negatively affect the development and commercialization of molecular tests. Their arguments are based on three reasons. First, patents are a useful instrument for coordinating multiple parties with complementary development skills, including marketers and scientific experts. Patents have this effect because “parties know that only those who strike deals with each other involving the patent can avoid being excluded by the patent in court.” Second, molecular tests are often easy to imitate and produce at a lower price than the original developer. Such imitating is often called “free riding” and is more likely to arise in the United States under *Myriad* and *Mayo* because patents have a narrower scope or are unavailable. Third, substantial investment, often funded by venture capitalists (VCs), is needed to develop and validate tests, and the weakening of patent protection for molecular tests will inevitably cause VCs to shift their investments to other sectors of the economy that they know have more robust patent protection.

In contrast, some question the need for patent protection. Between 2009 and 2010, the US Secretary’s Advisory Committee on Genetics, Health, and Society studied the role of patents in the development of genetic tests. The committee “concluded that patent-derived exclusive rights are neither necessary nor

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86. James E. Daily & F. Scott Kieff, *Anything Under the Sun Made by Humans: Patent Law Doctrines as Endogenous Institutions for Commercializing Innovation*, 62 EMORY L.J. 967, 980 (2013). The authors do not specifically discuss molecular tests, referring instead to “biotechnology.” However, it is quite clear that their analysis included it. For example, the authors discuss how *Mayo* affected *Myriad Genetics, Inc.* See id. at 978–80. It should also be noted that the authors published this article before *Myriad* was decided, meaning that they could not have considered the Supreme Court’s decision. The authors’ thesis in the article, however, makes it quite clear that they would have opposed the decision. See also Kieff, supra note 1, at 724–27.


88. Daily & Kieff, supra note 86, at 973.

89. *Id.* at 973, 980; see also Kieff, supra note 1, at 742, 747–48.

90. Holman, *supra* note 11, at 308.

91. *Id.*; see also Sanzo, *supra* note 11, at 20. Given Eisenberg stated that tests are not patent eligible, one might expect that she would then predict various specific harms to the development of tests. Interestingly, she didn’t. Rather, she “hope[d]” that the cases will do more to enhance test development than to suppress it. Eisenberg, *supra* note 10, at 286.

sufficient conditions for the development of genetic test kits and laboratory-developed tests."93 By “test kit,” the committee was referring to commercial products made for sale to multiple laboratories.94 Kits often include generic scientific materials (e.g., test tubes) as well as test-specific reagents (e.g., DNA test panels, software). However, this conclusion was based on estimated development costs of around $10,000,95 an unrealistically low assumption given that diagnostic executives estimate the cost to fully develop a test, including clinical education, between $20.1 and $106 million in the United States alone.96 That said, several factors do indicate that patent protection may not be important for development. For example, (i) developing molecular tests costs considerably less than developing pharmaceutical drugs;97 (ii) multinationals are increasingly supportive of open-science initiatives for genomics research;98 and (iii) patent holders often do not pay maintenance fees, meaning their rights lapse and become part of the public domain before the full twenty years of patent life is realized.99

Other commentators have different predictions about how Myriad and Mayo could affect test development. Some argue that innovators would turn to trade secret protection instead of patents,100

93. Id. at 35.
94. Id. at 12.
95. Id. at 94.
with the negative effect that innovations would be kept from society.\textsuperscript{101} One study explored this prediction by interviewing patent practitioners, legal academics, and scientists involved with genetic technology.\textsuperscript{102} It found increased interest in trade secrets but no instances of parties using trade secrets instead of patents.\textsuperscript{103} That said, the study interviewed people who might advise others to rely on trade secrets, not those who would actually make the decision.\textsuperscript{104}

The divergence between US and European patent-eligibility law led some commentators to question whether there would be ripple effects for Europe.\textsuperscript{105} Would European organizations be advantaged by the more generous European patentable subject-matter laws? Most commentators predicted that the effect, if any, would be negligible.\textsuperscript{106} The reasoning here was that US patent law applies equally to US and European organizations and that the United States is likely the most lucrative market for most tests.

This Section describes the leading commentary, predictions, and empirical studies analyzing the differences between US and European law. In particular, this Section focuses on commentators’ predictions of how Myriad and Mayo would adversely affect the development of molecular tests. These predictions build on orthodox justifications for patents and suggest that test developers now avoid developing tests due to narrower scope of protection and increased uncertainty that patents are valid.

III. RESEARCH QUESTIONS AND METHODS

This Part describes the research questions and methods in this Article. The research questions build on the predictions in the previous Section, and the methods primarily concern how the interviews were arranged and conducted.

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\textsuperscript{101} Anna B. Laakmann, \textit{The New Genomic Semicommons}, 5 U.C. IRVINE L. REV. 1001, 1013–16 (2015); Noonan, supra note 100; see also Robert Cook-Deegan et al., \textit{The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets?}, 21 EUR. J. HUM. GENETICS 585, 585 (2013).
\textsuperscript{103} \textit{Id.} at 553.
\textsuperscript{104} \textit{Id.} at 562.
\textsuperscript{105} LIDDELL, \textit{supra} note 98, at 6–7; Nicol et al., \textit{supra} note 6, at 535.
\textsuperscript{106} LIDDELL, \textit{supra} note 98, at 6–7.
\end{flushleft}
A. Research Questions

This Article’s study set out to explore whether any of the negative effects and consequences predicted by the commentators were evident in the development of molecular tests. The study also explored whether the effects were felt equally by US- and European-headquartered organizations.

Each interview was semistructured, meaning they were organized around a series of questions that permitted in-depth exploration of the various issues under research:

1. What role do patents and other intellectual property (IP) play in the development of molecular tests?
2. How (if at all) have patent prosecution strategies changed after Myriad and Mayo?
3. Does Myriad or Mayo create problematic uncertainty?
4. In what ways (if any) have developmental strategies altered due to Myriad and Mayo?
5. Does Myriad or Mayo create a disadvantage for US-headquartered organizations compared with European counterparts?

B. Methods

This study was designed to complement the results of previous empirical studies, which analyzed the impact of Myriad and Mayo at the macro level, by conducting semistructured interviews at the micro or organizational level. Semistructured interviews, which do not follow a rigorous set of questions but do cover the same set of topics with each interviewee, permit deep analyses of issues and flexibility based on interviewees’ responses. Thus, semistructured interview-based research is particularly useful in obtaining complex information about experiences and decision-making, especially from individuals who share similar interests and respond to the same events.107 Indeed, interview-based research, notwithstanding small sample sizes, has some advantages over other empirical methods, such as surveys, because it can identify and obtain context-rich data to explain previously unknown responses.108 These attributes of interview-based

research are particularly important in the molecular-test industry, where little is known about how organizations use patents in their development strategies and the development of tests can be complex.

C. Interviewee Inclusion Criteria and Characteristics

This Section gives an overview of the people that were interviewed, including the criteria that were used to determine if someone should be interviewed.

Three different categories of industry participants were interviewed: patent practitioners, executives at molecular-test companies, and technology-transfer office (TTO) managers at research institutes or universities. At least six interviews were conducted in each category in both the United States and Europe. Thirty-seven interviews were conducted in total.

Four interviews were conducted face-to-face and thirty-three were conducted via phone. Thirty-five interviewees agreed to have the interview recorded and transcribed. The other two interviewees agreed to have notes taken during the interview, which were supplemented immediately after the interview. The interviews were coded using NVivo 11 for Mac, according to the research questions, in order to perform thematic analysis, which refers to analyzing the data to find patterns and themes in responses to the questions, as well as latent content analysis, which looks to draw greater meaning from the interviews by combining responses from different questions.

Recruitment began in February 2017, and the last interview was conducted in July 2018. This seventeen-month period was primarily due to protracted recruitment of companies. Making contact with them was challenging, especially in the United States where contact details for potential interviewees are infrequently published online. Before any individual was invited to participate, their profile was checked to ensure they dealt with molecular-test technology and IP. No

109. See Ashish Arora & Suma Athreye, Introduction to the Special Section on Patent Use, 45 RES. POL’Y 1323, 1323 (2016). Some of the better explorations of how patents fit into organizations’ development strategies have been performed by the US Department of Health and Human Services. See SEC’YS ADVISORY COMM. ON GENETICS, supra note 92, at 20–35.


interviewee was offered an inducement to participate, and all were assured anonymity. All interviewees gave verbal consent to participate.

The average interview lasted forty-eight minutes, with a range of twenty-nine to seventy-six minutes. Although the interview times varied considerably, all topics were explored with each interviewee. Two reasons account for the range of interview times: (i) interviewees had varying experience with Mayo or Myriad, and (ii) interviewees engaged in discussion to varying degrees of detail.

Interviewee recruitment varied depending on the category. Patent practitioners were identified from lists of highly ranked practitioners.112 US practitioners were recruited from across the country, and European practitioners were recruited from the United Kingdom only. US practitioners included agents and attorneys, and UK practitioners included attorneys and solicitors. Interviewees with different training and different skills (e.g., drafting patents or drafting transactions) were included in order to ensure that all of the various issues at stake here were covered. All practitioners interviewed were partners except one who was an associate with seven years’ experience and was described by a partner as an expert in the field. All invitations to practitioners were sent via email.

Companies were recruited via online searches, attendee lists from conferences, and a specialized website.113 The companies interviewed were headquartered across Europe and the United States. The size of the companies interviewed varied: one company from the United States and one company from Europe identified as large; two from each territory identified as medium-sized; and the other companies identified as small. One small company in the United States and two from Europe had yet to launch a molecular test. All companies (from both territories) had at least one test they were developing that was “highly innovative” in the sense that it offered insights not currently available to medical practitioners and was based on new biomarkers or scientific techniques. Such tests would, for example, identify patients that would not benefit from surgery but are currently treated as patients that would.

TTOs were recruited only from leading biological science institutes, as indicated in research rankings (e.g., The Times Higher


Education World University Rankings). US TTOs were recruited from across the United States, and European TTO managers were recruited from the United Kingdom only, due to proximity and familiarity with English. All invitations to TTOs were sent via email.

IV. RESULTS: INTERVIEW DATA

This Part describes the results from the interviews, largely following the order of the research questions.\textsuperscript{114}

A. What Roles Do Patents and Other Intellectual Property Play in the Development of Molecular Tests?

To appreciate properly the importance of patents for molecular-test development (and therefore the implications of Myriad and Mayo), this Section begins by summarizing the responses on the technical and economic environment in which test developers operate. This Section then proceeds to describe how TTOs and companies use patents and other IP when developing molecular tests.

1. Background on Developing Molecular Tests

Companies and TTOs described developing tests as generally a high-risk proposition. No interviewee gave specific data on the chances of a new test making it to market, but they estimated a test had a worse chance of successfully reaching market than, for example, new mechanical equipment, but a better chance than a drug. Several companies also described how costs could vary substantially from $1 million to $150 million for the full development and launch of a test in multiple countries and could vary in duration from two to thirty years. These figures roughly align with the literature.\textsuperscript{115} They also explained that developing new molecular tests that rely on new biomarkers or new technical instruments is normally at the more expensive end of the spectrum. The novelty of the biomarker or instrument means that there is little scientific support at the outset; it must be generated.

\textsuperscript{114} Due to privacy concerns, the interviews cited in this Article are confidential. They remain on file with the Authors.

One company provided a relatively precise account of costs, based on the money it had raised for the development of a new test using a new platform. Overall, it had spent €130 million over ten years. Approximately 80 percent of that was spent on technical development, including clinical trials and scaled-up production. The remainder was spent on commercialization, including marketing, development of supply chains, and clinical education. On clinical education, the company commented that it is expensive and challenging to inform medical professionals about new tests and convince them to implement tests into their workflows, even with data showing the test is cost-effective and improves patient outcomes. Indeed, that company commented that it launched its product after five years of technical development but had continued to invest in work to demonstrate utility and to educate professionals.

The companies mentioned various other challenges surrounding the development of tests and their patent positions. Two challenges were described by every company, indicating common importance: regulation and reimbursement. In the United States, diagnostic kits are regulated by the Food and Drug Administration (FDA), and the regulatory challenges center on the data needed for FDA authorization (clearance or approval). Companies described various issues in obtaining authorization, including difficulties with clinical trial design and recruitment, not to mention results, which may or may not support authorization. Companies also described how it could take years to receive market authorization, especially in the case of technology and biomarkers unfamiliar to the FDA. This finding is echoed in the literature. European regulation for market authorization of molecular-test kits was considered a lower hurdle, although several companies said it could still pose a challenge because the regulator might ask for different data. They also said European regulation is set to change, with the In Vitro Diagnostic Medical Devices

116. See Ivanov, supra note 110, at e135.
117. The Authors did not interview people responsible for incorporating tests into medical practice. However, various sources describe the myriad concerns and evaluations that are often considered before a test is incorporated. See id.; Peeling et al., supra note 110; Steven M. Teutsch et al., The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: Methods of the EGAPP Working Group, 11 GENETICS MED. 3 (2009).
118. See Sackett & Haynes, supra note 110 (describing specific challenges at trials).
120. See MAKOWER ET AL., supra note 115, at 6; Kaplan et al., supra note 115, at 3071–72.
Regulation ushering in higher standards. Analysts suggest that under the earlier law the “majority” of test kits are self-certified, but under the new regime 80 percent will be reviewed by a regulator.

In many cases, the need for FDA clearance or approval can be avoided if companies choose to launch a laboratory-developed test (LDT) instead of a test kit. LDTs need to comply with less onerous clinical-laboratory laws. This means LDTs can generally be developed faster and cheaper than kits, but there are tradeoffs that may affect supply or demand. One tradeoff is that LDTs require a reference laboratory, where clients must send samples for processing. This might be inconvenient, or samples might degrade when they are sent to the reference laboratory for testing. Companies also described how LDTs typically have lower reimbursement rates, in part because the FDA has not reviewed them.

The respondents described reimbursement challenges as just as important, if not more important, than all other challenges. “Reimbursement” refers to the processes by which physicians and hospitals receive payments (usually from insurers) for the products and services they provide patients, such as molecular tests. Reimbursement determinations are made by private or public payors after analyzing clinical and economic data to determine the clinical value and effectiveness of a test. All companies with experience in US reimbursement determinations (five of six companies in the United States, and four of six in Europe) described them as complex and

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126. Id.
time-consuming, especially due to the different approaches for determining reimbursement. Companies noted that similar challenges were faced between European countries, due to different systems, and that some individual European countries presented US-like issues, but not on the same scale of complexity.

The molecular-test industry distinguishes between three types of data for molecular tests: (i) analytic validity, the ability to measure accurately and reliably the marker of interest; (ii) clinical validity, the strength of association between the biomarker(s) and the clinical outcome(s); and (iii) clinical utility, the effect the test has on patient management coupled with economic value. Companies noted that it was possible to launch tests in the United States and Europe without clinical-utility data and with no plans to produce any, thereby avoiding the cost and inconvenience of generating the data; but they advised that this was often not a prudent commercial decision, primarily because payors would be less willing to reimburse the test or only do so at a relatively low rate. All companies described how they conducted clinical trials and combined this data (or at least planned to) with economic analyses to produce clinical-utility data.

2. TTOs

TTOs stated unanimously that patents were core to their work. None aimed to launch a test themselves, and it was important to them to transfer the technology fairly early in its development to another organization either by licensing or assigning the technology. They described patents as core because they offered definable, exclusive, and transferable rights. Patents helped attract partners and VC funding for early development. Without patent protection, TTOs said they had little to offer in a deal because their researchers’ work would be

127. See id.
128. See Kaplan et al., supra note 115, at 3071–72.
129. Teutsch et al., supra note 117, at 6; Gold, supra note 125.
130. See generally Julia R. Trosman et al., Health Technology Assessment and Private Payers’ Coverage of Personalized Medicine, 7 J. ONC/OLOGY PRAC. 18s (2011); Gold, supra note 125. Similarly, FDA clearance does not guarantee clinical update either, especially without clinical-utility data. See Recommendations from the EGAPP Working Group: Testing for Cytochrome P450 Polymorphisms in Adults with Nonpsychotic Depression Treated with Selective Serotonin Reuptake Inhibitors, 9 GENETICS MED. 819 (2007).
Indeed, all TTOs thought that transferring test technology without a patent was unlikely.

TTOs also stated unanimously that they tended to avoid licensing strategies based on trade secret protection but did value know-how. The problem with licensing strategies based on trade secrets was that they could compromise researchers’ abilities to publish for the duration of the deal.\footnote{132} Know-how, which refers to practical knowledge or skill, is different because although researchers might not keep it a secret, the industry norm is not to write about it. Know-how can retain value because often only a few people know about it; examples included details of how to use a specific instrument or optimize an assay.\footnote{133}

TTOs discussed other types of IP but only occasionally identified them as valuable. For instance, copyright might sometimes play an important role, particularly if it protected compilations of data or algorithms. Generally, however, they said copyright conferred only a weak advantage because, as a matter of collaborative behavior, data were often shared and combined with other data without intending the use to be exclusive (especially in large research consortia) and, as a legal matter, copyright protection did not prevent similar algorithms being produced using the underlying ideas. Other forms of IP, including European database rights and trademarks, were briefly discussed but dismissed as generally not useful.

TTOs also discussed competitive advantages other than IP. Four TTOs describe how physical property could be important in deals. For example, they might have a reagent or instrument important for the molecular test that was known and used by their organization only or at most by a small number of other people worldwide. The TTOs acknowledged that other parties could probably make the property with a degree of effort, but given the TTOs’ existing expertise, the property could form a valuable competitive advantage. Other competitive advantages included scientific lead time and star scientists.\footnote{134} Without these, competitors would find it difficult to imitate tests. Star scientists with a track record of successful innovations added extra value.

\footnote{132} One TTO did describe licensing a test based on confidential data without a patent. They admitted, though, that this was the exception to the rule, and it arose as a concomitant of the research rather than a deliberate strategy.

\footnote{133} The importance of know-how (otherwise known as “tacit knowledge”) has been described elsewhere. See, e.g., Ashish Arora, Contracting for Tacit Knowledge: The Provision of Technical Services in Technology Licensing Contracts, 50 J. DEV. ECON. 233 (1996).

However, in all circumstances, the TTOs described how the value of these advantages varied and were not necessary for a deal.

The core nature of patents prompted discussions about patent prosecution strategies. The TTOs used slightly differing strategies but also shared some common elements. All TTOs preferred to transfer technology as early as possible in the patent’s lifecycle. One TTO said they preferred to license before a provisional application expired and before they had to make the more expensive full patent application, enabling them to pass on the patent filing costs. A number of TTOs described that they were generally happy to hold patents filed via the Patent Cooperation Treaty (PCT) until national-phase entry—that is, usually thirty months from the earliest priority date. The reason for this was that national-phase costs are significantly higher than those incurred when initially filing. Only two TTOs commented that they held patents longer than this on a regular basis without interest from a potential licensee.

One difference between US and European TTOs’ patenting strategies was the jurisdiction where protection was sought. All the US TTOs said they focused on the United States as their primary market and would always seek patent protection there. Five US TTOs added they would look at Europe as well as other territories (e.g., Canada, China, Japan, Australia) as secondary considerations. Obtaining foreign protection, however, depended on many variables, including

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135. A US practitioner stated that the practitioner knew of several TTOs that often used the date of a full application as a deadline for some projects. That is, if the test was not licensed by then, the TTOs’ role in developing the test would cease.


137. “National phase” is “the second of the two main phases of the PCT procedure. It follows the international phase and consists in the processing of the international application before each Office of or acting for a Contracting State that has been designated in the international application.” See Chapter 2: Entry into the National Phase (General), WIPO, https://www.wipo.int/pct/en/guide/nph02.html#_chapt2 [https://perma.cc/E9X7-ATTL] (last visited Mar. 23, 2020).


potential markets and potential licensees. The remaining TTOs stated they would consider patent protection outside the United States only if a licensee had shown interest in the test technology. All European TTOs, by contrast, stated that European and US patent protection were of similar importance. TTOs (in both territories) also stated there were exceptions to these strategies, such as when the test is specifically designed for use in developing countries. In general, however, European TTOs were likely to obtain both US and European patents as a top priority, whereas US TTOs would always obtain US protection and consider European patents (or patents elsewhere) as a secondary consideration.

TTOs described that their decisions on international patent protection were mostly determined by a sense of where profits could be made. Indeed, all interviewees, not just TTOs, commented that if a molecular test was launched around the world (or at least in the territories mentioned), US profits would be the most valuable, with sometimes half of the overall profit made there.

3. Companies

The companies interviewed were united in their view that patents were important for the development of molecular tests. None of them were developing a test without patent protection. However, they had different views on the role patents played, and they also relied on patents less than TTOs.

Companies often used patents in more than one role. The most common roles were that they could attract partners and investment (VC, private equity, or strategic investors). Eleven companies noted that patents were key for this function. Nine of these eleven companies also said that patents blocked, or potentially blocked, competitors from entering their markets and that the exclusive rights provided by a patent attracted partners and VCs.

All companies had some experience producing clinical-utility data and were able to speak about the connection between such data and patents. Five said that there was a direct connection between obtaining patents, funding, and partners (where necessary) and that, therefore, patents affected their ability to produce clinical-utility data. Another three companies also thought that patents had some

141. See also Kathleen Liddell et al., Patents as Incentives for Translational and Evaluative Research: The Case of Genetic Tests and Their Improved Clinical Performance, 2008 INTELL. PROP.
bearing on the production of clinical-utility data but that this work actually depended to a greater extent on other factors, such as the team behind the test, the potential profit of the test, and other competitive advantages.

Three of the companies that saw a connection between patents and the resources that went into producing clinical-utility data were critical of the emphasis that some partners and VCs placed on patents. In their experience, by the time products were launched, the patents offered limited or no protection. They also commented that competitors could often “invent around” patents and produce similar tests without infringing. At the same time, however, these companies acknowledged that patent protection was useful for deterring others from simply copying the test. They also noted that knowing in advance whether patent protection will be important for the test’s final market is often difficult; generally only in hindsight are there indications of whether patent protection was necessary or not. The final test market is often different from the market that was envisaged at the time of application for patent protection.

Two companies also thought that patents gave them confidence that they had freedom to operate (FTO). Part of the patenting process is to generate search reports and prior art analyses, and, in doing this, those companies become more confident that they are not infringing other patents. Other companies (and practitioners) were critical of this approach, insisting that conclusions about FTO should be drawn only after a formal FTO analysis and that search reports should not be used as proxies.

Corporate views about the jurisdictions for seeking patent protection followed a similar pattern to the TTOs. That is, US companies primarily focused on US patents, while European companies focused on both US and European patents. Three examples illustrate these approaches: (i) a US start-up let its European patents lapse because the company did not think it had the resources to pursue a European launch and because the patents were expensive to maintain; (ii) a midsize US company said it had launched in Europe but had not been able to make substantial profits there, despite holding a patent; and (iii) a midsize European company launched first in Europe and then in the United States, and then subsequently moved the bulk of its operations to the United States, where it was generating the most profit.

Q. 286, 287 (discussing whether the patent system provides an effective incentive for producing and disseminating genetic diagnostic tests with good clinical validity).
A distinguishing characteristic between TTOs’ and companies’ use of IP was that companies thought, in addition to patents, trade secrets could be particularly valuable. For example, they foresaw useful and valuable trade secrets in data, algorithms, reagents, methods, and ways to optimize tests. A trade secret reported by one company was a “dummy” component inserted into its kit to make copying more challenging and infringing activity easier to identify. One company even rated a trade secret as more valuable than its patents because, in its opinion, the trade secret was the key to copying the test.

Companies described several other types of competitive advantage. Like TTOs, they referred to star scientists, scientific lead time, and physical property, and they described how their approach to these advantages did not differ substantially. In addition, two companies commented that a type of clinician inertia gave them some advantage. That is, competitors had to convince medical professionals to “switch” to a new test kit, which could be difficult for them due to the goodwill in the test and the technology platform they had generated. These companies even admitted their technology was open to copying; the scope of their patent protection did not completely cover their tests, which had changed since the original patent applications, but no competitors had yet entered.

Other forms of competitive advantage available to companies included negotiating reimbursement rates and overcoming regulatory hurdles. Six companies described how these steps required significant time and expertise and that competitors could not enter their markets unless they too could address these challenges. These companies acknowledged that LDT providers could compete with kit providers but said that, in many ways, these were different markets. For example, a laboratory would be reluctant to send a test to a reference laboratory if it could perform the test more quickly and at a similar price using a kit.

B. Adapting to Myriad: Drafting Claims, Uncertainty, and Development Strategies

This Section details how interviewees adapted to issues presented by Myriad. It focuses on changes to drafting patent claims, certainty regarding the validity and the grant of patents, and changes to commercial strategies for developing molecular tests.

1. Practitioners

US practitioners stated that, in principle, they had a clear idea about what amounted to an eligible claim for molecular-test technology
in compliance with *Myriad*. This means that they thought they could draft claims that examiners were likely to consider patentable subject matter or that, if given a claim, they had a confidence in their assessment of whether it was valid. A consequence of *Myriad*, however, was that they generally thought that the individual claims were narrower in scope and thus offered less valuable protection. One practitioner agreed with this comment from the viewpoint of individual claims, but they also argued that the variety of different claims that they could obtain for nature-based products often meant that, cumulatively, their clients obtained a similar breadth of protection. One practitioner thought that there was still some uncertainty for some nature-based products, and another admitted to being “very cautious” when approaching claims that raised *Myriad* issues. Yet both were relatively confident in what they considered eligible.

The picture differed for patents granted before *Myriad* was decided. The practitioners thought that many patents were likely invalid, but only one practitioner had advised on one. That practitioner explained that the patent was identified in an infringement dispute. The litigants accepted it was invalid, so the case continued based on other patents. The practitioner also added that, even if valid, the patent was unlikely to have a bearing on the dispute because the technology was now quite old and had been superseded by noninfringing technology.

On test development strategies, all US practitioners described how *Myriad* had prompted more discussions with clients on trade secrets, but none knew of clients that had decided to use trade secrets *instead of* patents. Similarly, none of the practitioners knew of a client who had changed a development strategy due to the case.

European practitioners’ experience with *Myriad* was similar to their US counterparts, albeit they added that they probably encountered fewer *Myriad*-related issues because clients could raise them with US practitioners without involving European advisers. None of the European practitioners reported particular difficulties advising on *Myriad*-related issues. Likewise, none of the European practitioners reported that a client had changed development strategies due to the case.

Two European practitioners reported substantial issues with *Myriad* for nature-based products *unrelated* to molecular tests. One practitioner described how they had encountered ongoing difficulties obtaining claims for a cell-based therapeutic, elaborating that if the

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142. Many of the ways to draft *Myriad*-compliant claims have been described. *See, e.g.*, *After Myriad*, supra note 20, at 823–24.
claim to the compound was not granted, then third parties might be able to imitate the drug. The practitioner added that the method claims they were pursuing were probably valid and would probably provide their client with enough protection; nevertheless, the practitioner thought the case created an unnecessary risk for the drug’s development. The other practitioner reported that a US pharmaceutical client had abandoned development of a drug because Myriad limited the protection available for the compound and therefore made the project too risky.

2. Companies

Of the six US companies interviewed, four had not encountered Myriad-related issues. They commented that they had not needed to seek patent protection for products merely isolated from nature; therefore, the case passed largely unheeded. One of these companies recalled a situation when it could have obtained patent protection for a biomarker, assuming it was not recorded in prior art databases, but the respondent noted that the point was moot because it had obtained sufficient patent protection with other claims.

The remaining two US companies had encountered Myriad issues, but only one said its business operations had been affected by it. The company that had not been affected explained that, during the due-diligence process for a business deal, it found patent claims that were probably invalid pursuant to the case. However, it also decided that this had little consequence because even if the claims were valid, the patents would have provided limited protection for the molecular tests.

The sixth company had a much more complex story. It described a situation where it had a number of patents granted on Myriad-related subject matter before the decision, plus several pending patents where the examination process commenced before the decision and carried on afterwards. It also said that it had continued to apply for similar patents after the decision. The company said that, immediately after the case, patent examiners raised Myriad-based rejections that narrowed the pending patents. It lost claims the company desired for its business and thought that, even after examination concluded, there was a higher-than-normal degree of uncertainty about the validity of some claims. As for the patents granted before the decision, the company recognized that many of the claims had doubtful validity, but it had not amended them because of the difficulties and risks in that process. It also added there was some value in leaving these patents on the register, as the patents might discourage competitors from
researching in the area or encourage potential partners to contact the company. Despite the fact that *Myriad* had narrowed and introduced risks to its patent protection, the respondent said that this had not altered the company’s business strategies. That said, it was quite sure that the value of its deals had decreased. It was difficult, the company said, to quantify the impact because such deals included a variety of factors of which patents are only one part, albeit an important one.

European companies’ experiences with *Myriad* were similar to their US counterparts. Two described that they had never patented nature-based products, so the case had not affected them. A third company thought that it may have acquired some US patents covering isolated DNA in a deal five to ten years ago, but this had not become a prominent business issue, as the patents were not part of their current development strategies.

The remaining three European companies described more substantial interactions with the case. Two said they had prosecuted biomarker patents in Europe and the United States before and after *Myriad* was decided and, as a result of the decision, had amended US applications to obtain granted patents with narrower scopes of protection compared with the European patents. Despite the narrower US claims, they stated that their test development strategies remained unaltered. Part of the explanation was that, overall, the breadth of their US patent protection remained similar before and after *Myriad* when one considered the narrowed claims in combination with other claims. They also added that they had a normal degree of confidence (and doubt) in the validity of their granted US patents. The sixth company described a similar experience with the case, involving narrower US claims but unchanged development strategies. This company, however, raised another issue—namely, the narrower protection might devalue commercialization licenses in the United States, resulting in a lower royalty stream. The company considered that it might be overstating this possibility, as it had other types of patent protection and many other factors influence royalty calculations. Nevertheless, the company still thought this was a valid concern.

3. TTOs

US TTOs were more aware of, and more affected by, *Myriad* than the European TTOs. All the US TTOs commented that, after a short learning period, they were relatively confident applying the court’s ruling in *Myriad* and knowing what was and was not eligible. Four added, though, that claims to isolated naturally occurring
compounds were not particularly valuable or common (even prior to the case) and that the case had not affected their development strategies.

In contrast, two US TTOs described situations where the decision had affected their development strategies. The first said that a scientist had disclosed a molecular test based on a naturally occurring compound and that, together, they had decided that without a patent on the molecule they would have insufficient protection to develop the test. In response, they decided the scientist should conduct additional experiments to try to develop a slightly different test for which they could obtain commercially valuable claims. Possible claims included Myriad-compliant compounds (i.e., nature-based compounds that were markedly different from naturally occurring equivalents) and methods that covered different ways of performing the test and were Mayo-compliant. The TTO reported that this research had generated positive results; however, a patent was yet to be drafted. The other TTO stated that an invention was disclosed to them that could not be patented due to Myriad, and, therefore, they had forgone developing the test. The TTO thought it may have been possible to conduct additional experiments that could pave the way to a commercially valuable patent, but the scientist did not have the interest, funding, or time to commit to that possibility.

One US TTO also recounted a problem created by the Myriad decision for a patent that had been previously granted. The TTO described how a licensee contacted them shortly after the decision, informing them they would stop paying royalties on a patent because it was now invalid. The TTO expressed frustration at the fact that, in hindsight, they probably could have drafted Myriad-eligible claims but, due to the difficulties with reissue, this was never a viable option.

Echoing problems reported by European practitioners, two US TTOs described problems stemming from Myriad in relation to development of drugs. One described how the case stopped them from applying for a patent on a molecule, and, therefore, research had been redirected to assess whether they could produce a related molecule with markedly different characteristics from the naturally occurring molecule. The other TTO said that Myriad meant they could not patent an active ingredient, and, therefore, development of it had ceased.

European TTOs were, in contrast, relatively unaffected by Myriad. Two European TTOs were only vaguely aware of the case and said it had not affected their activities. A third was quite familiar with the case but only because it made headlines, not because the TTO had noticed a business impact. Another two, who had filed biomarker patents recently, said that issues surrounding the case had probably arisen during US prosecution and were dealt with by outside counsel,
but they could not recall any specific details. Both added that they had not altered their development strategies as a result.

The sixth European TTO described how *Myriad* had affected one development strategy but in an equivocal way. They narrowed some claims as a result of *Myriad*-based rejections, and this altered their business strategy for “deploying” the product. The interviewee chose not to describe how exactly deployment had changed but noted that the commercial value of the product and the patent claims had probably not changed.

### C. Adapting to Mayo: Drafting Claims, Uncertainty, and Development Strategies

This Section details how interviewees adapted to issues presented by *Mayo*. It focuses on changes to drafting patent claims, certainty regarding the validity and the grant of patents, and changes to commercial strategies for developing molecular tests.

#### 1. Practitioners

US practitioners were resoundingly clear that *Mayo* had a more significant impact on patent practice than *Myriad*. In particular, they pointed out the difficulties they had applying the case to new tests due to the legal uncertainty surrounding the decision and the need to narrowly draft claims that undermined potential commercial value. In response to these difficulties, the practitioners described what one practitioner called a “toolbox” of strategies for obtaining claims or delaying prosecution until a time when, they hoped, an event (e.g., a legal decision or change in USPTO practice) would allow the prosecution of claims with more clarity. The delay tactics involved filing continuation and divisional applications.143

The various strategies US practitioners deployed to obtain claims had drawbacks. One strategy was to draft more independent claims in a type of scattergun approach, hoping an examiner would grant one. A second strategy was to seek additional interviews with examiners to better understand the “idiosyncratic” way the examiner was applying the case and even, hopefully, to agree on valid claims. Other claim strategies focused on overcoming the “significantly more” element from the second limb of the *Mayo* test. This built on the principle that method claims directed to natural laws could be eligible if they include activities that are *not* well understood, routine, or

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143. Guerrini et al., *supra* note 102, at 550.
conventional. Practitioners reported drafting claims that incorporated reagents or scientific techniques or, alternatively, a series of conventional steps that on the whole created an unconventional method.\textsuperscript{144} The drawbacks to these fall into two categories. First, practitioners noted that drafting a large number of claims increased the cost of prosecution, as did seeking interviews with examiners. Second, they commented that including activities that were \textit{not} well understood, routine, or conventional usually resulted in a quite narrow scope and, therefore, did not always confer broad protection;\textsuperscript{145} for example, a competitor could supply a similar test by using a conventional reagent (not the patented unconventional reagent) or replacing one of the steps with a different step (or perhaps simply skipping the step).\textsuperscript{146}

The uncertainty of drafting claims that an examiner would accept as \textit{Mayo}-compliant flowed into uncertainty about the validity of granted claims. The US practitioners accepted that any granted claim could be invalid if challenged in court, but, in their view, there was a higher-than-normal risk that a court would disagree with examiners’ views on \textit{Mayo}-related issues.

Despite the legal uncertainty, the US practitioners described few instances where the case had affected clients’ development strategies. None could think of an instance in which a client had abandoned development of a test. Likewise, none knew of a client that had abandoned pursuing patent protection for a test, although two described protracted, ongoing prosecutions that had not yet been resolved. None of the practitioners knew of a client that had decided to use trade secrets \textit{instead of} patent protection. On the other hand, one described an instance where a client chose not to litigate to enforce a patent granted before the \textit{Mayo} decision because of the risk of

\textsuperscript{144} These and other drafting techniques have been previously reported. \textit{See, e.g.,} Miller \& Amos, \textit{supra} note 81, at 40–41; Nicholas J. Landau, \textit{Patenting Diagnostics and Biomarkers Six Years After Mayo}, \textit{Pat.} 213 (Nov. 29, 2018), https://www.patent213.com/2018/11/patenting-diagnostics-and-biomarkers-six-years-after-mayo/ [https://perma.cc/W7ZG-BMMZ].

\textsuperscript{145} Three US practitioners also raised challenges regarding the drafting of molecular-test claims that incorporated algorithms complying with the abstract ideas exclusion from \textit{Alice}. This topic was not pursued in this Article’s study, however, because there are not clearly different patent practices for abstract ideas and algorithms in the United States and Europe. \textit{See} Aboy et \textit{al.}, \textit{supra} note 64, at 1125.

\textsuperscript{146} Two practitioners raised the possibility that competitors might be able to avoid infringement-of-method claims by arranging performance of the test by more than one actor. The law concerning this issue has changed significantly in recent years. For a review, see Johnathon E. Liddicoat, \textit{Divided Performance of Patented Methods in Australia: A Call to Codify Procured Infringement}, \textit{41 U. New South Wales L.J.} 252, 255–62 (2018). The issue has been raised briefly elsewhere in the context of molecular tests. \textit{See, e.g.,} Guerrini \textit{et al.}, \textit{supra} note 102, at 551; Sachs, \textit{supra} note 19, at 1913–19. The practitioners commented that they raised this issue with clients but stated it was considered ancillary to obtaining valid claims.
invalidity. They chose instead to leave the granted patent “on the books.” Two practitioners thought the legal uncertainty reduced the value of business deals, but another two disagreed with this, stating that patent rights often played only a small role in the ultimate value of test transactions. The other three practitioners had no experience with this topic.

Mayo affected European practice as well, although not as profoundly. Only one patent attorney described consistent issues obtaining US patents for clients. They described similar concerns to those expressed by the US attorneys: (i) ongoing difficulties with drafting Mayo-compliant claims, (ii) concerns that the claims were too narrow, and (iii) concerns that the granted claims were actually invalid. Despite these issues, however, the practitioner said their clients had not adjusted their development strategies. A second practitioner explained that on one occasion when assisting with the filing of a US patent, a Mayo-based rejection had arisen but the test involved an unconventional technical step, and, therefore, they were able to overcome the rejection (on the second step of the Mayo test) and draft commercially valuable claims. A third practitioner noted that they were in the process of prosecuting a US patent and expected to receive a Mayo-based rejection, and they thought there was a high chance of protracted prosecution. The remaining European practitioners were aware of the issues Mayo raised but said they had not needed to study the decision.

2. Companies

US companies generally commented that Mayo had been a significant case for their businesses. Only one reported not being affected by Mayo. The company in question, a start-up, was granted patents after the decision but, prior to the interview for this study, was unaware of the case. After a brief discussion of the case with the interviewer, the company thought its patents were Mayo-compliant because the claims applied a sophisticated, unconventional algorithm that probed a range of relatively unknown biomarkers.

Each of the other US companies had been affected by Mayo, but the magnitude of impact varied. One company, when prosecuting its patents, described a similar scenario to the start-up mentioned in the preceding paragraph. When acquiring a test from another business, however, it took the view during due diligence that several key patents were probably invalid under Mayo, and, in response to this risk, the company abandoned the deal. Although quite an extreme response to the risk of invalidity, it decided it was necessary because the test, once
developed, would probably have been easy to imitate without patent protection.

The other four US companies encountered prosecution difficulties similar to those described by the US practitioners—for example, protracted prosecution, narrow claims, and inconsistent examiner application of Mayo. Despite these difficulties, though, none said that the lack of patent protection or uncertainty surrounding protection had stopped them from acquiring or developing a test. One company even stated that it is “unlikely any company would kill a product due to a patent.”

Although these four companies continued developing their tests, they reported other more nuanced effects. A common concern was that the value of their patents had decreased. The companies struggled to assign a numerical value, but their tone suggested it was a nontrivial amount. One of these companies, a small company yet to launch a test, explained that although it was content to develop its tests on a weak patent position, it was conscious that potential acquirers might have a different development strategy in mind requiring strong patents and that, in the absence of strong patent protection, these companies would no longer be interested.

The remaining three companies described different effects. The second company described how the narrower claims it obtained after Mayo led to lower reimbursement rates. It invests heavily in developing novel tests with large amounts of clinical-utility data. Prior to Mayo, the company used its patents to charge a premium by excluding competitors. Since Mayo, however, narrower claims has meant less certainty of excluding competitors. Therefore, when negotiating reimbursement rates, payors are more likely to refuse premiums because competitors could offer a similar test at a lower price.

The third company described how it had decided to use trade secrets instead of patents. It said that prior to Mayo it would have patented certain methods, but given the legal uncertainties of Mayo for these types of claims, it had decided to keep the methods secret. The company also noted that since it provides the test as an LDT, secrecy was feasible. On the other hand, trade secrecy made it more difficult to publish performance information about the test lest it reveal the secrets, which in turn made it more difficult to convince payors to pay a higher price or persuade medical professionals to use it.

For the last of these four companies, Mayo and a consequent shift to trade secret protection influenced its decision-making about releasing the test as an LDT or a kit. The company’s formal strategy was to launch a kit in addition to the LDT version of the test it already offered. The interviewee explained, however, that since Mayo had
weakened the company’s patent position, it was now advantageous to offer the test solely as an LDT to keep technical aspects of the test “hidden from view.” The company was hence contemplating abandoning the kit launch to preserve its trade secrets.

*Mayo* affected the European companies interviewed less than their US counterparts. Three had dealt with *Mayo*-related issues during prosecution. One company described how it had avoided a *Mayo* rejection by preemptively drafting narrower claims. The company’s test incorporated an unusual technique, and it explained that in these circumstances *Mayo* had not prevented it obtaining US patent claims that were sufficiently valuable for the company to develop its test. The other two companies described more drawn-out patent prosecution, but neither was particularly affected by the case. One thought that the narrower claims it obtained meant it might get a lower license rate in the United States but also that this was hard to predict. The other company was yet to obtain its US patent (it was still pending at the USPTO after two or three rejections) but was not perturbed. It intended to launch its test in Europe before the United States and expected this would provide other competitive advantages, including scientific lead time, comprehensive data, and goodwill in the test. In the company’s opinion, these advantages meant that any uncertainty or narrowness in its US claims would have a relatively trivial effect. Furthermore, its algorithm was still a trade secret. The company considered this particularly valuable because competitors would face difficulties trying to reverse engineer the algorithm despite its plans, by the time of launch, to publish on it and provide data to regulatory and reimbursement bodies.

The other three European companies had obtained US patents after *Mayo* was decided but were not aware of the case. After explaining the case and asking why they had not heard of it, all three suggested it was because their technology included clear advances over known techniques. Accordingly, the USPTO probably reached a swift view that the patent application included unconventional advances and fell outside the *Mayo* exception to patent eligibility. One company also opined that a reason why its patent did not receive a *Mayo* rejection may have been because the company directed its claim to an assay that detected the presence or absence of a pathogen. This may have been sufficient to avoid the first limb of the *Mayo* test because the patent was not directed to a medical correlation.
3. TTOs

Similar to the US companies and practitioners, US TTOs found Mayo a difficult case. As a starting point, all US TTOs echoed the points made by US practitioners in relation to prolonged prosecution, narrow claims, and uncertain validity of granted claims. Four TTOs also drew attention to the fact that patent costs for protecting molecular tests had increased substantially due to lengthier prosecution times.

They described a variety of drafting strategies to overcome Mayo-related issues, but none were uniformly adopted. One TTO described how they had claimed an assay for detecting a specific biomarker by focusing on specific “mechanical aspects” of the assay, instead of a diagnostic test that relied on a medical correlation. They even thought that the claims were probably as broad as they would have obtained pre-Mayo. The TTO noted, however, that this approach was not always feasible, as some tests could not be described as an assay. Five TTOs also discussed overcoming Mayo-related issues by incorporating tests into methods of medical treatments. One TTO described that they were able to obtain claims with minimal fuss by adopting this approach. Another two TTOs were critical of this approach, however, commenting that it was not feasible for them because they would need more data to support these types of claims and their researchers had no interest or capacity to redirect their research in this manner. The last two TTOs described this approach as feasible, but only when a researcher was interested and had the resources for the extra research.

While these experiences were similar to other interviewees’ experiences with Mayo, the challenges with patenting tests had more serious outcomes for the TTOs. Several TTOs abandoned or considered abandoning the development of tests. Five US TTOs said that they were looking very closely at molecular-test projects and had many concerns, and three of these TTOs had gone as far as abandoning patent filings and development of at least one test. Indeed, one of these TTOs said they were not developing “lots of promising products,” and another declared they “don’t translate diagnostics.” Three TTOs also reported having licensees contact them to cancel licenses because the patents were now invalid. The only TTO that had not lost a license or abandoned a test was the one who described successfully linking their tests to methods of medical treatments.

Although the US TTOs described different approaches for patenting and developing tests, two issues they all agreed on were that

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147. The TTO chose not to elaborate on this point.
they thought fewer VCs were interested in tests\(^{148}\) and that fewer companies were interested in partnering.

European TTOs described a very different experience with *Mayo* compared with their US counterparts. Their development strategies had not been affected by the case. Five said that they had no specific memory of the case arising during prosecution or development strategy meetings. They thought it was possible that the case had been raised during prosecution but, if it had, presumed it had been dealt with by external practitioners without raising concern. Indeed, two of the TTOs commented they were unaware of the case prior to the interview, even though they regularly dealt with molecular-test technology. One of the TTOs differed from the other four in that they had discussed the case with colleagues; they suggested that one reason the case had not arisen in (or at least had not been significant for) their development strategies was that their claims detailed unconventional instruments or incorporated an unconventional technique, such as a previously unpublished algorithm to diagnose a group of patients.

The sixth TTO described how the case had significantly prolonged the prosecution process for several of their patents, but eventually they obtained commercially valuable US claims and the delay had not affected their development strategies. This TTO outlined similar approaches to drafting claims as described above by the other TTOs. They also mentioned that they typically filed their patents “late” in order to generate more information about the delivery of the tests in medical practice. This strategy had a further advantage. They found it helped them overcome *Mayo*-related issues because the additional information often meant they had worked out unconventional reagents, instruments, or techniques that could be included in claims without affecting the commercial value of the claim.

**D. Does Myriad or Mayo Disadvantage US-Headquartered Organizations?**

Prior to this Article’s study, opinions differed on whether US-headquartered organizations were more strongly disadvantaged by *Myriad* or *Mayo* compared with European counterparts. It is often argued that patent protection is important to an innovative domestic economy. Yet, patent law applies equally to domestic and foreign organizations. This means that all organizations developing tests can seek patents in Europe, where they will engage with European patent law, which permits a broader range of subject matter. It also means that

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\(^{148}\) Taylor, *supra* note 9, at 229.
all organizations can seek patents in the United States, where they will have to deal with more restrictive patentable subject-matter law, as dictated by *Myriad* and *Mayo*.

As a general rule, US interviewees (practitioners, companies, and TTOs) thought that patentable subject-matter thresholds were easier to meet in Europe than in the United States. However, none thought the differences in patent law disadvantaged US-headquartered organizations compared with European counterparts. Explaining this view, the US interviewees offered four reasons.

First, European patents can be obtained by anyone, including US organizations. Thus, if European patents do confer a benefit, this benefit is available to organizations on both sides of the North Atlantic. Second, organizations that develop tests want, almost always, to launch in the United States because that is where they make most profits. Therefore, all organizations must engage with US patent law. Six US interviewees described this reason as a consequence of the globalized world. Third, although patent applications filed in Europe usually meet patent-eligibility thresholds, problems are often encountered with other patentability criteria (e.g., novelty, inventive step, nonobviousness). Accordingly, any benefit gained through patentable subject matter falls away during other stages of examination. Fourth, successful development of molecular tests involves many challenges, of which obtaining patent protection is only one. So even assuming European patents are broader and granted more easily, this benefit to the organization can be overridden by a milieu of other issues.

Despite such reasons, two US TTOs described how they had considered focusing their development activities in Europe in view of the differences in patent law. However, both went on to say that they had not actioned this plan. One of their primary reasons to continue focusing on the United States was that they had relatively limited knowledge of the potential European licensees or VCs that would be interested in their test.

European organizations had more diverse opinions on whether cross-Atlantic legal differences in patent eligibility brought about by *Myriad* and *Mayo* advantaged European organizations and disadvantaged US organizations. Four European practitioners thought that the cases did not disadvantage US-headquartered organizations, raising the same four arguments mentioned by US organizations. On the other hand, two European practitioners disagreed, taking the view that US organizations were at a disadvantage. One reasoned that US organizations tend to focus on their domestic markets, whereas European organizations tend to focus on territorial markets outside the United States. As a result, European companies could respond to
Myriad and Mayo in a more agile way, focusing attention on substantial, patent-friendly markets such as the United Kingdom and Germany. The other European practitioner, sharing the view that US organizations were at a disadvantage, had a client base with a high proportion of TTOs and start-ups compared to many other attorneys. The practitioner stated confidently that the cases, especially Mayo, created a disadvantage for US organizations because organizations working at the early stage of test development (like this practitioner’s clients) typically use patents to attract partners and VCs to develop their tests, and this is easier if they can obtain broad patent protection quickly and at low cost.

European companies were evenly split on the question. Two companies thought the cases created a disadvantage for US organizations. One of the explanations offered was that US companies typically regard strong US patent protection as necessary for early-stage test development, while molecular-test organizations in Europe had a more global vision and were content to obtain stronger patents in European markets (as well as other markets outside the United States). The second company articulated its ideas with less precision, merely stating that indirect benefits would flow to European companies because they could obtain patents quicker and often with broader scope. On the other hand, two European companies thought Myriad and Mayo did not create any particular advantage or disadvantage for European or US companies. One explained this with reference to the concept of the “globalized world,” and the other because it thought the extra scope and speed to grant offered minimal advantages. This company added that even if the cases did create a disadvantage for US companies, it was minor and, overall, US companies were still at an advantage because of the high number of VCs there. The remaining European companies did not comment on this topic, explaining that they were not familiar enough with the cases.

European TTOs were the only cohort where a clear majority thought the cases created a disadvantage for US companies.149 Only one European TTO thought that the cases did not create a disadvantage, basing this on the “globalized world.” The other five European TTOs offered several reasons why the legal position after Myriad and Mayo effectively disadvantaged US companies and advantaged European companies.

First, European organizations are more likely to file for patents in Europe than US organizations. And since patents are typically

149. Although two European TTOs were not familiar with Mayo before the interview, they felt they understood the case well enough by the end of the interview to answer this question.
necessary for the development of tests and procuring patent protection for tests is often easier and cheaper in Europe, European organizations are more likely to obtain the protection needed to develop tests in a protected market.

Second, most VCs and partners they engaged with were: (i) European, (ii) focused on European patent law, and (iii) (largely) oblivious to how severely the US cases had affected patent protection and practice there.\(^{150}\) Thus, the local European environment for tests had not changed,\(^ {151}\) whereas they were under the impression the US venture-capital environment had changed significantly with media coverage of *Myriad* and *Mayo*.\(^ {152}\)

Third, one of the most important elements for the success of any test is the data supporting it (e.g., data on its analytic and clinical validity), and typically such data are first gathered in an organization’s home market. Accordingly, since European organizations could launch in Europe with strong patent positions, then later launch in the United States when their data were stronger, this strategy might avoid the need for strong US patents because they would have the advantage of a good evidence base as well as strong reputation and other competitive advantages.

Fourth, pursuing a Europe-only launch of a test based on strong local patent protection was a legitimate and feasible business objective, particularly as a fallback from a US and European launch. These five TTOs admitted, though, that relative disadvantage for US organizations would not arise for every test, primarily because some test technology was still patent eligible in the United States.

V. DISCUSSION: INSIGHTS FROM THE INTERVIEW DATA

The following three topics distill the interview data and describe how the data provide insights into how *Myriad* and *Mayo* affect the development of molecular tests. The first topic is whether molecular tests can satisfy patentable subject-matter requirements in the United States. The second topic is the adverse effects of *Myriad* and *Mayo* on the development of molecular tests. The third topic is why the data show that organizations in the United States are now at a relative disadvantage compared to organizations in Europe.

\(^ {150} \) Taylor, * supra* note 9, at 229.

\(^ {151} \) One US practitioner did speculate that if VCs are only aware of local laws, then US VCs might be more reluctant to fund early-stage US organizations because of concerns about patenting, whereas European VCs’ activities will remain unchanged. After reflecting further on this possibility, though, the practitioner dismissed it.

\(^ {152} \) Taylor, * supra* note 9, at 229.
A. Molecular Tests and Patent Eligibility

In the immediate aftermath of Myriad and Mayo, senior legal commentators posited that molecular tests were no longer patent eligible in the United States. The interview data demonstrate that this is incorrect, at least as a blanket statement; many interviewees described a variety of ways to draft valuable claims. Indeed, Myriad’s effect on patenting tests appears to be quite limited, with US practitioners in particular describing how they were confident drafting claims that complied with Myriad, and all stating confidently that they had been able to obtain commercially valuable claims for clients. Although one US TTO chose not to develop a test because Myriad prevented them from patenting some biomarkers, all the other organizations (TTOs and companies) said Myriad had not stopped them from obtaining sufficient patent rights when required. These data accord with patent-register data identified by one study. It found that post-Myriad the numbers of gene-related patents continued to rise.\(^\text{153}\) Although the numbers of patents granted for isolated DNA sequences declined after Myriad, it found that these patents were already on a downward trajectory, which probably would have continued even without the Myriad decision.\(^\text{154}\)

Mayo’s impact on patent eligibility was more nuanced. The interview data show that commercially valuable patent claims can be obtained after Mayo, although experiences differed. Practitioners stated they were able to obtain claims for clients. In contrast, three TTOs stated they had forgone at least one patent application each due to concerns about legal uncertainty and claims being too narrow. One interpretation of these results is that commercially valuable claims are available for only some tests post-Mayo. Another interpretation is that valuable claims are generally available for all tests but only after protracted, resource-intensive prosecution. The interview data do not resolve this disagreement. But a consistent point with both interpretations is that Mayo’s most significant impact on patent practice was the way in which it increased legal uncertainty.

Uncertainty was a recurrent theme in interviews when discussing Mayo. Respondents raised three issues in particular: (i) whether claims could be drafted that were Mayo-compliant (and valuable); (ii) how USPTO examiners would apply Mayo to a patent application; and (iii) whether granted papers would survive judicial review, a concern which also applied to patents granted

\(^{153}\) Myriad’s Impact, supra note 20, at 1120.

\(^{154}\) Id. at 1120–22.
before the decision. Uncertainty was also a major finding in the first peer-reviewed study of Mayo-related patent filings and prosecutions. The study, analyzing a USPTO art unit related to molecular tests, found an allowance rate of 36 percent for applications that received a rejection citing Mayo, indicating that the majority of the applicants could not or chose not to overcome the rejections. Moreover, findings indicated that the number of annual Mayo-based rejections remained consistently high in the six years preceding the study, indicating that the patent profession had not worked out how to draft Mayo-compliant claims. Thus, from different perspectives, this study’s interview data and Aboy et al.’s data confirm that molecular tests remain patent eligible post-Myriad and post-Mayo but that there is ongoing and substantial uncertainty with the specific claims that are patent eligible. Mostly, the uncertainty stems from Mayo.

B. The Adverse Effects of Myriad and Mayo for the Development of Molecular Tests

This Section considers three types of adverse effects observed in this Article’s study. The first type, forgone test development, concerns interview data detailing organizations that abstained from or abandoned developing molecular tests. The second concerns how patents on molecular tests have reduced in financial value. The third concerns whether organizations are now using trade secrets instead of patents during the development of tests.

1. Forgone Test Development

Several patent-law theorists predicted that the decisions in Myriad and Mayo would adversely affect the development of tests. One theorist stressed that molecular tests are expensive to develop and validate and, therefore, typically require investment from VCs. Another stressed that few organizations have the necessary resources and skills in-house to develop tests by themselves and therefore require partners with complementary skills, which patents help attract. Both argued that § 101 law pre-Myriad and pre-Mayo was necessary for high rates of innovation because broad exclusive patent rights act as a type of security for investments, such as capital injections, as well as other resources, such as labor, and that they help prevent free riding. Thus,

155. Mayo’s Impact, supra note 20, at 515.
156. Id. at 516.
157. Holman, supra note 11, at 307–08.
158. Daily & Kieff, supra note 86, at 973–74.
Myriad and Mayo, which narrowed patent protection, would likely reduce the incentive to invest in test development.

The interview data show that (i) one TTO did not develop a test because of Myriad, (ii) three TTOs did not develop tests because of Mayo, and (iii) one company abandoned acquiring a test due to Mayo. These data, therefore, support the predictions. Furthermore, the data predominantly support their reasons: TTOs said that the most important role patents play in their organizations is attracting partners and VCs. In addition, however, the data bring to the fore some important nuances not mentioned by the patent-law theorists.

One nuance is that the data just summarized show TTOs are more affected than companies. TTOs and universities were not singled out by the theorists. A second detail, closely related to the first, concerns the roles that patents play for companies compared with TTOs. The interview data show that TTOs are more dependent on patents—they have fewer competitive advantages available to them—and, due to constraints on funding, are more sensitive to the cost of protracted patent prosecution. In effect, they are “patent precarious”: organizations that are particularly susceptible to changes in patent law that narrow protection or make patents difficult to obtain. This precariousness is exacerbated, too, by the fact that technologies emerging from TTOs are at their most immature and, therefore, their riskiest stage of development for investment.\footnote{159}

Patent precariousness also helps explain the difficulties two US companies experienced with transferring tests. One company stated that it abandoned acquiring a test from a start-up due to Mayo-related invalidity. The second, a small company, continued test development but anticipated more limited interest from potential partners due to Mayo. Both the start-up in the first scenario and the small company in the second scenario were yet to obtain regulatory approval, negotiate reimbursement, or scale up production of a test. The small company kept some trade secrets, but the start-up, according to the interviewee, had none of significance. These companies relied heavily on patents.

The idea that some organizations, particularly small ones, are patent precarious is consistent with other theoretical and empirical work. Economists in 1982 suggested that small companies might rely on patents because they lack other means to protect their development investments.\footnote{160} The point is also consistent with foundational literature...


\footnote{160} Richard C. Levin et al., Appropriating the Returns from Industrial Research and Development, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783, 797, 831 (1987); see also Roberto
on the competitiveness of firms that posits that companies need competitive advantages to gain market traction and that small organizations in resource-intensive industries find it particularly difficult to handle market forces without patent protection since they usually have access to only a small number of possible competitive advantages.161 At least two lines of empirical research support this idea. First, professors Ashish Arora and Marco Ceccagnoli conducted research on whether patent protection increases companies’ ability to license technology.162 The researchers found that licensing propensity correlated with increased patent protection but only when companies lacked “complementary assets,” a type of competitive advantage, which the authors defined as assets that are costly and time-consuming to acquire and which complement the product sold163 (e.g., trade secrets and manufacturing capabilities).164 Second, economist Scott Shane’s analysis of patents assigned to the Massachusetts Institute of Technology between 1980 and 1996 shows that wide patent scope correlated with new business formation. That is, the wider a patent’s scope, the more likely a business will be formed that acquires the patent from the university.165

Two further lines of empirical research support the more specific idea that patent precariousness is an issue for small molecular-test organizations. A 2008 survey of US start-ups found that medical device start-ups, a category that includes molecular-test start-ups, rated patents as 3.3 out of 4 on a scale of importance (with 4 being the highest importance) for capturing competitive advantage.166 The second piece of empirical research shows a different side of precariousness: when the prosecution of patents becomes expensive and difficult, precarious companies stop obtaining them. A study shows that the number of patents granted to small entities, which includes TTOs if they have not

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163. Id.

164. The cited study focused on manufacturing capabilities. Id. at 297.

165. See generally Shane, supra note 160, at 209.

licensed the patent,\textsuperscript{167} has declined after Myriad: prior to the decision, about one-third of applicants were small entities, and this has since dropped to almost zero.\textsuperscript{168}

Consequently, although this study’s findings—that Myriad and Mayo had negative effects on small organizations due to the increased precariousness of their patent portfolios—are based on a relatively modest number of interviews, the idea has substantial theoretical and empirical support.

2. Value Reduction

Four US companies reported that the financial value of their patents had reduced due to Mayo, and one US company and one European company reported patent value had reduced due to Myriad. The legal theorists did not specifically predict this effect, but practitioners did.\textsuperscript{169} Each of the companies describing this issue said reduced patent value resulted in reduced value of financial deals, including reimbursement, but none of the companies knew by how much.

This is clearly a negative effect for the individual companies interviewed, but whether it is an adverse effect from a public perspective of technology development is more complex. One could argue that if a transaction is modestly profitable for an organization that develops a test, then the laws influencing the value of the technology are operating sufficiently well. However, since one of the primary drivers of this reduction is the higher-than-normal level of uncertainty surrounding granted and pending patents, then to this extent at least the reduction in value is negative.

3. Trade Secrets

A number of commentators have argued that, from society’s perspective, changes in patent law have a negative impact when they fail to incentivize firms to disclose technological information and firms retain it as a trade secret.\textsuperscript{170} An interview-based study explored the adoption of this strategy in gene technology but found no instances of it

\begin{itemize}
\item \textsuperscript{167} 37 C.F.R. § 1.27 (2019).
\item \textsuperscript{168} Myriad’s Impact, supra note 20, at 1122.
\item \textsuperscript{170} Guerrini et al., supra note 102, at 544–45; W. Nicholson Price II, Big Data, Patents, and the Future of Medicine, 37 CARDOZO L. REV. 1401, 1418–19 (2016); see generally LANDES & POSNER, supra note 1, at 326–28; Bambauer, supra note 100, at 837–40.
\end{itemize}
occurring. The results of this Article’s study confirm increased interest in trade secret protection as a strategy for test development but found only one instance of it occurring. This supports the view that trade secrets hold increasing interest for test developers, but initial uptake appears low.

A related issue emerging from the interview data is that in response to *Myriad* and *Mayo*, companies were choosing to provide a test as an LDT instead of a kit to preserve trade secrets. The study recorded one instance of a US company choosing this strategy and another instance of a US company considering it. Unlike using trade secrets instead of patents, patent theorists have not previously predicted a shift to LDT technology nor the implications of this industry movement. In other fields the issue is familiar, and there is an active debate about whether the FDA should regulate LDTs, especially due to safety and accuracy concerns. In an environment where LDTs are arguably insufficiently regulated, it is a negative effect for *Myriad* and *Mayo* to have underpinned a shift in this direction.

**C. Explaining the Relative Disadvantage for US-Headquartered Organizations**

As previously mentioned, respondents had mixed views about whether *Myriad* and *Mayo* disadvantaged US-headquartered organizations more than their European counterparts. In the main, US organizations thought there was no noticeable difference. However, quite a number of European organizations, particularly TTOs, thought they were able to deal with the implications of *Myriad* and *Mayo* more easily than US organizations. It is also revealing that four US organizations decided against acquiring or developing a test due to *Mayo* and one decided against developing a test due to *Myriad*, whereas no European organization decided not to develop or acquire a test.

Notwithstanding the small sample size, the results on this issue speak to debates about whether local conditions of patent protection are significant for local innovation. On the one hand, patent

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173. SCHUTT, supra note 108, at 165.
protection appears to establish a level playing field, since the legal thresholds apply to any organization (local or foreign headquartered) seeking patent protection in the jurisdiction. However, several reasons emerged that support the view that Myriad and Mayo disadvantaged US-headquartered organization more than European counterparts, even though both groups must meet § 101 thresholds to acquire US patent protection.

First, US organizations commented that they primarily focus on the US market, whereas Europeans focus on US and European markets with roughly equal intensity; and some European organizations entertain business strategies that exclude the United States, whereas no US organization said they would do this. Second, US TTOs and companies described diminished VC and partner interest in molecular tests as a result of the cases,174 whereas no European organizations described this. The explanation is that local VCs and partners play important roles in innovation,175 especially for TTOs,176 and that European VC investors were less perturbed by, or perhaps less aware of, US legal developments.

Third, European organizations described business strategies that mitigated weak US patent rights, including relying on European and other non-US patent rights; relying on European and other non-US VCs; only partnering with European and non-US organizations; and launching tests in Europe before launching in the United States, using strong data generated in Europe. None of these strategies were mentioned by US interviewees.

Fourth, the interview data strongly indicate that Mayo generally made patent prosecution lengthier and more costly. This outcome, however, interferes with TTOs’ business strategy of prosecuting patents and transferring the technology swiftly and cheaply. European TTOs experienced Mayo’s effects on prosecution, but US TTOs were more

174. Taylor, supra note 9, at 229.
sensitive to the effects because they more precariously rely on US patents.

On balance, the results support the view that US organizations, particularly patent-precarious TTOs, have been more strongly disadvantaged by Myriad and particularly Mayo compared with European counterparts. The results, however, do not permit an assessment of how frequently the disadvantages arise.

VI. STUDY LIMITATIONS: REASONS FOR CAUTION PRIOR TO LAW REFORM

This Article’s study shows that Myriad and Mayo have adversely affected the development of some molecular tests and that the cases may create disadvantages for US-headquartered organizations. However, care must be taken before relying on this evidence as a basis for law reform. It is better to see it as indicative, but nonconclusive, evidence of overall trends. There are three reasons for careful reading of this evidence.

First, the sample size for the interviews is appropriate for an interview-based study but is small relative to the entire industry. The methodology does not accurately indicate the percentage of test organizations that have been negatively impacted in the wider population, nor the full number of tests that companies and TTOs chose not to develop, nor the amounts by which the value of molecular-test deals have reduced.

Second, there may have been some selection bias. The invitations sent to potential interviewees stated that this study was investigating the US Supreme Court cases of Myriad and Mayo. Some organizations may have ignored the invitations because they develop tests with little reliance on patent protection or have little interest in the Supreme Court cases. This is particularly plausible for tests that might be developed, for example, with public money or that build on existing technology, biomarkers, or clinical-utility data. A few interviewees illustrated this idea, pointing out that hospitals have been developing panel tests that are less innovative than their tests because the panels draw primarily on existing technology and publicly available data.

Third, this study was designed to assess the negative effects of Myriad and Mayo, not the positive ones that might balance out the adverse impacts. The most obvious potential positive effect of the decisions is the one argued by the Supreme Court: the decisions would unshackle “basic tools of scientific and technological work” from patent
protection, enabling wider and easier use.\textsuperscript{177} If the patent practice before the decisions did tie up these “tools,” then various fields of innovation may have flourished in the years afterward. To the Authors’ knowledge, research has not investigated this topic from an empirical perspective. Three US TTOs in this study volunteered information (it was not pursued by the interviewer) that they were developing projects that, at least in part, incorporated technology that was patented until \textit{Myriad} invalidated the protection.

Previous empirical studies found that biomedical scientists rarely become aware of protective patents and redirect research to avoid patent infringement.\textsuperscript{178} In contrast, the interview data suggest it might be more common for researchers to learn something is no longer patented, or that only a narrow patent exists, and subsequently deliberately move into that technical field. Thus, the potentially positive effects of \textit{Myriad} and \textit{Mayo} still need further examination before it can be concluded that the negative effects warrant law reform.\textsuperscript{179} Relatedly, \textit{Myriad} and \textit{Mayo} affect more than molecular-test development. For instance, they are having an impact on drug development. Two interviewees stated \textit{Myriad} had stopped development of a drug, one US TTO said \textit{Myriad} had redirected research on a drug, and one European practitioner said \textit{Myriad} posed a serious issue for the development of one of their client’s drugs. These points are consistent with a study that indicated that \textit{Myriad} is more frequently cited by the USPTO to reject non-DNA than DNA patent applications. Since \textit{Myriad} and \textit{Mayo} affect scientific research other than molecular-test technology, it would be prudent to understand these effects before devising any law reform.

Proceeding with policy or legislative reform before understanding the effects of the cases better is likely to be premature, poorly targeted, and insufficient and may even lead to more uncertainty. Further research is important.

\begin{itemize}
\item \textsuperscript{177} Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 589 (2013).
\item \textsuperscript{179} How exactly one should weigh innovation that has flourished with, for example, tests that were not developed is quite challenging.
\end{itemize}
VII. CONCLUSION

*Myriad* and *Mayo* significantly changed US patent practice and created significant divergence with European law on patentable subject matter. Previous studies of *Myriad* and *Mayo* have examined macrolevel effects, and this Article’s study aimed to examine the negative effects of *Myriad* and *Mayo* at the organizational level by interviewing patent practitioners, executives at molecular-test companies, and managers in technology-transfer offices at research institutes. The sample size of interviewees is small relative to the size of the molecular-test industry, meaning the results are only indicative of overall trends. However, since little is known about the molecular-test industry, this study provides context-rich information on how and when the negative effects arise. This information is vital to understanding the effects of the cases on the molecular-test industry and to developing evidenced-based patent law and policy.

This study has three main findings. First, *Myriad* and *Mayo* have negatively affected the development of tests in several ways. Notably, several organizations deliberately chose to forgo developing tests, and many have found the legal uncertainty following the cases problematic. Second, small patent-precarious organizations (those that rely heavily on patents for competitive advantage) have been more affected by the decisions than other organizations. Third, US-headquartered organizations have been more affected by the cases than European organizations, even though both types of organizations file US patents under the same eligibility law—a result that the majority of interviewees did not expect. The basis for this disadvantage is that European organizations do not, as a general rule, rely on US patents as significantly as US organizations do.

These results show that *Myriad* and *Mayo* have adversely affected the development of some molecular tests and that the cases may create disadvantages for US-headquartered organizations. Yet this Article does not recommend reform. A key reason for this unwillingness is that this study was designed to assess only the negative effects of *Myriad* and *Mayo*, not the positive ones. The most obvious potential positive effect is the one argued by the Supreme Court: that the decisions would unshackle “basic tools of scientific and technological work.” Until the positive effects are understood, reform is premature.