Marquette Intellectual Property Law Review

Volume 22 | Issue 2 Article 4

2018

NOA v. DOA: Increasing Medical Diagnostic Patentability After *Mayo*

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NOA v. DOA:

INCREASING MEDICAL DIAGNOSTIC PATENTABILITY AFTER MAYO

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INTRODUCTION

The medical diagnostics market is expected to reach 65 billion by 2018.[1] In March 2012, in *Mayo Collaborative Services v. Prometheus Labs, Inc.*, ("*Mayo*") the U.S. Supreme Court held that the Mayo Clinic (the "Clinic") had not infringed on Prometheus Labs' ("Prometheus") diagnostic patent because the Prometheus patent involved ineligible subject matter, and was therefore

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1. Jim Bustschli, *Diagnostic market growth expected to reach $65 billion by 2018*, HEALTHCARE PACKAGING, https://www.healthcarepackaging.com/article/trends-and-issues/vitro-diagnostics/diagnostic-market-growth-expected-reach-65-billion-2018 [https://perma.cc/RV44-3NM9]; *see also* TUFTS UNIVERSITY, CSDD IMPACT REPORT VOL. 17 NO. 6 (NOVEMBER/DECEMBER 2015).

invalid.[2] Section 101 of the Patent Act defines eligible subject matter as "any new and useful process, machine, manufacture, or composition of matter" as patentable subject matter.[3] Courts have held that Section 101 contains an implicit exception, making laws of nature, natural phenomena, and abstract ideas ineligible for patent protection.[4] Traditionally, applications to a structure or process have satisfied this exception.[5]

However, since the Court's unanimous decision in *Mayo*, the percentage of medical diagnostic patents allowed[6] by the U.S. Patent & Trademark Office (the "USPTO") has dropped to less than thirty-five percent, as compared to eighty-five percent before *Mayo*.[7] *Mayo* and its progeny[8] arguably had a significant impact on the multi-billion-dollar medical diagnostic industry—an industry focused on the laws of nature that occur within the human body. After *Mayo*, medical diagnostics developers have encountered less certainty for both issuance and in mounting a vigorous defense of infringement.

Although the topic of patentability has been avidly discussed in legal literature critiquing the Court's *Mayo* rationale, this article will analyze possible solutions to increase patentability, and the defense of medical diagnostic patents. Specifically, this article will examine: (1) how the Prometheus patent could have been altered during patent prosecution; (2) how these changes are affected by a challenge of invalidity elucidated through *Mayo* and its progeny; and (3) whether the Patent Trial and Appeal Board (the "PTAB") or subsequent Federal Circuit decisions have clarified the patentability of medical diagnostic patents. Finally, this article will draw conclusions regarding strategies to increase patentability in medical diagnostic patents and reduce the likelihood that the patent will be pronounced "Dead on Arrival" (DOA)[9] in district court.

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2. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 70 (2012).

3. 35 U.S.C. § 101 (2012).

4. Diamond v. Diehr, 450 U.S. 175, 185 (1981).

5. *Id.* at 187.

6. NOA is a "Notice of Allowance" in which, "[i]f on examination, it appears that the applicant is entitled to a patent under the law, a notice of allowance will be [issued]." *See* 37 C.F.R. § 1.311(a); U.S. PATENT & TRADEMARK OFFICE, MANUAL OF PATENT EXAMINING PROCEDURE § 1303 (2018).

7. Gaudry, Grab & McKeon, *Trends In Subject Matter Eligibility for Biotechnology Inventions*, IPWATCHDOG.COM, http://www.ipwatchdog.com/2015/07/12/trends-in-subject-matter-eligibility-for-biotechnology-inventions/id=59738/ [https://perma.cc/Q2ML-QED6].

8. Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013); Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014); Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371
(Fed. Cir. 2015).

9. DOA is a medical acronym commonly used in emergency room settings for a patient who was brought in by ambulance but was declared dead before receiving treatment in the emergency room; in other words, the patient was declared "Dead On Arrival."

I. PATENTABILITY OF MEDICAL DIAGNOSTICS

A. Dissecting the Prometheus Patent

The Prometheus patent assessed the proper therapeutic blood level of drugs used to treat Crohn's disease and ulcerative colitis.[10] Essentially, the patent applied principles of pharmacokinetics to customize the dosage for each individual patient, and therefore minimize toxicity while optimizing the therapeutic value of the medication.[11] The Clinic licensed the patented steps for determining these individualized dosages.[12] Eventually, the Clinic developed and used its own process; and Prometheus subsequently sued for infringement.[13] A U.S. District Court determined that the Clinic infringed on Prometheus's patents, but that Prometheus's patents were invalid. The U.S. Court of Appeals for the Federal Circuit overturned part of that decision, holding that Prometheus' diagnostic test *was valid*.[14] The Clinic subsequently appealed.[15]

The U.S. Supreme Court held that the processes in the diagnostic test were ineligible subject matter because the processes pertained to laws of nature under 35 U.S.C. § 101 of the Patent Act.[16] Although "an application of a law of nature . . . to a known structure or process may [deserve] patent protection," a law of nature cannot be transformed "into patent eligible [matter] . . . simply [by] stat[ing] the law [and] adding the words, 'apply it.'"[17] The Court therefore found that the "steps" Prometheus added to the process were not novel; instead they were merely instructions regarding a law of nature.[18] Thus, *Mayo* altered the landscape of the machine-transformation test, which up to that point, had been applied to other processes.[19] Medical diagnostics largely revolved around laws of nature played out within the human body and so long as a novel application was applied, the USPTO, the Federal Circuit, and Supreme Court did not cry foul. However, after *Mayo*, previously accepted additional requirements for process patentability to survive a law of nature invalidation

10. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 73 (2012).
11. *Id.*at 73–74.
12. *Id.* at 74–75.
13. *Id.* at 75–76.
14. *Id.* at 76 (emphasis added).
15. *Id.*
16. *Id.* at 76.
17. *Id.* at 72.
18. *Id.* at 77.
19. Computers, software, manufacturing and credit card company transactional software, for example.

would no longer be enough. In fact, simply adding the language "apply it" would not be enough.[20]

In light of this, the U.S. Supreme Court remanded *Mayo* to the Federal Circuit to determine whether transforming a law of nature was an adequate transformation to make Prometheus' diagnostic test patentable.[21] On remand, the Federal Circuit reasoned that it "is virtually self-evident that a process for a chemical or physical transformation of *physical objects or substances* is a patent-eligible subject matter[.]"[22] However, the Supreme Court found that the administering and determining steps of the Prometheus patent were not transformative, but merely "insignificant extra-solution activity[.]"[23] Additionally, the machine-or-transformation test must transform an ineligible material into eligible material.[24]

The Court addressed this complex transformation challenge, inherent within medical diagnostics, by discussing the risk of making overly broad claims and whether a claim has presented a "substantial practical application,"[25] reinforcing that "laws of nature, natural phenomenon, and abstract ideas" cannot be granted patent protection.[26] Historically, until the mid-2000's, 35 U.S.C. § 101 was interpreted quite broadly to include many types of subject matter; however, laws of nature were never patentable except for diagnostic methods claims that were routinely granted by the USPTO. Challenges to their status as patentable subject matter were not typically raised during litigation.

Mayo marks a distinct departure from this historical treatment of diagnostics. Reciting a process "is no more than a[n] . . . instruction to [read some numbers in light of medical knowledge]."[27] Upon review of Prometheus' '632 patent claims 1-54, the following claims construction language is repeated in claims 1, 7, 15, 25, 37 and 46:

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20. *Mayo*, 566 U.S. at 76. (quoting Bilski v. Kappos, 561 U.S. 593 (2010) ("which clarified that the 'machine-or-transformation test' is not a definitive test for finding patent eligibility, but only an important and useful clue.").

21. *Mayo*, 566 U.S. at 76–77.

22. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 628 F.3d 1347, 1356 (Fed. Cir. 2010), rev'd, 566 U.S. 66 (2012) (quoting In re Bilski, 545 F.3d 943, 962 (Fed. Cir. 2008) (emphasis in original).

23. *Mayo*, 566 U.S. at 78. *Compare to* Chen, Wan-Ling, *Patent-Eligibility after Bilski: Revisiting The Supreme Court's Prometheus Decision*, 1 NTUT J. OF INTELL. PROP. L. & MGMT. 94, 100 (2012) (asserting that the Grams test was found to be a merely a mathematical algorithm).

24. Diamond v. Diehr, 450 U.S. 175, 184 (1981).

25. *Id.* at 71.

26. *Id.* at 186 (holding that mathematical formulas are not patentable but when the claims are considered as a whole, and it is clear that it is an attempt to patent a process that implements or applies a mathematical formula—this is transformative and patentable). *Id.* at 191–93.

27. *Mayo*, 566 U.S. at 78.

> (1) A method of optimizing therapeutic efficacy for treatment of a . . . disorder:
> (a) administering a drug . . . to a subject having said . . . disorder; and
> (b) determining the level of [drug] in said subject having . . . disorder, wherein the level of [drug] less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount . . . 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 . . . drug subsequently administered.
> . . .
> (7) A method of reducing toxicity associated with treatment of a . . . disorder, comprising:
> (a) administering a drug providing 6-thioguanine to a subject having said . . . disorder;
> (b) determining the [amount of the drug] . . . in said subject having . . . disorder; and
> (c) determining the level of 6-methyl-mercaptopurine in said subject having said . . . disorder, wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of . . . drug subsequently administered.[28]

The claims construction language of "administering, determining, and administering," does not describe a non-conventional or novel activity. Indeed, this activity describes what is commonly known as pharmacokinetics and pharmacodynamics.[29] Arguably, what is missing from the '623 patent claims is some form of unique step that may have enabled a more effective adjustment of the blood levels of the drug in question. This could have been supported by a unique mathematical algorithm, a more discrete lab test with a higher degree of sensitivity and specificity than other tests on the market, or a process that was more advanced in regard to the accuracy of predicting toxicity and therapeutic levels in a specific population. Such a process of determining toxicity with a higher degree of sensitivity, could in turn allow, for example,

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28. U.S. Patent No. 6,355,623 col. 20-24 l. 10-12.

29. *See* Jennifer Le, *Overview of Pharmacokinetics,* MERCK MANUAL, http://www.merckmanuals.com/professional/clinical-pharmacology/pharmacokinetics/overview-of-pharmacokinetics [https://perma.cc/4TU8-4DA7] (noting that because of individual differences, drug administration must be based on each patient's needs—traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because it can delay optimal response or result in adverse effects. Knowledge of pharmacokinetic principles helps prescribers adjust dosage more accurately and rapidly. Application of pharmacokinetic principles to individualize pharmacotherapy is termed therapeutic drug monitoring).

less frequent blood draws, and more accurate determinations. However, this type of disclosure was absent in the '632 patent and was historically not required by the USPTO to issue a patent or the courts in the defense of diagnostic patents.

In contrast, *Classen v. Biogen Idec*, decided before *Mayo* but still relevant, claimed a method directed to immunizing a patient based on detection of markers in a screening step.[30] Although the screening step was based on a natural law, the immunization step was a non-conventional specific application of the screening principle,[31] and this claim was held as patentable.[32]

A similar diagnostic test that was based on natural law—yet, held as patentable—was the subject of litigation in *Ameritox Ltd. v. Millennium Health, LLC*.[33] The *Ameritox* invention was specifically directed "to quantify[] the metabolite concentration by adjusting the concentration for the patient's hydration status, and then statistically comparing the adjusted concentration to a set of known normative data."[34] In this way, the invention provided a method to improve medication monitoring and identify aberrant drug use. More importantly, the *Ameritox* '680 patent identified statistical analysis and normative data that increased the sensitivity and specificity of the test rendering it an inventive concept.[35]

B. Mayo and its progeny: Alice Corp, Myriad and Sequenom

Ameritox provides an excellent discussion of how *Alice Corporation v. CLS Bank International* outlines the framework for analyzing claims directed at an abstract idea.[36] *Alice Corp* provided a two-step test for patentability: (1) is the patent related to a law of nature; (2) if so, does the claim contain an inventive concept, element or combination of elements "sufficient to ensure that the patent . . . amounts to significantly more than a patent [on an] ineligible concept.[37] "Applications of concepts 'to a new and useful end' remain eligible for patent protection."[38] Undoubtedly, most diagnostic patents would satisfy step one of the *Alice Corp* framework. As the District Court noted in *Ameritox*, the "real heavy lifting" occurs in step two, which analyzes whether the process

30. Classen Immunotherapies, Inc. v. Biogen Idec, 659 F. 3d 1057, 1060 (Fed. Cir. 2011).

31. *Id.* at 1064–68.

32. *Id.*

33. Ameritox, Ltd. v. Millennium Health, LLC, 88 F. Supp. 3d 885, 917 (W.D. Wis. 2015), *reconsideration denied*, No. 13-CV-832-WMC, 2015 WL 1272280 (W.D. Wis. Mar. 19, 2015).

34. *Id.* at 909.

35. *Id.* at 911.

36. *Id.* at 903.

37. *Id.* (quoting *Alice Corp.*, 134 S. Ct. at 2355).

38. *Id.* at 911 (quoting, *Alice Corp.*, 134 S. Ct. at 2354).

sought to be patented includes an additional element or combination of elements that constitute an "inventive concept[.]"[39] For example, "*an element or combination of* elements that is sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."[40]

In the *Association for Molecular Pathology v. Myriad Genetics, Inc*., the Court analyzed claims to isolated genomic deoxyribonucleic acid (the "gDNA") segments associated with the breast cancer susceptibility gene (the "BRCA") and methods of diagnosing a propensity for cancer by detecting mutations in the genetic sequences.[41] The Court held that isolating a gDNA segment was insufficient to provide patent eligibility.[42] The Court reasoned that, while *Myriad* had discovered "an important and useful gene, . . . separating that gene from its surrounding genetic material is not an act of invention."[43] However, the complimentary deoxyribonucleic acid (the "cDNA"), which lacks non-coding regions of gDNA, was held to be patentable, because it was not a naturally occurring material.[44] Essentially, the *Alice Corp* framework was inapplicable.[45] This is similar to the results described *In re BRCA1– & BRCA2–Based Hereditary Cancer Test Patent Litig*., in which diagnostic tests to determine risk of breast cancer were found to be invalid.[46]

In *Ariosa Diagnostics, Inc. v. Sequenom, Inc*., the U.S. Court of Appeals for the Federal Circuit held that even a truly revolutionary medical test was patent ineligible.[47] The test at issue was one for detecting fetal genetic conditions in early pregnancy, which allowed the expectant mother to avoid more dangerous invasive techniques that could be potentially harmful to both the mother and the fetus.[48] The Federal Circuit concluded that the discovery was a significant contribution to the medical field, but the contribution did not matter as far as *patent eligibility* was concerned.[49]

The invention was embodied in U.S. Patent No. 6,258,540, which claimed certain methods for using cell-free fetal deoxyribonucleic acid (the "cffDNA")

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39. *Id.* at 903.

40. *Id.* (quoting *Alice Corp*., 134 S. Ct. at 2355) (emphasis in original).

41. Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 582–83 (2013).

42. *Id.* at 596.

43. *Id.* at 591.

44. *Id.* at 594–95.

45. *Id.*

46. In re BRCA1- & BRCA2–Based Hereditary Cancer Test Patent Litig., 774 F.3d 755, 758–65 (Fed. Cir. 2014).

47. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1377 (Fed. Cir. 2015).

48. *Id.* at 1373.

49. *Id.* at 1379 (emphasis added).

by teaching technicians to take maternal blood samples; keep the non-cellular portion (which was previously discarded as medical waste); amplify the genetic material so that only they had discovered what was present; and thereby identify paternally inherited sequences from fetal DNA that previously had not been known to be present in the maternal samples.[50] And it was therefore a novel discovery. In a separate concurrence, Judge Linn expressed his dissatisfaction with the "sweeping language of [the Court's decision] in *Mayo*."[51] Most notably, Judge Linn lamented on the Court's lumping together of the post-solution conventional activity as if it were qualitatively the same.[52]

In March of 2016, Sequenom, Inc. filed a Petition for Writ of Certiorari in the Supreme Court seeking to answer a single question: "[w]hether a novel method is patent-eligible where: (1) a researcher is the first to discover a natural phenomenon; (2) that unique knowledge motivates him or her to apply a new combination of known techniques to that discovery; and (3) he or she thereby achieves a previously impossible result without preempting other uses of the discovery?"[53] On June 27, 2016, the Court denied certiorari to Sequenom, Inc.[54] If the Court granted certiorari, however, it may have been forced to address the overwhelming breadth and scope of the decision in *Mayo*. At the very least, the Court may have provided more guidance to practitioners and inventors in the fields of medical diagnostics.

C. PTAB CASES & USPTO GUIDANCE

Since *Mayo*, the USPTO has taken up eligibility cases and also has offered guidance to practitioners. Under the authority of the American Invents Act (the "AIA"), the Patent Trial and Appeal Board (the "PTAB") has reviewed the validity of patents.[55] Some of these decisions may elucidate the contours of eligibility in diagnostic process patents beyond *Mayo* and its progeny. Of the sixty or more decisions from the Federal Circuit, the PTAB, or those decisions appealed to the U.S. Court of Federal Claims through May of 2016, only a small percentage involved diagnostic patents, and an even smaller amount originated at the PTAB.[56]

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50. US Patent no. 6,258,540 col. 1-3 l. 50-62.

51. Ariosa, 788 F.3d at 1380.

52. *Id.*

53. Petition for Writ of Certiorari, Sequenom, Inc. v Ariosa Diagnostics, Inc. 136 S. Ct. 2511 (2016) (No. 15–1182).

54. Sequenom, Inc. v. Ariosa Diagnostics, Inc. 136 S. Ct. 2511, 2511 (2016).

55. 35 U.S.C. § 135(b) (2012).

56. *See* U.S. PATENT & TRADEMARK OFFICE, CHART OF SUBJECT MATTER ELIGIBILITY COURT DECISIONS, https://www.uspto.gov/sites/default/files/documents/ieg-dec-2016-sme_crt_dec.xlsx [https://perma.cc/2L2M-BU6Z], (last visited March 22, 2017).

On May 4, 2016, the PTAB issued updated guidance to patent examiners on subject matter eligibility.[57] The instructions required examiners to articulate a reasoned rationale for any 35 U.S.C. § 101 rejections under both steps of the *Alice* and *Mayo* test.[58] These require the examiner to identify specific claim limitations in support of a rejection under both steps of the two-step analysis.[59] Additionally, the instructions establish that best practice for patent examiners is to cite the appropriate court decisions that support their conclusions.[60] Given that there are few cases that specifically govern diagnostic patents, the USPTO also provided subject matter eligibility guidelines for life science claims with the caveat that the examples are intended to show exemplary analysis and should not be the basis for a subject matter claim.[61]

The USPTO also issued a 2016 update to its "Index of Eligibility Examples" as well as an index of "Subject Matter Eligibility Court Decisions."[62] The USPTO guidance offers two life sciences examples provided of claims construction together with an analysis of the patent eligibility of those claims. First, a pigeon flu virus vaccine with claims construction listed as follows:

> Claims
> 1. A vaccine comprising live attenuated Pigeon flu virus.
> 2. A vaccine comprising inactivated Pigeon flu virus.
> 3. A vaccine comprising: Peptide F; and
> 4. A vaccine comprising: Peptide F; and
> a pharmaceutically acceptable carrier selected from the group consisting of a cream, emulsion, gel, liposome, nanoparticle, or ointment
> 5. A vaccine comprising: Peptide F; and
> an immuno-effective amount of an aluminum salt adjuvant.

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57. Robert W. Bahr, *Formulating a Subject Matter Eligibility Rejection and Evaluating the Applicant's Response to a Subject Matter Eligibility Rejection*, U.S. PATENT & TRADEMARK OFFICE (May 4, 2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-memo.pdf [https://perma.cc/352J-52TD]. *See generally* May 2016 Subject Matter Eligibility Update, 81 Fed. Reg. 27381 (May 6, 2016); July 2015 Update on Subject Matter Eligibility, 80 Fed. Reg. 45429 (July 30, 2015).

58. Bahr, *supra* note 57, at 1.

59. *Id.* at 2.

60. *Id.* at 2–3. *See* U.S. PATENT & TRADEMARK OFFICE, EXAMINATION AND TRAINING MATERIALS: BEST PRACTICES IN EXAMINATION (Jan. 3, 2017), https://www.uspto.gov/patent/laws-and-regulations/examination-policy/examination-guidance-and-training-materials (last visited March 22, 2017) [https://perma.cc/XYD3-ZKJ5].

61. *See* U.S. PATENT & TRADEMARK OFFICE, SUBJECT MATTER ELIGIBILITY EXAMPLES: LIFE SCIENCES (2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf [https://perma.cc/WAK5-Q6XZ] (last visited March 22, 2017)

62. *Id.*

> 6. A vaccine comprising: Peptide F;
> an immuno-effective amount of an aluminum salt adjuvant; and a pharmaceutically acceptable carrier.
> 7. A vaccine delivery device comprising a microneedle array that is coated with a vaccine comprising Peptide F. [63]

According to the USPTO best-practice analysis, Claims 1-2, and 4-7 were patent eligible, but Claim 3 was patent ineligible because, while there is no naturally occurring counterpart in nature, there is no indication that mixing these components changes the structure, function or other properties of the peptide or water.[64]

In contrast to Claim 3, Claim 5 was patent eligible because Peptide F and the adjuvant (e.g., aluminum phosphate) do not occur naturally together in nature, there is no naturally occurring counterpart mixture for comparison, and the mixture is different than the mere "sum" of the immunogenicity of its components.[65] When combined, the resultant mixture has an enhanced immunity of eighty percent seroprotection rate with respect to the virus.[66] The mixture's alteration in immunogenicity is a marked difference compared to the two items as they appear separately in nature (which has a poor immunogenicity of thirty percent).[67] Therefore, because the claims are not directed to a "product of nature exception," the claims qualify as patent eligible subject matter.[68]

The second example provided is a patent for Diagnosing and Treating Julitis.[69] Generally, it is diagnosed by physical observation during a medical examination.[70] However, it is commonly mistaken for other rashes caused by Rosacea; indeed, doctors often misdiagnose it as Rosacea which has a different treatment altogether.[71]

The applicant disclosed a method of detecting Jul-1 and using anti-Jul-1 antibody, which may use naturally and non-naturally occurring (porcine

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63. *Id.* at 2–3.

64. *Id.* at 3–4, 5–8.

65. *Id.* at 7.

66. *Id.*

67. *Id.*

68. *Id.* at 5–7 (quoting *Myriad Genetics*, 133 S. Ct. at 2117 (2013)) (explaining that the bacterial mixture of "Funk Brothers" was not patent eligible because the patent holder did not alter the bacteria in any way).

69. *Id.* at 9. Julitis is an auto-immune disease that affects more than 17 million people in North America and causes chronic inflammation of the skin resulting in itchy and extremely painful rash on the face, hands, and feet. *Id.*

70. *Id.*

71. *Id.*

antibodies)[72] to diagnose the disease.[73] The claims construction of the invention is as follows:

> 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.
>
> 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 a porcine anti-JUL-1 antibody and detecting binding between JUL-1 and the porcine antibody; and
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.
>
> 3. 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.
>
> 4. 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 antibody mAb-D33 and detecting binding between JUL-1 and antibody mAb-D33; and
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.
>
> 5. A method of diagnosing and treating julitis in a patient, said method comprising:

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72. *See generally*, Corinna Lau, et al., *Chimeric Anti-CD14 IGG2/4 Hybrid Antibodies for Therapeutic Intervention in Pig and Human Models of Inflammation*, 191 THE JOURNAL OF IMMUNOLOGY 191, 4769–4777 (2013), found at http://www.jimmunol.org/content/jimmunol/191/9/4769.full.pdf (discussing how porcine anti-bodies are non-naturally occurring in humans, but are useful in the detection of an immune response to a disease, and thus the detection of various inflammatory markers of disease) [https://perma.cc/DWN2-LQFA].

73. *See* SUBJECT MATTER ELIGIBILITY EXAMPLES *supra*, note 61, at 10.

a. obtaining a plasma sample from a human patient;
b. detecting whether JUL-1 is present in the plasma sample;
c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is
detected; and
d. administering an effective amount of topical vitamin D to the diagnosed patient.

6. A method of diagnosing and treating 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;
c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is
detected; and
d. administering an effective amount of anti-tumor necrosis factor (TNF) antibodies to the diagnosed patient.

7. A method of treating patients with julitis, the method comprising administering an effective amount of anti-TNF anti-bodies to a patient suffering from julitis.[74]

According to the USPTO best-practice guidance, the following claims are patent eligible: claims 1 and 3-7, while claim 2 is ineligible.[75] Claim 1 is eligible because, as a drug,[76] the anti-Jul-1 anti-body does not fall under the natural law exception discussed in *Mayo* and although the plasma is present in the sample, the claim on the whole, is not focused on the plasma product.[77] Therefore, the two-step analysis set by the *Alice* and *Mayo* test need not be performed.[78] Claim 2 is ineligible because it is aimed at a process that centers on the consequence of a law of nature that is the correlation or relationship between the presence of the Jul-1 in a patient's plasma and the present of julitis in a patient.[79] Claim 2 the essence of naturally occurring process and law of nature discussed in *Mayo.*

74. *Id.* at 10–11.

75. *Id.* at 11–15.

76. Here, "drug" comprises naturally occurring and or synthetically derived chemical compounds, which when injected or digested, have an effect on the human body, but are not naturally present in the body. Cambridge Online Dictionary, found at https://dictionary.cambridge.org/dictionary/english/drug [https://perma.cc/73GU-MQ9L].

77. SUBJECT MATTER ELIGIBILITY EXAMPLES *supra,* note 61 at 11.

78. *Id.* at 11.

79. *Id.*

II. RESOLUTION

Inferences can be drawn about the patentability of medical diagnostic patents, lessons learned from Prometheus, and subsequent patent decisions after *Mayo*. Namely, patent prosecution must adequately capture a novel transformative process to enable a diagnostic patent to secure a Notice of Allowance ("NOA"). Perhaps the Prometheus patent could have been saved by use of more creatively drafted patent claims that captured the novel mathematical processes, or the sensitivity and specificity of the lab work using normative data to establish the novelty of the method as in the case of *Ameritox*.

The probability of survival of a medical diagnostic patent under the *Mayo* framework, (e.g. process patents that involve laws of nature must be transformative in a meaningful and substantial way), requires more nuanced work on the patent prosecution side to ensure a NOA. Patent prosecution of medical diagnostic patents must accurately capture the novelty of the transformative process involved.

The second issue involves patent defense during claims construction. In order to ensure that a medical patent is not Dead on Arrival ("DOA") in federal court during patent litigation, the patent must contain a detailed explanation of the novel transformative process. Subject matter eligibility and claims construction challenges cannot begin and end with laws of nature. This may require patent prosecutors to educate themselves on the unique study designs and unique methods used early in the development stages of the disclosed invention. A detailed comparative analysis using normative data can ensure the survival of the independent patent claims. Statistical analysis and treatment algorithms may also be very valuable to distinguish the novelty of the accuracy of a proposed diagnostic test.

Congress intended that novelty applied to laws of nature would result in patentability. Issues with patent prosecution of medical diagnostic patents result in the lack of clarity of the novelty and transformation of laws of nature into a patentability. *Mayo* and its progeny have not provided a bright-line rule on how to prosecute claims to ensure patentability. However, if we examine the cases carefully, they provide insight *into what not to do*, and what to do to strengthen the patents chances of a NOA during prosecution and prevent invalidity (DOA) during claims construction. Therefore, increased care during prosecution may allow these patents to survive novelty, law of nature, transformation tests that *Mayo* and its progeny have imposed.

Whether the PTAB has added any insight to the patentability of medical diagnostic patents is still open for debate. The USPTO has offered guidance in this past year that offers a checklist of sorts to avoid invalidity claims. Proper prosecution should capture the transformation of the law of nature that reflects

a novel use. A careful study of the differences between a particular diagnostic test, examining what provides novelty over other tests or processes, is key.

CONCLUSION

In conclusion, patent prosecution can no longer be a recitation of broad claims 1-57 with the term "comprising" and "applied to." Patent prosecution of medical diagnostic patents must strive to understand the whole diagnostic process and the basis for the reliability, validity, sensitivity and specificity of the particular test as compared to what is known in the art. Claims themselves cannot be centered on the naturally occurring phenomenon like plasma, BRCA genes, blood cells, or principles of pharmacokinetics. Claims construction should not begin and end with the naturally occurring phenomenon, the patient, or the patients' cellular or physical reaction to the diagnostic test, but with a description of the *non-naturally* occurring process or transformative method that is being used as the means to more accurately detect and natural reaction to that created stimulus.

Unfortunately, the USPTO guidance does not offer examples of medical machinery diagnostics but is largely focused on vaccine or immune therapies that have a non-natural impetus that avoids the stickiness of the *Mayo-Alice* two-step. As we can see in the three medical diagnostic patents discussed, a critical step to survival is patent prosecution. *Mayo* had a chilling effect on the medical diagnostic patent industry. Increased care at the level of patent prosecution, and perhaps with an eye toward increased disclosure of a procedural algorithm or mathematical formula, or indicia that captures the unique individual patent reaction to the test, should be utilized in order to prevent a declaration of DOA during invalidity litigation at the district court, PTAB or Federal Circuit level.

APPENDIX

Prometheus Patent Claims Construction

The ‘623 patent had the following claims… We 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 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

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

2. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is inflammatory bowel disease (IBD).

3. The method of claim 2, wherein said subject having IBD is a pediatric subject.

4. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

5. The method of claim 1, wherein said level of 6-thioguanine is determined in red blood cells.

6. The method of claim 5, wherein said level is determined using high-pressure liquid chromatography.

7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

8. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is IBD.

9. The method of claim 8, wherein said subject having IBD is a pediatric subject.

10. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

11. The method of claim 7, wherein said toxicity associated with said drug treatment is hematologic toxicity.

12. The method of claim 7, wherein said toxicity associated with said drug treatment is hepatic toxicity.

13. The method of claim 7, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

14. The method of claim 13, wherein said level is determined using high-pressure liquid chromatography.

15. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

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

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

wherein the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

16. The method of claim 15, wherein said immune-mediated gastrointestinal disorder is IBD.

17. The method of claim 16, wherein said subject having IBD is a pediatric subject.

18. The method of claim 15, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic

colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

19. The method of claim 15, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

20. The method of claim 19, wherein said level is determined using high-pressure liquid chromatography.

21. The method of claim 15, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and

(b) determining the level of 6-thioguanine in said subject having said non-IBD autoimmune disease,

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

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

23. The method of claim 22, wherein said level of 6-thioguanine metabolite is determined in red blood cells.

24. The method of claim 23, wherein said level is determined using high-pressure liquid chromatography.

25. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

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

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000

pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

26. The method of claim 25, wherein said immune-mediated gastrointestinal disorder is IBD.

27. The method of claim 26, wherein said subject having IBD is a pediatric subject.

28. The method of claim 25, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

29. The method of claim 25, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

30. The method of claim 29, wherein said level is determined using high-pressure liquid chromatography.

31. The method of claim 25, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

32. The method of claim 1, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

33. The method of claim 7, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

34. The method of claim 15, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

35. The method of claim 22, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

36. The method of claim 25, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

37. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptoriboside to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine or 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder;

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

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

38. The method of claim 37, wherein said drug is 6-mercaptopurine.

39. The method of claim 37, wherein said drug is azathioprine.

40. The method of claim 37, wherein said immune-mediated gastrointestinal disorder is inflammatory bowel disease (IBD).

41. The method of claim 40, wherein said subject having IBD is a pediatric subject.

42. The method of claim 37, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

43. The method of claim 37, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

44. The method of claim 43, wherein said level is determined using high-pressure liquid chromatography.

45. The method of claim 37, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

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-methyl-mercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptoriboside, said subject having said immune-mediated gastrointestinal disorder;

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

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

47. The method of claim 46, wherein said drug is 6-mercaptopurine.

48. The method of claim 46, wherein said drug is azathioprine.

49. The method of claim 46, wherein said immune-mediated gastrointestinal disorder is IBD.

50. The method of claim 47, wherein said subject having IBD is a pediatric subject.

51. The method of claim 46, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

52. The method of claim 46, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

53. The method of claim 52, wherein said level is determined using high-pressure liquid chromatography.

54. The method of claim 46, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.