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Patentability of Diagnostic Methods in the United States and Abroad – Part I

By Jacquelyn Pariseau, Hadia S. Ahsan, Haley S. Ball, Shoshana Marvin and Gaby L. Longsworth

Patenting diagnostic methods poses a unique challenge to U.S. patent practitioners.

"Section 101" of the Patent Act, 35 U.S.C. §101, defines four statutory categories of subject matters eligible for U.S. patents: "[w]hoever 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." While this article focuses on diagnostic methods because the majority of 101 case law has developed around these technologies, we expect current and future 101 case law to affect the development of many other critical technologies, such as the development of sensor technology, artificial intelligence, and personalized medicine.

Section 101 is subject to "judicial exceptions," which preclude certain subject matter from patent eligibility; abstract ideas, laws of nature, and natural phenomena are not patentable. Navigating where diagnostic methods fit within Section 101 and its judicial exceptions can be challenging for applicants and practitioners. Nonetheless, it is vitally important for innovators of diagnostic methods and techniques to protect their intellectual property. In the Unites States, the tension between Section 101 and the judicial exceptions has played out with a patchwork of case law outlining the limited avenues to patentability for diagnostic methods.

Diagnostic methods often occupy a gray area in ex-U.S. jurisdictions as well. Some countries employ a similar approach as the United States, while others statutorily exclude certain diagnostic methods, e.g., methods of diagnosing human disease, from patentability. Practitioners who are well versed in ex-U.S.

Jacquelyn Pariseau, Hadia S. Ahsan, Haley S. Ball, Ph.D., Shoshana Marvin, M.Sc., and Gaby L. Longsworth, Ph.D., associated with Sterne, Kessler, Goldstein & Fox P.L.L.C., may be contacted at jpariseau@sternekessler.com, hahsan@sternekessler.com, hball@sternekessler.com, smarvin@sternekessler.com and glongs@sternekessler.com, respectively. The following persons contributed to the preparation of this article on their respective jurisdictions of expertise: Australia and New Zealand: Chris Vindurampulle and Naomi Pearce, Pearce IP; Canada: Selena Kim and Sarah Raja, Gowling WLG; Israel: Noam Blei and Tal Band, S. Horowitz & Co.; Brazil: Luiza Cotia, Roberto Rodrigues, and Rafaella Oliveira, Licks Attorneys; China: James Zhu and Yejun Wang, JunHe LLP; Europe: Alessandra Antonucci, Paolo Di Giovine, and Mario Pozzi, Società Italiana Brevetti S.p.A.; Sabine Agé, Hoyng Rokh Monegier; Koen Bijvank, Brinkhof; and Tobias Alexander Popp, Meissner Bolte (and also Germany); Japan: Yoichi Watanabe, Seiwa Patent & Law; Hideki Kodera, Shimizu Patent Office; Mexico: Eunice Lewis Velasco, Arochi & Lindner; UK and Europe: Alexander Crew and Gwilym Roberts, Kilburn & Strode LLP; South Korea: Jay J. Kim, Kim & Chang IP.

laws, however, can carefully draft diagnostic method claims to fit within the target jurisdiction's eligibility requirements.

This article summarizes the current landscape for subject matter eligibility of diagnostic methods in the United States and abroad.

THE SUPREME COURT'S *MAYO/ALICE* TEST

Since *Mayo Collaborative Services v. Prometheus Laboratories*[1] in 2012 and *Alice Corp. v. CLS Bank International*[2] in 2014, the Supreme Court has been applying a two-step test for determining whether subject matter is patent eligible. Step one asks whether the claimed invention is directed to one of the three judicial exceptions. If the answer is yes, step two asks whether the elements of the claimed invention, considered separately or in combination, contain an "inventive concept" that is "sufficient to ensure that the patent . . . amounts to significantly more than a patent upon the [judicial exception] itself." Important elements of the two-step test are discussed individually below.

Step One: The Judicial Exceptions

As noted earlier, abstract ideas, laws of nature, and natural phenomena are excluded from patent eligibility in the absence of an inventive concept that amounts to significantly more than the judicial exception itself.

Abstract Ideas

In re Board of Trustees of Leland Stanford Junior University,[3] the Federal Circuit held that the claimed invention was patent ineligible as a purely diagnostic claim directed to an abstract idea. The inventors claimed a computational method of determining which parent passed a specific gene to its offspring. The claim recited a "method for resolving haplotype phase" by processing allele data through multiple computational steps implemented by computer systems. The Patent Trial and Appeal Board (PTAB) found that the claims were directed to an abstract idea because the "steps for receiving and analyzing information, which humans could process in their minds, or by their mathematical algorithms, are mental processes within the abstract-idea category." Additionally, because the data collection, processing, storage, and output steps "did not go beyond the well-known, routine, and conventional," the independent claim was patent ineligible.

On appeal from the PTAB, the Federal Circuit confirmed the claim was patent ineligible.

On appeal from the PTAB, the Federal Circuit confirmed the claim was patent ineligible and merely provided already available genetic information after a series of routine mathematical steps.

Laws of Nature

In *Mayo Collaborative Services* (2012), the Supreme Court held that the recited diagnostic claims were unpatentable for "effectively claim[ing] the underlying laws of nature themselves."[4] The inventors discovered a correlation between the therapeutic efficacy of thiopurine drugs and a patient's resulting thiopurine metabolite levels after drug administration. High thiopurine metabolite levels suggested the drug dosage was too high and potentially toxic, while low levels suggested the drug dosage was too low to be effective. The claims at issue described a method of:

(1) Administering thiopurine drugs;

(2) Measuring the patent's resulting thiopurine metabolite levels; and

(3) Adjusting the dosage based on the resulting levels.

The Court held that the claims were unpatentable as directed to the underlying natural relationship between thiopurine drug metabolism and thiopurine metabolite levels, without involving any inventive or unconventional concepts.

Natural Phenomena

In *INO Therapeutics LLC v. Praxair Distribution Inc.*,[5] the Federal Circuit held that the claim at issue was not patent eligible because it was directed to a natural phenomenon and had no inventive concept. The inventors determined that newborns with left ventricular dysfunction (LVD) have an increased risk of pulmonary edema if administered inhaled

nitric oxide gas. The inventors observed that nitric acid causes an adverse event in the infants, and the claim recited a method of withholding nitric oxide from newborns with LVD. Specifically, the claim at issue recited:[6]

> 1. A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:
>
> (a) *identifying* … candidates for 20 ppm inhaled nitric oxide treatment…
>
> (c) *determining that a . . . patient* of the plurality *has left ventricular dysfunction*, so is at particular risk of increased PCWP leading to pulmonary edema upon treatment with inhaled nitric oxide . . . and
>
> (e) *excluding the second patient from treatment with inhaled nitric oxide*, based on the determination that the second patient has left ventricular dysfunction. . . .

The court reasoned that the claim covered a method in which "the body's natural processes [were] simply allowed to take place" and that, accordingly, the claim was directed to a natural phenomenon.[7]

The Federal Circuit held that claim 1 was not patent eligible because NR, a vitamin naturally present in cow milk, is a product of nature.

Like natural processes, natural products (even when isolated) are often not patent eligible. The claim at issue in *Chromadex Inc. v. Elysium Health, Inc.*,[8] recited a dietary supplement containing isolated nicotinamide riboside (NR). Specifically, the claim recited:

> 1. A composition comprising *isolated nicotinamide riboside* . . . wherein said composition is formulated for oral administration and *increased NAD^+ biosynthesis upon oral administration*.[9]

The Federal Circuit held that claim 1 was not patent eligible because NR, a vitamin naturally present in cow milk, is a product of nature. To reach its conclusion, the court compared the elements of claim 1 with the components of milk and held that the only difference between claim 1 and natural cow milk is that the NR is not isolated before being combined with other milk components. The court reasoned that milk and the claimed composition both "'increase[] NAD+ biosynthesis upon oral administration.'" Notably, the court distinguished its decision from *Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC*,[10] where it held that a method of using beta-alanine (a natural product) as a dietary supplement was patentable because the beta-alanine was present in "unnatural" concentrations that could "increase athletic performance in a way that naturally occurring beta-alanine [could not]."

Step Two: Inventive Concept

The second step of the *Mayo/Alice* test asks whether the claimed invention contains an "inventive concept" that is "sufficient to ensure that the patent . . . amounts to significantly more than a patent upon the [judicial exception] itself." This means that additional "inventive" elements of a claim may "transform" it into a patent-eligible application.[11] A discussion on inventive concepts is below.

Presence of an Inventive Concept

In *Illumina, Inc. v. Ariosa Diagnostics, Inc.*,[12] the Federal Circuit concluded that the claimed invention was patent eligible because the claim included an unconventional step. The claim at issue recited:[13]

> 1. A method, comprising: (a) extracting DNA comprising maternal and fetal DNA fragments from a substantially cell-free sample of blood plasma or blood serum of a pregnant human female; (b) producing a fraction of the DNA extracted in (a) by: (i) size discrimination of extracellular circulatory fetal and maternal DNA fragments, and (ii) *selectively removing the DNA fragments greater than*

> *approximately 300 base pairs*, wherein the DNA fraction after (b) comprises extracellular circulatory fetal and maternal DNA fragments of approximately 300 base pairs and less and a plurality of genetic loci of the extracellular circulatory fetal and maternal DNA fragments; and (c) analyzing DNA fragments in the fraction of DNA produced in (b).

In dicta, the court suggested that the size parameters Ariosa employed for separating cell-free fetal DNA (cffDNA) from maternal cell-free DNA were unconventional. The court stated there was no evidence demonstrating that "thresholds of . . . 300 base pairs were conventional for separating different types of cell-free DNA fragments" and stated, "conventional separation technologies can be used in unconventional ways."

In *Exergen Corp. v. Kaz USA, Inc.*, the Federal Circuit held that the claimed body temperature detector was patent eligible because, although the claim was directed to measuring a natural phenomenon (core body temperature), it recited an inventive concept.[14] The invention involved scanning a temperature detector across a patient's forehead, over the temporal artery, while a detector determined the peak temperature. The peak temporal artery temperature was then used to calculate the core body temperature. The court explained that this concept was inventive over prior art detectors because prior art detectors did not involve scanning across a target surface, taking multiple samples per second, or using a lateral scan rather than a pivoting scan. Therefore, the court concluded that the measurement method was not conventional, routine, or well-understood, and prior art temperature detectors did not provide the "unique combination of elements" that enabled the device to function. The court emphasized that the inventor successfully "transformed the process into an inventive application of the formula."

Absence of an Inventive Concept

In *Roche Molecular Systems, Inc. v. Cephied*,[15] the Federal Circuit determined that a method for detecting antibacterial-resistant *Mycobacterium tuberculosis* via conventional polymerase chain reaction (PCR) techniques was patent ineligible.[16] The claim at issue recited using PCR to detect mutations that conferred antibacterial resistance. Specifically, the claim recited:[17]

> 1. A method for detecting *Mycobacterium tuberculosis* in a biological sample suspected of containing *M. tuberculosis* comprising:
>
> (a) *subjecting DNA from the biological sample to polymerase chain reaction [PCR] using a plurality of primers* under reaction conditions sufficient to amplify a portion of a *M. tuberculosis* rpoB [gene] to produce an amplification product, wherein the plurality of primers comprises at least one primer that hybridizes under hybridizing conditions to the amplified portion of the [gene] at a site comprising at least one position-specific *M. tuberculosis* signature nucleotide selected, with reference to FIG. 3 (SEQ ID NO: 1), from the group consisting a G at nucleotide position 2312, a T at nucleotide position 2313, an A at nucleotide position 2373, a G at nucleotide position 2374, an A at nucleotide position 2378, a G at nucleotide position 2408, a T at nucleotide position 2409, an A at nucleotide position 2426, a G at nucleotide position 2441, an A at nucleotide position 2456, and a T at nucleotide position 2465; and
>
> (b) detecting the presence or absence of an amplification product, wherein the presence of an amplification product is indicative of the presence of *M. tuberculosis* in the biological sample and wherein the absence of the amplification product is indicative of the absence of *M. tuberculosis* in the biological sample.

The court held that the claims were directed to a natural phenomenon and lacked any inventive concept because they employed purely conventional techniques – PCR was already a well-known and commonly used method to detect gene mutations.

The court used similar reasoning in *Genetic Veterinary Sciences, Inc. v. LABOKLIN GmbH & Co. KG*,[18] in which the disputed claims involved a method of genotyping Labrador retrievers to determine if they were genetically predisposed to the canine disease Hereditary Nasal Parakeratosis. Specifically, the claim at issue recited:[19]

1. An in vitro method for genotyping a Labrador Retriever comprising:

a) obtaining a biological sample from the Labrador Retriever;

b) genotyping a SUV39H2 gene encoding the polypeptide of SEQ ID NO: 1[;] and

c) detecting the presence of a replacement of a nucleotide T with a nucleotide G at position 972 of SEQ ID NO: 2.

The method was deemed patent ineligible because it was directed to an application of the discovery of the "underlying natural phenomenon" and employed only conventional methods of genotyping that "have been around for years."

In *CareDx v. Natera, Inc.*,[20] the Federal Circuit held that a method for detecting transplant rejection or organ failure was invalid because there was no inventive concept. The method comprised:

(1) Isolating and genotyping a sample from a transplant recipient;

(2) Quantifying the levels of donor cell-free DNA (cfDNA) in the transplant recipient; and

(3) Diagnosing the transplant status based on the increase of donor cfDNA over time (where an increase in donor cfDNA over time was indicative of organ rejection, graft dysfunction, or organ failure).

Purely diagnostic claims continue to be held patent ineligible in the United States.

The Federal Circuit reasoned that the claims at issue were similar to those of *Ariosa* – collecting a bodily sample, measuring the cfDNA levels using conventional techniques, and using the natural correlation between heightened cfDNA levels and transplant health to identify a potential rejection. The Federal Circuit concluded that none of these steps were inventive and that the patent was invalid.

CONCLUSION

Purely diagnostic claims continue to be held patent ineligible in the United States. Practitioners should avoid typical diagnostic claim language unless they can incorporate an inventive concept that amounts to significantly more than a judicial exception into the claims. Method of treatment

Table 1. Summary of Patent Eligibility of Diagnostic Methods in the United States

Case	Claims Directed to	Patent Eligible (Y/N)	Reasoning
In re Board of Trustees of Leland Stanford Junior University (2021)	Abstract Idea	N	No inventive or unconventional concepts
Mayo Collaborative Servs. V. Prometheus Lab'ys, Inc. (2012)	Laws of Nature	N	No inventive or unconventional concepts
INO Therapeutics LLC v. Praxair Distributin Inc. (2019)	Natural Phenomena	N	No inventive or unconventional concepts
Illumina, Inc. v. Ariosa Diagnostics, Inc. (2020)	Method of Preparation	Y	Conventional technique used in an unconventional way
Exergen Corp. v. Kaz USA, Inc. (2018)	Natural Phenomena	Y	Inventive concept
Roche Molecular Systems, Inc. v. CEPHEID (2018)	Natural Phenomena	N	No inventive or unconventional concepts
Genetic Veterinary Sciences, INC. v. LABOKLIN GmbH & Co. KG (2019)	Natural Phenomena	N	No inventive or unconventional concepts
CareDx v. Natera, Inc. (2022)	Natural Phenomena	N	No inventive or unconventional concepts

claims remain patent eligible, but must include an affirmative administration step, and the claimed treatment regimen must be as specific as possible and directed to achieving a specific outcome. Finally, the Federal Circuit has suggested, in dicta, that inventive steps, which comprise using conventional techniques in unconventional ways, may be sufficient to transform patent ineligible subject matter into patentable subject matter at step two of the *Mayo/Alice* test. A summary of the U.S. cases discussed is provided in Table 1.

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Editor's note: The conclusion of this article will be published in the next issue of the *Intellectual Property & Technology Law Journal*.

Notes

1. Mayo Collaborative Servs. v. Prometheus Lab'ys, 566 U.S. 66 (2012).
2. Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. 208 (2014).
3. In re Bd. of Trs. of the Leland Stanford Junior Univ., 989 F.3d 1367 (Fed. Cir. 2021).
4. Mayo, 566 U.S. 66 at 92.
5. INO Therapeutics LLC v. Praxair Distrib. Inc., 782 F. App'x 1001(Fed. Cir. 2019).
6. U.S. Patent No. 8,795,741 B2
7. INO Therapeutics, 782 F. App'x at 1005.
8. Chromadex, Inc. v. Elysium Health, Inc., 59 F.4th 1280 (Fed. Cir. 2023), cert. denied, 144 S. Ct. 330 (2023).
9. U.S. Patent No. 8,197,807 B2.
10. Natural Alternatives Int'l, Inc. v. Creative Compounds, LLC, 918 F.3d 1338 (Fed. Cir. 2019).
11. Alice Corp., 573 U.S. at 217.
12. Illumina, Inc. v. Ariosa Diagnostics, Inc., 967 F.3d 1319 (Fed. Cir. 2020).
13. U.S. Patent No. 9,580,751 B2.
14. Exergen Corp. v. Kaz USA, Inc., 725 F. App'x 959 (Fed. Cir. 2018).
15. Roche Molecular Sys., Inc. v. Cepheid, 905 F.3d 1363 (Fed. Cir. 2018).
16. Roche Molecular Systems, Inc. v. Cepheid, 905 F.3d 1363 (Fed. Cir. 2018).
17. U.S. Patent No. 5,643,723.
18. Genetic Veterinary Scis., Inc. v. LABOKLIN GmbH & Co. KG, 933 F.3d 1302 (Fed. Cir. 2019).
19. U.S. Patent No. 9,157,114 B2.
20. CareDx, Inc. v. Natera, Inc., 40 F.4th 1371 (Fed. Cir. 2022).