A 12th Year 101 Update—Diagnostic & DNA Claims are Patent Eligible, but Pre-*Mayo* Patents May Continue to Fall

By Tamsen Valoir, PhD and Miranda Chavez, J.D., both of Boulware & Valoir, PLLC. Published in Biotechnology Law Report, Vol. 43, No. 4, (Aug. 2024), available online at https://doi.org/10.1089/blr.2024.89231.tv. Note: A new Guidance has issued since the publication of this paper, but relates to Artificial Intelligence, not at issue herein. See https://www.uspto.gov/patents/laws/examination-policy/subject-matter-eligibility.

The Supreme Court—driven perhaps by concern over patent trolls and the rising costs of healthcare—have transformed patent and economic policy through the blunt instrument of Section 101. Whatever their intent, the illogical analysis of *Mayo*[1] and the constitutionally dubious conclusion of *Myriad*[2] has resulted in older patents written before the change in law being poured out of the courts as invalid. This short note explores some of the ramifications of the current 101 analysis as applied in the life sciences.

The Statute

Invention is defined in the patent statute to mean invention or discovery.[3] That discoveries are patentable is echoed in the eligibility section 101, allowing patents for anyone who "invents" or "discovers" new and useful things:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.[4]

[1] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.,* 132 S.Ct. 1289, 566 U.S. 66 (2012) [hereinafter *Mayo*].

[2] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S.Ct. 2107, 569 U.S. 576 (2013) [hereinafter *Myriad*].

[3] 35 U.S.C. § 100.

[4] *Id*.

Throughout most of history, the 101 clause was read quite broadly, allowing one to patent "anything under the sun that is made by man."[5] Patent eligibility was not unlimited, however, as recited in the pivotal *Chakrabarty* case:

> This is not to suggest that § 101 has no limits, or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."[6]

Dr. Ananda Chakrabarty was originally denied a patent on his crude oil-eating genetically engineered bacterium because living organisms were thought to be patent ineligible. This was eventually reversed by the CCPA,[7] but the Patent Office appealed to the Supreme Court. The new bacteria—made by adding two plasmids to a natural bacteria—was held to be patentable in *Chakrabarty*, even if alive:

> [T]he patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101.[8]

Thus, the *Chakrabarty* case ushered in a new age sanctioning the patenting of biological inventions. It was pivotal in allowing the nascent biotechnology industry to flourish. Indeed, the total economic impact of the biosciences industry on the U.S. economy, as measured by overall output, totaled $2.9 trillion dollars in 2021.

However, what the statute giveth, the court may taketh away.

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[5] *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citation omitted) [hereinafter *Chakrabarty*].

[6] *Chakrabarty*, 447 U.S. at 309. (citation omitted).

[7] Application of Bergy, 596 F.2d 952 (C.C.P.A. 1979) (consolidated with Chakrabarty case). The full complex history of these cases is omitted.

[8] *Chakrabarty*, 447 U.S. at 310.

Laws of Nature not Patent Eligible

Laws of nature, natural phenomena, and abstract ideas are not patent eligible, at least under judicial doctrines,[9] but the *Mayo* opinion greatly extended this principle, noting that mere recitation of a patent ineligible concept (like a natural law) could render the entire claim unpatentable,[10] unless there was something more to transform the claim into a patent eligible application of that concept.[11]

The claims at issue in the *Mayo* case related to optimizing drug dosage levels by determining the levels of a metabolite of that drug. Certain drugs, such as 6-mercaptopurine (6-MP), are converted to 6-thioguanine (6-TG) in the body, and the inventors discovered how much 6-TG is too much, thus indicating a need to lower the dosage of 6-MP:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
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> (a) **administering** a drug providing [6-TG] to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) **determining** the level of [6-TG] in said subject having said immune-mediated gastrointestinal disorder,
>
> **wherein** the level of [6-TG] less than about [x] indicates a need to increase the amount of said drug subsequently administered to said subject and **wherein** the level of [6-TG] greater than about [y] indicates a need to decrease the amount of said drug subsequently administered to said subject.[12]

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[9] *Mayo*, 132 S.Ct. at 1293 ("'[L]aws of nature, natural phenomena, and abstract ideas' are not patentable.") (citations omitted).

[10] *Mayo*, 132 S.Ct. at 1297 (If a law of nature is not patentable, then neither is a process reciting a law of nature…"). This absurd concept results in a patent claim reciting that a corkscrew that uses F = MA, wherein F > the friction of the cork is not being even eligible for patents. **Every** corkscrew uses F = MA to overcome friction—how can merely **saying** so make it unpatentable?

[11] *Mayo*, 132 S.Ct. at 1294 ("We must determine whether the claimed processes have transformed these unpatentable natural laws into patent eligible applications of those laws.").

[12] U.S. Patent No. 6,355,623. Emphasis added in all cases unless noted otherwise. There was an additional patent and additional claims at issue, but for simplicity only a single claim is discussed.

The claim requires two active steps—first "administering" a drug, and second "determining" the level of metabolite. The "wherein" clauses merely identify an optimal dosage level. However, **no active step** of **changing** the dosage was affirmatively recited in the claim.

In fact, the drugs and the metabolite were both known, and assays for determining 6-TG had long been in use, even with inflammatory gastrointestinal disorders, such as Crohn's disease.[13] Thus, the claim should have been invalidated under the usual anticipation or obviousness analysis. The Supreme Court declined to do so, however,[14] instead holding that because the claims recited a "natural law" and little more they were not patent eligible.[15]

No "law of nature" is readily apparent in reading the claims. In fact, $F = MA$ and $E = mc^2$ are still free to be used by anyone on the planet, as are all of the other physical laws. However, the Court in *Mayo* seemed to believe that the correlation between metabolite levels and side effects was a "natural law" and thus not patent eligible.[16] Since the opinion, everyone now politely treats medical correlations as being laws of nature, in accordance with the opinion.

The *Mayo* court held that recitation of the "law of nature" made the entire claim unpatentable, unless transformed into a patent eligible application of the law.[17] The court then indicated that

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[13] Cuffari C*, et al.,* 6-Mercaptopurine metabolism in Crohn's disease: correlation with efficacy and toxicity, Gut. 39(3):401-6 (1996) ("blood was obtained prior to daily administration of 6-MP in 25 adolescent Crohn's disease patients … [and] 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) were measured…").

[14] *Mayo*, 132 S.Ct. at 1304 ("These considerations lead us to decline the Government's invitation to substitute §§102, 103, and 112 inquiries for the better established inquiry under §101.").

[15] *Mayo*, 132 S.Ct. at 1294 ("The claims purport to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects. We must determine whether the claimed processes have transformed these unpatentable natural laws into patent eligible applications of those laws. We conclude that they have not done so and that therefore the processes are not patentable.").

[16] *Mayo*, 132 S.Ct. at 1294 ("The claims purport to apply natural laws describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects.").

[17] *See* FN 10-11, *infra*.

routine and conventional activity is not enough for to transform an unpatentable law of nature into something patentable.[18]

Many have criticized this portion of the analysis because it appears to conflate patent eligibility under Section 101 with novelty and non-obviousness requirements under Sections 102 and 103. Indeed, more than one commentator has noted that any law student would receive a failing grade for an analysis that imports novelty and non-obviousness criteria into a patent eligibility analysis.[19]

Interestingly, the Supreme Court **intentionally** conflated these different concepts:

> We recognize that, in evaluating the significance of additional steps, the §101 patent-eligibility inquiry and, say, the §102 novelty inquiry **might sometimes overlap**. But that need not always be so. And to shift the patent eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do.[20]

In addition, the Supreme Court unraveled decades of patent jurisprudence and brought "synergism" requirement back into the patentability analysis, albeit under 101 instead of the

[18] *Mayo*, 132 S.Ct. at 1298 ("Purely 'conventional or obvious' '[pre]-solution activity' is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law.").

[19] *See e.g.*, http://www.ipwatchdog.com/2012/03/20/supreme-court-mayo-v-prometheus/id=22920/ ("If a student were to write such nonsense in a patent law paper or on a patent law final exam they would receive little, if any, credit.").

[20] *Mayo,* 132 S.Ct. 1289, 1304.

prior 103 analysis.[21] To even be eligible for patents, the invention as a whole must add something "significant **beyond the sum** of their parts taken separately."[22]

The damage potential of an eligibility test that conflates 102/103 issues with 101 issues and has a synergy requirement is very high. If we don't consider any routine, conventional steps as imparting anything significant more than the sum of the parts to a claim, what can be patentable in a well-developed industry that merely applies routine, conventional steps in new ways? Most patents rely on applying routine, conventional steps in new ways, and thus can be invalidated as not even eligible under the *Mayo* holding.

Natural Products Not Patent Eligible

In a subsequent case, the Supreme Court went deeper down the 101 rabbit hole to hold that natural products and discoveries are not patentable either. The Supreme Court stated in the *Myriad* case that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated."[23]

Of course, the naturally occurring DNA segments were **not** actually patented, but rather only the "isolated" DNA was patented—in other words, DNA that had been "uncovered" or cut away

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[21] The "Flash of Genius" test for patentability was formalized in *Cuno Engineering v. Automatic Devices*, 314 U.S. 84 (1941) which held that the inventive act had to come into the mind of an inventor in a "flash of creative genius" and not as a result of tinkering. "The new device, however useful, must reveal the flash of creative genius, not merely the skill of the calling. If it fails, it has not established its right to a private grant on the public domain." *Id.* at 91. The flash of genius test was rejected by Congress in its 1952 revision of the patent statute when 35 U.S.C. § 103 was amended to state the new standard of non-obviousness: "Patentability shall not be negatived by the manner in which the invention was made." Efforts to stamp out the "synergism" or "flash of genius" requirement continued, however, even after the 1952 revision. *See e.g., Chore Time Equipment Inc. v. Cumberland Corp.*, 713 F.2d 774, 781 (Fed. Cir. 1983) ("A requirement that an invention reflect 'synergism' or achieve a 'synergistic result,' before it may be held patentable appears nowhere in the statute . . . . References to synergism as a patentability requirement are, therefore, unnecessary and confusing.") (citations omitted).

[22] *Mayo*, 132 S.Ct. at 1298.

[23] *Myriad,* 133 S.Ct. at 2111

from the 3 billion or so bases of the genome, as well as from all of the proteins making up the chromatin structure in a chromosome.

The Supreme Court recognized that isolating the DNA from its normal chromatin and cellular environment meant the claimed product was in fact no longer a natural product.[24] Nonetheless, they opined that merely purifying the DNA was not enough to confer patentability, stating "[Myriad] found an important and useful gene, but . . . groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry."[25]

Discoveries Not Patentable?

Arguably, the statement that discoveries are not patentable is in direct conflict with the Constitution. Since the birth of our Nation, the United States Constitution has provided for patents for discoveries. Article 1, Section 8 of the Constitution of the United States of America, gives Congress the power "To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries…"

In reliance on this power, the Legislature provided for the patentability of discoveries in the original 1790 Patent Act. Although there were intervening amendments and changes, the current 1952 Patent Act still provides for patents on discoveries and in fact, the definition of "invention" includes discoveries.[26]

The definition of a "discovery" is "something found, invented or uncovered." Yet, "uncovering" a gene just isn't enough according to the Supreme Court. Regardless of the dubious constitutional grounds of the Supreme Courts holding that discoveries are not patentable, the Patent Office has no choice but to follow Supreme Court precedent, and has applied the Supreme Court's holding, rejecting claims to so-called "natural products" under section 101.[27]

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[24] *Myriad*, 133 S.Ct. at 2110 ("Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule.").

[25] *Myriad*, 133 S.Ct. at 2110.

[26] *See* FN 3-4, *infra*.

[27] cDNA, expression vectors, labelled primers and the like are still patentable.

Isolated Natural Products Have New Functionality

Actually, most isolated or purified natural products have significant medical functionality not even possible with the natural form of the product, and therefore should be patent eligible based on the new functionality imparted by isolation and/or purification.

Adrenaline is a good example. It was probably the first human hormone patented in 1906 in its purified form.[28] Adrenaline—also known as epinephrine—has saved countless lives and is still in use today. Indeed, many people carry an Epipen® and can testify to its life saving capabilities in the event of anaphylaxis.

The original adrenaline patent did not cover adrenaline in its natural form as found in a human being or animal. That could not be patented because it was not new. Instead, the patent only covered the purified form of the hormone, which in those early days was new.[29] In fact, Judge Learned Hand noted that the inventor "was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent."[30] Thus, Learned Hand recognized that adrenaline as found in an animal's glandular tissue had virtually no therapeutic use due to the low concentration and impurities, whereas the purified adrenaline had therapeutic (and commercial) value.

Insulin is another good example of a life-saving natural product. It was first patented when Banting partially purified it from dog pancreas[31] and has saved countless lives since. One could

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[28] *See* U.S. Patent No. 730,176 (1. A substance possessing the herein-described physiological characteristics and reactions of the suprarenal glands in a stable and concentrated form, and practically free from inert and associated gland-tissue.").

[29] *Id.*

[30] *Parke-Davis & Co. v. H. K. Mulford Co*., 189 F. 95, 103 (C.C.S.D.N.Y. 1911) (the cited quote was arguably only dicta, but the analysis was correct).

[31] *See* U.S. Patent No. 1,469,994, Extract obtainable from the mammalian pancreas or from the related glands in fishes, useful in the treatment of diabetes mellitus, and a method of preparing it. Claim 1: "A substance prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the gland practically free from

treat diabetes by eating raw pancreas,[32] but that isn't very practical in the event of diabetic coma. Thus, the discovery of at least partially purified insulin was a great therapeutic benefit to patients.

Vitamin B12 is another natural compound patented in purified form.[33] Prior to the patent, anemia was treated by eating raw liver, and thus the discovery of purified B12 was a great medical advance over consuming large quantities of raw liver.[34]

Even DNA has significant medical use when purified. Before any DNA was purified and sequenced it could not be used in any diagnostic method in the early days of biotechnology. Indeed, before whole genome sequencing was invented no gene diagnostics could be performed without a small piece of purified DNA. Thus, at the time of the *Myriad* patents, even DNA had significant medical uses not possible using DNA in its natural form.

While these examples are all historical, even today a significant percentage of small molecule drugs are natural products. Indeed, in a review of new drugs covering thirty years, authors David

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injurious substances and having a physiological characteristics of causing a reduction in blood sugar useful for the treatment of diabetes mellitus."

[32] George Graham G., Treatment Of Diabetes By Raw Fresh Gland (Pancreas), Br Med J. 1(3357): 859–860 (1925).

[33] U.S. Patent No. 2,563,794 ("The compound vitamin B12 an organic substance containing cobalt, together with carbon, nitrogen, hydrogen, oxygen, and phosphorus, said compound being a red crystalline substance soluble in water, methyl and ethyl alcohol and phenol, and insoluble in acetone, ether and chloroform, and exhibiting strong absorption maxima at about 2780 A 3610 A. and 5500 5., and an L. L. D. activity of about 11,000,000 L. L. D. units per milligram."). *See also Merck & Co. v. Olin Mathieson Chem. Corp*., 253 F.2d 156, 164 (4th Cir. 1958) (upholding Vitamin B12 patent U.S. Patent No. 2,703,302 and stating "The patentees have given us for the first time a medicine which can be used successfully in the treatment of pernicious anemia, a medicine which avoids the dangers and disadvantages of the liver extracts, the only remedies available prior to this invention, a medicine subject to accurate standardization and which can be produced in large quantities and inexpensively, a medicine which is valuable for other purposes, as well as for the treatment of pernicious anemia. It did not exist in nature in the form in which the patentees produced it and was produced by them only after lengthy experiments. Nothing in the prior art either anticipated or suggested it.").

[34] Whipple G.H. & Robscheit-Robbins F.S., Favourable influence of liver, heart and skeletal muscle in diet on blood regeneration in anemia. Am J Physiol. 1925; 72:408–18. Indeed, George Hoyt Whipple shared the 1934 Nobel Prize in Medicine with 1934 with George Richards Minot, and William Parry Murphy "for their discoveries concerning liver therapy in cases of anemia." *See* https://en.wikipedia.org/wiki/George_Whipple

Newman and Gordon Cragg showed that roughly 30 to 40% of new drugs each year are either natural products or directly derived therefrom.[35] That's a lot of patents that will either not come into existence, or if already in existence can be invalidated under the Supreme Court's 101 analysis.

Dancing the Two-Step

The Patent Office has interpreted *Mayo* to require a two-step approach to determining patent eligibility. First, determine "whether the claim is directed to a law of nature, a natural phenomenon, or an abstract idea (judicial exceptions)."[36] If not, the claim is eligible. If yes, then step two requires the Examiner determine "whether any element, or combination of elements, in the claim is sufficient to ensure that the claim as a whole amounts to significantly more than the judicial exception." If yes, the claim is eligible. If not, it is rejected as ineligible.

The two-step approach, however, can yield illogical results.

Consider, for example, that portions of the claim at issue in *Mayo*, *i.e.*, portions without the added offending natural correlation provided by the wherein clause, were not only patent eligible, but were in fact previously patented. *See* U.S. Patent No. 4,443,435 ("12. The method of eliciting the corresponding therapeutic response in a warm-blooded animal, which comprises administering to such animal an effective amount of a compound as defined by claim 1 [reciting prodrugs of MP, which would then be converted to TG in the body]."). Yet, when the natural correlation was added to a similar claim in U.S. Patent No. 6,355,623, the resulting claim became patent ineligible!

This result implies that patent ineligible concepts cast a long shadow—contaminating otherwise patent eligible material—and such toxic effect must be "significantly" overcome.[37] This analysis seems illogical when one realizes that all patent claims necessarily function in accordance with

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[35] David J. Newman & Gordon M. Cragg , Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010. J. Natural Prod. 75:311-335 (2012). See e.g., FIG. 5.

[36] *See* 2014 Interim Eligibility Guidance Quick Reference Sheet, available online at https://www.uspto.gov/patents/law/exam/2014_eligibility_qrs.pdf (underline in original).

[37] *Mayo,* 132 S.Ct. at 1297 ("The question before us is whether the claims do **significantly more** than simply describe these natural relations.") (emphasis added).

all natural laws, whether recited or not, yet the mere recitation of one is enough to poison the claim under *Mayo*.

To provide a hypothetical example—if Thomas Edison had had the misfortune to recite in his light bulb patent claim that increasing current or voltage would brighten the bulb, the recitation of such a natural law would poison the entire claim under the Mayo approach.[38] Hence, the light bulb would **no longer be patent eligible** under the proposed framework. Yet, whether recited or not, the light bulb must necessarily function in accordance with the natural law—that's **why** we refer to them as **laws**.

According to this "logic" all practitioners need do is avoid the recitation of any natural law (or any math) to circumvent *Mayo*, and indeed the current PTO guidance confirms this.[39] One of the (fictional) biotech examples relates to a skin rash called julitis, recently discovered to be correlated with the presence of the JUL-1 protein in patients. Using this new information, julitis could be definitively distinguished from other rashes, such as psoriasis.

ELIGIBLE

1. A method of detecting JUL-1 in a patient, said method comprising:
   a. obtaining a plasma sample from a human patient; and
   b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody.

INELIGIBLE

2. A method of diagnosing julitis in a patient, said method comprising:
   a. obtaining a plasma sample from a human patient;
   b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody; and
   c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.

Julitis claim 1 example provides that "detection" methods **without** conclusions are not "directed to" a judicial exception, and thus are patent eligible! However, adding the **diagnostic conclusion** in claim 2 renders the claim ineligible! This example indicates that practitioners with diagnostic inventions can simply avoid "diagnostic" language and stating any medical relevant conclusions to escape the *Mayo* result.

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[38] A bulb's brightness depends on the power being input into the bulb. Power, measured in watts, is the voltage and current product. The natural law governing the brightness of a bulb is thus Power (P) = voltage (V) x current (I) or P=VI.

[39] Subject Matter Eligibility Examples: Life Sciences (2016), available online at https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf.

The analysis of Julitis claim 2 is illogical—silly even—because substantively, claims 1 and 2 read on the **same** activities. Whether the conclusion is recited in the claim or not, it is inherently going to be made once the correlation is known.

Further, although promising an easy fix for side-stepping *Mayo*, to the extent that the JUL-1 protein and its antibodies were already known, the claim would not be novel or non-obvious. Thus, newly discovered medical correlations for known proteins probably cannot be patented this way.

Another example relates to the BRCA1 gene test for breast cancer, many patents of which were invalidated in the various Myriad cases.

INELIGIBLE

1. 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.

ELIGIBLE

70. The method of claim 1, wherein said comparing BRCA1 sequences further comprises:

hybridizing a wild-type probe to a BRCA1 gene isolated from said sample; and

detecting the presence of a hybridization product by measuring conformational changes in the probe that are indicative of hybridization to the BRCA1 gene with scanning near-field optical microscopy.

Claim 70 indicates that if one adds a plethora of claims, each reciting a different and very specific way to perform the method, they may escape the 101 hatchet during examination. However, all this does is increase the number of claims and the amount of fees, with no corresponding social benefit.

The Mayo Fallout

The damage potential in the two-step approach was realized in *Ariosa Diagnostics Inc. v. Sequenom, Inc.*,[40] which invalidated a patent for a very important medical advance under 101. The patents at issue in *Ariosa* related to diagnostic tests for fetal abnormalities, such as trisomy 21 or "Down's Syndrome."[41] The test used cell free maternal fluids, rather than fetal fluids, which were previously not known to even contain any fetal material. This was an important

[40] 788 F.3d 1371 (Fed. Cir. 2015) [hereinafter *Ariosa*].

[41] U.S. Patent No. 6,258,540.

advance because it reduced the need for invasive sampling methods, such as amniocentesis. Any woman who has ever undergone this painful needle biopsy procedure would certainly agree that testing maternal blood instead is a huge improvement.

Claim 1 is provided:

> 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
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> amplifying a paternally inherited nucleic acid from the serum or plasma sample and
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> detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.[42]

Ariosa filed a declaratory judgment action against Sequenom on these claims, and the District Court denied Sequenom's motion for preliminary injunction, based on a substantial question of invalidity under Section 101. On the second appeal, the Federal Circuit applied the two step *Mayo* analysis. It was undisputed in the record that the fetal DNA in the cell free maternal fluids was a natural phenomenon, and it was also undisputed that Sequenom did not create or alter any of these fetal DNAs. [43] Thus, the Federal Circuit concluded that the claim was "directed to matter that was naturally occurring."[44]

In the second step, the court found that the amplifying and detecting steps were conventional at the time of filing.[45] Indeed, the specification described sample preparation as using "standard techniques" and amplification was also described as "standard".[46] Further, during prosecution, the patentee described the detecting steps as "routine."[47] Thus, the Federal Circuit concluded that "the practice of the method claims does not result in an inventive concept that transforms the

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[42] There were many more claims at issue, but for simplicity we will only discuss one representative claim.

[43] *Ariosa,* 788 F.3d at 1373.

[44] *Id.* at 1376.

[45] *Id.* at 1377.

[46] *Id.* at 1377.

[47] *Id.* at 1377.

natural phenomenon of [cell free fetal] DNA into a patentable invention."[48] Therefore, the claim was not patent eligible:

> [I]n this case, appending routine, conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept. Where claims of a method patent are directed to an application that starts and ends with a naturally occurring phenomenon, the patent fails to disclose patent eligible subject matter if the methods themselves are conventional, routine and well understood applications in the art. The claims of the '540 patent at issue in this appeal are not directed to patent eligible subject matter and are, therefore, invalid.[49]

Judge Lynn said it best noting that "But for the sweeping language in the Supreme Court's *Mayo* opinion, I see no reason, in policy or statute, why this breakthrough invention should be deemed patent ineligible."[50]

Although requesting the Court rehear the case *en banc*, the Federal Circuit denied the petition.[51] Ariosa then appealed to the Supreme Court, but the *petition for certiorari* was denied, [52] even though many *amicus* briefs urged the case be taken up to correct some of the logical flaws of *Mayo*. Thus, Courts and the Patent Office are free to use the case to continue rejecting and invalidating claims.

The damage caused by the two-step approach became apparent early on. In his February 2017 update of Alice Storm[53], Robert Sachs indicated the percentage of invalidation of under the Federal courts and the percentage of 101 rejections in the Patent Office:

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[48] *Ariosa,* 788 F.3d at 1376.

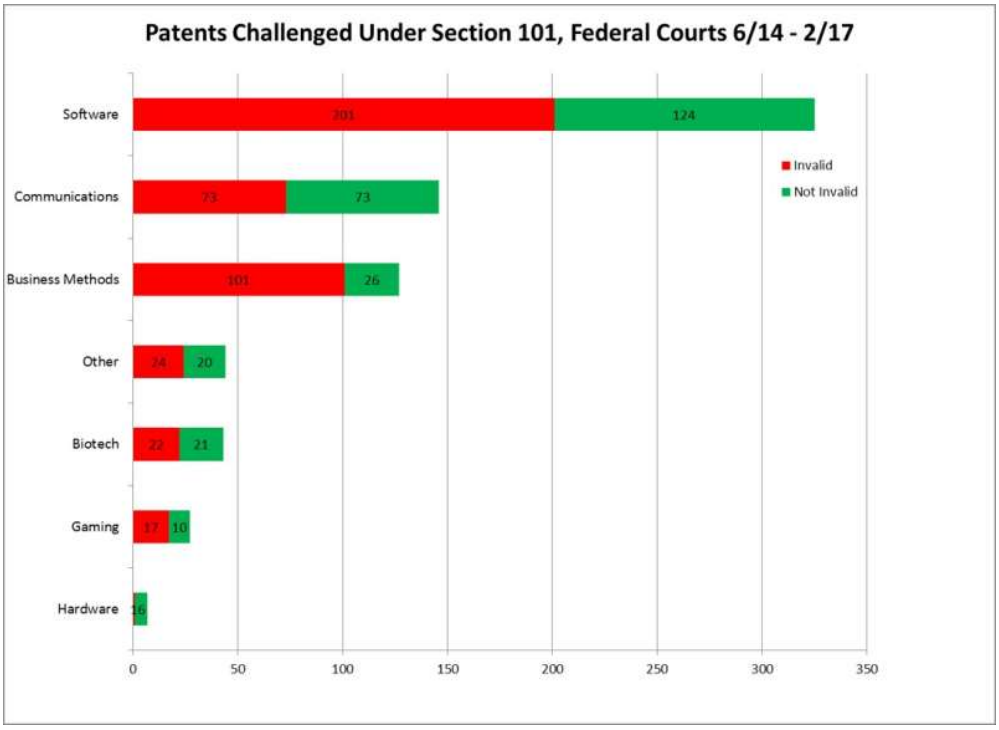
[49] *Id.* at 1378.

[50] *Id.* at 1381.

[51] *Id.* at 1381.

[52] *Sequenom, Inc. v. Ariosa Diagnostics, Inc.,* 579 US 928 (2016).

[53] http://www.bilskiblog.com/blog/alicestorm/. The Alice case is the computer and business method analog to the diagnostic and natural products cases but is not discussed in detail herein. See *Alice Corp. v. CLS Bank International,* 573 U.S. 208 (2014).



Art Unit	Art Unit Tech	Final Rejections		Non Final Rejections	
		Percent 101 Only	Percent 102/103 Only	Percent 101 Only	Percent 102/103 Only
1631	Molecular Biology	48.6%	7%	43%	8%
3696	Finance & Banking	47.9%	3%	44%	2%
3691	Finance & Banking	45.1%	3%	35%	5%
3694	Finance & Banking	42.1%	3%	29%	2%
3693	Finance & Banking	39.5%	2%	28%	1%
3692	Finance & Banking	38.1%	2%	31%	4%
3695	Finance & Banking	34.8%	4%	30%	2%
1600	Medicine	33.3%	0%	0%	0%
2857	Electrical Components, Devices & Systems	31.3%	22%	19%	14%
3623	Operations Research	30.3%	6%	22%	4%
2862	Electrical Components, Devices & Systems	30.3%	28%	14%	18%
3628	Cost/Price, Reservations	29.8%	11%	20%	7%
3625	E-Shopping	28.8%	6%	17%	6%
3714	Amusement & Education	28.2%	38%	18%	34%
2864	Electrical Components, Devices & Systems	28.2%	31%	18%	18%
3686	Health Care	28.1%	5%	18%	4%
3687	POS, Inventory, Accounting	26.3%	16%	23%	13%
3684	Operations Research	26.2%	7%	17%	4%
3682	Incentive Programs	25.3%	7%	15%	6%
3627	POS, Inventory, Accounting	25.3%	26%	16%	23%
3626	Health Care	23.0%	5%	17%	3%
3624	Operations Research	21.8%	5%	14%	3%
3715	Amusement & Education	20.5%	38%	13%	35%

As noted by Sachs "the highest rates of Section 101-only rejections were in Art Unit 1631, Microbiology. Not surprisingly, the business method art units are right behind, but they also they have the lowest rate of prior art rejections. How can it be then that these applications are so

"routine and conventional" as to support a Section 101 Rejection?" These authors posit the same question with respect to biotechnology. How can an unpredictable art that routinely garners enablement rejections at the same time be so routine and conventional as to have the highest rate of 101 rejections?

It seems that, while the Supreme Court cautioned us to "tread carefully in construing this exclusionary principle lest it swallow all of patent law,"[54] no one has been particularly cautious, with the result being administrative and judicial environments hostile to patent eligibility.

A Glimmer of Hope

Since the Supreme Court denied *certiorari* for the *Sequenom* case[55], the Federal Circuit—realizing that no help is forthcoming—has begun to try to rein in the chaos of *Mayo*. In *Rapid Litigation Management LTD v. Cellzdirect, Inc*.,[56] the Federal Circuit showed a willingness to apply the two-step method in a rigorous manner.

The claims at issue in *Cellzdirect* related to a method of preparing hepatocytes using a multiple freeze thaw method that retained some 70% of viable cells, where the art taught that they should only be freeze thawed once. The District court identified the "natural law" as being the cells ability to survive more than one freeze thaw cycle, and concluded that the patent was invalid.

The Federal Circuit didn't comment on this "labeling" of the natural law, but instead focused on the "directed to" aspect of the first step, noting 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."[57]

Thus, the Federal Circuit has attempted to make the first step in the two step analysis more rigorous than merely identifying a patent ineligible concept, but requiring that the claims be "directed to" that concept rather than just using it:

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[54] *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S.Ct. 2347, 2354, 573 U.S. 208 (2014).

[55] *Sequenom, Inc. v. Ariosa Diagnostics, Inc.,* 579 US 928 (2016).

[56] *Rapid Litig. Mgmt. v. CellzDirect, Inc*., 827 F.3d 1042 (Fed. Cir. 2016) [hereinafter *Cellzdirect*].

[57] *CellzDirect,* 827 F.3d at 1048.

> At step one, therefore, it is not enough to merely identify a patent-ineligible concept underlying the claim; we must determine whether that patent-ineligible concept is what the claim is "directed to." Here, the plain claim language shows that it is not.[58]

The Federal Circuit went further, noting that "Under step two, claims that are "directed to" a patent-ineligible concept, yet also "improve[] an existing technological process," are sufficient to "transform[] the process into an inventive application" of the patent ineligible concept." [59]

The Court also offers some useful language under the routine and obvious parts of the *Mayo* analysis:

> The 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. . . Repeating a step that the art taught should be performed only once can hardly be considered routine or conventional. [60]

Thus, the *Cellzdirect* case offers useful language that can rebut a 101 claim in either the PTO or the court. This emphasis on the "directed to" language was then echoed in the *Berkheimer*[61] and

[58] *CellzDirect,* 827 F.3d at 1050.

[59] *Id.*

[60] *Id.* at 1051.

[61] *Berkheimer v. HP Inc.,* 881 F.3d 1360 (Fed. Cir. 2018) [hereinafter *Berkheimer*].

Vanda[62] cases and picked up in a USPTO memo[63] and then reflected in its 2019 Guidance[64] and eventually in the Manual of Patent Examination Procedure.[65]

Current data indicates that the change in emphasis in the two step dance is having a positive effect. Indeed, the following graphic indicates that after a distressing increase in eligibility rejections in the aftermath of the *Mayo*/*Myriad* storm, eligibility problems are on the decline, at least in the Patent Office.

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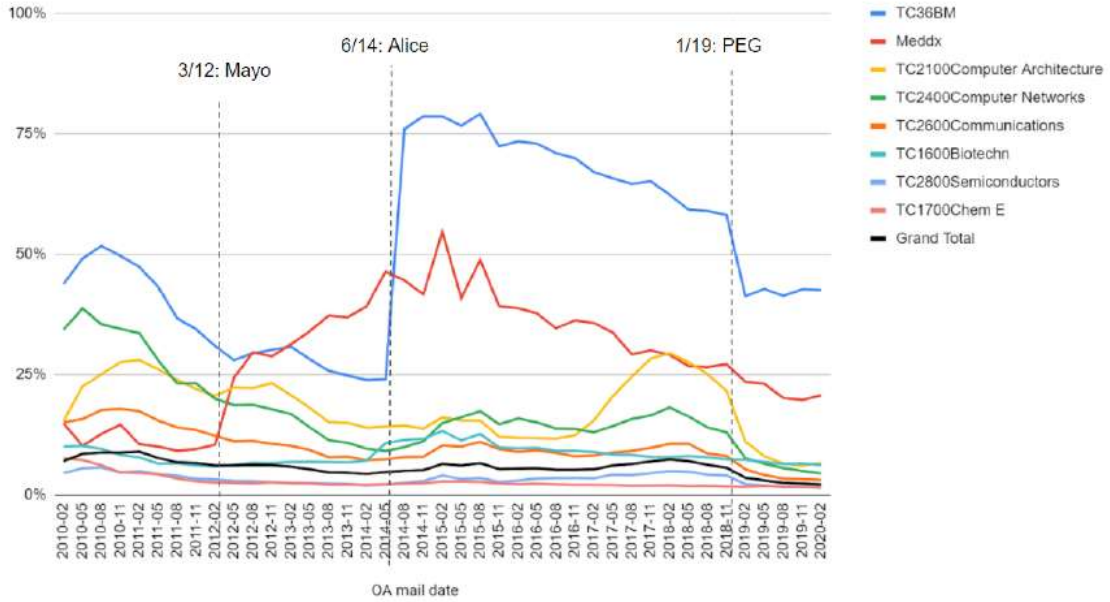
[62] *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals,* 887 F.3d 1117, 1134 (Fed. Cir. 2018) [hereinafter *Vanda*] ("the asserted claims are not directed to patent-ineligible subject matter. Claim 1 recites '[a] method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia.' Claim 1 requires specific steps: (1) determining the patient's CYP2D6 metabolizer genotype by (a) obtaining a biological sample and (b) performing a genotyping assay; and (2) administering specific dose ranges of iloperidone depending on the patient's CYP2D6 genotype.") (citations omitted).

[63] Memorandum: Recent Subject Matter Eligibility Decision: *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals*, June 7, 2018 ("[T]he Federal Circuit did not consider whether or not the treatment steps were routine or conventional when making its "directed to" determination. Since the claim was determined eligible in the step 2A "directed to" part of the test, there was no need to conduct a step 2B analysis. The US PTO' s current subject matter eligibility guidance and training examples are consistent with the Federal Circuit's decision in Vanda…").

[64] 2019 Revised Patent Subject Matter Eligibility Guidance, available online at https://www.federalregister.gov/documents/2019/01/07/2018-28282/2019-revised-patent-subject-matter-eligibility-guidance.

[65] Manual of Patent Examination Procedure (MPEP), Sections 2103 through 2106.07(c).

Fig. 1: Share of Office Actions with a Subject Matter Rejection



This graphic[66] shows the Patent Office rejections based on 101, with business methods being the top blue line, diagnostics the orange and biotech is turquoise. The dotted line for PEG is the Patent Eligiblity Guidance of 2019. Thus, we can see that as patent practitioners have learned how to circumnavigate the *Mayo*/*Myriad* analysis, the incidence of rejections has declined. Further, these authors indicate that there is no decrease in application filing in diagnostic or biotech filings as a result of *Mayo*.

Although Patent Office practice is very promising to ongoing patent issuance, *Mayo* and *Myriad* are still good law, and they can be expected to muddy the waters for years to come, at least for patents written before the *Mayo* decision.[67] Indeed, the biggest losses are likely the invalidation of diagnostic patents that recite medical correlations and were written **before** the *Mayo* mixing of 101, 102 and 103 concepts.[68] Some patents may be rescuable by reissue, provided the scope of

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[66] Excerpted from a guest post at PatentlyO: Patent Prosecution Trends Following the Patent Eligibility (101) and 112 Guidelines, by Colleen Chien, et al., Nov. 2, 2020, available online at https://patentlyo.com/patent/2020/11/prosecution-eligibility-guidelines.html or https://cdn.patentlyo.com/media/2020/11/PatentlyO-LJ-2020-11-02.pdf.

[67] *E.g.*, *CareDx, Inc. v. Natera, Inc,* 40 F.4th 1371, (Fed. Cir. 2022), *cert. denied. (2023)* (invalidating diagnostic patents written well before the *Mayo* decision).

[68] *CareDx, Inc. v. Natera, Inc, 22-1066, Petition For Writ Of Certiorari, p. 11 (2023)* ("the Federal Circuit has invalidated every single diagnostic method patent it has encountered since *Mayo*" and calling the courts 101 analysis of diagnostic patents "virtually a per se rule of

the claims isn't broadened, but this requires that the needed language be included in the specification, and therefore is not a solution for every patent.[69] For many, this has meant avoiding litigation and trying instead to work with licensees. For others, they stopped using the patent system and instead keep their diagnostic information secret, as Myriad has.[70]

To address this ongoing problem, Senators Thom Tillis (R-NC) and Chris Coons (D-DE) have attempted to fix the problem legislatively. In the last attempt, they introduced the Patent Eligibility Restoration Act ("PERA") of 2023.[71] The proposed law provides that "All judicial exceptions to patent eligibility are eliminated" and that the only ineligible subject matter is:

i) A mathematical formula that is not part of an invention…

ii) A mental process performed solely in the mind of a human being.

iii) An unmodified human gene, as that gene exists in the human body.

iv) An unmodified natural material, as that material exists in nature.

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invalidity"), *available online at* https://www.scotusblog.com/case-files/cases/caredx-inc-v-natera-inc/

[69] 35 U.S.C. § 251 ("Whenever any patent is, through error without any deceptive intention, deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent, the Director shall, on the surrender of such patent and the payment of the fee required by law, reissue the patent for the invention disclosed in the original patent, and in accordance with a new and amended application, for the unexpired part of the term of the original patent. No new matter shall be introduced into the application for reissue. . . No reissued patent shall be granted enlarging the scope of the claims of the original patent unless applied for within two years from the grant of the original patent.").

[70] Myriad Take Two: Can Genomic Databases Remain Secret?, Science 356(6338): 586-587 (2017), DOI: 10.1126/science.aal3224, ("Although Myriad initially disclosed variant data from test results, it began keeping the data secret in 2004. Myriad has never disclosed the algorithms and methods it uses to interpret those data. Now that Myriad's patents are invalid, competition in BRCA1/2 testing is growing. However, Myriad claims that other providers have not yet accumulated the quantity of data to match its interpretive accuracy. Thus, through maintenance of its database as a lawful trade secret, Myriad has continued to dominate the BRCA1/2 testing market.") (cites omitted).

[71] *See* https://www.congress.gov/bill/118th-congress/senate-bill/2140. The bill is stalled at introduced on 6/23/2022.

v) A process that is substantially economic, financial, business, social, cultural, or artistic.

Further, the bill prevents importing other statutes (102, 103, 112) into the eligibility analysis.

The bill is a commendable effort for fixing the *Mayo* mess, albeit not without some criticisms.[72] On January 23, 2024, The Committee on Intellectual Property (a subcommittee of The Senate Judiciary Committee) held a hearing to discuss the implications passing PERA into law. Of the eight witnesses that testified at the hearing, two expressed concerns with enacting PERA, while the rest spoke in support. While promising, given the legislative delays in providing a US budget, we anticipate that progress will continue to be slow. Since Congress only has until December in the second legislative session of the 118th Congress, it is likely that the bill will need to be reintroduced in the 119th session.

In conclusion, patents are still available in the diagnostic and natural product areas. Practitioners must camouflage the claims to avoid 101 rejections and are advised to use a variety of different claiming styles as the law continues to evolve. However, the Patent Office guidance and Federal Circuit case law continue to provide a roadmap for navigating the 101 morass. Unfortunately, older patents written well before the *Mayo* mess may continue to be invalidated in litigation.

[72] One criticism is that the proposed legislation doesn't address AI inventions. Recently in *Thaler v. Vidal*, 43 F.4th 1207, 1210, 1211 (Fed. Cir. 2022) the Federal Circuit held that "the Patent Act requires that inventors must be natural persons; that is, human beings." The court relied on inter alia, the fact that "the Patent Act has defined an 'inventor' as 'the individual . . . who invented or discovered the subject matter of the invention.'"