Patent Eligibility of Diagnostic Gene Signature Method Claims

A claim strategy assuring the patent subject matter eligibility of diagnostic gene signature method claims is discussed in light of last year's Risen (Suzhou) Pharma Tech. Co. Ltd. v. Alzheon, Inc., No. PATENT 11,191,742 Patent Trial and Appeal Board (PTAB) decision and prevailing judicial precedent.

Over the past 12 years, U.S. Supreme Court's jurisprudence on patent subject matter eligibility has profoundly affected the eligibility of patents with claims drawn to biomarker/gene mutation diagnostic assays.

For example, in *Mayo Collaborative Servs v Prometheus Lab'ys* (2012),[i] the claims of the diagnostic patents-in-suit were drawn to processes that help doctors who use thiopurine drugs to treat patients with autoimmune diseases, determine whether a given dosage level is too low or too high. The U.S. Supreme Court ruled that the patents were invalid because they merely described the natural correlation between a drug's metabolite levels in the blood and its effectiveness.

A year later, in *Association for Molecular Pathology v. Myriad Genetics, Inc.*,[ii] the U.S. Supreme Court held invalid U.S. patents obtained by Myriad Genetics on tests aimed at detecting mutations in a patient's BRCA1 and BRCA2 genes and thereby assessing whether the patient had an increased risk of cancer. The Court concluded that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated."

In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* (2015)[iii], the Federal Circuit affirmed the invalidity of claims in Sequenom's U.S. Patent No. 6,258,540 ("the ′540 patent"), which were drawn to a method for detecting paternally inherited cell-free fetal DNA (cffDNA) in maternal plasma or serum. The Court concluded the claims were generally directed at detecting the presence of a natural phenomenon, cffDNA, in maternal plasma or serum. Even if the invention created an alternative for prenatal diagnosis of developmental genetic mutations in fetal DNA that avoided the risks of widely used techniques that took samples from the fetus or placenta, the detecting steps merely appended routine and conventional steps (PCR) to a natural phenomenon and therefore failed to provide any inventive concept. The claims of Sequenom's '540 patent were found to be invalid under 35 U.S.C. §101. Sequenom's petition for a writ of *certiorari* to the U.S. Supreme Court was subsequently denied.

After *Mayo*, *Myriad,* and *Ariosa*, any assay that relies on the detection of genetic mutations or gene expression profiles is likely to be construed as merely a "natural phenomenon" and hence unpatentable in the United States. The consensus at the time was that the court's rulings were a death knell to the U.S. diagnostics industry.[iv]

The timing was unfortunate. With the advent of personalized medicine, gene signature panels were fast becoming an integral part of a patient's clinical evaluation.[v] This was especially true in oncology, where biomarker and mutational analysis were becoming mainstream for the definitive diagnosis of different forms of cancer, the evaluation of

treatment outcomes, the surveillance for resistance to targeted therapies, and the selection of second-round therapies that are the most likely to be effective. Without patent protection, it was difficult to see how companies in the diagnostic space could attract the investment needed to bring these assays to market and stave off the inevitable competition.

To remedy the uncertainty around patent subject matter eligibility, the USPTO adopted the *Alice/Mayo* threshold framework, first enunciated by the U.S. Supreme Court for determining if a claim is patent eligible under 35 U.S.C. §101, and subsequently incorporated into MPEP §2106. Under this test, a diagnostic claim is first given its broadest reasonable interpretation and then analyzed to determine:

- Step 1: if the claim falls within one of the four enumerated categories of statutory subject matter recited in 35 U.S.C. §101 (i.e., process, machine, manufacture, or composition of matter)

- Step 2A, Prong 1: if the claim recites a judicially recognized exception, e.g., "laws of nature," "natural phenomena," and "abstract ideas,"

- Step 2A, Prong 2: if so, does the claim recite additional elements that integrate the judicial exception into a practical application?

This last step ultimately provided the rationale for how a diagnostic claim, such as those method claims in *Myriad* that on their face were unpatentable for reciting a judicial exception, could still be transformed into patentable subject matter with judicious wording of the claims that demonstrates the claimed invention is directed to a practical application of the judicial exception, and not the judicial exception itself.

This was precisely the strategy employed in *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*[vi] *Vanda's* U.S. Patent 8,586,610 (the '610 patent) related to a method of treating schizophrenia patients with iloperidone, wherein the dosage range was based on the patient's genotype. At high doses, iloperidone can induce QT prolongation, a potentially life-threatening heart rhythm disorder. Iloperidone levels *in vivo* are dependent in part on the ability of the enzyme cytochrome P450 2D6 ("CYP2D6") to metabolize the drug. Claim 1, therefore, includes a genotyping assay to determine if the patient's genotype indicates the patient has a lower cytochrome P450 2D6 ("CYP2D6") activity with a reduced ability to metabolize iloperidone. If so, the claim requires that the dose of Iloperidone be lowered to avoid cardiac toxicity.

Allowed claim 1 of the '610 patent requires:

> A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:
>
> determining whether the patient is a CYP2D6 poor metabolizer by:
>
> obtaining or having obtained a biological sample from the patient; and

performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and

if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and

if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day,

wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount greater than 12 mg/day, up to 24 mg/day.

Vanda brought an infringement action against *West-Ward Pharm. Int'l Ltd*, a manufacturer of a generic version of the drug iloperidone, following the submission of an abbreviated new drug application (ANDA) by *West-Ward Pharm* and paragraph IV certification asserting the invalidity of the '610 patent. After the District Court found in favor of the Plaintiff, *West-Ward* appealed to the Federal Circuit, arguing *inter alia* that the asserted claims were directed to patent-ineligible subject matter under 35 U.S.C. §101 because they were directed to a natural relationship between iloperidone, CYP2D6 metabolism, and Q.T. prolongation, and add nothing inventive to those natural laws and phenomena.

The Federal Circuit ultimately agreed with the patentee, *Vanda*, stating:

> In this case, the '610 patent claims are directed to a method of using iloperidone to treat schizophrenia. ***The inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, <u>but that is not what they claimed</u>***. They claimed an application of that relationship. Unlike the claim at issue in Mayo, the claims here require a treating doctor to administer iloperidone in the amount of either (1) 12 mg/day or less or (2) between 12 mg/day to 24 mg/day, depending on the result of a genotyping assay.[vii]
>
> (emphasis added)

So, where does this leave the patentability of method claims implementing the use of gene signature diagnostics?

A recent example illustrates the challenge facing patent practitioners. Pending independent claim 1 is reproduced below:

> A method for treating a cancer in a subject in need thereof comprising:
>
> a) obtaining a biological sample comprising tumor cells from an extracellular fluid or compartment of the subject;
>
> b) detecting in the biological sample whether a checkpoint blockade therapy

> responder gene signature is expressed, said gene signature comprising the following genes: AARD, ACP1, ACTR2, ACTR3, ACTR6, AIMP1, ANP32B, AP2M1, APIP, APOD, APOL6, ARF1, ATAD2, ATP5G3, B2M, C1orf43, CALM1, CCT3, CCT4, CCT5, CCT6A, CD44, CD46, CD74, CHCHD2, COA6, COPS2, COX7A2, COX7C, COX8A, CP, EBNA1BP2, EIF2AK2, EIF5, EPRS, EZH2, FKBP3, GBP1, GTF3A, H2AFZ, HDGF, HIST1H1D, HIST1H4C, HLA-B, HLA-C, HNRNPA2B1, HSBP1, HSP90B1, IFI16, IFI27, IFI44L, IFI6, IFIH1, IFIT3, IFNAR1, IL6ST, ISG15, LAMP2, LMAN1, MAPKAP1, MDH1, MED10, MGP, MRPL13, MX1, NDUFA1, NDUFA4, NDUFB2, NUCB2, OAZ1, PAICS, PALLD, PAPOLA, PARP1, PARP9, PDCD5, PDHX, PDIA6, PEG10, PGRMC1, PKIB, PPM1G, PPP1CB, PSMA3, PSMB8, PSME1, PSME2, PTGES3, RAN, RARRES1, RHOA, RSRC1, S100A6, SEC61B, SEC62, SIVA1, SLC38A1, SMARCA5, SNX6, SRP72, SSR3, SSR4, STMN1, TAP1, TCP1, TM4SF1, TMCO1, TMEM59, TMEM97, TMPO, TRAM1, TSPO, TXNL1, UBE2J1, UBL5, UCHL5, UQCRH, USP1, VBP1 and XAF1,
>
> wherein expression of the gene signature is associated with a tumor capable of responding or continuing to respond to a checkpoint blockade therapy; and
>
> c) treating the subject with a checkpoint blockade therapy if the checkpoint blockade therapy responder gene signature is expressed in the biological sample.

Even if the example claim above is ostensibly a method-of-treatment claim, the Examiner nevertheless rejected the claim under 35 U.S.C. §101 as being directed to an abstract idea and natural phenomenon. Specifically, the Examiner contended the "natural phenomenon" was the expression of genes (and gene signatures) present in biological samples, and the abstract idea was the correlation of the expression of the genes (and gene signatures) with the response to therapy. The Examiner further alleged the treatment steps were not only optional, but they failed to integrate the judicial exception(s) into a practical application. The Examiner concluded, "administering an F.D.A. approved checkpoint inhibitor cancer therapeutic, such as ipilimumab, to a subject with cancer is well-known, conventional and routine in the art." Thus, according to the Examiner, the claims do not recite something "significantly more" than the judicial exception(s); instead, the claims "simply inform" the natural phenomenon to one performing routine active method steps and do not amount to significantly more than the judicial exception(s).

After reviewing recent PTAB decisions, Risen (Suzhou) Pharma Tech. Co. Ltd. v. Alzheon, Inc., No. PATENT 11,191,742,[viii] appeared to be on point. Specifically, the Petitioner *Risen* challenged *inter alia* claim 1 of *Alzheon*'s U.S. Patent No. 11,191,742 as being drawn to a law of nature and, hence, patent ineligible under 35 U.S.C. §101.

Claim 1 of the '742 patent required:

> 1. A method of treating Alzheimer's Disease in a subject, the method comprising administering to the subject a pharmaceutical composition comprising [Val-APS] or a pharmaceutically acceptable salt thereof, in

an amount effective to reduce cognitive decline, ***only if*** the subject is determined to

(i) be APOE4/4 homozygous; and

(ii) have a baseline [MMSE] score of ≥22,

wherein the MMSE was performed within sixty days prior to the first administration of the composition.

(emphasis added)

In their analysis, the PTAB agreed with the patent owner that "the challenged claims of the '742 patent are **not** ***directed*** to patent-ineligible subject matter and that the challenged claims are more similar to those in *Vanda* than those in *Mayo* because the claims in *Vanda* required a treating doctor to administer a drug to a patient in different amounts depending on the result of a genotyping assay."

The Board acknowledged:

> Similar to *Vanda*, ***the challenged claims are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome***. *Vanda*, 887 F.3d at 1136. Thus, as in *Vanda*, the instant claims recite "treatment steps," in contrast to Mayo, where "the metabolite level in blood simply 'indicate[d]' a need to increase or decrease dosage." *Id*. at 1135. Therefore, even though the claims may involve the natural phenomenon of a certain patient population responding better to treatment with ALZ-801, ***the claims are not directed to patent-ineligible subject matter because they require the treating doctor to administer ALZ-801 in an effective amount to this specific group of A.D. patients in order to reduce cognitive decline. Accordingly, we find that the claims integrate the recited judicial exception into a practical application***.
>
> (emphasis added)

Given this ruling, example claim 1 was amended to mirror the language of the *Risen* claim:

> A method for treating a cancer in a subject in need thereof comprising
>
> ***administering*** to the subject a checkpoint blockade therapy ***in an amount effective to prevent or reduce the progression of the cancer***
>
> > **only if** expression of a gene signature is detected in a biological sample comprising the subject's tumor cells, wherein said gene signature comprises one or more genes chosen from AARD, ACP1, ACTR2, ACTR3, ACTR6, AIMP1, ANP32B, AP2M1, APIP, APOD, APOL6, ARF1, ATAD2, ATP5G3, B2M, C1orf43, CALM1, CCT3, CCT4, CCT5, CCT6A, CD44, CD46, CD74, CHCHD2, COA6, COPS2, COX7A2, COX7C, COX8A, CP, EBNA1BP2, EIF2AK2, EIF5, EPRS, EZH2, FKBP3, GBP1, GTF3A, H2AFZ, HDGF,

> HIST1H1D, HIST1H4C, HLA-B, HLA-C, HNRNPA2B1, HSBP1, HSP90B1, IFI16, IFI27, IFI44L, IFI6, IFIH1, IFIT3, IFNAR1, IL6ST, ISG15, LAMP2, LMAN1, MAPKAP1, MDH1, MED10, MGP, MRPL13, MX1, NDUFA1, NDUFA4, NDUFB2, NUCB2, OAZ1, PAICS, PALLD, PAPOLA, PARP1, PARP9, PDCD5, PDHX, PDIA6, PEG10, PGRMC1, PKIB, PPM1G, PPP1CB, PSMA3, PSMB8, PSME1, PSME2, PTGES3, RAN, RARRES1, RHOA, RSRC1, S100A6, SEC61B, SEC62, SIVA1, SLC38A1, SMARCA5, SNX6, SRP72, SSR3, SSR4, STMN1, TAP1, TCP1, TM4SF1, TMCO1, TMEM59, TMEM97, TMPO, TRAM1, TSPO, TXNL1, UBE2J1, UBL5, UCHL5, UQCRH, USP1, VBP1 and XAF1.
>
> (emphasis added)

Here, the administration of the checkpoint blockade therapy to the cancer subject in an amount effective to prevent or reduce the progression of the cancer is ***contingent*** on the detection of a specific gene expression signature in a biological sample comprising the subject's tumor cells. Claim 1, as amended, fully integrates the detection of the specific gene expression signature into the method of treatment by requiring that the checkpoint blockade therapy be initiated ***only if*** the specific gene expression signature is detected. Thus, the treatment is not optional. The amendment of example claim 1 was found to be sufficient to overcome the rejection under 35 U.S.C. §101.

The state of patentable subject matter eligibility in the U.S. was summed up by Federal Circuit Judge Lourie in his denial of an *en banc* rehearing in Athena Diagnostics, Inc. v. Mayo Collaborative Services,[ix] in which he stated "[a]ccordingly, as long as the Court's precedent stands, the only possible solution [to patent eligibility of diagnostic claims] lies in the pens of claim drafters or legislators. We are neither."[x]

From a legislative perspective, Congress may still provide a revised statutory framework to 35 U.S.C. §101 whereby diagnostic gene signature method claims are patent eligible. The bipartisan Patent Eligibility Restoration Act (PERA)[xi] recently introduced to the House of Representatives and the Senate would eliminate "all judicial exceptions to patent eligibility."

In its present form, revised section 35 U.S.C. §101 of the bill would require:

> "(a) In general.—Whoever invents or discovers any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, may obtain a patent therefor, subject only to the exclusions in subsection (b) and to the further conditions and requirements of this title.
>
> "(b) Eligibility exclusions.
>
> "(1) IN GENERAL.—Subject to paragraph (2), a person may **not** obtain a patent for any of the following, if claimed as such:
>
> > "(A) A mathematical formula that is not part of a claimed invention in a category described in subsection (a).

"(B) (i) Subject to clause (ii), a process that is substantially economic, financial, business, social, cultural, or artistic, even though not less than 1 step in the process refers to a machine or manufacture.

"(ii) The process described in clause (i) shall not be excluded from eligibility for a patent if the process cannot practically be performed without the use of a machine or manufacture.

"(C) A process that—

"(i) is a mental process performed solely in the human mind; or

"(ii) occurs in nature wholly independent of, and prior to, any human activity.

"(D) An unmodified human gene, as that gene exists in the human body.

"(E) An unmodified natural material, as that material exists in nature.

"(2) CONDITIONS.—For the purposes of subparagraphs (D) and (E) of paragraph (1), a human gene or natural material shall **not** be considered to be unmodified if the gene or material, as applicable, is—

"(A) isolated, purified, enriched, or otherwise altered by human activity; or

"(B) otherwise employed in a useful invention or discovery.

(emphasis added)

The PERA bill would, therefore, overturn in part Association for Molecular Pathology v. Myriad Genetics, Inc. by asserting "***unmodified human genes***" are not eligible for patenting, but genes that are "***isolated, purified, enriched, or otherwise altered by human activity***" or "***employed in a useful invention or discovery***" shall not be considered unmodified, and hence would be patent eligible.

Even in the absence of congressional intervention, a diagnostic gene signature method claim can be patent eligible if the claim language is carefully crafted to clearly convey that the method of treatment is contingent on the detection of a specific gene signature; as the U.S. Supreme Court wrote in Alice,[xii] "we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent eligible application. We have described step two of this analysis as a search for an "inventive concept"'— i.e., 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."[xiii]

Further discussion of patentable subject matter related to a particular treatment and prophylaxis in Step 2A Prong Two of the *Mayo/Alice* test can be found in MPEP §2106.04(d)(2) .

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[i] *Mayo Collaborative Servs. v. Prometheus Lab'ys, Inc.,* 566 U.S. 66, 79–80 (2012)
[ii] *Ass'n for Molecular Pathology v. Myriad Genetics,Inc.,* 569 U.S. 576, 583 (2013)
[iii] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.,* 788 F.3d 1371, 1373 (Fed. Cir. 2015)
[iv] Gordon J. The impact of Myriad and Mayo: will advancements in the biological sciences be spurred or disincentivized? (Or was biotech patenting not complicated enough?). Cold Spring Harb Perspect Med. 2014 Dec 11;5(5):a020917. PMID: 25502748.
[v] Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, Mountzios G, Wistuba II, Swanton C, Peters S. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024 Mar 28;187(7):1617-1635. PMID: 38552610.
[vi] *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd*., 887 F.3d 1117 (Fed. Cir. 2018)
[vii] *Id*. at 1135.
[viii] *Risen (Suzhou) Pharma Tech. Co. Ltd. v. Alzheon, Inc.,* Patent Trial and Appeal Board. PGR2022-00051 Patent No. 11,191,742 B2
[ix] *Athena Diagnostics, Inc. v. Mayo Collaborative Services, LLC,* 927 F.3d 1333 (2019)
[x] *Id*. at 1336
[xi] S.2140 - 118th Congress (2023-2024): Patent Eligibility Restoration Act of 2023 | Congress.gov | Library of Congress (https://www.congress.gov/bill/118th-congress/senate-bill/2140/text)
[xii] Alice Corp. Pty. v. CLS Bank Int'l, 134 S. Ct. 2347, (2014)
[xiii] *Id.* at 2355.