Section 101: What's Left To Patent In The Life Sciences After *Myriad*, *Mayo,* And *Alice*?

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Introduction

Section 101 of the Patent Act (the Act)[3] states that the following categories of invention are eligible for patent protection, so long as the other standards of patentability are met: processes, machines, manufactures, and compositions of matter, as well as improvements thereof. In 1980, the Supreme Court ruled that a man-made microorganism was also eligible for patent protection under Section 101,[4] reaffirming at the same time that no patents should be granted on laws of nature, physical phenomena and abstract ideas. Instead, the Court emphasized that patent-eligible inventions must be generated by human ingenuity. Apart from its decision in 2001 that plants were also eligible for patenting,[5] the Supreme Court had not again addressed whether living organisms, or their natural components, were patent eligible until 2012.

Although the courts have grappled for years with the "abstractness" of software claims, after about 2010 the courts turned their attention to life sciences patents, finding that many diagnostic claims were patent-ineligible as abstract ideas,[6] while others were patent-ineligible for patenting as embracing natural phenomena.[7] Shortly after the *Bilski* decision[8] held that claims to a method of hedging commodity risk were patent-ineligible under Section 101 as an attempt to patent an abstract idea, the Supreme Court granted certiorari and remanded the *Classen* case[9] involving an appeal of claims to immunization schedules, and then decided two biotech/pharma cases, the *Mayo* case[10] in 2012 and the *Myriad* case[11] in 2013. The application of the Supreme Court's *Mayo* decision by the Federal Circuit to the prenatal testing claims in the *PerkinElmer* case[12] and in the *Ariosa* case,[13] as well as the Federal Circuit's own rejection of the Myriad diagnostic

[1] See, Warren's Patents4Life blog at http://www.patents4life.com/ for further discussion of these and other biotechnology issues.
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[3] 35 U.S.C. §101, et seq.
[4] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[5] *J.E.M. Ag Supply Inc. v. Pioneer Hi-Bred International, Inc*., 534 U.S. 124 (2001).
[6] *Association for Molecular Pathology v. U.S. Patent and Trademark Office,* 702 F.Supp.2d 181, 94 USPQ2d 1683 (S.D.N.Y. March 29, 2010); *The Association for Molecular Pathology* v. *Myriad Genetics Inc.,* 653 F.3d 1329 (Fed. Cir. 2011) (collectively the "*Myriad*" case).
[7] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. ___, 132 S.Ct. 1289, 182 L. Ed. 2d 321 (2012)(the "*Mayo*" case).
[8] *Bilski v. Kappos*, 561 US __, 130 S. Ct. 3218, 177 L. Ed. 2d 792 (2010).
[9] *Classen Immunotherapies, Inc. v. Biogen IDEC*, et al., 130 S. Ct. 3541; 177 L. Ed. 2d 1119 (2010)(remanded); *Classen*, 659 F.3d 1057 (Fed. Cir. 2011); *GlaxoSmithKline v. Classen Immunotherapies, Inc.*, 133 S. Ct. 973; 184 L. Ed. 2d 751 (2013)(cert. denied).
[10] *Prometheus Labs. Inc. v. Mayo Collaborative Servs.,* 628 F.3d 1347 (Fed. Cir. 2010); *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. ___, 132 S.Ct. 1289, 182 L. Ed. 2d 321 (2012).
[11] *Association for Molecular Pathology v. U.S. Patent and Trademark Office,* 702 F.Supp.2d 181, 94 USPQ2d 1683 (S.D.N.Y. March 29, 2010); *The Association for Molecular Pathology* v. *Myriad Genetics Inc.,* 653 F.3d 1329 (Fed. Cir. 2011); *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc.* 133 S. Ct. 2107, 186 L. Ed. 2d 124 (US 2013).
[12] *PerkinElmer, Inc. v. Intema Ltd.*, 496 Fed. Appx. 65, 73 (Fed. Cir. Nov. 20, 2012)(nonprecedential). Intema filed a petition for certiorari with the Supreme Court, which has been denied.
[13] *Ariosa Diagnostics Inc. v. Sequenom Inc*., 788 F.3d 1371 (Fed. Cir. 2015).

claims suggests that claims directed to the use of biomarkers in personalized medicine have increasingly become vulnerable to attack by litigants as not constituting patent-eligible inventions. The U.S. Patent and Trademark Office has also issued a series of their own Memoranda outlining the patent eligibility of natural products, natural phenomena, and laws of nature.[14]

This paper discusses and reflects on what the courts and the Patent Office have said illustrating the recent evolution of biotechnology-related court decisions on patent eligibility. A table is provided at the end of the chapter showing the language of various biotech patent claims and how the courts have ruled.

I. *Mayo* and *Classen*: Their Importance and Analysis

Prometheus Laboratories, Inc. v. Mayo Collaborative Services.

In the *Mayo* case,[15] the Federal Circuit held in 2010 that claims directed to a method of optimizing the dosing of a drug are eligible for patenting where the method involved observing whether or not the level of 6-thhiopurine in the patient's blood is above or below specific levels. According to the Federal Circuit, steps in the claims involving "administering" the drug or "determining" the level of the metabolite in the blood satisfied the machine or transformation (MOT) test devised by the Federal Circuit in its Bilski opinion.[16] However, in *Bilski*, the Supreme Court had refused to anoint the MOT test as the sole test for patentability and rather ruled that the *Bilski* claims failed to satisfy Section 101 because they were an impermissible attempt to claim an abstract idea.[17] This was the second time the Federal Circuit had found that the Prometheus claims were eligible for patenting.[18]

In its 2010 ruling, the Federal Circuit reasoned that the claims were not an attempt to impermissibly patent a natural phenomenon – the correlation between metabolite levels and efficacy – and they did not wholly preempt all uses of the phenomenon. In addition, the Federal Circuit again held that the administering and determining steps were sufficiently transformative to meet the MOT test, recognizing that while the "indicative" steps were patent-ineligible mental steps, the claims, taken as a whole are directed to a patent eligible method of optimizing therapeutic efficacy.[19]

In finding the Prometheus claims patent-eligible, the Federal Circuit declined to discuss the *"Metabolite Labs, dissent*"[20] in which Justice Breyer and two other now-retired Justices urged the Court to find a claim to a diagnostic method patent-ineligible. The Metabolite Laboratories' claims involved assaying the level of an amino acid naturally occurring in the body and

[14] *See*, https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility.
[15] *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 628 F.3d 1347 (Fed. Cir. 2010)(on remand from the Supreme Court).
[16] *Mayo*, 628 F.3d 1347; *In re Bilski*, 545 F.3d 943, 88 U.S.P.Q.2d 1385 (Fed. Cir. 2008).
[17] *Bilski*, 130 S. Ct. 3259; 177 L. Ed. 2d 837.
[18] *Prometheus Labs. Inc. v. Mayo Collaborative Servs.,* 581 F.3d 1336 (Fed. Cir. 2009).
[19] *Mayo*, 628 F.3d 1358-59.
[20] *Mayo*, 628 F.3d 1356; *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 126 S. Ct. 2921 (2006).

correlating that level to the presence or absence of a vitamin deficiency.[21] Unlike the Metabolite Laboratories' claims, the Prometheus claims required actual administration of a drug. In finding Prometheus claims patent-eligible, the Federal Circuit ruled that such methods of optimizing therapeutic efficacy did not wholly preempt all uses of the recited correlations but instead transformed the human body by administration of a synthetic drug or measurement of a metabolite that would not be present but for the administration of the drug.[22]

The Supreme Court again granted certiorari to Mayo's appeal and reversed the Federal Circuit holding on March 20, 2012.[23] Justice Breyer, writing for a unanimous court, found that the claims were no more than an attempt to patent a natural phenomenon by surrounding it with steps conventional in medical treatment, such as administering the "old" drug, or by mental steps that were not patent-eligible.[24]

While the Court indicated that new compounds, and new uses for old compounds, would remain patent-eligible,[25] this ruling that administration of a drug followed by determining the drug metabolite levels in the blood is patent-ineligible may tempt courts to terminate opportunities to patent certain treatment regimens. After all, the Prometheus claim could be easily rewritten as a method of treatment claim:

> "A method of treating an immune disorder comprising administering to a subject afflicted with said disorder, an amount of a 6-TG-supplying drug sufficient to provide a blood level in said subject of 6-TG that is between x and y ng/ml [the optimal range]."

Could such a dosage-related claim be subjected to a 101 challenge? It would probably be easy to anticipate, but would it fail a 101 challenge as well? Justice Breyer implicitly denigrates method-of-treatment claims by quoting from amici briefs that note that such methods also involve the body's natural reaction to the treatment agent, and notes that methods of medical treatment are not patentable in many foreign jurisdictions.[26]

The key phrase in the decision may be that the adjunct steps were "specified at [too] high a level of generality."[27] But how much generality is too much generality? The reader of the opinion keeps waiting for Justice Breyer to provide some hint of the degree of unconventionality or amount of significance that would suffice in the context of a diagnostic test "to transform an unpatentable law of nature into a patent-eligible application of such a law,"[28] but none is forthcoming. Finally, although this decision did not address diagnostic methods involving the detection and measurement of endogenous biomarkers, the Federal Circuit invalidated an "If a/Then b" diagnostic claim based on a gene mutation in its *Myriad* decision, discussed below.

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[21] *See, e.g.,* U.S. Patent 4,940,658 claim 13.
[22] *Mayo*, 628 F.3d at 1355-1356.
[23] *Mayo Collaborative Services v. Prometheus Labs., Inc.,* 132 S. Ct. 1289, 182 L. Ed. 2d 321 (U.S. 2012).
[24] *Mayo*, 132 S. Ct. 1297-98.
[25] *Mayo*, 132 S. Ct. 1302.
[26] *Mayo*, 132 S. Ct. 1304-05. Claims to administering a drug to a patient are not patent-eligible in many foreign countries. However, claims to a method of using a drug to treat a condition, or to make a medicament to treat a condition are widely patent eligible.
[27] *Mayo*, 132 S. Ct. 1302.
[28] *Mayo*, 132 S. Ct. 1290, 1294, 1298.

Thus, diagnostic claims that were thought to be eligible for patenting prior to 2010 can now be threatened during litigation and those now drafting diagnostic claims will find little guidance from the Supreme Court's ruling.

Classen Immunotherapeutics, Inc. v. Biogen Idec.

Those watching the evolving Section 101 standards prior to 2010 saw that courts were finding natural phenomena in other patented diagnostic or treatment methods. For example, in 2006 the district court noted in the *Classen*[29] case:

> Clearly, the correlation between vaccination schedules and the incidence of immune mediated disorders that Dr. Classen claims to have discovered is a natural phenomenon. The issue, therefore, is whether the Classen patents simply describe this correlation.

The district court stated that the claims[30] "describe little more than an inquiry of the extent of the proposed correlation between vaccines and chronic disorders,"[31] and granted summary judgment of invalidity to Biogen.

In 2008, the Federal Circuit affirmed the district court's grant of summary judgment that Classen's claims are invalid under Section 101, holding that claims involving a method to lower immunization risks[32] failed the MOT test and so were patent ineligible.[33] However, in August of 2011, a three judge panel of the Federal Circuit revisited *Classen*[34] following the grant of certiorari, vacated decision and remand (in other words "GVR") discussed above. The panel accepted, at least for purposes of this review of summary judgment, that method claims from two of Classen's patents, involving a specific, tangible, physical step of immunization on the determined schedule, traverse the coarse eligibility filter of Section 101.[35] These two claims generally involved screening immunization schedules and then immunizing a subject pursuant to the lower risk immunization schedule. According to the panel, such claims are not directed to a law of nature, like gravity, or to a physical phenomenon, like lightning. The panel also reaffirmed, as in *Mayo*, that the presence of a mental step in a claim is not fatal to patent-eligibility under Section 101.[36] Thus, the panel held that the claims of two out of three patents were not directed to abstract ideas:

> "The claims of the [two] patents are directed to a method of lowering the risk of chronic immune disorder, including the physical step of immunization on a determined schedule. These claims are directed to a specific, tangible application, as in *Research Corporation* [*v. Microsoft*, 627 F.3d 859 (Fed. Cir. 2010)] and in accordance with *Bilski v. Kappos*... exclusions from patent eligibility should be

[29] *Classen Immunotherapies, Inc. v. Biogen Idec,* 2006 U.S. Dist. LEXIS 98106 at *13 (D. Md. Aug. 16, 2006).
[30] See chart following this discussion for selected Classen claims.
[31] *Classen,* 2006 U.S. Dist. LEXIS 98106 at *13-14.
[32] *See,* Classen's U.S. Patent 6,638,739 claim 1, provided in part within the chart following this discussion.
[33] *Classen Immunotherapies, Inc. v. Biogen Idec*, 304 Fed. Appx. 866 (Fed. Cir. 2008).
[34] *Classen Immunotherapies, Inc. v. Biogen Idec*, 659 F.3d 1057 (Fed. Cir. 2011).
[35] *Classen,* 659 F.3d 1066.
[36] *Classen,* 659 F.3d 1065.

applied 'narrowly', 130 S. Ct. at 3229, we conclude that the subject matter of these two patents traverses the 'coarse eligibility filter' of § 101".[37]

The majority of the panel unfortunately found the third patent's main claim is an abstract idea because it requires no more than referring to known information about the effects of various immunization protocols but does not require immunization in light of that information.[38] However, Judges Rader and Newman cautioned that "judges should tread carefully when imposing new limits on the protection for categories of human innovation."[39] The Supreme Court denied certiorari, thus implicitly recognizing that a method of improving the outcome of an immunization protocol which involves transforming subjects from a nonimmune state to an immune state is a sufficiently "unnatural act" so that it is not excluded from 101 as was Prometheus′ treatment regimen – which, as noted above, can be considered an "old use for an old compound."

II. *Myriad* Decision: Its Importance and Analysis

Association of Molecular Pathologists et al. v. *USPTO et al. ("Myriad").*

On May 12, 2009, a group of plaintiffs ranging from professional medical organizations to individual researchers, apparently assembled and certainly represented by the ACLU, filed suit in the SDNY, seeking, *inter alia,* a declaratory judgment that the claims of a number of patents controlled by Myriad were invalid as improperly attempting to claim natural phenomena, such as genetic mutations, or natural products, such as isolated DNA.[40] The patents were generally drawn to tests offered by Myriad that identified mutations in a patient's BRCA1 or BRCA2 genes and, in at least one claim, correlated the presence of mutations to an increased risk of breast or ovarian cancer. Also challenged were claims to isolated human genes, or fragments thereof, and cDNA derived from the wild-type genes.[41]

The suit did not attract much attention at the time, since *Bilski* had been decided by the Federal Circuit in 2008,[42] and was making its way to the Supreme Court. Many commentators opined that the plaintiffs did not even have standing[43] because Myriad had contacted only a few of the plaintiffs ten years or more before the suit was brought and Myriad had not yet sued anyone for infringement. So the biotech IP world was rocked on March 29, 2010 when Judge Sweet agreed with the plaintiffs and held that claims directed to isolated BRCA2 DNA, BRCA2 cDNA, methods of identifying mutations in a subject's BRCA2 gene, methods of correlating the mutations to an increased risk of cancer, and even a claim to a method of using transgenic cells comprising the BRCA2 DNA to screen test compounds for anti-cancer activity, all fell under the

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[37] *Classen,* 659 F.3d 1066 (Judge Moore entered a vigorous dissent, arguing that such an immunization step "is nothing more than post-solution activity." *Id.* 659 F.3d 1079).
[38] *Classen,* 659 F.3d 1067-68.
[39] *Classen,* 659 F.3d 1074.
[40] Complaint, *The Association for Molecular Pathology* v. *Myriad Genetics Inc.,* 09-Civ-4515 (SDNY May 12, 2009) (http://docs.justia.com/cases/federal/district-courts/new-york/nysdce/l :2009cv04515/345544/1/).
[41] See, the chart following this discussion for some of the patent claims at issue.
[42] *In re Bilski,* 545 F.3d 943, 88 U.S.P.Q.2d 1385 (Fed. Cir. 2008); *Bilski v. Doll*, 556 U.S. 1268, 129 S. Ct. 1735 (Jun. 1, 2009)(cert. granted).
[43] *See, e.g.,* John Conley, ACLU and Myriad Both Seek Further Federal Circuit Review, http://www.genomicslawreport.com/index.php/category/badges/myriad-gene-patent-litigation/page/2/ (Sep. 2, 2011).

prohibition against patenting natural products or abstract ideas.[44] Judge Sweet stated that "it is irrelevant to the § 101 analysis whether Applicants' claimed process is novel or nonobvious,"[45] but accepted plaintiffs' arguments that the isolated DNA sequences were simply repositories of genetic information that performed the same function as they did in the intact genome of the subject.[46] The primary rationale for the decision was that "products of nature do not constitute patentable subject matter absent a change that results in creation of a fundamentally new product."[47] Judge Sweet relied on the Supreme Court's language in *Diamond* v. *Chakrabarty*[48] to require that a claimed composition present in nature must be "a product of human ingenuity having a distinctive name, character [and] use."[49]

Myriad appealed both the standing challenge and the decision on the merits to the Federal Circuit, and on July 29, 2011, a divided panel found that the isolated DNA molecules were patent-eligible.[50] Judge Lourie, writing for the majority, gave weight to the fact that covalent chemical bonds are broken at both ends of a native DNA molecule when the DNA is removed from the human genome,[51] and this point was ably emphasized and amplified by Judge Moore.[52] As stated by Judge Lourie, a chemist: "[W]e conclude that the challenged claims are drawn to patentable subject matter because the claims cover molecules that are markedly different—have a distinctive chemical identity and nature—from compounds that exist in nature."[53] Judge Lourie further emphasized that "isolated DNA is not purified DNA," instead "when cleaved, an isolated DNA molecule is not a purified form of a natural material [like adrenalin purified from adrenal gland material] but a distinct chemical entity."[54] Judge Lourie also noted that natural or novel DNA sequences can be chemically synthesized from scratch, and thus require no isolation in any way from nature.[55] The use of cells transformed with isolated BRCA2 in claim 20 to screen potential anti-cancer agents was also found to be patentable.[56] This was not surprising, as claim 20 is analogous to a claim to the use of the Chakrabarty cells to "eat oil."

However, the claims directed to comparing a subject's BRCA2 DNA sequence with a wild-type ["normal" or "reference"] sequence did not survive a review by the Federal Circuit under the new *Bilski* standard,[57] even one including the recitation that "an alteration in the germline sequence of the BRCA2 gene or the sequence of its RNA indicates a predisposition to cancer."[58] The panel members agreed that all of these mutation/wild-type comparison claims were

[44] *Association for Molecular Pathology v. U.S. Patent and Trademark Office,* 702 F.Supp.2d 181, 94 USPQ2d 1683 (S.D.N.Y. March 29, 2010) ("*Myriad*").
[45] *Myriad,* 702 F.Supp.2d at 220 (citing *Bilski,* 545 F.3d at 958).
[46] *Myriad,* 702 F.Supp.2d at 229-231.
[47] *Myriad,* 702 F.Supp.2d at 222.
[48] *Diamond v. Chakrabarty,* 447 U.S. 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980).
[49] *Myriad,* 702 F.Supp.2d at 223.
[50] *The Association for Molecular Pathology* v. *Myriad Genetics Inc.,* 653 F.3d 1329 (Fed. Cir. 2011).
[51] *Myriad,* 653 F.3d 1351-53.
[52] *Myriad,* 653 F.3d 1362-63.
[53] *Myriad,* 653 F.3d 1351.
[54] *Myriad,* 653 F.3d 1352. The Federal Circuit made it clear that it was not addressing the patentability of "natural products" such as adrenaline or certain microorganisms, that exist in nature in complex systems, and that must be extracted and purified in order to make them commercially useful. The Supreme Court did not address this type of "natural product" when it found that genomic DNA is a natural product.
[55] *Id.*
[56] *Myriad,* 653 F.3d 1357-58.
[57] *Myriad,* 653 F.3d 1355-57.
[58] U.S. Patent No. 6033857, claim 2.

impermissible attempts to claim abstract ideas - even claim 2 of U.S. Patent 6,033,857, which is clearly an "If (a)/Then (b)" correlative diagnostic claim.

In December 2011, the Association for Molecular Pathology petitioned the Supreme Court for certiorari, presumably to void the isolated DNA claims. However, after reversing *Mayo* in March 2012[59] as discussed above, the Court then vacated the Federal Circuit *Myriad* decision[60] and remanded (in other words GVR'd) it back to the Federal Circuit. On Aug. 16, 2012, the original Federal Circuit panel again held that claims to isolated genomic DNA sequences were patent-eligible under § 101 as directed to discrete chemical molecules.[61]

The panel spent little time on the method claims but reaffirmed that they were invalid attempts to claim an abstract idea. Judge Lourie again found that the method claims which only involve "comparing" and "analyzing" DNA sequences fail the MOT test and are no more than abstract ideas. In addition, at least one "diagnostic method" claim was also found patent-ineligible.[62] Claim 2 of the '857 patent reads:

> "A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA indicates a predisposition to said cancer."

This claim goes beyond simply comparing a patient sequence with a reference sequence to see if there are differences – it requires the "comparer" to draw a conclusion from the comparison, and a rather important one at that. The train of logic that might have, but did not, lead Judge Lourie to a conclusion that this claim is sufficiently concrete to be patent-eligible includes the following:

> "Limiting the comparison to just the BRCA genes or…to just the identification of particular alterations, fails to render the claimed process patent eligible. As the Supreme Court has held, 'the prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' [citing *Bilski* and *Diehr*, quoting Flook]. Although the *application* of a formula or abstract idea in a process may be patentable subject matter…Myriad's claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process claimed."[63]

It is simply not the case that claim 2 does not "apply the step of comparing two nucleotide sequences in a process," whether or not obtaining and sequencing the patient's DNA is a step of

[59] *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. ___, 132 S.Ct. 1289, 182 L. Ed. 2d 321 (2012).
[60] *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (Mar. 26, 2012).
[61] *Myriad*, 689 F.3d 1303 (Fed. Cir. 2012).
[62] *Myriad*, 689 F.3d 1335.
[63] *Myriad*, 689 F.3d 1334-35. After making this statement, Judge Lourie goes on to reject the argument that the steps of extracting DNA and sequencing it are inherently present in the claims.

the process. The claim is to a method of making a diagnosis. It goes beyond "mere data gathering steps." There is absolutely no prohibition to including a "thinking step" in a method claim. It could be that the panel did not address this claim specifically because Myriad did not argue its concreteness separately from its other arguments. It may prove the most significant loss to the biotechnology industry and to "personalized medicine" in recent years. Worse yet, coupled with *Cybersource v. Retail Decisions*[64] (processes that can be carried out entirely mentally are patent-ineligible), it grades the bumpy road for the Supreme Court to eventually hold – the question is not presented in *Mayo* – that patents on diagnostic methods using single, or a few, biomarkers are patent ineligible.

The Supreme Court again granted *certiorari* after the Federal Circuit's 2012 *Myriad* decision and on June 13, 2013, in a unanimous opinion, found that claims to isolated stretches of genomic DNA, e.g., to the BRACA1/2 genes, were invalid as directed to "products of nature."[65] The Court rejected a general rule that breaking covalent bonds to yield a novel DNA molecule would always create a patent-eligible compound. The Court reasoned that the "human gene" claims focused on the information encoded in the DNA sequence and ignored the plain language of the claims, stating that the claims were "simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section DNA."[66]

The composition claims expressly directed to cDNA were found to be patent-eligible because cDNA preparation requires significant human manipulation.[67] If the Courts had engaged in careful scrutiny of Myriad's claim language, and the underlying support for such language in its specifications, they might have noticed that the term "gene" does not appear in any of the claims at issue, and that the application discloses little, if any, genomic DNA. Instead, the Myriad patents disclose cDNA sequences. If this fact had been presented in a "Question," the Court would probably have found it difficult to rule on the patent-eligibility of "isolated human genes."

The DNA "comparison" method claims were not considered by the Court. Interestingly, the Court spoke approvingly about the patent-eligibility of applications of knowledge about the native genes and stated that many of Myriad's unchallenged claims were limited to such applications.

Thus, after the *Myriad* decision, we are left with a Supreme Court ruling that genomic DNA is not eligible for patenting because it is a product of nature, and with a Federal Circuit panel ruling that claims to comparison of nucleic acid sequences, without more, are also ineligible as an impermissible effort to patent abstract ideas.

[64] 654 F.3d 1366 (Fed. Cir. 2011).
[65] *Association for Molecular Pathology, et al. v. Myriad Genetics, Inc.* 133 S. Ct. 2107, 186 L. Ed. 2d 124 (US 2013).
[66] *Myriad*, 133 S. Ct. at 2118, 186 L. Ed. 2d 136.
[67] *Myriad*, 133 S. Ct. at 2119, 186 L. Ed. 2d 136-37.

III. *Alice* Decision: Its Importance and Analysis

The focus of this paper is on biotechnology-related cases. However, the *Alice* decision[68] is often cited by the courts and the Patent Office when evaluating the patent eligibility of claims. Hence, we summarize the Supreme Court findings in the *Alice* case.

Alice's claims are drawn to a computer-implemented scheme for mitigating "settlement risk." The patents in suit claim (1) methods for exchanging obligations (the method claims), (2) a computer system configured to carry out the method for exchanging obligations (the system claims), and (3) a computer-readable medium containing program code for performing the method of exchanging obligations (the media claims). All of the claims are implemented using a computer; the system and media claims expressly recite a computer, and the parties have stipulated that the method claims require a computer as well. Claim 33 of U.S. Patent 5,970,479 is a representative method claim.

> 33. A method of exchanging obligations as between parties, each party holding a credit record and a debit record with an exchange institution, the credit records and debit records for exchange of predetermined obligations, the method comprising the steps of:
>
> (a) creating a shadow credit record and a shadow debit record for each stakeholder party to be held independently by a supervisory institution from the exchange institutions;
>
> (b) obtaining from each exchange institution a start-of-day balance for each shadow credit record and shadow debit record;
>
> (c) for every transaction resulting in an exchange obligation, the supervisory institution adjusting each respective party's shadow credit record or shadow debit record, allowing only these transactions that do not result in the value of the shadow debit record being less than the value of the shadow credit record at any time, each said adjustment taking place in chronological order, and
>
> (d) at the end-of-day, the supervisory institution instructing on[e] of the exchange institutions to exchange credits or debits to the credit record and debit record of the respective parties in accordance with the adjustments of the said permitted transactions, the credits and debits being irrevocable, time invariant obligations placed on the exchange institutions.

The court followed the *Mayo* two step patent eligibility test.[69] First, the Court concluded that it followed from the *Gottschalk v. Benson*,[70] *Parker v. Flook*,[71] and *Bilski* cases, and *Bilski* in particular, that the claims at issue were directed to an abstract idea. According to the Court, the concept of 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

[68] *Alice Corporation Pty Ltd. v. CLS Bank International*, 134 S. Ct. 2347, 189 L. Ed. 2d 296 (U.S. 2014).
[69] *Mayo Collaborative Services v. Prometheus Labs. Inc.,* 132 S. Ct. 1289, 1297 (U.S. 2012); *Alice*, 134 S.Ct. at 2355.
[70] *Gottschalk v. Benson,* 409 U.S. 63 (1972).
[71] *Parker v. Flook,* 437 U.S. 584 (1978).

block of the modern economy, so intermediated settlement (like the hedging against risk claims in the Bilski case) is an abstract idea beyond the scope of section 101.[72]

For the second step of the *Mayo* analysis, the Court considered whether the claims contain an "inventive concept" sufficient to "transform" the claimed abstract idea into a patent-eligible application.[73] To illuminate the issues, the Court reviewed the *Diehr* case,[74] noting that the claim at issue employed a "well-known" mathematical equation, but it used that equation in a process designed to solve a technological problem in "conventional industry practice." According to the Court, the invention in *Diehr* used a thermocouple to record constant temperature measurements inside the rubber mold--something the industry had "not been able to obtain" and the temperature measurements were then fed into a computer, which repeatedly recalculated the remaining cure time by using the mathematical equation.[75] It was these additional steps that "transformed the process into an inventive application of the formula" and the claims in *Diehr* were patent eligible because they improved an existing technological process--not because they were implemented on a computer.[76]

Thus, the Court stated that mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention.[77] The Court found that the method claims, which require only generic computer implementation, do not transform that abstract idea into a patent-eligible invention. The representative method claim, the Court decided, does no more than simply instruct the practitioner to implement the abstract idea of intermediated settlement on a generic computer. When taking the claim elements separately, the function performed by the computer at each step--creating and maintaining "shadow" accounts, obtaining data, adjusting account balances, and issuing automated instructions—is, according to the Court, purely conventional.[78]

Similarly, because Alice's system and media claims add "nothing of substance to the underlying abstract idea," the Court held that they too are patent ineligible under section 101.[79]

IV. *Myriad*, *Mayo,* and *Alice* Rulings Applied

PerkinElmer, Inc. v. Intema, Ltd. ("*PerkinElmer*").

In the *PerkinElmer* case, a panel of the Federal Circuit reversed the district court and invalidated all of the claims of U.S. Patent No. 6,573,103 as patent-ineligible[80] in view of its *Myriad* decision and the Supreme Court's ruling in the *Mayo* case. The Intema claims were found to both "claim a law of nature" and to recite "the mental process of comparing data to determine a risk

[72] *Alice*, 134 S.Ct. at 2356.
[73] *Alice*, 134 S.Ct. at 2357.
[74] *Diamond v. Diehr,* 450 U.S. 175, 187, 101 S. Ct. 1048 (1981); *Alice*, 134 S.Ct. at 2358.
[75] *Alice*, 134 S.Ct. at 2358.
[76] *Id*.
[77] *Id*.
[78] *Alice*, 134 S.Ct. at 2359.
[79] *Alice*, 134 S.Ct. at 2360.
[80] *PerkinElmer, Inc. v. Intema Ltd.,* 496 Fed. Appx. 65, 73 (Fed. Cir. Nov. 20, 2012)(nonprecedential). Intema filed a petition for certiorari with the Supreme Court, which was denied.

level."[81] The November 2012 *PerkinElmer* decision was deemed to be nonprecedential by the Federal Circuit, at least in part because the Supreme Court had not yet handed down its *Myriad* opinion.

The claims at issue are directed to an improved method to diagnose Down's syndrome by measuring known biomarkers and/or ultrasound data taken during both the first and the second trimesters of pregnancy, and then subjecting the data to multivariate analysis based on reference parameters to determine the odds that the fetus has Down's syndrome. The method was "improved" because some markers are more predictive at different stages of pregnancy.[82]

It is not easy to tell if the Federal Circuit panel applied the Supreme Court *Mayo* ruling or the Federal Circuit's *Myriad* ruling as the dominant precedent, in part because these two cases found ineligibility on different grounds.

Thus, the *PerkinElmer* panel relied on the *Myriad* reasoning in characterizing the claims as involving only mental steps, stating that "[t]he stricken claims [in *Myriad*] are indistinguishable from those before us… The [*Myriad*] claims were not over an *application* of the mental process of comparing. 'Rather, the step of comparing two DNA sequences [was] the entire process that [was] claimed.'"[83]

In relying on *Mayo* reasoning, the panel found a law of nature in claimed subject matter: "Intema also claims a law of nature: the relationship between screening marker levels and the risk of fetal Down's syndrome."[84]

As in *Myriad* and *Mayo*, the *PerkinElmer* panel noted that claims involving only analysis without action predicated on such analysis were defective, stating that in the Intema claims "data are compared to known statistical information. No action beyond the comparison is required."[85] According to the *PerkinElmer* panel, "[A]s in *Prometheus*, there is no requirement that a doctor act on the calculated risk,"[86] and "[h]ere no 'further act' moves the recited concepts to a specific application."[87]

In suggesting that preemption[88] might be a concern, the panel referred to the Supreme Court's *Mayo* decision, stating that "anyone who wants to use this mental step or natural law must follow the claimed process."[89]

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[81] *PerkinElmer*, 496 Fed. Appx. 70.
[82] U.S. Patent No. 6,573,103, col. 2, lines 37-56.
[83] *PerkinElmer*, 496 Fed. Appx. 70 (citing *Myriad*, 689 F.3d at 1335). We note that this statement is only true if the diagnostic conclusion reached in one of the disputed claims is completely ignored as a limitation.
[84] *PerkinElmer*, 496 Fed. Appx. 70.
[85] *Id.* at 70.
[86] *Id.* at 71.
[87] *Id.* at 71 nn. 2.
[88] The Supreme Court has indicated that claims wholly preempting the use of a mathematical formula are patent-ineligible. *Gottschalk v. Benson*, 409 U.S. 63, 67-68 (1972). "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right." *Id*. (citing *LeRoy v. Tatham*, 55 U.S. 156 (1852)).
[89] *PerkinElmer*, 496 Fed. Appx. 71 (citing *Mayo*, 132 S. Ct. at 1298).

But which prohibition was applied? Apparently both mental steps and natural laws, since the *PerkinElmer* panel concludes: "Because the asserted claims recite an ineligible mental step and natural law, and no aspect of the method converts these ineligible concepts into patentable applications of those concepts, the claims cannot stand."[90]

Thus, patent applicants must now search for a "further act" or "aspect" that confers patent-eligibility, because the *Mayo* decision found that simply discovering and claiming an indicative correlation (If "a", then "b") is an impermissible attempt to claim (and thus to monopolize) a natural phenomenon, or law of nature, unless the claim contains another feature that adds something beyond a statement of the correlation.[91] The Court simply denigrated and disregarded the other steps present in the claims[92] – administering the reference drug, measuring the levels of its metabolites and drawing a conclusion about appropriate dosing from the levels that are measured:

> In particular, the steps in the claimed processes [in Prometheus's patents] (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field…upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries.[93]
>
> * * *
>
> [D]o the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that apply natural laws?[94]

Of course, the Court said that the answer was "No." However, the Court provided no guidance as to what that "enough" might be, except to discuss the facts of three older decisions that have nothing to do with modern medicine.[95]

So what action or application might be enough to satisfy a court on the facts available in *PerkinElmer*?[96] The Federal Circuit seems to be edging toward a definition of what is sufficient "to transform an unpatentable law of nature into a patent-eligible application of such a law."[97] The *PerkinElmer* panel tries to explain how the *Mayo* Court distinguished *Diamond v. Diehr*[98] as follows: "The key distinction, which bears on our decision today, is between claims that recite ineligible subject matter, and no more, and claims that recite specific inventive applications of the subject matter."[99] In referring to *Mayo*, the *PerkinElmer* panel noted "that the claims in *Diehr* were patent-eligible 'because of the way the additional steps of the process integrated the [ineligible] equations into the process as a whole,'"[100] and the panel notes that the *Diehr* court

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[90] *Id.* at 73.
[91] *Mayo*, 132 S.Ct. at 1297-98; L. Ed. 2d at 331-32.
[92] *Id*., 132 S. Ct. at 1297; L. Ed. 2d at 331.
[93] *Id.*, 132 S. Ct. at 1294; L. Ed. 2d at 328.
[94] *Id*., 132 S. Ct. at 1297; L. Ed. 2d at 331.
[95] *Id*., 132 S. Ct. at 1298-99; L. Ed. 2d at 332-33.
[96] Would an amniocentesis step be enough? Or would it merely be 'purely conventional'?
[97] *PerkinElmer,* 496 Fed. Appx. 71 (citing *Mayo*, 132 S. Ct. at 1299).
[98] 450 US 175 (1981).
[99] *PerkinElmer,* 496 Fed. Appx. 68 (citing *Diamond v. Diehr*, 450 U.S. 175, 187 (1981).
[100] *Id*. at 70.

"nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use or purely conventional."[101]

However, in *Diehr*, the algorithm functioned in the context of curing shaped rubber widgets and caused the heated mold to open when the widgets were optimally cured.[102] Apart from the algorithm, the molding process was apparently "purely conventional."[103]

Unfortunately, *PerkinElmer* makes it clear that the step of drawing a diagnostic conclusion – the purpose of the method – is to be given no weight as a specific inventive application of a natural law in the patent-eligibility analysis. It is not an "inventive concept" to use a term from *Mayo*, but an "ineligible concept."[104]

Therefore, practitioners are tasked with the nearly impossible burden of claiming two inventions or discoveries in one claim – the first is based on the underlying discovery of an indicative correlation that permits a diagnosis to be drawn, and the second is some as-yet undefined "aspect" or "action" akin to opening the heated mold in *Diehr* and taking out the cured widget. But wouldn't the doctor's adjusting the dose in *Mayo*, suggesting breast removal in *Myriad,* or ordering an amnio in this case be conventional medical activity? The Supreme Court may think they will know what "aspect" or "action" is sufficient when they see it, but their recent decisions have not communicated a discernible standard to patent applicants.

Perkin-Elmer is the first decision in which the Federal Circuit invalidated claims that recited correlating levels of specific biomarkers to the presence or absence of a specific medical condition (Down's syndrome).[105] Although the decision was labeled "nonprecedental," probably in view of the then-pending *Myriad* appeal, it certainly won't be the last. The Supreme Court denied Intema's petition for certiorari on October 7, 2013,[106] signaling agreement with the Federal Circuit that such correlations are not patent-eligible subject matter under Section 101.

Claims 7-9 of the '103 patent recited the specific biomarkers that are measured, and they were apparently all known biomarkers for Down's syndrome. How would the Federal Circuit rule if the inventor had discovered a new biomarker and then claimed its use to diagnose a specific pathology? Since the *de facto* reversal of *In re Durden*[107] by *In re Ochiai*[108] and *In re Plueddemann*,[109] any use, even an obvious one, of a patentable compound is itself patentable.

Since the Supreme Court in the *Myriad* case affirmed that at least cDNA is patentable subject matter, the courts have created a situation in which a compound can be patented, but its use in a diagnostic procedure cannot—at least in view of the guidance that has been provided to date.

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[101] *Id*.
[102] *Diamond v. Diehr*, 450 U.S. 175, 178 (1981).
[103] *Id*., 450 U.S. at 180-81.
[104] *PerkinElmer*, 496 Fed. Appx. 68.
[105] *See, e.g*., U.S. Patent No. 6,573,103, claims 8-9.
[106] *Intema Ltd. v. PerkinElmer, Inc.,* 134 S. Ct. 102, 187 L. Ed. 2d 34, (U.S. 2013). In its petition for certiorari, Intema argued that evaluating multiple samples taken at different times was a novel "inventive step" in its diagnostic claims, but this did not induce the Supreme Court to grant their petition.
[107] 763 F.2d 1406 (Fed. Cir. 1985).
[108] 71 F.3d 1565 (Fed. Cir. 1995).
[109] 910 F.2d 823 (Fed. Cir. 1990).

This is probably not what the Supreme Court intended because, *in dicta*, it stated that useful applications of DNA molecules may well be patentable,[110] but this may conflict with the Federal Circuit's apparent hostility to patents claiming diagnostic methods based on new uses of "old-biomarkers."

BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp.

The *Ambry* case[111] revisits some of the issues and claims that were not fully adjudicated in the *Myriad* case. Myriad and its business partners asserted against Ambry various composition and method claims of patents not previously considered by the Supreme Court or the Federal Circuit.

Claim 16 of U.S. Patent No. 5,747,282 is representative of the composition claims at issue.

> 16. A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

The Federal Circuit found that such primers are not distinguishable from the isolated DNA ruled patent-ineligible products of nature in the *Myriad* case and such primers are not similar to the cDNA that was found to be patent-eligible by the Supreme Court.[112] It made no difference to the Federal Circuit that the primers were synthetically replicated.[113] The Federal Circuit was also not swayed by Myriad's arguments that primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body, or that primers have a fundamentally different function (starting material for polymerization) than when they are part of a DNA strand (storing biological information).[114]

The Federal Circuit also considered the patent eligibility of claims of U.S. Patent 5,753,441, where claim 7 (which depends from and includes the subject matter of claim 1) is recited below.

> A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject[,]

[110] *Myriad*, 133 S. Ct. at 2119-210, 186 L. Ed. 2d 137.
[111] *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp*., 774 F.3d 755 (Fed. Cir. 2014).
[112] *Ambry*, 774 F.3d at 760.
[113] *Id*.
[114] *Ambry*, 774 F.3d at 760-61.

> wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

Claim 8 also depends from claim 1 and states the germline nucleic acid sequence is compared by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids.

The Federal Circuit treated the first paragraphs of claims 7 and 8 separately from the second paragraphs, noting that they had already found claim 1 (i.e., the first paragraph) patent-ineligible.[115] According to the Federal Circuit, these methods for identification of alterations of the gene merely require comparing the patient's gene with the wild-type and identifying any differences that arise, and because of its breadth, the comparison step covers detection of yet-undiscovered alterations.[116] Hence, claims 7 and 8 were found to be abstract ideas.

With respect to whether the second paragraphs of claims 7 and 8 are a "further inventive concept to take the claim into the realm of patent-eligibility," the court agreed with the findings of the lower court that the elements of the second paragraphs of claims 7 and 8 "set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications" and these elements to not add "enough" to make the claims as a whole patent-eligible.[117]

Myriad had argued that claims should be patent eligible because they are similar to claim 21 of the '441 patent, which Judge Bryson suggested was patent eligible in his separate opinion in the 2012 Federal Circuit opinion,[118] and that the Supreme Court had approved of Judge Bryson's suggestion.[119] But, according to the Federal Circuit, claim 21 of the '441 patent is qualitatively different from method claims 7 and 8.[120] The Federal Circuit noted that claim 21 is a method of detecting alterations in which the alterations being detected are expressly identified in the specification by tables 11 and 12, which expressly identify ten predisposing mutations of the BRCA1 gene sequence discovered by the patentees. Hence, the Federal Circuit asserted that claim 21 is limited to the particular mutations the inventors discovered, whereas claims 7 and 8 are significantly broader and more abstract, as they claim all comparisons between the patient's BRCA genes and the wild-type BRCA genes.[121]

Thus, Myriad's claims were found to be directed to ineligible subject matter in violation of 35 U.S.C. § 101.

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[115] *Ambry*, 774 F.3d at 762.
[116] *Ambry*, 774 F.3d at 763.
[117] *Ambry*, 774 F.3d at 764-65.
[118] *Myriad*, 689 F.3d at 1349. Judge Bryson indicated that, "[a]s the first party with knowledge of the sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications."
[119] *Myriad,* 133 S.Ct. at 2120.
[120] *Ambry*, 774 F.3d at 765.
[121] *Id.*

In re Roslin Institute

The issue in the *Roslin Institute* case was whether the Patent Office should find that claims to cloned mammals in U.S. Patent Application No. 09/225,233, patent eligible.[122] One such cloned mammal is Dolly the sheep, which was made by fusing the nucleus of an adult, somatic mammary cell with an enucleated oocyte, stimulating cell division to generate an embryo, and then implanting the embryo into a surrogate mammal, where it develops into a baby animal. Claims 155 and 164 are representative:

> 155. A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats.
>
> 164. The clone of any of claims 155-159, wherein the donor mammal is non-foetal.

The Federal Circuit affirmed the Patent Trial and Appeal Board finding that these claims were ineligible for patenting because such clones are constituted a "natural phenomenon" that did not possess "markedly different characteristics than any found in nature,"[123] and because the claims were anticipated and obvious by the prior art because they were indistinguishable from clones produced through prior art cloning methods, i.e., embryotic nuclear transfer and *in vitro* fertilization.[124]

The Federal Circuit contrasted the facts of the *Roslin Institute* case with the *Chakrabarty*[125] case, where non-naturally occurring bacterium were made by adding four plasmids to a specific strain of bacteria. In *Chakrabarty,* the Supreme Court held that such a modified bacterium was patentable because it was "new" with "*markedly different characteristics from any found in nature* and one having the potential for significant utility."[126]

The Roslin Institute argued that its claimed clones were patent eligible because they are distinguishable from the donor mammals used to create them, contending that "environmental factors" lead to phenotypic differences that distinguish its clones from their donor mammals.[127] However, Roslin acknowledged that any phenotypic differences came about or were produced "quite independently of any effort of the patentee."[128] The Roslin Institute also argued that the clones are distinguishable from their original donor mammals because of differences in mitochondrial DNA, which originates from the donor oocyte rather than the donor nucleus.[129] The Federal Circuit did not buy these arguments because such factors, phenotypic differences, and mitochondrial DNA differences were not recited in the claims.[130] Finally, the Roslin Institute argued that its clones were patent eligible because they are time-delayed versions of their donor

[122] *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014).
[123] *Roslin Institute*, 750 F.3d at 1335, 1339.
[124] *Roslin Institute*, 750 F.3d at 1335, 1339.
[125] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[126] *Roslin*, 750 F.3d at 1336.
[127] *Roslin*, 750 F.3d at 1337-38.
[128] *Roslin*, 750 F.3d at 1338.
[129] *Id.*
[130] *Id.*

mammals, and therefore different from their original mammals. But the Federal Circuit again found that this distinction cannot confer patentability because such a time-delayed characteristic is true of any copy of an original.[131]

Ariosa Diagnostics Inc. v. Sequenom Inc.

In the *Ariosa* case, a panel of the Federal Circuit in June 2015 affirmed the district court ruling that the asserted claims U.S. Patent No. 6,258,540 (the '540 patent) were ineligible for patenting.[132] Claim 1 of Sequenom's '540 patent reads as follows:

> 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
>
> amplifying a paternally inherited nucleic acid from the serum or plasma sample and
>
> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

The panel followed a two-step method outlined by the Supreme Court in the *Mayo* case[133] to find these claims patent ineligible. First, the panel found that the claims were directed to a patent-ineligible concept, noting that it was undisputed that the existence of cffDNA in maternal blood is a natural phenomenon and that that the location of the nucleic acids existed in nature before Drs. Lo and Wainscoat found them.[134] The panel referred to several statements from the specification as evidence to support their finding of such a natural phenomenon.[135]

> "It has now been discovered that foetal DNA is detectable in maternal serum or plasma samples."
> '540 patent, col. 1, ll. 50-51.
>
> "This is a surprising and unexpected finding; maternal plasma is the very material that is routinely discarded by investigators studying noninvasive prenatal diagnosis using foetal cells in maternal blood."
> '540 patent, col. 1, ll. 51-55.

Even such benign statements as these can therefore be problematic in a patentee's specification when patent eligibility issues are raised.

The panel then considered whether claim 1 contains an inventive concept sufficient to "transform" the claimed naturally occurring phenomenon into a patent-eligible application.[136]

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[131] *Id.*
[132] *Ariosa Diagnostics Inc. v. Sequenom Inc*., 788 F.3d 1371 (Fed. Cir. 2015).
[133] *Mayo Collaborative Services v. Prometheus Labs. Inc.,* 132 S. Ct. 1289, 1297 (U.S. 2012); *Ariosa*, 788 F.3d at 1375.
[134] *Ariosa*, 788 F.3d at 1376.
[135] *Id*.
[136] *Id.*

The panel found no such transformation stating that methods like PCR were well-understood, routine, and conventional activity in 1997, and that the same applied to the detecting step.[137] With respect to the detection step, the panel cited to statements made during the prosecution of the '540 patent; the following is one example of such a statement.[138]

> [O]ne skilled in the art is readily able to apply the teachings of the present application to any one of the well-known techniques for detection of DNA with a view to analysis of foetal DNA…

Thus, a patentee's assertions that any step or aspect of a claimed inventions is "well-known" can fuel a patent-ineligibility finding.

Sequenom argued that the particular application of the natural phenomena embraced by the '540 patent claims were narrow and specific, and hence the claims should be patent eligible because they did not preempt all uses of cffDNA.[139] However, the panel found that while preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility. According to the panel, in this case, Sequenom's attempt to limit the breadth of the claims by showing alternative uses of cffDNA outside of the scope of the claims did not change the conclusion that the claims are directed to patent ineligible subject matter.[140]

Judge Linn concurred but stated he did so only because he was bound by the "sweeping language" of *Mayo*. According to Judge Linn, the '540 patent claims should be patent eligible. He noted that while the instructions in the claims at issue in *Mayo* had been widely used by doctors, the amplification and detection of cffDNA had never before been done. He called the Sequenom invention "ground-breaking" and "nothing like the invention at issue in *Mayo*."[141]

Despite Judge Linn's strong concurrence, the Federal Circuit declined to review the panel decision en banc.[142] Judge Newman wrote a strong dissent, while Judges Lourie and Dyk wrote separate concurrences of the denial of en banc review.

Judge Lourie, joined by Judge Moore, urged that laws of nature are exact statements of physical relationships, all physical steps of human ingenuity utilize natural laws or involve natural phenomena, and such steps cannot be patent-ineligible solely because they are laws of nature, because nothing in the physical universe would then be patent-eligible.[143] According to Judge Lourie, methods that utilize laws of nature do not set forth or claim laws of nature. Judge Lourie also reasoned that abstract steps are, axiomatically, the opposite of tangible steps, and that which is not tangible is abstract. Hence, Judge Lourie noted that steps that involve machines are tangible, steps that involve transformation of tangible subject matter, and tangible implementations of ideas or abstractions should not be considered to be abstract ideas.[144] Judge

[137] *Ariosa*, 788 F.3d at 1377.
[138] *Ariosa*, 788 F.3d at 1377-78.
[139] *Ariosa*, 788 F.3d at 1378.
[140] *Ariosa*, 788 F.3d at 1379.
[141] *Ariosa*, 788 F.3d at 1381.
[142] *Ariosa Diagnostics Inc. v. Sequenom Inc.*, 809 F.3d 1282, 117 U.S.P.Q.2D (BNA) 1153 (Fed. Cir. 2015)
[143] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1154.
[144] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1155.

Lourie also noted that there may be some truth to concerns that the whole category of diagnostic claims is at risk and that a crisis of patent law and medical innovation may be upon us.[145]

Judge Dyk thought that the framework of *Mayo* and *Alice* is an "essential ingredient of a healthy patent system" but he expressed concerns that are shared by some of his colleagues that a too restrictive test for patent eligibility under 35 U.S.C. § 101 with respect to laws of nature (reflected in some of the language in Mayo) may discourage development and disclosure of new diagnostic and therapeutic methods in the life sciences, which are often driven by discovery of new natural laws and phenomena.[146] Judge Dyk stated that the Federal Circuit was bound by the language of *Mayo*, and any further guidance must come from the Supreme Court.[147] According to Judge Dyk Mayo/Alice framework works well when the abstract idea or law of nature in question is well known and longstanding, but a problem exists with *Mayo* insofar as it concludes that an inventive concept cannot come from discovering something new in nature such as the identification of a previously unknown natural relationship or property.[148] Judge Dyk stated that this is especially true in the life sciences, where development of useful new diagnostic and therapeutic methods is driven by investigation of complex biological systems, and he worried that method claims that apply newly discovered natural laws and phenomena in somewhat conventional ways are screened out by the Mayo test.[149] Judge Dyk provided a partial solution to this problem by limiting the scope of patents based on new discoveries to narrow claims covering applications actually reduced to practice.[150] He reasoned that primary concern with a patent on a law of nature is undue preemption--the fear that others' innovative future applications of the law will be foreclosed – and that limiting the scope of claims to those reduced to practice would avoid the preemption issue.

Judge Newman flatly stated that the *Ariosa* case was wrongly decided and declared that she did not share the view of her colleagues such an incorrect decision is required by Supreme Court precedent. [151] According to Judge Newman, the facts of the *Ariosa* case are different from those in *Mayo*. Whereas both the claimed medicinal product and its metabolites were previously known in the *Mayo* case, the Sequenom method was not previously known, nor was the diagnostic knowledge and benefit implemented by the method.[152] In addition, Judge Newman asserted that patenting of this new diagnostic method does not preempt further study of this science, nor the development of additional applications.[153]

In view of the concerns expressed by the Federal Circuit judges, which capture many of those of the diagnostics and biotechnology industry, it would seem that the *Ariosa* ruling could be poised for review by the Supreme Court. A petition for *certiorari,* was filed in mid-March, asking for clarification of the scope of the *Mayo* opinion. As Harold Wegner has cautioned, there are serious dangers raised for the patent community if this case is taken for review by the Supreme

[145] *Id*.
[146] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1156.
[147] *Id.*
[148] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1158.
[149] *Id*.
[150] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1160.
[151] *Ariosa*, 117 U.S.P.Q.2D (BNA) at 1161.
[152] *Id*.
[153] *Id*.

Court, including a potential for a binding, precedential Supreme Court affirmance of the Federal Circuit decision.[154] However, the petition for cert. was denied.

Notably, not all of the claims in the Sequenom patent were diagnostic claims. The claim of the '540 patent summarized below is only directed to the amplification and detection of cffDNA. Invalidation of such claims, coupled with statements about the ineligibility of claims to nature-based products in *Roslin*, comes perilously close to a general repudiation of "*Bergy II*", 596 F.2d 952 (CCPA 1979) in which a "biologically pure culture" of a microorganism useful to produce an antibiotic was found to be patent-eligible despite its existence in the "complex jungle of microorganisms" in the soil sample from which it was isolated. When the Supreme Court decided *Chakrabarty*, it remanded the CCPA's decision in *Bergy II* for dismissal as moot. However, the CCPA decision may have precedential weight, since the Supreme Court cited it in *Diehr*.

Genetic Technologies Ltd. v. Merial LLC

In the *Genetic Technologies* case, a panel of the Federal Circuit in April 2016 affirmed the district court ruling that the asserted claims of U.S. Patent No. 5,612,179 (the '179 patent) (amongst others) were not eligible for patenting.[155] Claim 1 of the '179 patent recites:

> 1. A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising:
>
> a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and
>
> b) analyzing the amplified DNA sequence to detect the allele.

According to Genetic Technologies, the methods of the '179 patent had various advantages over prior art methods involving direct analysis of a coding region. For example, Genetic Technologies stated that "analysis of relatively short regions of non-coding sequences, of a size which can be amplified, can provide more information than prior art analyses such as cDNA RFLP analyses which involve the use of significantly larger DNA sequences...." '179 Patent Prosecution History, Applicant's Amendment and Remarks of Jan. 14, 1993, at 6.

The district court granted defendants' motions, holding that claim 1 of the '179 patent is invalid for claiming a law of nature, which is patent-ineligible subject matter. "A claim is unpatentable if it merely informs a relevant audience about certain laws of nature, even newly-discovered ones, and any additional steps collectively consist only of well-understood, routine, conventional

[154] Harold C. Wegner, *A Sequenom White Paper,* http://www.laipla.net/wp-content/uploads/2016/02/SequenomFeb23.pdf (Feb. 23, 2016). He has also noted that the Court may not grant the petition, since there are, as yet, no conflicting opinions below, or within the Court.

[155] *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016) (cert. denied).

activity already engaged in by the scientific community. The claim involved here, claim 1 of the '179 patent, does just that and no more."

The Federal Circuit used the *Mayo/Alice* test and ask first whether claim 1 is directed to a patent-ineligible concept, finding that it was. The Federal Circuit then examined the physical steps by which claim 1 implements the natural law of linkage disequilibrium between coding and non-coding regions to determine whether they provide more than "well-understood, routine, conventional activity" already engaged in by those in the field under the second step of the *Mayo/Alice* test. According to the Federal Circuit, claim 1 contains two implementation steps, "amplifying genomic DNA with a primer pair" and "analyzing the amplified DNA sequence to detect the allele."

The Federal Circuit found that "amplifying" genomic DNA with a primer pair and the "analyzing" step of the amplified DNA to provide a user with information about the amplified DNA were well known, routine, and conventional in the field of molecular biology as of 1989, when the first precursor application to the '179 patent was filed.

Rapid Litigation Mgmt. LTD v. Cellzdirect, Inc.

In the *Cellzdirect* case, a panel of the Federal Circuit in July 2016 vacated and remanded the district court ruling that the asserted claims of U.S. Patent No. 7,604,929 (the '929 patent) were not eligible for patenting.[156] Claim 1 of the '929 patent reads as follows:

> 1. A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes being capable of being frozen and thawed at least two times, and in which greater than 70% of the hepatocytes of said preparation are viable after the final thaw, said method comprising:
>
> (A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes,
>
> (B) recovering the separated viable hepatocytes, and
>
> (C) cryopreserving the recovered viable hepatocytes to thereby form said desired preparation of hepatocytes without requiring a density gradient step after thawing the hepatocytes for the second time,
>
> wherein the hepatocytes are not plated between the first and second cryopreservations, and wherein greater than 70% of the hepatocytes of said preparation are viable after the final thaw.

The Federal Circuit reversed the lower court, stating the following.

> The district court identified in these claims what it called a "natural law" —the cells' capability of surviving multiple freeze -thaw cycles. We need not decide in this case whether the court's labeling is correct. It is enough

[156] *Rapid Litigation Mgmt. LTD v. Cellzdirect, Inc.*, 827 *F.3d* 1042 (Fed. Cir. 2016).

> in this case to recognize that the claims are simply not directed to the ability of hepatocytes to survive multiple freeze- thaw cycles. Rather, the claims of the '929 patent are directed to a new and useful laboratory technique for preserving hepatocytes. This type of constructive process, carried out by an artisan to achieve "a new and useful end," is precisely the type of claim that is eligible for patenting.

The panel delved into the prosecution history of the patent to evidence that "[T]he individual steps of freezing and thawing were well known, but a process of preserving hepatocytes by repeating those steps was itself far from routine and conventional," concluding that "[r]epeating a step that the art taught should be performed only once can hardly be considered routine or conventional." (Citing Diehr with approval.) "To require something more [than Diehr] at step two [of the Mayo/Alice test] would be to discount the human ingenuity that comes from applying a natural discovery in a way that achieves a 'new and useful end.'"

Cleveland Clinic v. True Health Diagnostics

In the *Cleveland Clinic* case, a panel of the Federal Circuit in June 2017 affirmed the district court ruling that the asserted claims of U.S. Patent No. 7,223,552 (the '552 patent) (amongst others) were eligible for patenting.[157] Claim 11 of Cleveland Clinic's '552 patent reads as follows:

> 11. A method of assessing a test subject's risk of having atherosclerotic cardiovascular disease, comprising
>
> comparing levels of myeloperoxidase in a bodily sample from the test subject with levels of myeloperoxidase in comparable bodily samples from control subjects diagnosed as not having the disease, said bodily sample being blood, serum, plasma, blood leukocytes selected from the group consisting of neutrophils, monocytes, sub-populations of neutrophils, and sub-populations of monocytes, or any combination thereo[f];
>
> wherein the levels of myeloperoxidase in the bodily [sample] from the test subject relative to the levels of [m]yeloperoxidase in the comparable bodily samples from control subjects is indicative of the extent of the test subject's risk of having atherosclerotic cardiovascular disease.

The Federal Circuit found that the claims are directed to multistep methods for observing the law of nature that myeloperoxidase correlates to cardiovascular disease. The court therefore proceeded to consider step 2 of the Mayo/Alice test by examining the elements of the claims to determine whether they contain an inventive concept sufficient to transform the claimed naturally occurring phenomena into a patent eligible application.

[157] *Cleveland Clinic v. True Health Diagnostics*, 859 F. 3d 1352 (Fed. Cir. 2017).

The Federal Circuit concluded that the practice of the method claims does not result in an inventive concept that transforms the natural phenomena of myeloperoxidase being associated with cardiovascular risk into a patentable invention. According to the Federal Circuit, the *Mayo* and *Ariosa* decisions make clear that transforming claims that are directed to a law of nature requires more than simply stating the law of nature while adding the words "apply it."[158]

Exergen Corp. v. Kaz USA

In the *Exergen* case, a panel of the Federal Circuit in March 2018 affirmed the district court ruling that the asserted claims of U.S. Patent No. 7,787,938 (the '938 patent) were eligible for patenting.[159] Claim 14 of Exergen's '938 patent reads as follows:

> 14. A method of detecting human body temperature comprising making at least three radiation readings per second while moving a radiation detector to scan across a region of skin over an artery to electronically determine a body temperature approximation, distinct from skin surface temperature.

The parties had agreed that the claims are directed to a patent-ineligible concept, so the sole issue remaining for the panel was to decide if the distinct court properly found that the claims contained a further inventive concept that was not "well-understood, routine [and] conventional activity previously engaged in by researchers in the field." This is the second step the patent office's path for resolving the 101 question.

The panel concluded:

> "Even if the concept of [the measurement of a natural phenomenon (core body temperature)] is directed to a natural phenomenon and is abstract at step one [the MPEP's Step 2A], the measurement method here was not conventional, routine, and well-understood. Following years and millions of dollars of testing and development, the inventor determined for the first time the coefficient representing the relationship between temporal-arterial temperature and core body temperature and incorporated that discovery into an unconventional method of temperature measurement. As a result, the method is patent-eligible, similar to the method of curing rubber held eligible in *Diehr*."

Mayo and *Ariosa* were distinguished as employing well-known, existing methods to determine the existence of natural phenomenon. The panel recognized that, while section 101 patent eligibility is a legal question, "sometimes the inquiry may contain underlying factual issues, citing *Mayo* for the proposition that the 101 inquirey 'might sometimes overlap' with other fact-intensive inquiries like novelty under section 102.

[158] In June 2018, the Supreme Court has declined to grant Cleveland Clinic's petition for certiorari.
[159] *Exergen Corp. v. Kaz USA, Inc.*, 725 F. App'x 959 (Fed. Cir. 2018).

The Patent Office issued a Memorandum entitled "Changes in Examination Procedure Pertaining to Subject Matter Eligibility, Recent Subject Matter Eligibility Decision (*Berkheimer v. HP, Inc*.)(April 19, 2019), citing the *Exergen* decision as "concluding that the district court's fact finding that the claimed combination was not proven to be well-understood, routine, [or] conventional was not clearly erroneous." The Memorandum stated that, in a Mayo/Alice 2B analysis, "an additional element (or combination of elements) is not well-understood, routine or conventional unless the examiner finds, and expressly supports a rejection in writing with references to facts such as concessions by applicant, citation to relevant court decisions, citations to relevant publications or the examiner properly takes official notice of the well-known, etc., nature of the additional elements."

In re Urvashi Bhagat

In the *In re Urvashi Bhagat* case, [160] the PTAB affirmed an Examiner's rejection of claims drawn to a lipid-containing formulation. Claim 65 of U.S. Patent Application Ser. No. 12/426,034 (the '034 application) was at issue.

> 65. A lipid-containing formulation, comprising a dosage of omega-6 and omega-3 fatty acids at an omega-6 to omega-3 ratio of 4:1 or greater, contained in one or more complementing casings providing controlled delivery of the formulation to a subject, wherein at least one casing comprises an intermixture of lipids from different sources, and wherein
>
> > (1) omega-6 fatty acids are 4–75% by weight of total lipids and omega-3 fatty ac-ids are 0.1–30% by weight of total lipids; or
> >
> > (2) omega-6 fatty acids are not more than 40 grams.

The examiner found that the claimed "intermixture of lipids from different sources" is "structurally indistinct" from lipid formulations derived from a single source referring to the prior art as proof. The examiner also found that the claims are directed to natural products of walnut oil and olive oil, and that the additional limitations in the claims do not change the characteristics of the products or add "significantly more" to the claims.

The Federal Circuit simply dismissed the claim element "casing" as meaning "any orally accepted form", in the anticipation section of the decision, that does not provide patentability to the compositions because the specification states that the term is not claim-limiting and that it does not describe any novel characteristics of the components or their formulations.

This analysis may be appropriate in a patentability analysis under sections 102/103, it is unclear how a mixture of lipid from different sources encased in casings providing controlled delivery is a natural product.

[160] *In re Urvashi Bhagat*, Appeal 2016-2525 (March 16, 2018).

Ex Parte Buck

In the *Ex Parte Buck* case, [161] the PTAB upheld an Examiner's rejection of claims drawn to a kit comprising vitamin D. Claim 7 of U.S. Patent Application Ser. No. 13/446,128 (the '128 application) was at issue.

> 7. A kit comprising multiple, separate weekly or monthly dosages of
> a) Vitamin D, and
> b) 25-OH D3, wherein a dosage ratio of the Vitamin D3 to the 25-OH D3 is from about 6:1 to 1:6; a single weekly dosage contains from 7μg to 350 μg each of Vitamin D and 25-OH D3; and a single monthly dosage contain from 30 μg.

The Examiner asserted that the vitamin D and 25-OH D3 of the kit were both natural products, and that the characteristics of each component were not significantly different from their naturally-occurring counterparts because they have the same structure and function as they do in nature.

The Board the Examiner has failed to provide a single example of a natural product, that comes in multiple separate weekly or monthly dosages, and which satisfies all the features of the claims.

According to Appellants, the two claimed compounds, Vitamin D3 and 25-0H D3, exhibit in combination synergistic effects, synergistically raising and sustaining 25-OH D3 levels in an individual and allowing weekly and/or monthly dosing, which is not possible using the single ingredients. not persuaded by Appellants' arguments.

However, the Board found that it was indisputable that both vitamin D3 and 25-OH D3 are naturally-occurring chemicals that co-exist in biological systems and, by themselves, are products of nature and consequently unpatentable. While all inventions, at some level, embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas, the Board found that they could not structurally distinguish the chemical compositions recited in the claims from those occurring naturally in biological systems. The Board also found that the fact that Appellants claim different dosage amounts or ratios did not suffice to add significantly more to the naturally-occurring substances than the administration of the same naturally-occurring substances themselves.

[161] *Ex parte Buck,* Appeal No. 2017-005470 (PTAB, April 20, 2018).

Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l Inc.

In the *Vanda* case, a panel of the Federal Circuit in April 2018 affirmed the district court ruling that the asserted claims U.S. Patent No. 8,586,610 (the '610 patent) were ineligible for patenting.[162] Claim 1 of Vanda's '610 patent reads as follows:

> 1. A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:
>
> determining whether the patient is a CYP2D6 poor metabolizer by:
>
> obtaining or having obtained a biological sample from the patient; and
>
> performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and
>
> if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and
>
> if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day,
>
> wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.

The Federal Circuit panel distinguished the S. Ct.'s decision in *Mayo* stating: "The *Mayo* claim was not a treatment claim, it was 'not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable." The majority discussed the importance of the specificity of the dosages recited in the Vanda claims. The Federal Circuit panel concluded:

> "At bottom, the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome….[t]hey recite a method of treating patients based on this relationship that makes iloperidone safer by lowering the risk of [the heart condition]."

Hence this decision appears to broadly hold that method of treatment claims are patent eligible, and the Patent Office has endorsed this position in a Memorandum entitled "Recent Subject Matter Eligibility Decision, Vanda Pharmaceuticals, Inc. v. West-Ward Pharmacueticals (June 7, 2019)/

[162] *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l Inc.*., 887 F.3d 1117 (Fed. Cir. 2018).

Ex Parte Young

In the *Ex Parte Young* case,[163] the PTAB reversed an Examiner's rejection of claims drawn to a method of manipulating the huge amount of DNA sequence information. Claim 1 of U.S. Patent Application Ser. No. 14/489,198 (the '198 application) was at issue.

> 1. A method comprising:
>
> amplifying one or more nucleotide sequences in a sample using a PCR amplification process to produce an amplified sample;
>
> using a massively parallel sequencing (MPS) instrument to read the one or more nucleotide sequences of the amplified sample and generate one or more text strings based on the amplified sample;
>
> selecting a first plurality of text strings from the one or more text strings read by the MPS instrument, wherein each of the selected first plurality of text strings represent a nucleotide sequence that-corresponds to a first target locus in the amplified sample;
>
> comparing the selected first plurality of text strings to one another to determine an abundance count for each unique text string included in the selected first plurality of text strings;
>
> identifying a first number of unique text strings included in the selected first plurality of text strings as representing noise responses; and
>
> determining a method detection limit (MDL) as a function of the abundance counts for the first number of unique text strings identified as representing noise responses.

The Board noted that in addition to the claimed "comparing," "identifying," and "determining" steps identified by the Examiner as constituting data manipulation, the claims recite the steps of "using a massively parallel sequencing (MPS) instrument to read the one or more nucleotide sequences of the amplified sample and generat[ing] one or more text strings based on the amplified sample[, and] selecting a first plurality of text strings from the one or more text strings read by the MPS instrument."

The Board did not address the Examiner's initial finding that the claims are drawn to an "abstract process." Instead, the PTAB reversed the rejection as incorrectly applying the Mayo/Alice test at step two:

> "Thus, even if we were to agree with the Examiner that the rejected claims involve an abstract idea, i.e. manipulation of nucleic acid sequence data, we are not persuaded that the preponderance of

[163] *Ex Parte Young*, Appeal 2017-007443 (July 18, 2018).

> evidence on this record supports a factual finding that other features of the claims, MPS in particular, were well-understood, routine conventional activities already engaged in by skilled artisans in the field, given the evidence cited by the Examiner to support such a finding, and given [statements in the specification that MPS is not routinely used to analyze DNA for forensic purposes](citing *Berkheimer v HP Inc*.)."

Ex Parte Nagy

In the *Ex Parte Nagy* case, [164] the PTAB affirmed an Examiner's rejection of claims drawn to a method for early diagnosis of Alzheimer's disease (AD). Claim 2 of U.S. Patent Application Ser. No. 14/223,113 (the '113 application) was at issue.

2. A method of assessing the risk of AD progression in a human subject suspected of having AD, which method comprises:

> (i) obtaining lymphocytes from said human subject suspected of having AD and from an age-matched healthy subject with normal cognitive ability;
>
> (ii) inducing cell division in the lymphocytes taken from the human subject suspected of having AD;
>
> (iii) separating the dividing lymphocytes of (ii) into two pools and treating one pool of lymphocytes with rapamycin;
>
> (iv) assaying the level of protein of at least one interleukin selected of interleukin ("IL") 1 beta (IL1B), IL-2, IL-6 or IL-10 in the pool of lymphocytes treated with rapamycin and in the untreated pool;
>
> (v) comparing the level of protein of the at least one interleukin obtained in (iv) for the pool of rapamycin-treated lymphocytes and the untreated lymphocyte pool to quantify the change in protein levels in response to rapamycin;
>
> (vi) repeating steps (ii)-(iv) using control lymphocytes taken from the age-matched healthy subject with normal cognitive ability; and
>
> (vii) determining that said human subject suspected of having AD is at increased risk of AD progression when (a) the reduction of IL1B or IL10 protein levels in response to rapamycin is higher in control lymphocytes as compared to lymphocytes taken from the human subject suspected of having AD [and/or] (b) the reduction of IL-2 or

[164] *Ex Parte Nagy*, Appeal 2017-008793 (July 30, 2018).

> IL-6 protein levels in response to rapamycin is lower in control lymphocytes as compared to lymphocytes taken from the human subject suspected of having AD….

Claim 27 used the same methodology to determine that m-Tor signaling in a human lymphocyte is decreased if there is a decrease in the protein level of at least one of the interleukins in response to rapamycin.

The core of the Board's reasoning bears repeating:

> "Thus, here as in Mayo, the claims are not directed to a method of treating a disease. To the contrary, Appellant's claims are similar to those in *Mayo*, which "were directed to a diagnostic method based on the 'relationships between concentrations of certain metabolites [of the administered thiopurine drug] in the blood and the likelihood that a dosage of the thiopurine drug will prove ineffective or cause harm.'" *Vanda Pharms*., *Inc. v. West-Ward Pharms. Int'l Ltd*., 887 F.3d 1117, 1134 (Fed. Cir. 2018), quoting *Mayo*, 132 S.Ct. at 1289. "This 'relation is a consequence of the ways in which thiopurine compounds are metabolized in the body–entirely natural processes. And so, a patent that simply describes that relation sets forth a natural law.'" Thus, here, as in *Mayo*, the relationship between certain [IL] protein levels and either the risk of [AD] progression or the decrease in mTOR signaling are entirely natural processes and Appellant's claims do no more than simply describe that relationship, thereby setting forth a natural law." [citing *Mayo*, 132 S. Ct. 1289 (2012)].

However, the main claims appear to recite more than a relationship between certain protein levels and either the risk of Alzheimer's progression or a decrease in mTOR signaling. The main claims are more complicated, for example, including recitation of inducing lymphocyte division, creating two pools of lymphocytes obtained from both Alzheimer's disease suspects and controls, treating one pool from each pair with rapamycin, and quantifying the change in protein levels in response to the rapamycin treatment.

Ex Parte Schwartz

In the *Ex Parte Schwartz* case,[165] the PTAB reversed an Examiner's rejection of claims drawn to a method of modulating expression of a target gene in the genome of a human cell. Claim 21 of U.S. Patent Application Ser. No. 14/482,950 (the '950 application) was at issue.

> 21. A method [of] selectively modulating expression of a target gene in the genome of a human cell determined to be in need thereof comprising:

[165] *Ex Parte Schwartz*, Appeal 2017-004975 (August 2, 2018).

> determining the presence of an encoded antisense transcript overlapping a promoter of the target gene;
>
> contacting the antisense transcript with an exogenous gapmer or double-stranded ag[“antigene”]RNA; and
>
> detecting a resultant modulation of expression of the target gene,
>
> the gapmer comprising a DNA insert complementary to a sequence in the antisense transcript upstream relative to the transcription start site of the gene, and the agRNA being 18-28 bases and complementary to a portion of the antisense transcript upstream to a portion of the antisense transcript upstream relative to the transcription start site of the gene.

The Examiner rejected the claims under section 101 as directed to the “abstract idea of determining the presence of an encoded antisense transcript overlapping a promoter of a target gene.” Having concluded that the claim failed Step 2A of the Mayo/Alice step, the Examiner conducted the Step 2B inquiry and ruled that the additional claim elements do not add “‘significantly more'” than this abstract idea because they describe “‘conventional techniques that do not add meaningful limits to practicing the abstract idea.'”

Considering the claims as a whole, the PTAB determined that they are directed not to a method of “determining the presence ... “but to a method of "selectively modulating expression of a target gene.” Hence, the PTAB disagreed with the Examiner's finding that the claims were directed to the abstract idea of determining the presence of an encoded antisense transcript overlapping a promoter of a target gene, and because the Examiner had not identified another applicable judicially recognized exception, the PTAB reversed the Examiner's rejection of claims 21-40.

Ex part Ho

In the *Ex Parte Ho* case, [166] the PTAB reversed an Examiner’s rejection of claims drawn to an isolated cell population of human bone marrow-derived cells. Claim 133 of U.S. Patent Application Ser. No. 11/797,322 (the ‘322 application) was at issue.

> 133. An isolated cell population of human bone marrow-derived cells, wherein said cell population has been cultured in vitro at cell seeding densities of about 30 cells/cm^2 under about 5% oxygen conditions for more than 30 population doublings, wherein said cell population continues to maintain a population doubling time of about 30 hours per doubling and wherein greater than 91% of the cells in said cell population continue to co-express cell surface markers CD49c and CD90, and wherein said cell population does not express cell surface

[166] *Ex Parte Ho,* Appeal no. 2016-007472 (PTAB, Aug. 7, 2018).

> markers CD34 or CD45, and wherein said cell population expresses telomerase at a relative expression of between about 1 transcript of telomerase per 10^6 transcripts of an 18s rRNA and about 10 transcripts of telomerase per 10^6 transcripts of an 18s rRNA.

Examiner asserted that the claimed cell population was patent ineligible because it is not markedly different from a progenitor cell population that exists *in vivo*. According to the Examiner, the claimed cell population is "obtained from a naturally occurring human body," and "[t]here is no indication in the specification that the isolated cells have been modified by applicants or the claimed cells have any characteristics (structural, functional or otherwise) that are markedly different from naturally occurring counterparts."

Appellants argued that the Examiner had not identified a naturally occurring counterpart of the claimed cells and that the Examiner had not provided any references showing that a cell population exists *in vivo* having the features of the claimed cell population. Appellants also asserted that the culturing step recites that the cell population has been cultured *in vitro* at cell seeding densities of about 30 cells/cm^2 under about 5% oxygen conditions for more than 30 population doublings, but that the Examiner had not established that the culturing features recited in the claims were routine or conventional.

Appellants contended that the characteristics of the claimed cells were the direct result of the inventor's experimentation with low oxygen and low-density culture conditions. A Declaration by Dr. Ragaglia referred to multiple reports showing the "profound influence of culture conditions" on the mesenchymal stem cell (MSC) phenotype and behavior, and that once a cell is removed from its native environment, its phenotype and behavior are subject to change. For example, Dr. Ragaglia cited a reference by Javazon as teaching that discrepancies in the phenotypes of isolated and cultured MSCs arise due in part to differences in isolation and culture conditions. Dr. Ragaglia cited a document by Zhang as teaching that "MSCs cultured without confinement have higher levels of osteogenic markers"; a document by Kiefer as teaching that different culture media have different effects on cellular phenotype, doubling time, cytokine production, and ability to differentiate into stromal lineages; and a document by Bain as teaching that even very brief culture can alter the attachment and chemotactic behavior of MSCs. Dr. Ragaglia acknowledged that "an MSC is different and distinct from the cell population recited in claim 133 but asserted that "[t]he conclusions regarding the structural differences between in vivo and in vitro MSCs can be extrapolated to the claimed cell population."

The Board found that the Examiner had not persuasively identified any inadequacy in Appellants' rebuttal evidence, and that the Examiner had not provided scientific reasoning or evidence sufficient to support a finding that the claimed isolated cell population was a product of nature, lacking markedly different characteristics from a naturally occurring counterpart. Hence, the Board reversed the rejection under section 101.

Ex parte Parenteau

In the *Ex Parte Parenteau* case,[167] the PTAB reversed an Examiner's rejection of claims drawn to isolated tumor C-RC cell populations. Claim 17 of U.S. Patent Application Ser. No. 13/774,644 (the '644 application) was at issue.

> 17. An isolated tumor C-RC cell population prepared by
>
> (a) obtaining a tumor sample from an individual;
>
> (b) cultivating the tumor sample under conditions that induce a stress response in non-C-RC differentiating and differentiated cells leading to apoptosis and necrosis but permit C-RC cells to propagate through the activation of a regenerative response;
>
> (c) isolating the dominant actively expanding, most rapidly dividing population of cells from step (b); and
>
> (d) culturing the cells to obtain a population of 51 % to 100% C-RC, in a serum-free, defined cell culture medium containing agents selected from the group consisting of agents inducing the apoptosis and/or necrosis of the cells, cAMP elevating agents, agents inhibiting cell-cell adhesion, nitric oxide, tumor necrosis factor-alpha (TNF-α), interleukin I-beta (ILI-α), interferon-gamma (IFN-γ), agents disrupting cell adhesion, agents interfering with survival of more differentiated cells, and calcium in a concentration of less than about 1 mM calcium,
>
> wherein 80-100% of the C-RC population consists of actively expanding and dividing VSEC, SDEC and SCEC cells and abnormal transit amplifying cells.

The Board found that the Examiner failed to establish an evidentiary basis to support a finding that that such culture media was well known, routine and conventionally used in the art at the time of Appellants' claimed invention. Hence, the Board reversed the rejection under section 101 and found that the tumor C-RC cell population prepared as recited in the claim was eligible for patenting.

Roche Molecular Systems, Inc. v. Cepheid

In the *Cepheid* case, a panel of the Federal Circuit in October 2018 affirmed the district court ruling that the asserted claims U.S. Patent No. 5,643,723 (the '723 patent) were ineligible for patenting,[168] illustrating that the Federal Circuit is bound by precedent to maintain that most diagnostic and DNA claims are not eligible for patenting.

Claim 17 of the '723 patent is drawn to primers, as shown below.

[167] *Ex parte Parenteau,* Appeal no. 2017-002191 (August 22, 2018).
[168] *Roche Molecular Systems, Inc. v. Cepheid*, ___ F.3d ___ (Fed. Cir. 2018).

> 17. A primer having 14-50 nucleotides that hybridizes under hybridizing conditions to an *M. tuberculosis* rpoB gone at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting of:
>
> a G at nucleotide position 2312,
>
> a T at nucleotide position 2313,
>
> an A at nucleotide position 2373,
>
> a G at nucleotide position 2374,
>
> an A at nucleotide position 2378,
>
> a G at nucleotide position 2408,
>
> a T at nucleotide position 2409,
>
> an A at nucleotide position 2426,
>
> a G at nucleotide position 2441,
>
> an A at nucleotide position 2456, and
>
> a T at nucleotide position 2465.

Primers are short pieces of DNA that have hydroxyl groups on their ends. Despite Roche's arguments that such primers are not found in nature, for example, because *M. tuberculosis* has a circular genome so there is no "end" to the natural *M. tuberculosis* DNA, and hence from a chemical perspective no 3'-hydroxyl groups naturally present in *M. tuberculosis* DNA, the Court ruled that such primers "are not chemically or structurally different from the primer that we held patent ineligible" in *Based Hereditary Cancer Test Patent Lit.*, 774 F.3d 755 (Fed. Cir. 2014)(referred to by the Court as *BRCA1*, discussed as *Ambry* above.).

Similarly, the Court held that the diagnostic claims were ineligible for patenting as a naturally occurring phenomenon. Claim 1 of Roche's '723 patent reads as follows:

> 1. A method for detecting Mycobacterium tuberculosis in a biological sample suspected of containing M. tuberculosis comprising:
>
> (a) subjecting DNA from the biological sample to polymerase chain reaction using a plurality of primers under reaction conditions sufficient to simplify a portion of a *M. tuberculosis* rpoB gone to produce an amplification product, wherein the plurality of primers comprises at least one primer that hybridizes under hybridizing conditions to the amplified portion of the gone at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ D NO:1), from the group consisting
>
> a G at nucleotide position 2312,
>
> a T at nucleotide position 2313,

an A at nucleotide position 2373,

a G at nucleotide position 2374,

an A at nucleotide position 2378,

a G at nucleotide position 2408,

a T at nucleotide position 2409,

an A at nucleotide position 2426,

a G at nucleotide position 2441,

an A at nucleotide position 2456, and

a T at nucleotide position 2465; and

(b) detecting the presence or absence of an amplification product, wherein the presence of an amplification product is indicative of the presence of M. tuberculosis in the biological sample and wherein the absence of the amplification product is indicative of the absence of M. tuberculosis in the biological sample.

The Court characterized the method claims as a diagnostic test containing two steps: the amplification step and the determination of the presence of *M. tuberculosis* based on the presence or absence of the PCR amplification product. Following step 2 of the Mayo/Alice analysis, the court found nothing inventive about the amplification step and that the "detecting step is similarly devoid of an inventive concept because it involves a simple mental determination of the presence of MTB based on the presence of absence of a PCR amplification product."

Roche essentially argued this point: "[T]hat to use its primers to detect MTB 'is no less an inventive act than to make a specific artificial drug that is effective to treat an MTB infection."' The court dismissed this argument as not involving "a significantly new function for the primers."

Judge O'Malley filed a ten-page concurrence stating that that the BRCA1 decision forced her to concur: "Specifically I believe that our holding there was unduly broad for two reasons: (1) the question raised in BRCA1 was narrower than our holding in that case; and (2) our interpretation of the nature and function of DNA primers lacked the benefit of certain arguments and evidence that the patent owner presented in this case."

As to point 1, O'Malley noted that in the BRCA1 case, the district court had specifically stated that it had not resolved the section 101 issue since the record was necessarily incomplete, because for example the issue there was whether the district court had abused its discretion in denying the patent owner a preliminary injunction. O'Malley noted that in the present case, the question before the district court on summary judgment was the validity of the claims in view of a much more complete record.

As to point 2, O'Malley noted that the Fed. Cir. in BRCA1 had been primarily guided by the Supreme Court's decision in *Myriad,* 569 US 576 (2013), where the S. Ct. concluded that the patent owner's "principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13…. Critically, the Court recognized that claims are not 'saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule': the 'claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA.'"

Quoting from the *Myriad* (2013) decision regarding the patent-eligibility of cDNA, O'Malley noted "[T]he lab technician unquestionably creates something new when cDNA is made…DNA is distinct from the DNA from which it was derived" because the intron sequences are removed., O'Malley stated that the Federal Circuit's conclusion in *BRCA1* was based on the "two facts" that "[p]rimers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind" and that "[t]hey are structurally identical to the ends of DNA strands found in nature."

O'Malley attacks this sort of fact-finding: "but it is not clear from the *BRCA1* opinion or record why we reached this conclusion…Specifically *BRCA1* concludes that primers have 'identical sequences' to the natural DNA strands directly opposite the strands to which they bind, but, as the record in this case reveals, a finding that the two have identical sequences does not entirely resolve the question of whether they are structurally identical because structure is not defined solely by nucleotide sequence.. Nor is it clear how primers 'are structurally identical to the ends of DNA strands found in nature." In other words, the fact that the isolated BRCA1 gene has an identical sequence to its genomic counterpart does not force the conclusion that a short ssDNA primer is structurally the same as the genomic ssDNA sequence to which it is designed to bind.

Judge O'Malley summarizes the structural/functional differences between the claimed primers and the nature MTB rpoB gene, and states that the primers are "markedly different" from any DNA molecules "typically found in nature." The markedly different "requirement" to avoid the natural product label is from the *Chakrabarty* decision that found genetically modified bacteria patent eligible in part because they have "potential for significant utility." Judge O'Malley concludes:

> "For these reasons, while I agree with the majority that the broad language of our holding in *BRCA1* compels the conclusion that the primer claims in this case are ineligible under 35 U.S.C. § 101, I believe that holding exceeded the confines of the issue raised on appeal and was the result of an underdeveloped record in that case. I believe accordingly, that we should revisit out conclusion in *BRCA1* en banc."

Hence, if Judge O'Malley can sway the Court in the future we may see some more decisions that are more supportive of biotechnological innovation.

Summary

While tangible molecular structures and active steps that go beyond mere thought exercises may still be sufficient to overcome the patent eligibility hurdle, the court and PTAB rulings suggest that manipulation of a known natural product to diagnose or treat disease may no longer be patent eligible, unless such manipulation involves new and non-obvious method steps. The Supreme Court ruling in the *Myriad* case was limited to genomic DNA, but Patent Office Examiners find that other natural products (proteins, antibodies, primers, etc.) are no longer eligible for patenting. Each step of the claims at issue in *Mayo* and the concept of adjusting dosage was known in the prior art, but the courts are using the *Mayo* standards to find patent ineligibility of claims drawn to important new discoveries such as those in *Ariosa*, where the concept of checking maternal serum for fetal DNA was previously inconceivable. Section 101 now provides litigants with a potent tool for invalidating claims to pharma- or biotech-based methods and materials without the need to argue more complex, fact-driven issues such as anticipation, obviousness or the increasingly tangled requirements of 35 U.S.C. § 112(1).

The primary rationale for finding patent claims ineligible for patenting is that they might preempt all uses of a natural product or correlation and thereby stifle innovation. But even claims that do not preempt the totality of uses of such a natural product or correlation are ruled ineligible for patenting because, "While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility."[169] The Patent Office and the courts now routinely find that the steps for achieving new and potentially life-saving diagnostic results are conventional or routine in medicine. Claims containing such steps are deemed *per se* patent-ineligible with little or no evidentiary support of such a conclusion, even when the reagents have never before been employed in such steps.

Increasingly, the locus of early stage innovation is within universities and small start up companies, where the only assets are typically patents or patent applications. Through their slavish adherence to rejecting any claim that recites a natural product or correlation the courts and the Patent Office are more likely to inhibit patenting by early innovators whose innovations have broad implications. The result will likely be no development of promising technologies because patenting is blocked, and no funding will be then available to such innovators. Development of promising technologies will be only be carried out by large corporations who can successfully avoid rewarding the original innovator.

The following table shows how the courts have ruled on some biotechnology patent claims.

Biotech Diagnostic Claims: Which Ones are Eligible for Patenting under § 101?	
Metabolite's U.S. Patent 4,940,658 claim 13: A method for detecting a deficiency of	**Claim 13 is eligible for patenting pursuant to the Federal Circuit (2004) ruling:**[170] This

[169] *Ariosa Diagnostics Inc. v. Sequenom Inc*., 788 F.3d 1371, 1379 (Fed. Cir. 2015) (*cert. denied*)
[170] *Metabolite Labs. Inc.* v. *Lab. Corp. of Am. Holdings,* 370 F.3d 1354 (Fed. Cir. 2004).

cobalamin or folate in warm-blooded animals comprising the steps of: – assaying a body fluid for an elevated level of total homocysteine; and – correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.	claim is valid under Sections 102, 103 and 112. [No discussion of patent eligibility of the claims.] **Problem: Supreme Court granted, then withdrew, certiorari in 2006** to determine whether the patent claim is invalid on the ground that it improperly seeks to "claim a monopoly over a basic scientific relationship." But the Supreme Court withdrew the writ of certiorari as improvidently granted. **Three Justices wrote a strong dissent.**[171]
Classen's U.S. Patent 6,638,739 claim 1.[172] A method of immunizing a mammalian subject which comprises: (I) *screening* a plurality of immunization schedules, by (a) *identifying* a first group of mammals and at least a second group of mammals, ... each group of mammals having been immunized according to a different immunization schedule, and (b) *comparing* the effectiveness of said first and second screened immunization schedules in protecting against or inducing a chronic immune-mediated disorder in said first and second groups, as a result of which one of said screened immunization schedules may be identified as a lower risk screened immunization schedule and the other of said screened schedules as a higher risk screened immunization schedule with regard to the risk of developing said chronic immune mediated disorder(s), (II) *immunizing said subject*.... in accordance with said lower risk screened immunization schedule ...	**Claim 1 is eligible for patenting pursuant to the Federal Circuit (2012) ruling**[173] because: • this claim includes the physical step of immunization on the determined schedule. • precedent has recognized that the presence of a mental step is not of itself fatal to § 101 eligibility. • Section 101 is only a coarse filter.
Classen's U.S. Patent 5,723,283 claim 1. A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, which	**Claim 1 is <u>not</u> eligible for patenting pursuant to the Federal Circuit (2011) ruling**[174] because this claim does not require an active step after determining the effects of immunization: • this method simply collects and compares

[171] *Laboratory Corporation of America Holdings* v. *Metabolite Laboratories Inc.,* 548 U.S. 124; 126 S. Ct. 2921 (2006).
[172] The language of this claim was shortened somewhat. Note that claim 1 of Classen's US Patent 6420139 is similar to the language of this '739 patent claim in that both claims require immunization <u>after</u> screening for a lower risk screened immunization schedule.
[173] *Classen Immunotherapies, Inc. v. Biogen Idec,* 659 F. 3d 1057 (Fed. Cir. 2011).
[174] *Id.*

comprises immunizing mammals in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.	data, without applying the data • the abstraction of the claim is unrelieved by any movement from principle to application
Prometheus' U.S. Patent 6,355,623 claim 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 $8x10^8$ 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 $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject. **U.S. Patent 6,355,623 claim 46.** A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising: (a) *determining* the level of 6-thioguanine or 6-methylmercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathiopurine, 6-thioguanine, and 6-methyl-mercaptoriboside, said subject having said immune-mediated gastrointestinal disorder,	**These claims are <u>not</u> eligible for patenting pursuant to the Supreme Court ruling[175] because**: • relationships between concentrations of certain metabolites in the blood and the likelihood that a thiopurine drug dosage will prove ineffective is a natural law or a natural phenomenon that is not patent-eligible; • the administering step simply identifies a group of people who will be interested in the correlations • doctors have long been using these drugs for treatment of autoimmune disorders and the determining step is well known in the art • the 'wherein' clause simply tells doctors about relevant natural laws and does not require any therapeutic intervention • such well-known administering and determining steps are not sufficient to transform an unpatentable law of nature into a patent-eligible claim **The Federal Circuit[176] had found these claims to be patent-eligible because:** • the claims do not preempt all uses of the natural correlations involved (other drugs might be administered to optimize the therapeutic efficacy of the claimed treatment); • the claimed methods transform the human body and its components via chemical and physical changes to the drugs • even claims without an administration step thought to be patent-eligible because the determining step, which is present in each of the asserted claims, is transformative and central to the claimed methods. Determining

[175] *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 566 U.S. ___, 132 S.Ct. 1289, 182 L. Ed. 2d 321 (2012).
[176] *Prometheus Laboratories, Inc. v. Mayo Collaborative Services,* 628 F.3d 1347 (Fed. Cir. 2010).

wherein the level of 6-thioguanine less than about 230 pmol per 8x108 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 $8x10^8$ red blood cells or a level of 6-methylmercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation. **Federal Circuit also stated:** "we do not view the disputed claims as merely claiming natural correlations and data-gathering steps. The asserted claims are in effect claims to methods of treatment, which are always transformative when one of a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition." **However, the Supreme Court overruled the Federal Circuit's decision.**
Myriad's U.S. Patent 5,710,001 claim 1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises *comparing* a first sequence (i.e., a BRCA1 gene, RNA or cDNA) from said tumor sample, with a second sequence (i.e., a BRCA1 gene, RNA or cDNA) from a non-tumor sample of said subject, wherein a difference in the sequence ... indicates a somatic alteration in the BRCA1 gene in said tumor sample.	**The Federal Circuit[177] has found this claim to be patent ineligible because** claims to "comparing" or "analyzing" two gene sequences fall outside the scope of § 101 because they claim only abstract mental processes.
Myriad's U.S. Patent 6,033,857 claim 2 A method for diagnosing a predisposition for breast cancer in a human subject which comprises *comparing* the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer.	**The Federal Circuit[178] has ruled that this claim is patent ineligible because** claims to "comparing" or "analyzing" two gene sequences embrace only abstract mental processes. The Court gave no weight to the diagnostic step where alteration in the germline sequence indicates a predisposition for cancer.
Myriad's U.S. Patent 5,747,282 claim 20. A method for screening potential cancer therapeutics which comprises:	**The Federal Circuit[179] has ruled that this claim is patent <u>eligible</u> subject matter because** he claim includes transformative steps

[177] *The Association for Molecular Pathology v. Myriad Genetics Inc.,* 689 F.3d 1303 (Fed. Cir. 2012).
[178] *Id.*
[179] *Myriad,* 689 F.3d 1303, 1334-35 (Fed. Cir. 2012).

growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, *growing* said transformed eukaryotic host cell in the absence of said compound, *determining* the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.	(e.g., growing and determining), and the use of a transformed cell, which is made by man.
Myriad's U.S. Patent 5,747,282 claim 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2. **Myriad's U.S. Patent 5,747,282 claim 5.** An isolated DNA having at least 15 nucleotides of the DNA of claim 1.	**The Supreme Court[180] has ruled that these claims are <u>not</u> eligible for patenting because** these claims embrace genomic DNA, which is a product of nature.
Myriad's U.S. Patent 5,747,282 claim 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.	**The Supreme Court[181] had held that this claim is patent <u>eligible</u> because:** This claim embraces cDNA, which is a product of human intervention.
Intema's U.S. Patent No. 6,573,103 Claim 1: A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, comprising: --measuring the level of different markers from the first and second trimester of pregnancy by: (i) assaying a sample . . .; and/or (ii) measuring an ultrasound screening marker from an ultrasound scan; and determining the risk of Down's syndrome by comparing the measured levels with those in non-Down's	**The Federal Circuit[182] has ruled this claim ineligible for patenting** because it claims "a law of nature" and recites "the mental process of comparing data to determine a risk level." **Intema has filed petition for cert.**;[183] one question posed to the Supreme Court: Is a useful, novel and non-obvious diagnostic, screening or personal medicine test patent eligible under 35 U.S.C. § 101 if: a) the inventive concept is in the selection, combination and timing of the data collected in the data-gathering steps;

[180] *The Association for Molecular Pathology v. Myriad Genetics Inc.,* 133 S. Ct. 2107; 186 L. Ed. 2d 124 (2013).
[181] *Id.*
[182] *PerkinElmer v. Intema Ltd*., 496 Fed. Appx. 65, 70 (Fed. Cir. Nov. 20, 2012)(nonprecedential).
[183] *Intema Ltd. v. PerkinElmer*, 2012 U.S. Briefs 1372; 2013 U.S. S. Ct. Briefs LEXIS 2395 (May 16, 2013).

pregnancies.	and/or b) the final step is calculating a new and useful test result from data collected by novel data-gathering steps, but does not involve a physical activity?
Myriad's U.S. Patent 5,753,441 claim 7: A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA or cDNA from a tissue sample from said subject with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject, wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.	**The Federal Circuit[184] has ruled this claim ineligible for patenting** because: The comparison step = a patent-ineligible abstract idea involving comparing BRCA sequences and determining the existence of alterations; and The non-patent-ineligible elements do not add "enough" to make the claim as a whole patent-eligible.
Myriad's U.S. Patent 5,753,441 claim 16: A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the	**The Federal Circuit[185] has ruled this claim ineligible for patenting** because: the primers are not distinguishable from the isolated DNA ruled patent-ineligible products of nature in the *Myriad* case and not similar to the cDNA that was found to be patent-eligible by the Supreme Court; it made no difference that the primers were

[184] *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp*., 774 F.3d 755 (Fed Cir. Dec. 17, 2014).
[185] *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp*., 774 F.3d 755 (Fed Cir. Dec. 17, 2014).

synthesis of DNA having all or part of the sequence of the BRCA1 gene.	synthetically replicated; and the Federal Circuit was not swayed by Myriad's arguments that primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body, or that primers have a fundamentally different function (starting material for polymerization) than when they are part of a DNA strand (storing biological information).
Roslin Institute's U.S. Ser. No. 09/225,233 claims 155 and 164: 155. A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats. 164. The clone of any of claims 155-159, wherein the donor mammal is non-foetal.	**The Federal Circuit[186] has ruled this claim ineligible for patenting** because such clones are constituted a "natural phenomenon" that did not possess "markedly different characteristics than any found in nature." The claims were also unpatentable over the prior art because they were indistinguishable from clones produced through prior art cloning methods, i.e., embryotic nuclear transfer and *in vitro* fertilization.
Sequenom's U.S. Patent 6,258,540 claim 1: A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.	**The Federal Circuit[187] has ruled the claim ineligible for patenting** because the claims were directed to a patent-ineligible concept - it was undisputed that the existence of cffDNA in maternal blood is a natural phenomenon and that that the location of the nucleic acids existed in nature before the inventors found them; and methods like PCR and the detecting step were well-understood, routine, and conventional activity in 1997.
Genetic Technologies' U.S. Patent 5,612,179 claim 1: 1. A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising:	**The Federal Circuit[188] has ruled the claim ineligible for patenting** because amplifying genomic DNA with a primer pair and the analyzing the amplified DNA to provide a user with information about the amplified DNA were well known,

[186] *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014).
[187] *Ariosa Diagnostics Inc. v. Sequenom Inc*., 788 F.3d 1371 (Fed. Cir. 2015).
[188] *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369 (Fed. Cir. 2016) (cert. denied).

a) amplifying genomic DNA with a primer pair that spans a non-coding region sequence, said primer pair defining a DNA sequence which is in genetic linkage with said genetic locus and contains a sufficient number of non-coding region sequence nucleotides to produce an amplified DNA sequence characteristic of said allele; and b) analyzing the amplified DNA sequence to detect the allele.	routine, and conventional in the field of molecular biology as of 1989, when the first precursor application to the '179 patent was filed.
Rapid Litigation's U.S. Patent No. 7,604,929 Claim 1: 1. A method of producing a desired preparation of multi-cryopreserved hepatocytes, said hepatocytes being capable of being frozen and thawed at least two times, and in which greater than 70% of the hepatocytes of said preparation are viable after the final thaw, said method comprising: (A) subjecting hepatocytes that have been frozen and thawed to density gradient fractionation to separate viable hepatocytes from non-viable hepatocytes, (B) recovering the separated viable hepatocytes, and (C) cryopreserving the recovered viable hepatocytes to thereby form said desired preparation of hepatocytes without requiring a density gradient step after thawing the hepatocytes for the second time, wherein the hepatocytes are not plated between the first and second cryopreservations, and wherein greater than 70% of the hepatocytes of said preparation are viable after the final thaw.	**The Federal Circuit[189] has ruled the claim eligible for patenting** because the claims are simply not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims of the '929 patent are directed to a new and useful laboratory technique for preserving hepatocytes. This type of constructive process, carried out by an artisan to achieve "a new and useful end," is precisely the type of claim that is eligible for patenting.

[189] *Rapid Litigation Mgmt. LTD v. Cellzdirect, Inc.*, 827 *F.3d* 1042 (Fed. Cir. 2016).

Cleveland Clinic's U.S. Patent No. 7,223,552 claim 11: 11. A method of assessing a test subject's risk of having atherosclerotic cardiovascular disease, comprising comparing levels of myeloperoxidase in a bodily sample from the test subject with levels of myeloperoxidase in comparable bodily samples from control subjects diagnosed as not having the disease, said bodily sample being blood, serum, plasma, blood leukocytes selected from the group consisting of neutrophils, monocytes, sub-populations of neutrophils, and sub-populations of monocytes, or any combination thereo[f]; wherein the levels of myeloperoxidase in the bodily [sample] from the test subject relative to the levels of [m]yeloperoxidase in the comparable bodily samples from control subjects is indicative of the extent of the test subject's risk of having atherosclerotic cardiovascular disease.	**The Federal Circuit[190] has ruled the claim ineligible for patenting** because the claims are directed to multistep methods for observing the law of nature that myeloperoxidase correlates to cardiovascular disease and the practice of the method does not result in an inventive concept that transforms the natural phenomena of myeloperoxidase being associated with cardiovascular risk into a patentable invention.

[190] *Cleveland Clinic v. True Health Diagnostics*, 859 F. 3d 1352 (Fed. Cir. 2017).

Exergen's U.S. Patent No. 7,787,938 claim 14: 14. A method of detecting human body temperature comprising making at least three radiation readings per second while moving a radiation detector to scan across a region of skin over an artery to electronically determine a body temperature approximation, distinct from skin surface temperature.	**The Federal Circuit[191] has ruled the claim eligible for patenting** because **e**ven if the concept of the measurement of a natural phenomenon (core body temperature) is directed to a natural phenomenon and is abstract at step one, the measurement method here was not conventional, routine, and well-understood. Following years and millions of dollars of testing and development, the inventor determined for the first time the coefficient representing the relationship between temporal-arterial temperature and core body temperature and incorporated that discovery into an unconventional method of temperature measurement. As a result, the method is patent-eligible,
Urvashi Bhagat's Application Ser. No. 12/426,034 claim 65: 65. A lipid-containing formulation, comprising a dosage of omega-6 and omega-3 fatty acids at an omega-6 to omega-3 ratio of 4:1 or greater, contained in one or more complementing casings providing controlled delivery of the formulation to a subject, wherein at least one casing comprises an intermixture of lipids from different sources, and wherein (1) omega-6 fatty acids are 4–75% by weight of total lipids and omega-3 fatty ac-ids are 0.1–30% by weight of total lipids; or (2) omega-6 fatty acids are not more than 40 grams.	**The Board[192] found the claim ineligible for patenting** because the intermixture of lipids from different sources was structurally indistinct from prior art lipid formulations and the casing not provide patentability to the compositions because the specification stated that the term is not claim-limiting and did not describe any novel characteristics for the formulations.
Buck's Application Ser. No. 13/446,128 claim 7: 7. A kit comprising multiple, separate weekly or monthly dosages of	**The Board[193] found the claim ineligible for patenting** because it was indisputable that both vitamin D3 and 25-OH D3 are naturally-occurring chemicals that co-exist in biological systems and, by themselves,

[191] *Exergen Corp. v. Kaz USA, Inc.*, 725 F. App'x 959 (Fed. Cir. 2018).
[192] *Cleveland Clinic v. True Health Diagnostics*, 859 F. 3d 1352 (Fed. Cir. 2017).
[193] *Ex parte Buck,* Appeal No. 2017-005470 (PTAB, April 20, 2018).

a) Vitamin D, and b) 25-OH D3, wherein a dosage ratio of the Vitamin D3 to the 25-OH D3 is from about 6:1 to 1:6; a single weekly dosage contains from 7µg to 350 µg each of Vitamin D and 25-OH D3; and a single monthly dosage contain from 30 µg.	are products of nature and consequently unpatentable. While all inventions, at some level, embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas, the Board found that they could not structurally distinguish the chemical compositions recited in the claims from those occurring naturally in biological systems. The Board also found that the fact that Appellants claim different dosage amounts or ratios did not suffice to add significantly more to the naturally-occurring substances than the administration of the same naturally-occurring substances themselves.

Vanda's U.S. Patent 8,586,610 claim 1: 1. A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of: determining whether the patient is a CYP2D6 poor metabolizer by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.	**The Federal Circuit[194] has ruled the claim eligible for patenting** because the S. Ct.'s decision in *Mayo* was distinct. The Federal Circuit stated that "The *Mayo* claim was not a treatment claim, it was 'not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable." This decision appears to broadly hold that method of treatment claims are patent eligible.
Young's Patent Application claim 1: 1. A method comprising:	**The Board[195] found the claim eligible for patenting** because even if the judges were to agree with the Examiner that the rejected claims involve an abstract idea (i.e.

[194] *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l Inc.*., 887 F.3d 1117 (Fed. Cir. 2018).
[195] *Ex parte Buck,* Appeal No. 2017-005470 (PTAB, April 20, 2018).

amplifying one or more nucleotide sequences in a sample using a PCR amplification process to produce an amplified sample; using a massively parallel sequencing (MPS) instrument to read the one or more nucleotide sequences of the amplified sample and generate one or more text strings based on the amplified sample; selecting a first plurality of text strings from the one or more text strings read by the MPS instrument, wherein each of the selected first plurality of text strings represent a nucleotide sequence that-corresponds to a first target locus in the amplified sample; comparing the selected first plurality of text strings to one another to determine an abundance count for each unique text string included in the selected first plurality of text strings; identifying a first number of unique text strings included in the selected first plurality of text strings as representing noise responses; and determining a method detection limit (MDL) as a function of the abundance counts for the first number of unique text strings identified as representing noise responses.	manipulation of nucleic acid sequence data), they were not persuaded that the preponderance of evidence on the record supported a factual finding that other features of the claims, MPS in particular, were well-understood, routine conventional activities.
Nagy's Application Ser. No. 14/223,113 claim 2: 2. A method of assessing the risk of AD progression in a human subject suspected of having AD, which method comprises: (i) obtaining lymphocytes from said	**The Board[196] found the claim ineligible for patenting** because as in *Mayo*, the claims were not directed to a method of treating a disease and to the contrary, Nagy's claims were similar to those in *Mayo*, which "were directed to a diagnostic method based on the 'relationships between concentrations of certain metabolites [of the administered thiopurine drug] in the

[196] *Ex Parte Nagy*, Appeal 2017-008793 (July 30, 2018).

human subject suspected of having AD and from an age-matched healthy subject with normal cognitive ability; (ii) inducing cell division in the lymphocytes taken from the human subject suspected of having AD; (iii) separating the dividing lymphocytes of (ii) into two pools and treating one pool of lymphocytes with rapamycin; (iv) assaying the level of protein of at least one interleukin selected of interleukin ("IL") 1 beta (IL1B), IL-2, IL-6 or IL-10 in the pool of lymphocytes treated with rapamycin and in the untreated pool; (v) comparing the level of protein of the at least one interleukin obtained in (iv) for the pool of rapamycin-treated lymphocytes and the untreated lymphocyte pool to quantify the change in protein levels in response to rapamycin; (vi) repeating steps (ii)-(iv) using control lymphocytes taken from the age-matched healthy subject with normal cognitive ability; and (vii) determining that said human subject suspected of having AD is at increased risk of AD progression when (a) the reduction of IL1B or IL10 protein levels in response to rapamycin is higher in control lymphocytes as compared to lymphocytes taken from the human subject suspected of having AD [and/or] (b) the reduction of IL-2 or IL-6 protein levels in response to rapamycin is lower in control lymphocytes as compared to lymphocytes taken from the human subject suspected of having AD….	blood and the likelihood that a dosage of the thiopurine drug will prove ineffective or cause harm.'"

Schwartz' Application claim 21: 21. A method [of] selectively modulating expression of a target gene in the genome of a human cell determined to be in need thereof comprising: determining the presence of an encoded antisense transcript overlapping a promoter of the target gene; contacting the antisense transcript with an exogenous gapmer or double-stranded ag["antigene"]RNA; and detecting a resultant modulation of expression of the target gene, the gapmer comprising a DNA insert complementary to a sequence in the antisense transcript upstream relative to the transcription start site of the gene, and the agRNA being 18-28 bases and complementary to a portion of the antisense transcript upstream to a portion of the antisense transcript upstream relative to the transcription start site of the gene.	**The Board[197] found the claim eligible for patenting** because they disagreed with the Examiner's finding that the claims were directed to the abstract idea of determining the presence of an encoded antisense transcript that overlapped a promoter of a target gene, and because the Examiner had not identified another applicable judicially recognized exception. Hence, the Board reversed the Examiner's rejection of the claims.
Ho's Application claim 133: 133. An isolated cell population of human bone marrow-derived cells, wherein said cell population has been cultured in vitro at cell seeding densities of about 30 cells/cm^2 under about 5% oxygen conditions for more than 30 population doublings, wherein said cell population continues to maintain a population doubling time of about 30 hours per doubling and wherein greater than 91% of the cells in said cell	**The Board[198] found the claim eligible for patenting** because Appellants provided information showing that the characteristics of the claimed cells were the direct result of the inventor's experimentation with low oxygen and low-density culture conditions. The Board found that the Examiner had not persuasively identified any inadequacy in Appellants' rebuttal evidence, and that the Examiner had not provided scientific reasoning or evidence sufficient to support

[197] *Ex Parte Schwartz*, Appeal 2017-004975 (August 2, 2018).
[198] *Ex Parte Ho,* Appeal no. 2016-007472 (PTAB, Aug. 7, 2018).

population continue to co-express cell surface markers CD49c and CD90, and wherein said cell population does not express cell surface markers CD34 or CD45, and wherein said cell population expresses telomerase at a relative expression of between about 1 transcript of telomerase per 10^6 transcripts of an 18s rRNA and about 10 transcripts of telomerase per 10^6 transcripts of an 18s rRNA.	a finding that the claimed isolated cell population was a product of nature, lacking markedly different characteristics from a naturally occurring counterpart. Hence, the Board reversed the rejection under section 101.
Parenteau's Application claim 17: 17. An isolated tumor C-RC cell population prepared by (a) obtaining a tumor sample from an individual; (b) cultivating the tumor sample under conditions that induce a stress response in non-C-RC differentiating and differentiated cells leading to apoptosis and necrosis but permit C-RC cells to propagate through the activation of a regenerative response; (c) isolating the dominant actively expanding, most rapidly dividing population of cells from step (b); and (d) culturing the cells to obtain a population of 51 % to 100% C-RC, in a serum-free, defined cell culture medium containing agents selected from the group consisting of agents inducing the apoptosis and/or necrosis of the cells, cAMP elevating agents, agents inhibiting cell-cell adhesion, nitric oxide, tumor necrosis factor-alpha (TNF-α), interleukin I-beta (ILI-α), interferon-gamma (IFN-γ), agents disrupting cell adhesion, agents interfering with survival of more differentiated cells, and calcium in a concentration of less than	**The Board[199] found the claim eligible for patenting** because the Examiner failed to establish an evidentiary basis to support a finding that that such culture media was well known, routine and conventionally used in the art at the time of Appellants' claimed invention. Hence, the Board reversed the rejection under section 101 and found that the tumor C-RC cell population prepared as recited in the claim was eligible for patenting.

[199] *Ex parte Parenteau,* Appeal no. 2017-002191 (August 22, 2018).

about 1 mM calcium, wherein 80-100% of the C-RC population consists of actively expanding and dividing VSEC, SDEC and SCEC cells and abnormal transit amplifying cells.	
Roche's U.S. Patent 5,643,723 claims 1 and 17: 1. A method for detecting *Mycobacterium tuberculosis* in a biological sample suspected of containing M. tuberculosis comprising: (a) subjecting DNA from the biological sample to polymerase chain reaction using a plurality of primers under reaction conditions sufficient to simplify a portion of a *M. tuberculosis* rpoB gone to produce an amplification product, wherein the plurality of primers comprises at least one primer that hybridizes under hybridizing conditions to the amplified portion of the gone at a site comprising at least one position-specific M. tuberculosis signature nucleotide selected, with reference to FIG. 3 (SEQ D NO:1), from the group consisting a G at nucleotide position 2312, a T at nucleotide position 2313, an A at nucleotide position 2373, a G at nucleotide position 2374, an A at nucleotide position 2378, a G at nucleotide position 2408, a T at nucleotide position 2409, an A at nucleotide position 2426, a G at nucleotide position 2441, an A at nucleotide position 2456, and	**The Federal Circuit[200] found the claims ineligible for patenting** because despite Roche's arguments that such primers are not found in nature, for example, because *M. tuberculosis* has a circular genome so there is no "end" to the natural *M. tuberculosis* DNA, and hence from a chemical perspective no 3'-hydroxyl groups naturally present in *M. tuberculosis* DNA, the Federal Circuit found that such primers "are not chemically or structurally different" from the primer that they held patent ineligible in *Based Hereditary Cancer Test Patent Lit*., 774 F.3d 755 (Fed. Cir. 2014)(referred to by the Federal Circuit as *BRCA1*). Similarly, the Federal Circuit held that the diagnostic claims were ineligible for patenting as a naturally occurring phenomenon. The Federal Circuit characterized the method claims as a diagnostic test containing two steps: the amplification step and the determination of the presence of *M. tuberculosis* based on the presence or absence of the PCR amplification product. Following step 2 of the Mayo/Alice analysis, the court found nothing inventive about the amplification step and that the "detecting step is similarly devoid of an inventive concept because it involves a simple mental determination of the presence of *M. tuberculosis* based on the presence of absence of a PCR amplification

[200] *Roche Molecular Systems, Inc. v. Cepheid*, ___ F.3d ___ (Fed. Cir. 2018).

a T at nucleotide position 2465; and (b) detecting the presence or absence of an amplification product, wherein the presence of an amplification product is indicative of the presence of *M. tuberculosis* in the biological sample and wherein the absence of the amplification product is indicative of the absence of *M. tuberculosis* in the biological sample.	product."