Myriad Post-*Myriad*

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Genes as Data

Charting the course of science and human destiny, Nobel Laureate James Watson announced: "We used to think our future was in the stars. Now we know our future is in the genes."[1] If "our future" meant the future of business and industry, the prediction would have ended with "our future is in data." The battle over gene patenting, as I argue here, is largely about data. While many welcome limitations on gene patenting and putting genes into the public domain, the benefits of data-mining and the emerging markets for precision medicine through genomics should not be ignored.

The US Supreme Court's 2013 decision, holding patent claims to isolated, endogenous DNA sequences to be invalid, seemed to have limited negative impact on Myriad Genetics whose patent on the isolated BRCA1 and BRCA2 genes were at the heart of the case. This paper explains this minimal impact in two ways. First, the Court's decision still left synthetic DNA patentable, leaving that as a fruitful source for commercialization by companies like Myriad. The Federal Circuit's subsequent decision, however, invalidated Myriad's product claims over the synthetic PCR primers based on the isolated DNA sequences were unpatentable. Nonetheless, it is open how far future courts may go in invalidating products based on isolated or synthetic DNA sequences.[2] Second, the Court's decision did not address the patentability of mined genetic data for diagnostic and therapeutic purposes. This field of genetic data-mining is precisely where Myriad has moved in its patenting activity. Although the Supreme Court's 2014 decision in *Alice*[3] placed seemingly insurmountable limits on process patents, Myriad has been successful in obtaining at least one datamining patent in 2017 and several more applications are pending. This paper explores the shift from genes to data in the aftermath of the *AMP v Myriad* decision.

It is not an overstatement to conclude that Myriad, the company, may have actually benefitted from the *AMP v Myriad* decision. By putting isolated, endogenous DNA sequences into the public domain, the Supreme Court made these sequences available for companies to mine and develop therapeutic and diagnostic techniques that could lead to synthetic DNA molecules that might be patentable even though endogenous, isolated DNA sequences are unpatentable under the *AMP v Myriad* decision The Supreme Court's decision has supported an emerging industry for

[1] Quoted without citation in Shobita Parthasarathy, 'Building Genetic Medicine: Breast Cancer, Technology, and t he Comparative Politics of Health Care' 199 (2012)(MIT Press, Cambridge).
[2] See In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig., 774 F.3d 755 (Fed. Cir. 2014).
[3] See Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347, 189 L. Ed. 2d 296 (2014).

precision medicine, aka personalized medicine, even while limiting the diagnostic market that Myriad had developed in the 2000's through its now invalidated patents. Genes are refashioned into mineable data. Supporting this claim is the series of data-mining patents that Myriad has pursued over the past decade, from even before the *AMP v Myriad* decision.

Starting with an analysis of the lawsuit leading up to the Supreme Court decision and the details of the Supreme Court's decision itself, this Article moves to an assessment of the decision in light of precedent on the exception to patenting for natural phenomena. Through this exception, I argue, the Court makes a distinction between inventive activity, that can be subject to patenting, and extractive activity, that cannot be subject to patenting. An analysis of the case law gives way to a discussion of Myriad's recent patenting activity, after the Myriad decision, which has been in the area of data analytics. This shift, I argue, is consistent with the unpatentability of isolated DNA sequences. With the denial of the patent right in isolated DNA, the Court, unintentionally, created a readily exploitable resource for data mining and analytics. While the success of patenting data analytics may be in question after the 2014 Supreme Court decision in Alice, the uncertainty of that decision still leaves room for patenting in fields of artificial intelligence, robotics, and data science. A study of Myriad's recent annual reports shows that these fields are precisely the ones Myriad currently touts. The Article ends with a discussion of further developments in the area of genomic medicine that go beyond Myriad's activities and concludes with thoughts on the future direction of law and policy in genomic medicine.

Myriad the Case, Science, and Policy

On June 13, 2013, the United States Supreme Court addressed the question of the patentability of isolated endogenous DNA sequences in a challenge to Myriad's breast cancer gene patent brought by the Association for Molecular Pathology.[4] The Court's answer seems straightforward. Isolating a naturally occurring DNA sequence does not give rise to patentability while creating a synthetic DNA sequence might be patentable.[5] In subsequent litigation involving challenges raised by Myriad's licensees in the wake of the Supreme Court decision, the Federal Circuit ruled that PCR primers based on the isolated DNA sequences were not patentable subject matter.[6]

In 1997 and 1998, Myriad Genetics was granted three patents related to identifying genetic sequences associated with susceptibility to breast and ovarian cancer.[7] These patents covered the complementary DNA sequences (cDNA), useful both for identifying the presence of the various alleles of the cancer gene in patients and for diagnosing the susceptibility to breast and ovarian

[4] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S.Ct. 2107 (2013).

[5] *Id.* at 2119–20.
[6] See supra note 2.
[7] *Id.* at 2113.

cancers. as well as the broader isolated DNA sequence.[8] Based on these patents, Myriad marketed a diagnostic test for detecting the presence of the gene sequences.[9]

Myriad's practices became the subject of media scrutiny. Medical practitioners, patient rights' advocates, and health care access proponents raised critical issues of high medical costs and patient's right to know in questioning Myriad's business and litigation strategies. In 2009, the Association for Molecular Pathology sued Myriad, challenging the validity of its patents.

Spring 2010 marked the Federal District Court's decision in the Myriad litigation and a turning point for biotechnology patenting. Judge Sweet of the Federal District Court for the Southern District of New York ruled that Myriad's patent claims to isolated DNA sequences and methods were not patentable.[10] The ruling rested on the court's interpretation of precedent that natural phenomena are not patentable. This precedent, and the controversial interpretation, are discussed in a later part of this Article. Judge Sweet, working with a biotechnology-trained clerk, reasoned that all DNA sequences whether isolated or synthetic were products of nature, indistinguishable from naturally occurring DNA sequences.[11] Therefore, Myriad's patents should not have been granted.

Judge Sweet may have tapped into anti-patent sentiment. In June, 2010, the Supreme Court published its long awaited decision in *Bilski v. Kappos*, dealing with business method patents.[12] While there was unanimity as to holding invalid the particular business method at issue (a method for hedging risk in commodities markets), four of the justices would have gone further and ruled that all business methods were unpatentable.[13] In 2012, in what is probably its most far-reaching decision in this area, the Supreme Court reviewed a patent on a medical diagnostic procedure to treat Crohn's Disease held by the company Prometheus, which was alleging patent infringement by the Mayo Clinic.[14] The Court ruled that the patent was invalid because it entailed using a correlation that would be an unpatentable law of nature.[15] Judge Sweet's 2010 ruling preceded these developments. Upon appeal to the United States Court of Appeals for the Federal Circuit in 2011, which hears appeals of patent cases, Judge Sweet's decision was overturned with respect to

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[8] *Id.* at 2112–13.

[9] *Id.*

[10] *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1314 (Fed. Cir. 2012), *aff'd in part, rev'd in part sub nom. Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 133 S. Ct. 2107 (2013).

[11] Id.

[12] *Bilski v.* Kappos, 561 U.S. 593, 130 S. Ct. 3218, 177 L. Ed. 2d 792 (2010).

[13] *See*, *Id.* at 626, 130 S. Ct. at 3239 (Justice Stevens, with whom Justice Ginsburg, Justice Breyer, and Justice Sotomayor join, concurring in judgment).

[14] *Mayo Collaborative Servs. v. Prometheus Labs., Inc*., 132 S. Ct. 1289 (2012).

[15] *Id.* at 1294.

the patent-eligibility of the isolated DNA sequence.[16] Upon appeal to the Supreme Court, the case was sent back to the Federal Circuit in 2012 for reconsideration in light of the Court's ruling in *Mayo v. Prometheus*.[17]

This back and forth of a case is not atypical in controversial areas of law. In 2012, the Federal Circuit once again upheld the patentability of the DNA sequences identified by Myriad.[18] In its second review of the Myriad patents, the judges agreed that cDNA, or synthetic DNA sequences, would be patent-eligible since they were not natural phenomena.[19] The basis for this ruling was the finding that research scientists at Myriad had to engage in inventive activity in constructing the synthetic DNA sequence.[20] Two of the three Federal Circuit judges ruling on the case also found that there was inventive activity in isolating the DNA sequence from its naturally occurring state.[21] One of the three, however, reasoned there was no difference between the isolated DNA sequence and the naturally occurring sequence.[22] Therefore, one dissenting judge concluded that isolated endogenous DNA sequences were not patentable.[23] The Supreme Court decided to review this opinion and issued its own, final opinion in June, 2013.[24]

Two words describe the 2013 Supreme Court opinion: anticlimactic and frustrating. The anticlimax was in the Court's conclusion that isolated, endogenous DNA was not patentable while synthetic DNA could be. This conclusion, it was argued, followed from the Court's precedent. What is frustrating is the reasoning supporting this conclusion.

In 1948, the Supreme Court ruled in *Funk Brothers v. Kalo Inoculant Co*. that a patent covering a combination of bacteria that facilitated nitrogen fixation in plants was a product of nature and therefore unpatentable.[25] The purported inventor in that case had simply combined naturally occurring bacteria and had not invented anything.[26] This ruling was important in the Supreme Court's 1980 decision, *Diamond v. Chakrab*arty, in which the Court addressed the question of

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[16] *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Offic*e, 653 F.3d 1329, 1334 (Fed. Cir. 2011).

[17] *Association for Molecular Pathology v. Myriad Genetics, Inc*., 132 S.Ct. 1794 (2012) (granting cert. to remand).
[18] *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1309 (Fed. Cir. 2012).
[19] *Id.* at 1326.
[20] *Id.* at 1349 (discussing how Myriad's patents transform natural phenomenon).
[21] *Id.* 1348 (describing Myriad's patent as being "inspired by nature" and the steps needed to create the isolated DNA sequence).
[22] *Id.* at 1353.
[23] *Id.* at 1356.
[24] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 133 S.Ct. 2107 (2013), *aff'g in part, rev'g in part Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303 (Fed, Cir. 2012).
[25] *Funk Bros. Seed Co. v. Kalo Inoculant Co*., 333 U.S. 127, 132 (1948). Judge Learned Hand is often cited for saying that the product of nature exclusion does not exist. See his opinion in *Parke-Davis v. Mulford*, 189 F. 95 (CCSDNY 1911). But this interpretation has been contested and Hand's analysis has been questioned. See Jon M. Harkness, Dicta on Adrenalin(e): Myriad Problems with Learned Hand's Product-of-Nature Pronouncements in Parke-Davis v. Mulford, 93(4) Journal of the Patent and Trademark Office Society 363 (2011).
[26] *Id.* at 130.

whether a genetically modified bacterium was an unpatentable product of nature or a patentable invention.[27] The Court held that the inventor had modified the organism to create a new life form that did not exist in nature.[28] Therefore, the new organism could be patented.[29] The *Diamond v Chakrabarty* decision is famous for the oft repeated line (deriving from the legislative history of the 1950s revision of the US Patent Law) that "anything under the Sun made by man" is potentially patentable.[30]

The Myriad decision is a logical extension of these precedents. The Supreme Court had to determine whether the DNA sequences at issue were natural phenomena or man-made.[31] Its conclusion was that isolated fragments of naturally-occurring DNA are a natural phenomenon but that non-endogenous DNA or cDNA is man-made.[32] The Court's opinion, not surprisingly, parallels the Solicitor General's Brief recommending invalidation of the patent claims relating to isolated DNA sequences, but not cDNA, based on the exception for natural phenomenon.[33] This surprising parallel suggests that the Myriad decision is the product of politics, or a policy judgment.[34]

I would contend that the Myriad decision is in fact policy masked as science. The flaw in the Court's decision is the explicit discussion of patent policy. Instead, the Court seems to rely on expert scientific testimony that was part of the record.[35] The opinion is steeped in a summary of the underlying science. Interestingly, Justice Scalia refused to sign onto the scientific exegesis although he agreed with the result.[36] In his brief concurrence, Justice Scalia rests his decision on a syllogism. Natural phenomena are not patentable. The record shows isolated DNA sequences are

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[27] *Diamond v. Chakrabarty*, 447 U.S. 303, 307 (1980).
[28] *Id.* at 309-10.
[29] *Id.* at 310.
[30] *Id.* at 309 (quoting Senate hearings).
[31] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S.Ct. 2107, 2111 (2013).
[32] *Id.* at 2111.
[33] "Synthesized genetic materials such as cDNA are patent-eligible subject matter because they do not occur in nature but instead are the product of significant human creativity. By contrast, isolated but otherwise unmodified DNA is not patent-eligible. The public's ability to study and use native DNA would be unduly compromised if changes caused by the extraction of naturally-occurring substances from their native environments were sufficient to trigger patent-eligibility. And while the process of isolating DNA entails physical changes, those changes do not significantly alter the structure or function of the relevant DNA segments." See Brief of United States in Association for Molecular Pathology v. Myriad Genetics, Inc., 2013 WL 390999 (U.S.), 9 (U.S.,2013). The Solicitor General's Brief was submitted as a neutral one, not supporting either party, because it offers a compromise position on the validity of Myriad's patents. The Court in turn adopted this compromise in its decision.
[34] "Instead, the distinction looks more like the product of compromise, conveniently advanced in the Solicitor General's brief and happily grasped by the Court. Arriving at a decision that creates the perception of moderation--of compromise--serves the Court's purpose in legitimizing patent law, and, indeed, in legitimizing the Court's institutional role in the patent system, at least among audiences which are unlikely to attempt to deconstruct the gDNA/cDNA distinction as a matter of molecular biology." Timothy R. Holbrook & Mark D. Janis, Expressive Eligibility, 5 UC Irvine L. Rev. 973, 981 (2015)
[35] *Id.* at 2111-12.
[36] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

natural phenomena. Therefore, the patent claims pertaining to isolated DNA sequences are not patentable. Since there is no legal or policy discussion of the first proposition of the syllogism and no extensive analysis of the second, except for a regurgitation in the majority opinion of the science, attorneys, policymakers, and people in industry are left to wonder: What lessons for future cases about DNA sequences, whether human, animal, or plant?

Two possibilities emerge from the opinion. One is a comparison between the claimed DNA sequence and its natural counterpart. If they are identical, then the claimed sequence is a natural phenomenon and unpatentable.

The second possible approach to determining when a DNA sequence is patentable is to focus on the method for uncovering the sequence.[37] The Court emphasizes that isolating DNA sequences snipping the relevant sequence from its natural state, like extracting a mineral from the earth.[38] Constructive synthetic DNA involves scientific activity. With respect to the isolated DNA, the Court rejects the approach of the Federal Circuit that a researcher has to determine where to snip the natural sequence in order to derive the isolated one.[39] That decision was enough to make the isolated sequence man-made for the Federal Circuit. But the Supreme Court does not view that decision as inventive enough. Extraction is not invention while synthesizing is.[40] That distinction seems to be the clearest answer the Supreme Court provides for distinguishing naturally occurring sequences from man-made ones.[41]

In short, the Supreme Court characterized its decision as applying a rule that natural phenomena are not patentable in reaching its decision in the Myriad case. But it is far from clear how this rule was derived and how it is to be applied in practice. On the day the Supreme Court opinion was announced, within hours, the United States Patent and Trademark Office (USPTO) issued a short memorandum to patent examiners summarizing the decision.[42] The memo tracks the Supreme Court's reasoning by stating that patents would not be issued for merely isolating DNA sequences but patents were available for synthetic sequences.[43]

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[37] *See* Pila, *infra* note 56 at 356-60.

[38] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2119 (2013).

[39] *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1365 (Fed. Cir. 2011) cert. granted, judgment vacated sub nom. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794, and opinion vacated, appeal reinstated sub nom. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 467 F. App'x 890 (Fed. Cir. 2012)

[40] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2117 (2013)

[41] *See* JUSTINE PILA, THE REQUIREMENT FOR AN INVENTION IN PATENT LAW 6-7 (2010).

[42] *See* Memo available at http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf

[43] *Id.*

The USPTO has provided guidelines on how to implement *Myriad* in the prosecution of patent applications.[44] The Supreme Court ruling suggests is that merely identifying naturally DNA sequences cannot be the basis for a patent. Interpreted in this way, researchers and inventors will have to put more effort in creating synthetic forms and in developing inventions that tap the DNA sequences that have been mined. Arguably, such efforts can only enrich the industry and make the field more competitive and innovative. It would have been more devastating if the *AMP v Myriad* decision had issued twenty-five years ago when identification of genomes, human, animal, and plant, was in its infancy. At that earlier stage, limitations on patenting, as we see in Myriad, might have altered the field. But since the future is in synthetic DNA and in applications of isolated sequences,[45] two areas of invention left untouched by the opinion, the Supreme Court may have just shut the barn door when the naturally occurring horse has been let loose. Instead of bemoaning lost patents, attention should turn towards the future. In that way, the *AMP v Myriad* decision may actually be ushering in the next stage of the genomic revolution.

One indication of the controversy over the Supreme Court's decision in Myriad is the 2014 opinion by the Australian High Court in New South Wales rejecting the Supreme Court's analysis in favor of the Federal Circuit's in a challenge to Myriad's Australian patent on the isolated breast cancer gene.[46] The High Court quoted the Supreme Court's language that "such important and useful genes had never been located or isolated from surrounding genetic materials."[47] In finding invention in the identification and isolation of the gene mutation, the High Court rejected the Supreme Court's emphasis on the information content of the isolated gene sequence.[48] Even if the information content in the isolated and naturally occurring genes were identical, the High Court concluded that the chemical compositions of the two sequences were different.[49] Citing the Federal Circuit majority opinion, the Australian High Court concluded that the chemical difference was enough to make the isolate sequence patentable.[50]

Genes as Natural Phenomena and the Implications for Genes as Data

"We merely hold that genes and the information they encode are not patent eligible under s. 101 simply because they have been isolated from the surrounding genetic material," announced the Supreme Court in its *AMP v Myriad* decision.[51] What is striking is the use of the word "merely." Understatement in part as the adverb diminishes the broad implications of the Court's ruling for

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[44] *See* 2014 Memo at http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf. The USPTO tries to translate the judicial decision into a flowchart that an examiner can apply almost mechanically, following the language of the decision. See https://www.uspto.gov/sites/default/files/documents/wrksht-sme-blnk-nbp.pdf

[45] *See, e.g.*, Eyal Karzbrun, Alexandra M. Tayar, Vincent Noireaux, & Roy H. Bar-Ziv, *Programmable On-Chip DNA Compartments as Artificial Cells*, 345 SCIENCE 829.

[46] *D'Arcy v Myriad Genetics In*c [2014] FCAFC 115..

[47] I*d.* at ¶ 135.

[48] *Id.* at ¶ 155

[49] *Id.* at ¶ 149.

[50] *Id.* at ¶ 211-12.

[51] Myriad, supra note 22 at 2107.

patenting isolated DNA sequences, the word choice is accurate as to the implications of the decision. The Court leaves open patenting of synthetic DNA sequences, which is the future for biotechnology. Although undefined by the Court, synthetic DNA includes modifications of isolated, naturally occurring DNA sequences for therapeutic purposes and the creation of synthetic compounds, such as Humulin, or synthetic insulin. Invention of synthetic DNA can require access to naturally occurring DNA, which is now unpatentable and therefore readily available (absent other protections) for researchers in industry and universities. In short, the *AMP v Myriad* decision merely made available a key component for the synthetic DNA industry.

The decision also merely provided a boon to the emerging data mining industry for the development of new drugs and therapies. As the Supreme Court stated in *AMP v My*riad: "[T]his case does not involve patents on new *applications* of knowledge about the BRCA 1 and BRCA2 genes."[52] One new application is to genomic medicine. Myriad's patenting behavior since 2007 shows a shift towards genetic data mining as an innovative business strategy. By merely finding isolated naturally occurring DNA sequences unpatentable, the Court's *AMP v Myriad* decision actually benefitted Myriad the company. This section examines this assertion. The next, and final, section sets forth possible legal and policy responses to this industry shift.

Myriad's patenting behavior provides evidence of the company's shift from isolating DNA sequences to methods for analyzing DNA for the purposes of therapy and prognosis. In 2014, the USPTO published a Myriad patent application for identifying hereditary cancer genes. In 2015, a patent application for "Gene signatures for cancer prognosis" was published, followed by the publication in 2017 of a continuation application.[53] Other published patent applications include "Gene signatures for renal cancer prognosis" in 2016;[54] "Genes and gene signatures for diagnosis and treatment of melanoma" in 2017;[55] "Methods and materials for assessing allelic imbalance" in 2017[56]; and "BRCA deficiency and methods of use" in 2014.[57] While these applications are pending review, the USPTO has granted a patent covering "Screening methods and sequences relating thereto" in 2017,[58] numerous design patents covering medical forms and labels to tabulate and analyze genetic data in 2015 and 2016,[59] and uses of the BRCA2 mutation in 2013.[60] These are just some examples of Myriad's patenting behavior in the United States, and there are corresponding applications in Japan, the European Patent Office, and at WIPO.[61] These patents

[52] Id.
[53] See US Patent Application No. 15/331076 (Jun 1, 2017); US Patent Application No. 14/713636 (Sep 3, 2015).
[54] See US Patent Application No. 15/171993 (Sep 29, 2016).
[55] See US Patent Application No. 15/388979 (Jul 13, 2017).
[56] See US Patent Application No. 15/412404 (May 11, 2017).
[57] See US Patent Application No. 13/852129 (Jan 23, 2014).
[58] See US Patent Application No. 12/572121 (granted Apr 18, 2017).
[59] See, e.g., US Patent Application No. 29/487239 (granted Jun 2, 2015); U.S. Patent Application No. 29/487249 (granted Aug 23, 2016).
[60] See US Patent Application No. 13/167481 (granted Jul 2, 2013).
[61] Data available from author upon request.

and applications show research and development activity and business interests in the field of data mining. Myriad's activity parallel data mining and data processing patenting more broadly. For example, Microsoft was granted a patent for a "Method and Apparatus for Exchanging Data with a Database"[62] and Google, a patent for "Searching Structured Geographical Data."[63] Microsoft's patent is a component of its smart phone product and its applications while Google's patent is related to its map and direction guidance products. Myriad's data mining patent relates to genomic diagnostics and therapies. I discuss these patent applications and patents in the next section to illustrate the direction of research and development activity subsequent to the Myriad decision.

One might suspect that the Supreme Court's 2014 decision in *Alice*, which raised the requirements for process patents like the ones Myriad has been seeking, would affect the success of datamining patenting. However, the last three patent applications resulted in issued patents after the 2014 decision. The 2015 and 2016 patents covered the design of various forms for the purpose of tabulating and analyzing genetic data. The 2017 patent was for a method patent that had been initially rejected by the examiner for lack of novelty before the *Alice* decision. The Patent Trial and Appeal Board reversed the examiner's findings and the patent was granted. While the Alice decision may dampen Myriad's efforts to patent inventions covering the mining of genetic data, it seems clear that in the wake of the *Myriad* decision, Myriad the company was charting a course of research and development that would rely upon access to isolated DNA sequences. The Supreme Court's decision making isolated DNA sequences unpatentable would facilitate this direction of research and development.

The direction of Myriad's business enterprise is found in its activities challenging granting patents of potential rival companies. In 2011, with the passage of the *America Invents Act*, Congress introduced the Inter Partes Review (IPR), an administrative proceeding that allows an affected party to challenge granted parties on grounds of lack of novelty or non-obviousness. Myriad has initiated several IPR petitions challenging granted patents in the field of data-mining. In 2014, Myriad challenged nine patents involving sequence detection and data analytics relating to various types of cancers. These nine patents had been granted to GeneDX, Inc., a company engaged in precision medicine. Myriad settled its dispute with GeneDX, Inc., as permitted under the *America Invents Act.* Johns Hopkins' patents were the target of Myriad's IPR petitions in 2017. Four patents involving data analytics of gene sequences were at issue, and once again Myriad settled with Johns Hopkins.[64] The terms of these settlements are confidential. Settlement, however, keeps the patents alive. We can only speculate about the terms of settlement between Myriad and GeneDX and Johns Hopkins respectively. Nonetheless, the filing of the petitions is revealing of where Myriad sees its business interests and complements the company's patenting strategy in the field of genetic data analytics.

[62] Patent No. 7877417 (2011).
[63] Patent No. 7836085 (2010).
[64] Data available upon request from author.

Brendan Frey, CEO of Deep Genomics, provides an insightful picture of the market landscape for genetic patenting after the *AMP v Myriad* decision:

> The core idea of Deep Genomics is that the pharmaceutical company of the future is going to look like a computer science company with an amazing team of biologists and chemists and experts in clinical trials rather than a traditional pharmaceutical company with biologists and chemists who are using computational tools. It's a question of culture; it'll be a culture of computer science.[65]

Whether Myriad has engaged the culture of computer science is a question that can only be answered by those inside the company. But Mr. Frey's description points to the synthesis of biology and data analytics that is one possible future for genomic based medicine. One indication of what is on the horizon is the development of artificial intelligence patents. A search of the USPTO patent database for computation-directed inventions uncovered 7524 applications since 2011 with a general allowance rate of 87.5 per cent (a total of 6583 granted AI related patents).[66] These patents were examined in two USPTO Art Units (i.e. groups of patent office examiners), numbers 2121 and 2129, responsible for reviewing inventions relating to artificial intelligence. Unit 2121 deals with all AI-related inventions that are software based and has an allowance rate of 72.6 per cent. Unit 2129, by contrast, deals with artificial intelligence that is part of a system of electronic control and has an allowance rate of 80.6 per cent. Since AI patents are general use technology and not platform specific, AI inventions tied particularly to biotechnology and genomics are not identifiable. But one might predict that AI applications to genetic data-mining may be the next generation of biotechnology patenting.

One study of the impact of the Alice decision showed that "the class with the greatest percentage of applications with Alice rejections is class 705, which handles 'data processing: financial, business practice, management, or cost/price determination' applications. After class 705, the rate at which applications contain Alice rejections drops significantly."[67] Research on the Artificial Intelligence class of patents support a decline in the patent allowance rate after the Alice decision. Studying patent class 706, which covers "Data Processing: Artificial Intelligence" inventions reveals a 31.2% allowance rate in 2018, and allowance rates of 50.7% (2017), 60.3% (2016), 65.7% (2015), 66% (2014), 65.5% (2013), 71.5% (2012), and 75.3 (2011). These data are consistent with a decreased allowance rate post-Alice. However, breaking down the classification

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[65] Allison Proffitt, "Deep Genomics Shifts Focus to Genetic Medicines," Bio-IT World (May 12, 2017) available at http://www.bio-itworld.com/2017/05/12/deep-genomics-shifts-focus-genetic-medicines.aspx.

[66] Data available at www.uspto.gov, compiled and analyzed by author in September, 2017. These statistics are before the Supreme Court's *Alice* decision in 2014, which limited the patentability of method claims. One would predict that the allowance rates would have decreased since 2014.

[67] See James Cosgrove, Alice Three Years Out (July 19, 2017) available at https://blog.juristat.com/2017/7/19/alice-three-years-on.

shows the impact may be mixed across inventions even within the Artificial Intelligence category. An examination of related classes, 700 (Data Processing: Generic Control Systems or Specific Application), with an additional small percentage of 711 (Memory (electrical computers and digital processing systems)) and 713 (Support (electrical computers and digital processing systems)), reveals little change in the allowance rate from 2014 to 2018.[68] The Supreme Court's limitations on process patents in its Alice decision has had an effect on allowance rates in the fields of e-commerce, Artificial Intelligence, and data mining, but the magnitude of the effect varies by class of invention and may not be as dramatic in the aggregate. Consequently, the decision may not dissuade companies seeking patents in field of genetic data-mining.

Myriad's turn towards data-mining patents is consistent with the Supreme Court's analysis in *AMP v Myriad*. While the decision is heavy on the science, a point I return to in the conclusion of this Article, the Supreme Court's decision rests on the principle that natural phenomenon are not patentable. The Court has restricted patentable subject matter on the basis of this principle, not least from 1874 decision in *American Wood Paper Co. v. Fibre Disintegrating Co*.,[69] which found refined cellulose caused by decomposition to be unpatentable. The cellulose in question was a product of nature, and *not* the product of human invention. A decade later, the Supreme Court found unpatentable an artificial version of a red dye in *Cochrane v. Badische Fabrik*.[70] Once again, the alleged invention was a product derived from nature rather than the product of human ingenuity. In its first decision on natural phenomenon in the twentieth century, the Court found unpatentable a method for treating the skin of fruit with mold-resistant borax in *American Fruit Growers v. Brogdex*.[71] As discussed earlier, a patent for a mixture of naturally occurring bacteria was rejected in the 1948 *Funk Brothers* decision.[72] Only in 1980, did the perspective on natural phenomenon change when the Supreme Court found patentable a man-made bacterium because it did not exist in nature. More importantly, the genetically modified bacterium in *Diamond v Chakrabarty* was not simply taken from or discovered in nature.[73]

What the items found to be unpatentable have in common in the line of 'products of nature' cases is that the alleged inventions were taken from nature. They were extracted from the natural world rather than being the product of human invention. The Supreme Court case law draws a line between two types of industries, one the product of human invention and hence patentable subject matter, and the other the product of human mining and extraction and hence unpatentable. One can understand this distinction in terms of diverging property rights systems. Extractive industries, such as mining gems or drilling for oil, are protected by their own unique property system. Patent law would be redundant and unnecessary because of the alternative system of legal rights.

[68] Data collected and analyzed by author, on file with author.
[69] 90 US 566 (1874).
[70] 111 US 293 (1884).
[71] 283 US 1 (1931).
[72] See supra note 42.
[73] See supra note 44.

Inventive industries however require a different property right regime, one provided by the rules of patent.

The distinction between extraction industries and inventive industries explains what the US Supreme Court has done with naturally occurring DNA sequences. Isolating such DNA sequences involve extraction, not invention. As we see, patenting activity turns to methods and tools for extracting and analyzing naturally occurring DNA sequences for the creation of therapeutic and diagnostic techniques grounded in data analytics. Naturally occurring genes are the object of extraction with data analysis being the potential source of invention. Current patenting activity is evidence for the future of this industry of data-extracting and data-processing, with patents supporting the latter.

A Closer Look at Myriad's Patenting Activity and Business Practices

The previous section described some recent patent applications filed by Myriad as support of their activities in developing data-mining inventions. In this section, these applications, particularly ones that have resulted in granted patents, are discussed in further detail. A deeper exploration of these applications shows a direction for the future of genomic medicine after the 2013 Myriad decision. With isolated genetic sequences unpatentable, genetic data becomes a resource for the data-mining industry. Further evidence for this direction of inventive activity is provided by a an examination of Myriad's annual reports before and after the Myriad decision.

Myriad's application for "Screening Methods and Sequences Thereto" resulted in an issued patent in 2017.[74] The abstract for the issued patent states: "Disclosed are screening methods and sequences related thereto. Disclosed are methods for detecting mutations in the MYH gene of an individual. Also disclosed are methods of genotyping and methods of predicting for an individual the likelihood of developing certain cancers, such as colorectal cancer." The first independent claim covers: "A method for screening a sample for a mutation in an MYH nucleic acid comprising: obtaining a sample of an individual; analyzing an MYH nucleic acid in said sample; and detecting a mutation in said MYH nucleic acid of said sample resulting in the amino acid variant Y165C." The 2017 patent covers a method of diagnosis that involves identifying a mutation in a sample of nucleic acid to detect a variant. This variant, as several dependent claims set forth, is correlated with family medical history to determine likelihood of colorectal cancer. The last independent claim sets forth the synthesizes the steps: "A method of genotyping, comprising: detecting, in a sample of an individual identified as (a) diagnosed with colorectal cancer, (b) diagnosed with colorectal adenomas, (c) having at least one family member diagnosed with colorectal cancer, or (d) at an increased risk for colorectal cancer, that the individual has a

[74] U.S. Pat.No. 9624546.

nucleotide variant in an MYH nucleic acid of the individual that results in the amino acid variant Y165C." There are no claims covering isolated DNA sequences or the mutation, consistent with the Court's 2013 ruling. However, the patent does grant Myriad rights over a method of identifying and analyzing data for diagnostic purposes.

A few weeks after the Supreme Court's decision ruling against its isolated DNA patents, Myriad obtained a utility patent on the use of BRCA2 mutations. Although not covering the gene sequence, the patent provides protection in the area of medical diagnostics, consistent with the 2017 patent discussed in the previous paragraph. An independent claim in the 2013 patent covers: "A method of genotyping, comprising: obtaining a tissue sample or cells from a human patient identified as, or suspected of, having an increased predisposition to breast and ovarian cancer; and performing a nucleic acid-based assay to detect in said tissue sample or cells a deletion of five nucleotides in a BRCA2 allele beginning at the cDNA position of 7,044."[75] As with the 2017 patent, the 2013 patent covers a method for analyzing genetic sequences to make a medical diagnosis.

Myriad's other issued patents relevant to data-mining are in the design area. It is unusual for a genetics company to obtain design patents, but their issuance supports the pursuit of a data-mining and analytics strategy. Both design patents cover a form, specifically one for organizing and representing data. The 2014 patent claims a particular layout and color scheme for demarcating the presentation of data.[76] The 2016 patent claims a variation of the 2014 design patent with a different color coding and diagonal representation of data.[77] The pursuit of such design patents for a genomics company indicates an interest in developing valuable forms of data visualization and representation, consistent with the goals of developing data analytics.

A look at Mryiad's annual reports shows how the company has been moving into data analytics and, to use the company's term, "robotics."

Other Notable Developments in the Law of Genomic Medicine

In 2012, the US Supreme Court ruled on the patentability of a therapeutic method for the treatment of Crohn's disease in a dispute between patent owner Prometheus Labs and alleged infringer the Mayo Clinic.[78] The patent covered the adjustment of dosage for a drug therapy in response to biometrics taken from a Crohn's patient obtaining treatment.[79] As a therapeutic method, the patent directly covered a method of administering personalized medicine since the adjustment in dosage was based on specific biometric characteristics of the patient, namely the

[75] U.S. Pat. No. 8476020.
[76] US Pat.No. D730981.
[77] US Pat. No. D764481.
[78] *Mayo Collaborative Servs. v. Prometheus Labs., Inc*., 132 S. Ct. 1289, 182 L. Ed. 2d 321 (2012).
[79] *Id.* at 1295.

level of vitamin B-12 measured after an initial administration of the drug.[80] The Court invalidated the patent on the therapeutic method because the claims covered a law of nature, specifically the statistical correlation between the amount of drug administered and the level of vitamin B-12.[81] The Court also expressed concerns with the policy of interfering in medical treatment by limiting the ability of the medical practitioner to calculate a correlation in her head while treating a patient.[82]

One example of the compounding effects of *AMP v Myr*iad and *Prometheus v Mayo* is provided by the 2014 decision in the United States Federal District Court for Delaware, invalidating a patent for identifying and selecting genetic characteristics associated with athletic ability. Owned by the Australian company, Genetic Technologies Limited, the patent covered "a method to predict potential springing, strength or power performance in a human."[83] The claims covered processes for identifying specific alleles in genes and making a prediction about athletic ability based on the presence of the alleles in the identified genetic sequence.[84] On a motion to dismiss, the court ruled that there was no plausible basis for the patentability of this claim under the standards of *Prometheus v Mayo* and *AMP v Myriad*.[85] The magistrate judge recommended that the claims covered laws of nature and natural phenomena, and the inventor had added little inventiveness beyond the identification of a correlation between a naturally occurring sequence and athletic ability.[86]

What is striking about the Delaware Court's opinion is its ruling on a pretrial motion to invalidate the patent. Although a magistrate's decision, the opinion rested on the plausibility of the invention being patentable in light of the Supreme Court's limitations on patentable subject matter.[87] This decision is one of the few applying the Twombly/Iqbal standard[88] for motions to dismiss for failure to state a claim in the patent context.[89] While the plausibility ostensibly rests

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[80] *Id.* at 1296.
[81] *Id.*
[82] *Id.* at 1302.
[83] *Genetic Tech. Ltd. v. Lab. Corp. of Am. Holdings*, No. 12-1736-LPS-CJB, 2014 WL 4379587, at *3 (D. Del. Sept. 3, 2014).
[84] *Id.*
[85] *Id.*
[86] *See id.* at 26 (explaining that merely pointing out someone will have relatively greater performance due to the presence of the genetic variation does not amount to an "application of the law of nature to a new and useful end").
[87] *Id.* at 9.
[88] *See Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009).
[89] *See* Arthur Miller, *From Conley to Twombly to Iqbal: A Double Play on the Federal Rules of Civil Procedure*, 60 DUKE L.J. 1, 14 (2010); *see also* Chris Morrison & J. Patrick Elsevier, *Macronix Ruling Revives Twombly Questions in Patent Cases*, LAW360 (Mar. 25, 2014), http://www.law360.com/articles/520186/macronix-ruling-revives-twombly-questions-in-patent-cases?article_related_content=1 (explaining that in the context of patent cases, the strict Twombly/Iqbal standard has not been regularly used).

on applying the legal standard for patentability,[90] implicit is an assessment of the scientific basis for the invention. In other words, given the science, the court was examining the claimed invention in light of the scientific background to conclude the viability of the patent owner's claim of ownership of patentable subject matter.

The problems with knowledge and information in personalized medicine also provides the basis for the FDA's investigation of 23andMe, a company that provides through the mail prognoses of proclivities to disease based on personalized genetic samples.[91] The case of 23andMe was the motivating example in the introduction to this article and serves as the final example of the travails of personalized medicine companies.

Until a complaint was brought by the Food and Drug Administration in November, 2013, 23andMe sold direct-to-consumer genetic testing.[92] The Mountain View, California, company, founded in 2006, operates at the intersection of biotechnology and information technology by combining "potential of personal genetic information and web-based interactive tools" to "empower individuals to access and understand their own genetic information while also holding the potential of accelerating research in the field of genetics."[93]

To what extent does such a company empower individuals? The ideal is one of providing individuals with personal information about their genetic ancestry and disease proclivities. An individual, armed with such information, can make better decisions about health care over one's lifetime. The information includes a tracing of genetic ancestry and identification of proclivities to disease based on ethnicity.[94] However, empowerment comes at a cost. 23andMe collects the information into a database that would arguably be proprietary. The construction and use of such a database creates issues of privacy as well as ownership over data. Furthermore, a company like 23andMe largely determines how the genetic information is packaged and communicated to the consumer. In turn, the packaging of information shapes how individual consumers and the medical profession may understand the health characteristics of patients. Industry marketing and packaging shape the vocabulary for personal identity in genetic categories.

In a letter to 23andMe, published on the FDA website, the agency stated that "even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS [Personal Genome Service] for its intended uses, which

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[90] *See* Damon C. Andrews, *Iqbal-ing Seagate: Plausibility Pleading of Willful Patent Infringement*, 25 BERKELEY TECH. L.J. 1955, 1967-68 (2010).
[91] *See* Warning Letter from Alberto Gutierrez, Dir., Office of In Vitro Diagnostics & Radiological Health, Food & Drug Admin., to Ann Wojcicki, CEO, 23andMe, Inc. (Nov. 22, 2013), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm (accessed November 10, 2014).
[92] *Id.*
[93] Matthew Rimmer, *23andMe, Inc.: Patent Law and Lifestyle Genetics*, 22(1) J. OF L., INFO., & SCI. 25, EAP 2 (2012).
[94] *Id.* at EAP 4.

have expanded from the uses that the firm identified in its submissions [for marketing approval]."[95] According to the agency, there is no scientific support for the claims made by 23andMe in its advertising for diagnosing or informing consumers about the predictions made from genetic testing.[96]

The lack of scientific basis and explanation for the reports made by the company is echoed in a complaint filed by a nationwide class of consumers against 23andMe shortly after the FDA complaint. The class action plaintiffs alleged that the company advertises that it provides " 'health reports on 240+ conditions and traits', 'drug response', 'carrier status', among other things, when there is no analytical or clinical validation for the PGS for its advertised uses."[97] The class action complaint further alleges that 23andMe "uses the information it collects from the DNA tests consumers pay to take to generate databases and statistical information that it then markets to other sources and the scientific community in general, even though the test results are meaningless."[98]

Because of these complaints, 23andMe ceased providing health related reports, but continues to provide ancestry reports and raw genetic data based on the samples provided by customers.[99] As with the other examples of personalized medicine related companies, the story of 23andMe demonstrates the differences in information between companies and consumers and the controversies over the underlying science supporting the services being advertised and provided. These two concerns—information differences and uncertainty as to the science—define the market failures providing the basis for policy reform.

Patent Policies: Looking Forward

By categorizing isolated DNA sequences as a natural phenomenon, the Supreme Court has aligned patent doctrine with current developments in biotechnology and genomic medicine. Data-mining facilitates algorithmic study of natural DNA sequences for the development of medical diagnostics and therapies, including synthetic DNA which the Supreme Court clarified was patentable subject matter. Patenting patterns and scientific developments are consistent with this legal and business environment. How should patent policy respond? This question is the motivation for this concluding section.

One important policy objective is to avoid creating obstacles to scientific and medical research. Genetic data are a resource for new medical understanding and approaches to medical treatment. Artificial intelligence, for example, can scan biometric data, including gene sequences,

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[95] *See* FDA WARNING LETTER, *supra* note 79.
[96] *Id.*
[97] Class Action Complaint at 1, No. 13-CV-2847-H-JMA, 2013 WL 6687874 (Nov. 27, 2013).
[98] *Id.* at 2.
[99] 23ANDME, https://www.23andme.com (last visited Jan. 28, 2015) (displaying company's disclaimer at the top of the website that health-related genetic reports are no longer provided).

to supplement clot-busting drugs and surgery as a way to treat potential stroke victims. Higher accuracy and productivity in health care are predicted.[100] Artificial intelligence technologies, for example, "might also make medicine more specific, by being able to draw distinctions that elude human observers."[101] Genomic medicine has been limited by focusing on only portions of the DNA sequence that are loci of weaknesses and cancer markers. Advances in techniques arising from the intersection of computer and genetic science allow for analysis of the full DNA sequence and more precise medical diagnoses.[102] Patent policy, and patent politics, should work closely with scientific communities in addressing the concerns of constituencies with these new medical techniques.

The Supreme Court's decision in *AMP v Myriad* rests heavily on recitations of science, so much so that Justice Scalia felt compelled to write a concurrence in which he expressed discomfort in signing onto most of the heavily scientific discussion in the majority opinion while agreeing with the result. The Court's embrace of science, in part, provides a factual basis for identifying isolated DNA sequences as a natural phenomenon. Deference to the scientific community is implicit in the Court's exegesis of the science of DNA. What is unsatisfactory is the lack of any engagement with patent policy and concerns over the effects of DNA patenting on access to genetic diagnostics. The Court consciously avoids the policy questions by appealing to a legal rule ("natural phenomena are not patentable") and drawing on scientific facts to apply the rule.

But the policy questions persist. Professor Shobita Parthasarthy has documented the policy debates and market politics following *AMP v Myriad* and DNA patenting in the path leading to the Supreme Court's decision.[103] As she concludes from the battles over Myriad's BRCA patents, "citizens are deeply concerned about who owns technology and about the power that this ownership confers."[104] A recurring concern is data privacy and misuse of patent records.[105] But the concerns will also extend to the costs and access to the new medical technologies. The *AMP v Myriad* decision, as I have argued, has made possible, among other developments, this new medical landscape. The Court's overemphasis of science and lack of attention to the doctrinal and policy details makes the decision a weak basis for how to address citizen concerns over data-mining and algorithmic medicine. Future research must pay attention to the markets arising in this

[100] "From A&E to AI," The Economist 69 (June 9, 2018).
[101] Id.
[102] Viktor Mayer-Schonberger & Kenneth Cukier, Big Data: A Revolution That Will Transform How We Live, Work, and Think 25 (2013).
[103] Shobita Parthasarathy, Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care (2007); Patent Politics: Life Forms, Markets & the Public Interest in the United States & Europe (2017).
[104] Patent Politics, supra note 90 at 197.
[105] See, e.g., Adam Tanner, Our Bodies, Our Data: How Companies Make Billions Selling Our Medical Records 56-57 (2017),

new era of data-driven medicine. This Article has set forth the parameters for this future research.[106]

[106] For a discussion of possible policy responses, see Ghosh, supra note 2; Shubha Ghosh, Decentering the Consuming Self: Personalized Medicine, Science, and the Market for Lemons, 5 Wake Forest J.L. & Pol'y 299, 300 (2015).