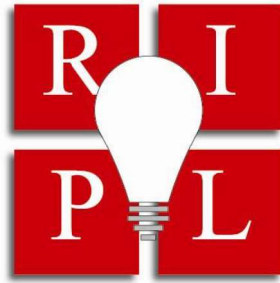


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THE PATENTING OF GENE BASED DIAGNOSTIC ASSAYS IN A POST MAYO AND MYRIAD WORLD

MICHAEL A. SANZO

ABSTRACT

Recent advances in biotechnology have given researchers the ability to comprehensively examine the genetic basis of disease in unprecedented ways and will undoubtedly result in many new and valuable gene based diagnostic assays in the near future. These advances came during a period of roughly thirty years during which the patent eligibility of such assays was essentially unquestioned. Then, beginning in 2010, the Supreme Court embarked on a series of decisions that will, in almost all cases, preclude the patenting of diagnostic assays that rely on genetic mutations or gene expression patterns. This article suggests that reason that the issue of patent eligibility went unquestioned in the biotechnology industry for so long is due to early Supreme Court decisions that took conflicting approaches to analyzing patent eligibility. It also examines why the patent eligibility test that has now been adopted by the Supreme Court is so devastating to the patenting of gene based assays.

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AND MYRIAD WORLD

MICHAEL A. SANZO

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THE PATENTING OF GENE BASED DIAGNOSTIC ASSAYS IN A POST MAYO AND MYRIAD WORLD

MICHAEL A. SANZO*

I. INTRODUCTION

On April 14, 2003, the International Human Genome Sequencing Consortium announced that it had completed sequencing the approximately 3 billion nucleotides making up the human genome. The project had taken about 10 years, involved over 200 researchers and had cost about 3 billion dollars.¹ By 2014, the time needed for the complete sequencing of a genome had been reduced to 50 hours, at a cost of \$6,500 and there are currently procedures available that can purportedly obtain a complete sequence in 26 hours at \$1,000–\$1,500 per person.² For the first time, scientists are able to comprehensively compare the genomes of diseased and normal individuals and, as a result, gene based diagnostic methods are poised to enter an unparalleled period of discovery.

This remarkable advancement has occurred during a 30-year period in which court decisions established, and then repeatedly confirmed, the patentability of genes and gene based diagnostic methods. Then, in a rapid series of cases beginning in 2010, isolated genes were declared unpatentable products of nature and criteria were established that essentially ensure that nearly all gene based diagnostic tests will be found to be patent ineligible. As a result of these cases, thousands of patent claims have been invalidated and companies operating in the diagnostic field have struggled to develop new strategies for protecting intellectual property.

This paper will examine exactly where we are now with respect to the patenting of genes and gene based diagnostic methods and how an entire industry got things so wrong for so many years.

* © Michael A. Sanzo 2016. Ph.D., J.D., and is a patent attorney working in the areas of chemistry, biotechnology, and pharmaceuticals. The opinions expressed herein are solely those of the author and do not necessarily reflect those of any organization with which he is associated.

¹ Gina Kolata, *Human Genome, Then and Now*, N.Y. TIMES, Apr. 16, 2013, at D3; International Consortium Completes Human Genome Project, All Goals Achieved; New Vision for Genome Research Unveiled, National Human Genome Research Inst., <https://www.genome.gov/11006929/2003-release-international-consortium-completes-hgp/> (last visited Aug. 31, 2016); Erika Hayden, *Technology: The \$1,000 genome*, 507 NATURE 294-295 (March 2014).

² Neil A. Miller et al., *A 26-hour system of highly sensitive whole genome sequencing for emergency management of genetic diseases*, 7 GENOME MEDICINE 100 (2015); Claire Maldarelli, *We Can Now Sequence A Whole Human Genome In 26 Hours*, POPULAR SCIENCE (Sept. 30, 2015), <http://www.popsci.com/scientists-can-now-sequence-whole-genome-in-26-hours>; ; Michele Munz, *New Genome Technology Opens Door to Large-Scale Disease Studies*, ST. LOUIS POST DISPATCH, May 5, 2015.

II. HISTORICAL PERSPECTIVE

Historically, there are four major Supreme Court cases that are usually recognized as being of particular importance with respect to patent eligibility: *Funk Bros. Seed Co. v. Kalo Inoculant Co.*,³ *Parker v. Flook*,⁴ *Diamond v. Chakrabarty*,⁵ and *Diamond v. Diehr*.⁶ These cases all agree with the basic premise that a law of nature, an abstract principle or a product of nature are not themselves patent eligible but may sometimes become patent eligible if they are part of a broader claim. Where the cases differ is in the way that they analyze claims and reach conclusions regarding eligibility.

Two of the cases, *Funk Bros.* and *Flook*, analyze patent eligibility by “claim dissection.” In this form of analysis, each individual element in a claim is separately reviewed to determine whether it would be considered patent ineligible if claimed alone. If such subject matter is present, then the other claim elements are examined to determine whether they are “inventive” when considered in the absence of the patent ineligible elements. Concepts of patentability and patent eligibility tend to be mixed together in these cases in a way that, as we shall see, will almost inevitably lead to a conclusion that a gene based diagnostic method is patent ineligible.

In contrast, the *Chakrabarty* and *Diehr* cases begin analysis by asking whether a claim as a whole is directed to a law of nature⁷ or is limited to a particular application of the law. Claim elements are not separated from one another; concepts of patent eligibility and patentability are kept distinct and contributions of laws of nature to inventiveness are considered. For the purposes of the present discussion, this approach will be referred to as “whole claim analysis.” Although these decisions have been characterized as following *Funk Bros.* and *Flook*, the cases are, in fact, essentially incompatible with one another and produce diametrically opposed results.

The sections that follow examine how the different approaches taken by the Supreme Court have contributed to the crisis that now exists with respect to the patentability of gene based diagnostic methods.

A. Analysis by Claim Dissection (*Funk Bros.* and *Flook*)

Probably the best starting point in discussing patent eligibility is with *Funk Bros. Seed Co. v. Kalo Inoculant Co.*⁸ This decision occurred in 1948, four years prior to the 1952 revisions in patent law, and at a time when courts often mixed together different criteria of patentability.⁹ At issue was the validity of claims to an inoculant composition made up of distinct strains of bacteria, each with the ability to infect a

³ 333 U.S. 127 (1948).

⁴ 437 U.S. 584 (1978).

⁵ 447 U.S. 303 (1980).

⁶ 450 U.S. 175 (1981).

⁷ Natural processes may be regarded as laws of nature and genes as products of nature. For the purposes of the present analysis, all patent ineligible subject matter is considered as a whole. It will be understood that, unless otherwise indicated, reference to one form of patent ineligible subject matter includes the other forms as well.

⁸ 333 U.S. at 127.

⁹ *See id.*

single type of leguminous plant and serve as a source of nitrogen. Apart from the bacteria having been selected so as to not interfere with one another's ability to carry out this function, they were unchanged from their state in nature.

The approach taken by the Supreme Court in this case exemplifies the claim dissection approach and can be seen in the following comments by the Court:

Each of the species of root-nodule bacteria contained in the package infects the same group of leguminous plants which it always infected. No species acquires a different use. The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.¹⁰

The Court does not simply ask whether the claimed inoculum is found in nature, but instead begins by considering each element of the inoculum, i.e., each strain of bacteria, and asking whether it is acting in a new and distinct way. The focus is on whether the composition changes the activity of each bacterial strain and not on whether the composition itself is performing in a different way than compositions found in nature. In this regard, it is worth noting that the patent did not claim individual bacterial strains and that the Court never suggests that the claimed combination exists in nature.

The opinion then continues with, what today, would most closely resemble an analysis of the novelty and nonobviousness of the inoculum:

Even though it [the inoculum] may have been the product of skill, it certainly was not the product of invention. There is no way in which we could call it such unless we borrowed invention from the discovery of the natural principle itself. That is to say, there is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed. All that remains, therefore, are advantages of the mixed inoculants themselves. They are not enough.¹¹

The prohibition on borrowing "invention" from a law of nature is an important characteristic of cases following the *Funk Bros.* model.¹² In this view, once subject matter is deemed to be a law or product of nature, it cannot itself make a contribution to the novelty and nonobviousness (or "invention") of a claim. The effect of this on claims to gene based diagnostic assays is devastating. The "inventiveness" of these

¹⁰ See *id.* at 131.

¹¹ See *id.* at 132.

¹² The meaning of the term "invention" in pre and post 1952 cases is discussed by Judge Rich in *In re Bergy*, 596 F.2d 952, 959 (1979). As used in the *Funk Bros.* case, the term appears to be closer to "patentability" than "nonobviousness" in today's parlance.

assays is usually based on a discovery of a relationship between mutations or gene expression patterns and disease and these relationships are considered to be laws of nature. Eliminating their contribution to “invention” goes to the very heart of claims to these assays.

Finally, it is important to recognize the way in which this case mixes different aspects of patent law to produce a muddled result in which neither patentability nor patent eligibility is clearly addressed. Justice Douglas seems to find the claimed composition to be unpatentable because all of the bacterial components that make it up are products of nature and the products of nature to be patent ineligible because the claim is unpatentable.

A second case that has served prominently as a precedent in patent eligibility cases is *Parker v. Flook*,¹³ a decision in which the Supreme Court considered the patent eligibility of claims to a method for determining an “alarm limit.” In the context of the case, alarm limits are values used during chemical reactions to signal that a parameter such as temperature or pressure is exceeding a point where the reaction can proceed in a safe and efficient manner. The claimed method consisted of: (a) monitoring the parameter of interest, e.g., temperature; (b) using an algorithm to calculate an alarm limit based on changes in the parameter; and (c) setting the alarm limit based on the calculation. The only thing distinguishing the invention from prior art procedures was the use of the algorithm.

Even though *Flook* was decided in 1978, long after the 1952 revisions to patent law had clarified and separated different aspects of patentability, it took the same approach to analyzing patent eligibility as used in the *Funk Bros.* case. Concepts of patent eligibility and patentability are mixed together and contributions of the purported law of nature (or in this case, the algorithm) are excluded from consideration. This is illustrated in the decision as follows:

Mackay Radio and *Funk Bros.* point to the proper analysis for this case: The process itself, not merely the mathematical algorithm, must be new and useful. Indeed, the novelty of the mathematical algorithm is not a determining factor at all. Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the “basic tools of scientific and technological work,” it is treated as though it were a familiar part of the prior art.¹⁴

The idea that laws of nature should be considered to be part of the prior art in analyzing claims in the U.S. appears to have its origin in the 1853 case of *O’Reilly v. Morse*¹⁵ and this is the source cited in *Flook*.¹⁶ The most relevant portion of *Morse* with respect to patent ineligibility involves the Court’s review of the English case *Neilson v Harford*,¹⁷ which concerned the discovery by Nielson that the functioning of a blast furnace could be improved if air was heated before being passed through molten metal in the furnace. A primary issue was whether the claims encompassed anything more

¹³ 437 U.S. 584 (1978).

¹⁴ See *id.* at 591-592.

¹⁵ 56 U.S. 62 (1853).

¹⁶ 437 U.S. at 592.

¹⁷ 151 ER 1266 (1841); summarized at: www.bustpatents.com/CASELAW/NEILSON.html.

than the “principle” (for our purposes “law of nature”) that hot air promotes ignition better than cold air. Commenting on this issue, the *Morse* court stated:

But after much consideration it was finally decided that this principle must be regarded as well known, and that the plaintiff had invented a mechanical mode of applying it to furnaces, and that his invention consisted in interposing a heated receptacle between the blower and the furnace, and by this means heating the air after it left the blower and before it was thrown into the fire.

Undoubtedly the principle that hot air will promote the ignition of fuel better than cold was embodied in this machine. But the patent was not supported because this principle was embodied in it. He would have been equally entitled to a patent if he had invented an improvement in the mechanical arrangements of the blowing apparatus or in the furnace while a cold current of air was still used. But his patent was supported because he had invented a mechanical apparatus by which a current of hot air, instead of cold, could be thrown in. And this new method was protected by his patent. The interposition of a heated receptacle in any form was the novelty he invented.¹⁸

The Court is saying essentially that if Nielson had tried to base his patent on having discovered the effect of heating gas on promoting ignition and nothing more, the claim would be directed to the law itself and would be patent ineligible. However, Nielson had instead applied this law as part of a mechanical invention that was patentable for other reasons. Thus, the idea of judging patent eligibility based on claim elements considered in the absence of the law of nature is present in the *Morse* decision. As set forth, however, by Judge Rich speaking for the Court of Customs and Patent Appeals (the forerunner of the Federal Circuit), this approach creates serious problems:

Another principle stated in *Flook* is that a “mathematical algorithm” or formula is like a law of nature in that it is one of the “basic tools of scientific and technological work” and as such must be deemed to be “a familiar part of the prior art,” even when it was not familiar, was not prior, was discovered by the applicant for patent, was novel at the time he discovered it, and was useful. This gives to the term “prior art,” which is a very important term of art in patent law, particularly in the application of § 103, an entirely new dimension with consequences of unforeseeable magnitude.

It is one thing to say that a principle, natural cause, or formula, per se, is not within the categories of § 101, but quite another to say it is “prior art” in determining the nonobviousness of an invention predicated on it even though the inventor discovered it.¹⁹

¹⁸ 56 U.S. at 116.

¹⁹ *Bergy*, 596 F.2d at 965-966.

B. Whole Claim Analysis (Chakrabarty and Diehr)

In *Diamond v. Chakrabarty*,²⁰ the Supreme Court held that microorganisms engineered to express genes giving them the ability to digest oil spills were patent eligible:

Judged in this light, respondent's microorganism plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter--a product of human ingenuity "having a distinctive name, character [and] use." The point is underscored dramatically by comparison of the invention here with that in *Funk*.²¹

Although the Court couches the decision as following *Funk Bros.*, the cases could not have been decided more differently. In *Chakrabarty*, the Court began by looking at the claimed invention as a whole and the question of whether the genes used to engineer the microorganisms were different from their natural counterparts never arose. Once it was decided that the engineered bacteria were not found in nature, the only remaining issues with respect to patent eligibility were whether they fell within one of the classes recited in 35 U.S.C. § 101, i.e., a process, machine, manufacture or composition of matter, and whether they had a practical utility.

The attempt to maintain consistency with the *Funk Bros.* decision by distinguishing the cases based on the characteristics of the inventions is ill-advised. The parallels are almost exact. The genes isolated in *Chakrabarty* are just as much products of nature as the bacteria isolated in *Funk Bros.*, and the recombinant bacteria of *Chakrabarty* are equivalent to the inoculum of bacterial strains in *Funk Bros.* The advantage of the *Chakrabarty* composition was that it replaced the multiple strains of bacteria used on oil spills with a single strain, and the advantage of the *Funk Bros.* composition was that it replaced multiple strains of bacteria used in treating plants with a single inoculum. Finally, the genes used in *Chakrabarty*, just like the bacteria in *Funk Bros.*, performed the same function in the claimed invention that they performed in nature (i.e., they generated hydrocarbon digesting enzymes in the recombinant bacteria).

Given these similarities, it is not difficult to see what the results in the *Chakrabarty* and *Funk Bros.* cases would have been if the approaches taken by the Court were switched. Using the claim dissection approach of *Funk Bros.* in *Chakrabarty*, the analysis would proceed by first concluding that each gene was structurally and functionally the same in the recombinant bacteria as in nature.²² The next question would be whether, not counting the contribution of the genes, the recombinant bacteria were patentable. Here the answer would clearly be "no" since the only thing that made the bacteria different from their natural counterpart was the presence of the recombinant genes. Thus, *Chakrabarty's* invention would be found to be patent ineligible using the analytic approach of *Funk Bros.*

²⁰ 447 U.S. at 303.

²¹ See *id.* at 309-310 (internal quotation marks omitted).

²² The genes performed the same function in producing enzymes after transformation as before.

Using the whole claim analysis approach of *Chakrabarty* in the *Funk Bros.* case, the first question would be whether the claimed inoculum had a counterpart in nature. Since the patent had already issued at the time of the litigation and this would not have occurred if there had been a comparable prior art inoculum known during prosecution, and since there was no suggestion in the case of any such inoculum, it is highly likely that the answer would be “no.” In addition, the inoculum constituted a composition of matter and had a clear utility. It would therefore almost surely be found to be patent eligible. Thus, at least with respect to patent eligibility, an opposite result would be obtained. The prospects that the Court would find the invention patentable also seem quite good since the prohibition on borrowing “invention from the discovery of the natural principle” would no longer exist and the Court had acknowledged that the patentee had discovered that there were strains of root-nodule bacteria which do not exert a mutually inhibitive effect on each other.²³

In light of these considerations, the notion that *Chakrabarty* follows *Funk Bros.* seems strained at best. The cases use fundamentally different approaches to evaluating patent eligibility that produce opposite results. The basic principle that emerges from *Chakrabarty* is that: although a law of nature is not itself patent eligible, a composition of matter with “markedly different characteristics” from that found in nature and with the potential for significant utility is. This is true even if the composition includes a product of nature that is structurally and functionally unchanged when considered in isolation and even if the markedly different characteristics are due entirely to contributions from the product of nature.

The approach taken in *Chakrabarty* was confirmed and clarified in *Diamond v. Diehr*,²⁴ a case in which the Supreme Court considered claims to a process for molding rubber products. The process involved: (a) measuring the temperature inside a mold where raw rubber was being cured; (b) feeding this information to a computer which used a well-known mathematical formula (the Arrhenius equation) to calculate and revise cure time; and (c) signaling by the computer to open the press at the appropriate time. According to the Court:

[T]he respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process of curing synthetic rubber. Their process admittedly employs a well-known mathematical equation, but they do not seek to pre-empt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.²⁵

As in *Chakrabarty*, the Court in *Diehr* begins its analysis by looking at the claimed invention as a whole and asking if there is a counterpart in nature. Even though the mathematical equation is an element in the claims, the Court does not separate it out and look at it in isolation. It also does not go through the dissection of claim elements that characterized the *Funk Bros.* and *Flook* cases. In fact, for the first time, the Court expressly repudiates this approach:

²³ See *Funk Bros.*, 333 U.S. at 129-130.

²⁴ 450 U.S. 175 (1981).

²⁵ See *id.* at 187.

In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made. The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.²⁶

Finally, the Court makes it clear that patent eligibility and patentability are separate concepts that should be analyzed individually: the question therefore of whether a particular invention is novel is "wholly apart from whether the invention falls into a category of statutory subject matter."²⁷

III. RISE AND FALL OF THE PATENTABLE GENE AND GENE BASED DIAGNOSTICS

A. "Establishment" of the Patentability of Genes and Related Subject Matter

During the period between the Supreme Court's decision in *Diehr* and its 2012 *Mayo* decision, the Federal Circuit consistently held that DNA was a chemical compound and treated it accordingly.²⁸ During this period, the status of isolated genes and nucleic acids as patent eligible subject matter was not so much established as assumed.²⁹

Doing so was not unreasonable. *Chakrabarty* and *Diehr* had both taken a whole claim analysis approach to patent eligibility that, as discussed above, is likely to view this subject matter favorably and these were the most recent major Supreme Court decisions of relevance at the time. Moreover, *Chakrabarty* was the only one of the four primary Supreme Court patent eligibility cases that dealt with recombinant technology, i.e., the transferring of genes from one organism to another. It therefore better matched the technology in most of the recombinant DNA cases decided by the Federal Circuit.

²⁶ *See id.* at 188-189.

²⁷ *See id.* at 190 (citations omitted).

²⁸ *See, e.g.,* Amgen v. Chugai, 927 F.2d 1200, 1206; (1991); *In re Deuel*, 51 F.3d 1552, 1557-1559 (1995); University Cal. v. Eli Lilly, 119 F.3d 1559, 1168 (1997). This is more important than it might appear. Chemical compounds are defined largely in terms of the structural features that affect the way that they react with other compounds. DNA that has been cleaved from a larger sequence and isolated can be used in ways that would otherwise not be possible and which is the result of differences in the end groups available. As discussed in text that follows, the Supreme Court today seems to view DNA as being more a passive repository of genetic information than an active chemical compound.

²⁹ Amgen v. Chugai, 927 F.2d 1200 (1991); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993); *In re Bell*, 991 F.2d 781 (1993); *In re Deuel*, 51 F.3d 1552 (1995); University Cal. v. Eli Lilly, 119 F.3d 1559 (1997).

The Federal Circuit not ignore the risk of preemption³⁰ but dealt it with under the written description and enablement provisions of patent law. Specifically, the Federal Circuit held that a gene must be characterized in terms of its specific structure and that the disclosure of sequence information for a single gene or protein is not sufficient to support a claim to a “class” of genes or proteins based on similarity of function.³¹ By 2001 it was widely accepted that the isolation of a gene was sufficient to distinguish it from a natural counterpart and, in that year, the USPTO published Utility Guidelines that stated:

An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.³²

B. Supreme Court Intervention

1. *Bilski v. Kappos*

One of the first indications that there might be a problem with respect to the patent eligibility of gene based diagnostic methods came from a case that, on its face, has little to do with genes. In *Bilski v. Kappos*³³ the Supreme Court considered claims covering a process for hedging the risk of price changes in business transactions. The Federal Circuit had previously heard the case and had given an opinion suggesting that it might consider the “machine-or-transformation test” to be the sole basis for assessing whether a process meets the patent eligibility requirements of 35 U.S.C. § 101. Under this test, a claimed process is patent-eligible only if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing.³⁴ Since gene based diagnostic assays typically do not require the use of a particular machine or apparatus or involve a transformation of one thing into something else, the adoption of this test would invalidate many existing claims in this area.

However, *Bilski* turned out to be a false alarm. The Supreme Court affirmed the Federal Circuit’s decision, but made it clear that the machine-or-transformation test

³⁰ Preemption (i.e., the preclusion of the use of a natural law by others due to its being present in a patent claim) has often been cited as a primary rationale for excluding laws of nature from being patent eligible. See Katherine Strandburg, *Much Ado About Preemption*, 50 HOUS. L. REV. 567 (2013).

³¹ *Amgen*, 927 F.2d at 1209-1210; *Fiers*, 984 F.2d at 1168-1170; *In re Bell*, 991 F.2d at 783-784; *Eli Lilly*, 119 F.3d at 1566-1569.

³² Utility Examination Guidelines, 66 Fed. Reg. 1092–02 (Jan. 5, 2001).

³³ 130 S. Ct. 3218 (2010).

³⁴ See *id.* at 3224.

was not the sole test for determining the patent eligibility of a claimed process.³⁵ Although the immediate threat to the patentability of gene based assays was averted, *Bilski* did not specifically address the question of how patent eligibility should be evaluated in the context of the life sciences. This would soon be resolved in a way that most patent practitioners involved in biotechnology would not have thought possible.

2. *Mayo Collaborative Services v. Prometheus Laboratories and Association for Molecular Pathology v. Myriad Genetics*

The first case in the demise of patentable gene based diagnostic methods was *Mayo Collaborative Services v. Prometheus Laboratories*.³⁶ The claims in *Mayo* concerned a method for adjusting the dosage of thiopurine drugs based on metabolite levels in a patient's blood. A claim typical of those under consideration read:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
 - (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
 - (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

*wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

*wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.³⁷

The Court held that the above claim was not patent eligible because it was directed to a law of nature—the relationship between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective (or cause harm) and the other elements present in the claimed process did not add enough to make the claim inventive. A primary factor that the Court relied on was that the steps in the process (considered in the absence of the natural law itself) involved only well-understood, conventional activity previously engaged in by researchers in the field.³⁸

Examining each step separately, the Court concluded that: (a) the “administering step” did not add anything to the law of nature, because it referred to doctors who by

³⁵ See *id.* at 3226-3227. The Court did not completely reject the machine-or-transformation test and went so far as to suggest that test may provide a useful and important clue with regard to patent eligibility. Presumably, it should still be available during as an argument during prosecution.

³⁶ 132 S. Ct. 1289 (2012).

³⁷ See *id.* at 1295.

³⁸ See *id.* at 1294.

definition were already treating patients with thiopurine drugs; (b) the two “wherein” steps did not add anything because they were “at most . . . a suggestion that the physician should take those laws into account when treating his patient;” and (c) the “determining step” did not limit the doctors in any way, because they could “determine the level of the relevant metabolites . . . through whatever process” they chose to use. Finally, considering all the claim elements together, the Court concluded that the three steps in combination added “nothing to the law of nature that is not already present when the steps are considered separately.”³⁹

Overall, the Court basically followed the procedures set forth in the *Funk Bros.* and *Flook* cases and reached the predictable conclusion that the claimed assay was patent ineligible. Had the procedures of *Chakrabarty* and *Diehr* been used, the Court would have immediately found that the claimed diagnostic method does not exist in nature (nature does not administer drugs and test metabolite levels), that the method falls into one of the classes of patentable subject matter recited in 35 U.S.C. § 101 (it is a process) and that it has a practical utility (it tells physicians how to adjust drug levels in a patient being treated). The next step would have been to analyze the novelty and nonobviousness of the method without further consideration of eligibility issues.

The *Mayo* decision was concerned solely with method claims; there were no holdings concerning the patent eligibility of claims to nucleic acids with sequences corresponding to all, or a portion, of a gene. This left open the possibility of protecting diagnostic assays indirectly by drafting claims covering compositions needed to carry out the assays. However, in *Association for Molecular Pathology v. Myriad Genetics*⁴⁰ the Court foreclosed this possibility as well.

Myriad had identified mutations in two human genes (BRCA1 and BRCA2) that were correlated with a greatly increased risk of a woman developing breast cancer and obtained patents covering DNA molecules that could be used in assays for the mutations. Representative claims were:

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
2. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.⁴¹

The Court held that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated. The fact that the claimed DNA sequences were *in vitro* and in a different environment from corresponding natural sequences was of no apparent significance. Similarly, the fact that the isolated sequences could perform functions not possible for genes in cells was insufficient for them to be considered something other than a product of nature. It appears that the sole criterion that the Court relied on to conclude that the isolated DNAs and their counterparts in nature were the same is their having a common sequence. Thus, unlike the Federal Circuit in the cases discussed previously herein, the Supreme Court does not appear to consider DNA to be a chemical compound but rather a passive transmitter of information. Under this view, DNA’s are the same if their sequences are the same.

³⁹ 132 S. Ct. at 1297-1298.

⁴⁰ 133 S. Ct. 2107 (2013).

⁴¹ See *id.* at 2113.

One common misconception is that the Court indicated that cDNA would, in general, be patentable even when DNA corresponding to the cDNA was patent ineligible. What the Court actually said was:

As a result, cDNA is not a “product of nature” and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.⁴²

Thus, cDNA is only patent eligible to the extent that it differs substantially from a related gene, *e.g.*, due to the elimination of introns. Short cDNA sequences, such as probes, that do not represent sequences in which introns have been deleted and cDNA derived from genes that lack introns, *e.g.*, genes as generally found in bacteria, would not be patent eligible.

The *Myriad* decision essentially ends the possibility of covering a gene based diagnostic assay by claiming probes or primers required for its performance. Between this decision and that of *Mayo*, there is very little left for businesses that depend on the patenting of gene based diagnostic assays.

3. *Alice Corp. v. CLS Bank Int'l*

The Supreme Court position expressed in the *Mayo* and *Myriad* decisions was further solidified in *Alice Corp. v. CLS Bank Int'l*.⁴³ This case was concerned with a patented method for mitigating “settlement risk,” *i.e.*, the risk that only one party to an agreed-upon financial exchange will satisfy its obligation. In particular, the patents in suit claimed: (1) a method for exchanging financial obligations, (2) a computer system configured to carry out the method for exchanging obligations, and (3) a computer-readable medium containing program code for performing the method of exchanging obligations.⁴⁴

The Supreme Court indicated that assessing the patent eligibility of claims under 35 U.S.C. § 101 involves a two-step process. First, a determination must be made as to whether the claims are directed to patent-ineligible subject matter (*e.g.*, an abstract idea, fundamental law or product of nature). If so, the next step is to determine if the claims include other elements, either individually or as an ordered combination, that are sufficient to transform the subject matter in a way that makes it patent-eligible.⁴⁵

Applying the first step of this test to the specific patent on appeal, the Court concluded that its claims were directed to a patent-ineligible concept: the abstract idea of an intermediated settlement. The Court stated that, like the risk hedging strategy in *Bilski*, the concept of an intermediated settlement is a fundamental economic practice long prevalent in our system of commerce and the use of a third-party intermediary (or “clearing house”) is a building block of the modern economy.⁴⁶

⁴² *See id.* at 2119.

⁴³ 134 S.Ct. 2347 (2014).

⁴⁴ 134 S.Ct. at 2353.

⁴⁵ *See id.* at 2355-2357.

⁴⁶ *See id.* at 2357.

Turning to the second step, the Court concluded that the method claims merely required generic computer implementation, and, as such, failed to transform the abstract idea of an intermediated settlement into a patent-eligible invention. In this regard, the Court stated, “simply appending conventional steps, specified at a high level of generality, to a method already ‘well known in the art’ is not enough to supply the inventive concept needed to make this transformation.”⁴⁷

This is essentially the approach taken in the *Funk Bros* and *Flook* cases. The Court uses claim dissection, muddles together concepts of patent eligibility and obviousness, and omits contributions made by the accused natural element. For the great majority of gene based diagnostic assays, the end result will be a finding of patent ineligibility.

C. Subsequent Developments at the Federal Circuit

Subsequent to the Supreme Court decisions discussed above, there have been four biotechnology cases decided by the Federal Circuit dealing with the patent eligibility of claims in the area of recombinant DNA technology.⁴⁸ All of these have resulted in a finding that claims were patent ineligible. Representative of these cases are *In re BRCA1- & BRCA2-Based Hereditary Cancer Test* and *Arisoa v. Sequenom*, each of which is discussed below.

1. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*

After the Supreme Court’s decision in *Association for Molecular Pathology v. Myriad*, Ambry Genetics, a California company specializing in gene based diagnostic assays for inherited and non-inherited diseases, began selling kits that included assays for mutations in the BRCA 1 and BRCA2 genes. In response, the University of Utah and Myriad filed suit in district court and the case was subsequently appealed to the Federal Circuit.⁴⁹

The composition claims at issue were directed to single-stranded DNA primers with sequences corresponding to those present on the human chromosome where the BRCA genes are located. The primers were used to amplify the genes as part of a procedure for determining if a patient carried mutations indicative of an increased risk of developing breast cancer. In considering the patent eligibility of the claims, the court stated:

⁴⁷ See *id.*

⁴⁸ The cases are: *In re BRCA1- & BRCA2-Based Hereditary Cancer Test*, 774 F.3d 775 (Fed. Cir. 2014); *Arisoa v. Sequenom*, 788 F.3d 1371 (Fed. Cir. 2015); *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016) and *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333 (2014). The first three of these were directed, essentially, to diagnostic methods and the forth to cloned animals. There was also a fifth case in the area of biotechnology, *Rapid Litigation Management, Ltd. v. CellzDirect, Inc.*, 2016 U.S. App. LEXIS 12352 (Fed Cir. 2016), in which claims were found to be patent eligible (Slip opn. No. 2015-1570 (July 5, 2016)). However, this case was concerned with a method of cryopreserving hepatocytes and not recombinant DNA technology or diagnostic assays.

⁴⁹ *In re BRCA1-*, 774 F.3d 755.

The primers before us are not distinguishable from the isolated DNA found patent-ineligible in Myriad and are not similar to the cDNA found to be patent-eligible. Primers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature.⁵⁰

Beyond this, the court ruled that: (a) the fact that gene sequences were chemically synthesized was of no consequence in distinguishing them from sequences in nature;⁵¹ (b) the fact that short, single-stranded DNA cannot be found in the human body is of no consequence since, in the view of the court, isolating separate strands of DNA is no different from isolating DNA from other cellular components,⁵² and (c) the fact that primers do not participate in the coding of a sequence translated into a protein is of no consequence since they still bound to complementary sequences which is a function that they perform in cells.⁵³

These rationales do not bode well for companies interested in patenting gene based diagnostic methods. They suggest that, in order to transform a DNA strand into something that is patent eligible, there will need to be a disruption of the natural DNA sequence itself and, in order to distinguish primers based on function, the primers will need to be doing something other than hybridizing to complementary sequences. However, the structural and functional characteristics dismissed by the court are the ones that most prominently differentiate DNA primers and probes from DNA found *in vivo* and cannot generally be substantially changed without ruining their diagnostic value.

The court's rulings on method claims are equally disturbing. Here, the court held that the "comparing" of BRCA gene sequences from tissue samples with control BRCA sequences represented an abstract idea that had the potential to severely impede research on the BRCA genes and that the remaining claim elements were "well-

⁵⁰ See *id.* at 760. The position of the Federal Circuit is consistent with that of the Supreme Court regarding isolated gene sequences. Structural differences relating to the excision of sequences from a larger strand and differences in the environment in which the primers are found appear to be regarded as insignificant.

⁵¹ See *id.* The court stated, "[c]ontrary to Myriad's argument, it makes no difference that the identified gene sequences are synthetically replicated. As the Supreme Court made clear, neither naturally occurring compositions of matter, nor synthetically created compositions that are structurally identical to the naturally occurring compositions, are patent eligible." *Id.* at 2117.

⁵² See *id.* The court stated:

Myriad argues that primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body. But, as the Supreme Court made clear, "separating [DNA] from its surrounding genetic material is not an act of invention." The Supreme Court held ineligible claims directed to segments as short as 15 nucleotides, the same length as the primer claims at issue here, suggesting that even short strands identical to those found in nature are not patent eligible. *Id.* (citations omitted).

⁵³ See *id.* at 761. The court stated:

One of the primary functions of DNA's structure in nature is that complementary nucleotide sequences bind to each other. It is this same function that is exploited here—the primer binds to its complementary nucleotide sequence. Thus, just as in nature, primers utilize the innate ability of DNA to bind to itself. *Id.*

understood,” “routine” and “conventional.”⁵⁴ Since essentially all diagnostic tests involve comparing the characteristics present in diseased or potentially diseased individuals, with their normal counterparts, the court’s decision suggests that the issue of patent eligibility will be present in almost all patent applications claiming such tests. Unless there are other claim elements that are new and unconventional, which is rarely the case with diagnostic assays, the claims are likely to be found patent ineligible.

2. *Ariosa v. Sequenom*

In the past, there have been instances when the Supreme Court has made decisions that initially seemed to destroy well-established patent principles but which were later tempered by Federal Circuit decisions.⁵⁵ To the extent that people in the patent community may have maintained any lingering hope for something similar after the decision discussed above, this hope was badly damaged by the Federal Circuit’s decision in *Ariosa v. Sequenom*.⁵⁶

Sequenom had discovered that it was possible to perform prenatal, genetically based diagnostic tests for paternally derived cell free fetal DNA (“cffDNA”) circulating in a woman’s blood. Although cffDNA was known to exist in the prior art, Sequenom was the first company to recognize the diagnostic potential of this material and to demonstrate that existing techniques could be successfully used to obtain clinically useful results. The great advantage of the methodology lay in the fact that it could replace more dangerous tests based on the analysis of placental samples.

Nevertheless, the court found that Sequenom’s tests were unpatentable under the analysis set forth in *Mayo*. After concluding that the DNA sequences found in maternal blood are products of nature, the court states:

Like the patentee in *Mayo*, Sequenom contends that the claimed methods are patent eligible applications of a natural phenomenon, specifically a method for detecting paternally inherited cffDNA. Using methods like PCR to amplify and detect cffDNA was well-understood, routine, and conventional activity in 1997. The method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA. Because the method steps were well-understood, conventional and routine, the method of detecting paternally inherited cffDNA is not new and useful. The only subject matter new and useful as of the date of the

⁵⁴ See *id.* at 763-764.

⁵⁵ For example, in 2007, the Supreme Court issued a decision in the *KSR v. Teleflex* (127 S.Ct. 1727 (2007)) which was initially perceived by many to open the door to arbitrary and unanswerable obviousness rejections. However, in a series of subsequent decisions, the Federal Circuit established new principles that returned obviousness criteria to nearly the same place as before the Supreme Court’s decision.

⁵⁶ 788 F.3d 1371 (Fed. Cir. 2015). See also *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282 (Fed. Cir. 2015) (denied rehearing en banc). More recent confirmation may be found in *Genetic Technologies*, 818 F.3d 1369.

application was the discovery of the presence of cffDNA in maternal plasma or serum.⁵⁷

The importance of techniques being routine, well-understood and conventional are concepts that, under *Chakrabarty* and *Diehr* (and under the Federal Circuit decisions prior to *Mayo*) would have been relevant to the obviousness of an invention but not to patent eligibility. As in the *Funk Bros.* and *Flook* cases, the invention in *Ariosa* is considered in a piecemeal manner and the contribution of the purported products of nature to inventiveness is ignored.

D. PTO Guidelines

On March 4, 2014, the U.S. Patent and Trademark Office (“PTO”) released guidelines for examiners in analyzing subject matter eligibility under the tests set forth in the *Mayo* and *Myriad* Supreme Court decisions⁵⁸, which included many examples of how the mandated test would be applied to different claims. Although the guidelines just represent the views of the PTO and have no actual legal authority, there are aspects to them that should be of interest to patent practitioners.

The first is that the PTO indicates that examiners do not need to provide evidence to support patent ineligibility rejections; simply articulating the reason why the claimed invention is not eligible is sufficient.⁵⁹ This may amount to little more than asserting that all claim elements, other than the natural product itself, are well known in the art. Since this will be true in most cases involving claims to diagnostic procedures, rejections in this area will be common.

On perhaps a more optimistic note, it appears that the PTO regards the labeling of primer or probe sequences as sufficient to make them patent eligible, even if their sequence corresponds to that of a sequence found in nature.⁶⁰ If this is correct, and that is far from certain, it would mean that applicants should be able to validly claim a broad array of labelled probes and thereby provide a modicum of protection for many common types of assays.⁶¹

⁵⁷ 788 F.3d at 1377.

⁵⁸ DEP’T OF COMMERCE, UNITED STATES PATENT AND TRADEMARK OFFICE: 2014 INTERIM GUIDANCE ON PATENT SUBJECT MATTER ELIGIBILITY (2014) [hereinafter 2014 INTERIM GUIDANCE]; DEP’T OF COMMERCE, UNITED STATES PATENT AND TRADEMARK OFFICE: JULY 2015 UPDATE: SUBJECT MATTER ELIGIBILITY (2015) [hereinafter JULY 15 UPDATE], available at <http://www.uspto.gov/patent/laws-and-regulations/examination-policy/2014-interim-guidance-subject-matter-eligibility-0>.

⁵⁹ See JULY 15 UPDATE. On page 6, under section IV entitled “Requirements Of A Prima Facie Case,” the PTO states in paragraph 2:

For subject matter eligibility, the examiner’s burden is met by clearly articulating the reason(s) why the claimed invention is not eligible, for example by providing a reasoned rationale that identifies the judicial exception recited in the claim and why it is considered an exception, and that identifies the additional elements in the claim (if any) and explains why they do not amount to significantly more than the exception.

⁶⁰ See 2014 INTERIM GUIDANCE, *supra* note 58, at 9.

⁶¹ There is good reason to at least question whether this is actually the case. The Supreme Court was certainly willing to overlook structural changes associated with the isolation of a gene in *Myriad* and the Federal Circuit found primers to the BRCA1 gene to be patent ineligible irrespective of the

IV. CONCLUSION

A. *The Patent Eligibility Standard as it Exists Today*

The Supreme Court has provided a two-step test for patent eligibility. In the first step, a decision is made as to whether an abstract idea, fundamental law or product of nature is present in the claims of a patent. If this type of subject matter is found, the next step is to determine whether the remaining claim elements are sufficient to provide an “inventive concept.”⁶² The term “inventive” suggests that the claim elements are being compared to the prior art to determine if they are new and nonobvious and, in fact, this seems to be the way in which the courts are proceeding. However, the test differs from an obviousness analysis in two important respects.

First, in an obviousness analysis, all of the elements in a claim must be taken into account in the context of the invention as a whole, whereas in the patent eligibility test, the purported law of nature is excluded from consideration and analysis takes place on an element by element basis. Since the relationship between gene mutations or gene expression and disease is considered to be a law of nature, the single most inventive aspect of most gene based diagnostic claims is thrown out before analysis for inventiveness begins.

Second, it is not clear how, or if, any of the standard arguments used by patent applicants to rebut an allegation of unpatentability on obviousness grounds, i.e., under 35 U.S.C. § 103, apply in the context of patent ineligibility. Findings by both the Supreme Court and Federal Circuit consist mainly of conclusory allegations unsupported by specific citations or evidence. Moreover, the PTO has instructed examiners that they do not need to provide evidence to support patent ineligibility rejections. It appears that essentially all that is needed is for an examiner to say why he or she thinks a claim is not patent eligible. Thus, in addition to a claim being stripped of the one element that is likely to be most critical to inventiveness, patent applicants are left without any clear means for responding to allegations concerning the claim elements that remain.

To see the shortcomings of the *Myriad* and *Alice* test, one need only to step back and look at the results produced. Clinical procedures have become indistinguishable from products of nature for the purposes of patent eligibility, leaving one with the sense that they have not been through a legal analysis so much as an exercise in making inventions disappear. Yes, the relationships relied on exist in nature. But these are diagnostic tests ordered by physicians and performed on samples taken from patients, with analyses made on machines and results compared to controls! How can they possibly be products of nature?

If, in *Mayo* and *Myriad*, the Supreme Court had followed the approach taken in *Chakrabarty* and *Diehr* and asked whether a claimed invention (considered as a whole and taking into account the contribution of *all* elements) is found in nature, then the

fact that the DNAs could be used solely for binding to DNA sequences to prime PCR reactions and could no longer encode a natural protein. The PTO guidelines were published before *In re BRCA1- & BRCA2-Based Hereditary Cancer Test* was decided but the PTO did not revise their statements in the update published in July of 2015.

⁶² See *Mayo*, 132 S. Ct. at 1294; *Alice*, 134 S. Ct. at 2355.

absurdity of concluding that diagnostic assays are essentially a part of nature could have been avoided. Concerns about preemption are not new and could have been addressed by the written description and enablement sections of the law. In addition, safe harbors have been created and could be expanded if necessary.⁶³

So why didn't the Supreme Court do this? After all, the *Chakrabarty* and *Diehr* decisions were more recent than *Flook* and much more recent than *Funk Bros.* In addition, there had been thirty years of the de facto following of *Chakrabarty* and *Diehr* by the Federal Circuit and an entire industry that had developed under these decisions.

One possibility is that the Court may not have fully appreciated the repercussions of the decisions. In the *Myriad* decision, Justice Thomas seemed, at one point, to indicate that the Court's decision may have been different if the case had involved method claims:

Similarly, this case does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson aptly noted that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications."⁶⁴

This suggests that, perhaps, the Court wanted to leave open the possibility of diagnostic claims based on genes being patentable even if the genes themselves are not. Of course, the Court had already expressed an unfavorable view of diagnostic tests in the *Mayo* case and it would soon confirm the patent eligibility test of *Myriad* in *Alice*.

Another possibility is that the Court understood that it was destroying thousands of patent claims and the underpinnings of many diagnostic biotechnology companies, but simply thought that effectively reducing the cost of diagnostic tests to patients and ensuring that everyone would be free to practice and develop tests was more important. If this is the case, then it is basically a repudiation of the patent system (at least insofar as it applies to diagnostic medicine). Under these circumstances, companies would be well advised to invest their time and talent elsewhere.

B. The Future of Gene Based Diagnostic Tests

There are, of course, those that do not view the effect of the recent patent eligibility decisions on gene based diagnostic assays as being destructive at all. The result that they see from the *Mayo* and *Myriad* decisions is a greater availability of diagnostic tests at much lower prices and unimpeded further development of assays by whoever chooses to do so. Perhaps these people envision a system in which exploratory research is essentially the exclusive domain of public sector institutions and private industry, to the degree that it participates at all, implements and markets

⁶³ See 35 U.S.C. § 271(e)(1); *Merck v. Integra*, 545 U.S. 193 (2005).

⁶⁴ 133 S. Ct. at 2120.

tests on a non-proprietary basis. The extent to which this is likely, or even sensible, may be debated.

What is clear, however, is that the biotechnology industry has developed and thrived in an atmosphere in which companies were able to develop patentable inventions and this has now been severely compromised in at least one important area. The decisions in *Mayo* and *Myriad* are more than simply findings that claims to a test for adjusting drug levels and a test for cancer susceptibility are invalid. They are, essentially, the end of gene based assays as patentable subject matter. If the Supreme Court did not intend this, then they need to rectify matters as soon as possible. If it was deliberate, then they need to reconsider the wisdom and justice of their rulings. A place to start would be with the comments made by Justice Moore when the *Myriad* case was at the Federal Circuit:

The Patent Office has, for more than a decade, affirmatively stated its belief that isolated DNA is patentable for the same reasons as isolated vitamins or hormones. There is no indication from Congress that this view is wrong; to the contrary, it appears Congress also believes DNA is patentable. This long-term policy of protecting isolated DNA molecules has resulted in an explosion of innovation in the biotechnology industry, an industry which, unlike the financial services industry or even the software industry, depends on patents to survive. Holding isolated DNA not patentable would destroy long settled industry expectations for no reason other than a gut feeling that DNA is too close to nature to be patentable, an arbitrary decision based on a judge-made exception.

We cannot, after decades of patents and judicial precedent, now call human DNA fruit from the poisonous tree, and punish those inquisitive enough to investigate, isolate, and patent it . . . The patents in this case might well deserve to be excluded from the patent system, but that is a debate for Congress to resolve. I will not strip an entire industry of the property rights it has invested in, earned, and owned for decades unchallenged under the facts of this case.⁶⁵

Assuming that the patent eligibility standards of the Supreme Court remain as they are, we will not return to a system of trade guilds and secret knowledge in the area of diagnostic tests. That is not possible in a world of regulated products and lawsuits. What is likely to occur will hardly be noticed; companies will simply not invest in these areas in the U.S. in the future. The tests that never became available will not be missed and patients will never know what their prognosis might have been if only their disease had been detected sooner.

⁶⁵ Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, 689 F.3d 1303, 1348 (Fed. Cir. 2012).