Take A Walk on the Bio Side:

Patent Eligibility of Biotechnological Inventions

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Recent court decisions regarding patent eligible subject matter have radically changed the availability of patent protection for biotechnology in the United States. While patent protection remains available for some biological materials and methods, it is clearly not available for many diagnostic and therapeutically significant inventions. More troubling is the challenge of discerning logically coherent principles to guide the identification of which technologies are patent eligible. Those engaged in patent prosecution continue to explore the extent to which claim drafting strategies can create eligibility out of chaos.

This paper offers an overview of the current state of patent eligibility and guidance for identifying patent eligible subject matter in biotechnology. Both case law and guidance provided by the United States Patent and Trademark Office (USPTO) are considered. Examples of claim strategies that have and have not succeeded in prosecution before the USPTO are provided.

Legal Basis for Subject Matter Eligibility: Plain Meaning With Exceptions

Section 101 of Title 35 of the United States Code provides the statutory definition of patent eligible subject matter:

> 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.[1]

Congressional intent of the scope of patentable subject matter under this Section was to include "anything under the sun that is made by man, but it is not necessarily patentable under section 101 unless the conditions of the title are fulfilled." S. Rep. No. 82-1979 at 5 (1952). This phrasing suggests a basic low threshold requirement for subject matter, with a reliance on other statutory provisions to limit patentability.

While this language is clear and unambiguous in its identification of the type of subject matter that can be patented, the courts have long held that certain exceptions to this list remain. These "judicial exceptions" to patent-eligible subject matter are laws of nature, abstract ideas, mathematical algorithms, and natural phenomena[2]. Under the guise of adhering to precedent by

[1] 35 U.S.C. §101.

[2] It is this author's personal view that these listed exceptions are not really exceptions, in that a claim that was truly to a product or law of nature would not be "made by man", and would also fail to meet the requirement for novelty

continuing to reference these exceptions using the same language, the courts in recent years have radically expanded the qualifications for what sort of products and processes are regarded as laws or products of nature and abstract ideas.

Biological Products: Myriad Interpretations

Many had considered any controversy about the patentability of biological subject matter to have been settled by a 1980 decision by the United States Supreme Court. That case, *Diamond v. Chakrabarty*, held that patent law does not distinguish between "living and inanimate things..." but rather between" products of nature, whether living or not, and human-made inventions."[3] *Chakrabarty* asserted that "anything under the sun that is made by man" may be patentable if it meets the Patent Office's legal requirements.

The Chakrabarty patent was not the first U.S. patent directed to recombinant DNA, nor was it the first U.S. patent on a living organism. Patenting of living organisms began with the patent for purified yeast cells that issued to Louis Pasteur in 1873.[4] Following *Chakrabarty*, more developments in biotechnical subject matter were patented. In 1988, the PTO issued the first patent for a transgenic animal, widely known as the "Harvard Mouse".[5]

The mere "discovery" of some product does not give rise to patentable subject matter unless the product was created, or manmade. In a 1931 case, *American Fruit Growers, Inc., v. Brogdex Co*., the court held that a patent on a fruit whose skin is impregnated with a chemical compound is not patentable because the fruit is not transformed into a new and different name, character, or use. [6] On the other hand, a known biological material has been held patentable if it is in a purified or concentrated form and thus not previously described. In 1970, in *In re Bergstrom*, the court said pure materials are by definition novel as compared to impure materials.[7] Thus, claims directed to purified prostaglandins were found patentable.

What was once considered settled law regarding the patentability of isolated DNA molecules became unsettled in 2013, with the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.* The Court held that Myriad Genetics' patent claims to isolated genomic DNA are not drawn to patent-eligible subject matter, while claims to complementary DNA ("cDNA") qualify as patent-eligible (the latter because the nucleotide sequences differ from those found in nature).[8] Myriad's patents claimed the isolated genes BRCA1 and BRCA2, which genes contain mutations that can be used to detect a person's predisposition to breast and ovarian cancer, as well as related DNA molecules and methods of

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under §102. Likewise, an abstract idea would not be a "process" under §101, and would likely fail the requirement in §112 for definiteness in claim language.

[3] 447 U.S. 303 (1980).

[4] U.S. Patent No. 141,072.

[5] U.S. Patent No. 4,736,866.

[6] "Addition of borax to the rind of natural fruit does not produce from the raw material an article for use which possesses a new or distinctive form, quality, or property. The added substance only protects the natural article against deterioration by inhibiting development of extraneous spores upon the rind. There is no change in the name, appearance, or general character of the fruit. It remains a fresh orange, fit only for the same beneficial uses as theretofore." *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), 11-12.

[7] 427 F.2d 1394 (C.C.P.A. 1970).

[8] *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

detecting the mutations and screening for relevant drugs.[9] The Court explicitly stated that the claims cannot be saved by the fact that a non-naturally occurring molecule is created by isolating DNA from the human genome and severing chemical bonds, noting that the claims did not recite the DNA in terms of a chemical composition, nor did the claims rely on the chemical changes that result from the isolation of a particular section of DNA.[10] This language leaves open the question of what effect the *Myriad* decision will have on other types of isolated biological material, such as proteins and peptides.

Method Claims: Hold the Mayo

The Supreme Court took the analysis of diagnostic method patent eligibility in a whole new direction with its 2012 decision in *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*[11] Remarkably, the *Mayo* Court characterized a correlation between the level of a non-natural thiopurine drug metabolite in a patient's blood and the optimal drug dosage for that patient as a "law of nature." Although this administration of drug requires human action, the relationship between the drug administration and the way the drug is metabolized by the body exists in principle apart from the human action.

The Court held that a method claim based on the discovery of a law of nature must incorporate an "inventive concept" above and beyond the newly discovered law of nature to be patent eligible. The steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity preciously engaged in by researchers in the field. The requirement for an "inventive concept" means the claimed method must also contain other elements or a combination of elements sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself. The Court also held that a method claim is patent ineligible if it "preempts" a newly discovered law of nature.

> Claim 1 of the Prometheus U.S. Patent No. 6,355,623 (now invalidated):
>
> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

[9] The BRCA1 and BRCA2 genes are referred to as the "breast cancer genes" (**BR**east **CA**ncer) because mutations in these genes correlate with an increased risk of breast cancer and ovarian cancer in women. The patents at issue include other DNA claims as well, such as cDNA and fragments of isolated genes with at least 15 nucleotides. The Court refers to "isolated DNA" as a separate category from the cDNA and the fragments.

[10] *Id.* at 14. Note the Court did not appear to understand that, when working with isolated DNA, one does not use literally the same DNA sequence that came from the natural source. Instead, the literally isolated natural DNA is amplified into a large number of copies ("clones"). Thus, recombinant proteins are made from copies of the natural sequence, typically cDNA, and do not use the original source DNA.

[11] *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 132 S. Ct. 1289, 1294 (2012).

wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

The Court took issue with each of the steps of the claimed method. The "administering" step was regarded as "simply refer[ring] to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs. That audience is a pre-existing audience; doctors used thiopurine drugs to treat patients suffering from autoimmune disorders long before anyone asserted these claims."[12] The "determining" step simply tells doctors to engage in "well-understood, routine, conventional activity." "Conventional or obvious" activity cannot transform unpatentable law of nature into patent-eligible application.[13]

Oh, *Diehr*, What Can It Mean?

Mayo does leave room for some diagnostic testing and personalized medicine method claims to remain patent eligible. Significantly, the Court did not overrule *Diamond v. Diehr*, a decision that found a method for operating a rubber molding press patent eligible.[14] The *Mayo* Court regarded the *Diehr* claims[15] as patent eligible because the *Diehr* majority never suggested that all the steps, or at least the combination of steps recited in the claims "were in context obvious, already in use, or purely conventional."[16] According to *Mayo*, "[t]hese other steps apparently added to the formula something that in terms of patent law's objectives had significance—they transformed the process into an inventive application of the formula.". The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the §101 categories of possibly patentable subject matter.

That said, *Mayo* seems to give *Diehr* a benefit of the doubt on whether the claimed method involved steps that were routine and conventional, and already in use, without seriously

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[12] *Id.* at 1297.
[13] *Id.* at 1298.
[14] 450 U.S. 175 (1981).
[15] Claim 1 of U.S. Patent No. 4,344,142:

A method of operating a rubber-molding press for precision molded compounds with the aid of a digital computer, comprising:

providing said computer with a data base for said press including at least,

natural logarithm conversion data (1n),

the activation energy constant (C) unique to each batch of said compound being molded, and

a constant (x) dependent upon the geometry of the particular mold of the press,

initiating an interval timer in said computer upon the closure of the press for monitoring the elapsed time of said closure,

constantly determining the temperature (Z) of the mold at a location closely adjacent to the mold cavity in the press during molding,

constantly providing the computer with the temperature (Z),

repetitively performing in the computer, at frequent intervals during each cure, integrations to calculate from the series of temperature determinations the Arrhenius equation for reaction time during the cure, which is where v is the total required cure time,

repetitively comparing in the computer at frequent intervals during the cure each said calculation of the total required cure time calculated with the Arrhenius equation and said elapsed time, and

opening the press automatically when a said comparison indicates completion of curing.

[16] *Mayo*, 132 S. Ct at 1299.

considering the very real likelihood that the method claimed in *Diehr* actually involved routine and conventional steps for operating a rubber molding press, save for the use of the Arrhenius equation to control the timing of the curing process. On the one hand, we can accept that the method of *Diehr* satisfactorily integrated the unpatentable equation into the series of steps in a manner that amounted to "significantly more" than merely claiming the unpatentable equation itself. On the other hand, a serious question can be raised about the ability of the claims found eligible in *Diehr* to pass the now-standard *Mayo-Alice* test.[17]

Go Ask Alice

The 2014 Supreme Court decision, *Alice v. CLS Bank*[18], dealt with a method of mitigating settlement risk, but has become the namesake of the current patent eligibility test applied across all subject matter, although primarily employed to invalidate patents and reject patent applications in the software and biotechnology arts. The *Alice* test (or *Mayo/Alice* test) is a two-part test that actually has three parts. In step one, the test asks whether the claims at issue are directed to one of the four statutory categories (process, machine, manufacture, or composition of matter). The second step asks whether the claim is directed to subject matter encompassing one of the judicial exceptions to patentable subject matter. In the second part of the second step, if the claims are directed to patent-ineligible subject matter, the Court must then 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.

Although the *Alice* Court did not define what constitutes an "abstract idea", this notion that a claim directed to an abstract idea is ineligible for patenting has since been applied widely to invalidate many patents.[19]

Adios, Ariosa

Ariosa Diagnostics, Inc. v. Sequenom, Inc.[20] provided the final nail in the coffin for hopeful interpretations of *Mayo* and its successors that the ineligibility disease would not spread beyond the "natural correlation" cases. The patent at issue here was directed to a break-through invention based on the discovery of cell-free fetal DNA in maternal blood. The invention applied this discovery to providing a rapid analysis of paternally-inherited fetal genes via amplification. The Federal Circuit felt obliged to analyze the claims under the *Mayo/Alice* test and concluded that the presence of fetal DNA in maternal serum is a natural phenomenon, and the recited steps of DNA isolation and amplification were conventional.

Even though the claimed method involved making use of material that, under "routine and conventional" practice, would have been discarded, and provided the key to a non-invasive, safer method for prenatal genetic testing, the recitation of routine process steps meant the claim was not patent-eligible. Instead of looking at the claim as a whole, which combined known

[17] See http://www.usptotalk.com/the-main-event-alice-v-diehr/ for a blog post by David Stein that lays out quite nicely this failure to pass the *Alice* test.
[18] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347 (2014).
[19] According to this blog post by Gene Quinn, http://www.ipwatchdog.com/2016/04/21/what-should-we-do-about-alice/id=68478/, 65.75% of patents challenged in the District Courts have been invalidated under Section 101, and 91% of patents before the Federal Circuit have been invalidated since *Alice*.
[20] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d (Fed. Cir. 2015).

techniques of amplifying genetic material with using what those skilled in the art considered waste (the non-cellular material that would have been discarded), the Federal Circuit looked at each element separately and found each one wanting. Most alarming about this approach is that it can be used to deconstruct any invention and conclude that it amounts to nothing more than applying routine and conventional steps to a method that is directed to a natural phenomenon. It seems the court could just have easily opted to consider the claim as a whole, and recognized the novelty of performing the amplification using previously discarded material as a patent eligible application of the inventive concept.

Alas, SOME Biotechnology Inventions Are Patentable

Myriad also dealt with method claims. While the methods of detecting BRCA mutations in patients or tumor samples were found ineligible, one method claim did pass muster. The ineligible method claims recited "analyzing" or "comparing" DNA sequences, which are considered "abstract mental processes" that are not patent-eligible. On the other hand, the claim directed to a method of screening potential cancer therapeutics was found patent-eligible. The eligible claim required growing a cell transformed with a BRCA mutation that causes cancer, and determining how a compound affects the growth rate of the transformed cell. The key was that the engineered cell is a patent-eligible composition of matter, and this transformed cell provided that something "more" than merely reciting a natural law and adding the words "apply it". Therefore, even if the screening steps recited in the method claim are "conventional," the method is patent-eligible.

Another Federal Circuit decision that found a biotechnology method patent-eligible was *Rapid Litigation Management Ltd. V. Cellzdirect, Inc*.[21] At issue were claims to a method for producing pure cultures of mature liver cells (hepatocytes) useful "for testing, diagnostic, and treating purposes."[22] The invention was based on an unexpected discovery that certain hepatocytes could be frozen and thawed repeatedly and remain viable. The claimed method overcame a problem in the prior art with low yield and an inability to use hepatocytes that had been subjected to more than one freeze-thaw cycle.

The method claims had been found invalid under §101 by the District Court based on the Mayo/Alice two-step analysis. The discovery that hepatocytes could be subjected to multiple freeze-thaw cycles was regarded as an ineligible law of nature. The routine, well-understood freezing process was regarded as failing to recite an inventive concept that would provide the necessary "something more" to survive step two of the *Mayo/Alice* test.

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[21] 827 F.3d 1042 (Fed. Cir. 2016).

[22] Claim 1 of U.S. Patent No. 7,604,929 recites:

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

The Federal Circuit vacated and remanded, having found that the District Court erred at step one of the *Mayo/Alice* test. The claims were not directed to an ineligible law of nature because they were not directed to the ability of hepatocytes to survive multiple freeze-thaw cycles. Instead, the claims are directed to a new and useful technique for preserving hepatocytes, achieving a "new and useful end", which the panel considered "precisely the type of claim that is eligible for patenting".

These claims were distinguished from those found ineligible in other recent cases (*Myriad III*[23], *Sequenom*[24], and *Merial*[25]), which were characterized as cases in which the natural law is used to identify genetic information, cell free DNA, or mutations using an "abstract mental process". Rather than simply observing or detecting the ability of hepatocytes to survive multiple freeze-thaw cycles, the patent claims result in a better way of preserving hepatocytes. The decision makes the point that this distinction between the natural ability of the subject matter to undergo the natural process and claims that are directed to that natural ability is the key to preserving patent eligibility for such methods as making a new compound or treating cancer with chemotherapy.

USPTO Approach: Markedly Different Molecules or Diagnosis With A Side of Treatment

Three key guidance documents relating to the USPTO's approach to evaluating biotechnology claims for patent eligibility have been released: two in 2014, and one in 2016 (plus some subsequent memoranda addressing more recent court decisions)[26]. The March 4, 2014 "Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena and/or Natural Products" was the first document in this series. According to the guidelines, a natural product must be "markedly different" from how it appears in nature to rise to the level of patent-eligible subject matter. It was revealed during a USPTO forum on May 9, 2014 that the USPTO's definition of "markedly different" required a difference in structure and that a difference in function will not suffice.

The December 15, 2014 Interim Guidance on Patent Subject Matter Eligibility ("Interim Eligibility Guidance") and Examples provided some examples of nature based products, and how such claims are to be analyzed. Notably, the examples include a section dealing with purified proteins, and makes the following point:

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[23] *In re BRCA1- and BRCA2-based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014).
[24] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d (Fed. Cir. 2015).
[25] Genetic Technologies Ltd. v. Laboratory Corp. of America Holdings, 818 F.3d (Fed. Cir. 2016), finding ineligible claim 1 of U.S. Patent No. 7,615,342:

> 1. A method to predict potential sprinting, strength, or power performance in a human comprising:
> a) analyzing a sample obtained from the human for the presence of one or more genetic variations in α-actinin-3 (ACTN3) gene;
> b) detecting the presence of two 577R alleles at the loci encoding amino acid number 577 of the α-actinin-3 (ACTN3) protein; and
> c) predicting the potential sprinting, strength, or power performance of the human, wherein the presence of two copies of the 577R allele is positively associated with potential sprinting, strength, or power performance.

[26] All of the USPTO guidance documents, including examples and memoranda, can be accessed at https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility.

> This example illustrates that changes in physical/chemical structure (claims 2-5) as compared to a product's natural counterpart can demonstrate markedly different characteristics, whether or not accompanied by changes in biological/pharmacological function or chemical/physical properties.[27]

In contrast to the previous position that a marked difference requires a structural difference, the Interim Eligibility Guidance makes it clear that a marked difference may be the result of a structural or functional difference. If the product is markedly different, then the claim does not recite a product of nature exception, therefore the subject matter is patent-eligible and it is not necessary to proceed to Step 2B.

In another departure from the previous procedures, claims that recite a judicial exception, but clearly do not seek to monopolize the judicial exception, are subject to a streamlined eligibility analysis, in which the markedly different characteristics analysis is not necessary. In this practitioner's experience, guidance phrased in terms of ascertaining whether a claim is seeking to monopolize a judicial exception results in quite variable examiner treatment of claims. All an examiner need do to reject a claim as seeking to monopolize a judicial exception is to narrowly define the judicial exception.

The next update to the USPTO's subject matter eligibility guidance was released in May 2016.[28] This update addresses the examination of claims for subject matter eligibility, taking into account the U.S. Supreme Court's decisions in *Alice Corp.*, *Myriad*, and *Mayo* and the Federal Circuit's decisions in *Enfish v. Microsoft Corp.*[29] and *TLI Communications LLC v. A.V. Automotive LLC.*[30] The guidance deals with rejections and applicant responses using the two-part *Mayo/Alic*e test as it applies in the life sciences. Examples are provided that concern vaccines, diagnostics, methods of treatment, and screening for genetic alterations. This set of examples is noteworthy in that it includes more claims that are considered to recite patent eligible subject matter.

Example 1's Takeaway: Make your natural products unnatural

The vaccine example includes a pair of claims to the virus, one to attenuated virus, and the other to inactivated virus. Both are deemed eligible as not directed to a judicial exception because these viruses differ from their naturally-occurring counterparts due to mutation or chemical alteration. All of the other vaccine claims in this example recite a "Peptide F" (a naturally-occurring peptide isolated from the flu virus) together with a carrier and/or aluminum salt adjuvant or as a coating on a microneedle array. Each is found eligible except for the one that fails to define a specific carrier. That one is ineligible because water is considered a pharmaceutically acceptable carrier, failing to add the requisite "something more" beyond the naturally-occurring peptide. The other claims are eligible because each recites a combination of substances that do not occur together in nature.

[27] MDC Examples (Nature-Based Products) at 5.
[28] https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-memo.pdf
[29] *Enfish LLC v. Microsoft Corporation*, 822 F.3d 1327 (Fed. Cir. 2016).
[30] 823 F.3d 607 (2016).

Example 2's Takeaway: Recite an unconventional assay or reagent

The next example addresses diagnosis and treatment of the hypothetical disease "julitis". The first four claims in the example are all directed to detecting/diagnosing julitis using routine and conventional methods of obtaining a plasma sample from a patient and detecting presence of the protein newly-discovered by the applicant and named "JUL-1" by contacting the sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody. In this example, the JUL-1 protein was not previously known, and the inventors created a new specific monoclonal antibody "mAb-D33" by injecting pigs with JUL-1. The introduction also tells us that the use of porcine antibodies to detect human proteins was not routine and conventional.

The only differences between claims 1 (eligible) and 2 (ineligible) of the julitis example are the preamble, and the addition of a third step to claim 2. Claim 1 is directed to a method of **detecting JUL-1** in a patient, comprising two steps: (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 the two. Claim 2 is directed to a method of **diagnosing julitis** in a patient, and adds step (c), "diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected." The USPTO's analysis notes that claim 1 does not recite or describe a judicial exception, so the analysis does not even reach the last step of the Mayo/Alice test in which one looks for "significantly more" than the judicial exception. Claim 2, one the other hand, describes and "is focused on" a correlation or relationship between the presence of JUL-1 in a patient's plasma and the presence of julitis. The analysis further notes that step (c) could be performed using mental steps, which are considered to represent abstract ideas.

The next two claims in the example are identical to claim 2, except that they recite the antibody to JUL-1 with more specificity. Claim 3 requires a porcine anti-JUL-1 antibody, and claim 4 requires the mAb-D33 antibody. Because each of these recites an unconventional step by using an antibody not routinely used by those in the field, the requirement for something "significantly more" than the judicial exception has been satisfied. Thus, if the method avoids reciting a disease condition or diagnosis, it is treated as merely a claim to an assay. If the claim does recite a disease condition or mention diagnosis, then it must involve reagents and/or steps that are not routine and conventional.

Two more claims appear in the julitis example that involve treatment of julitis. Claim 6 is structured like claim 2, except it recites merely detecting JUL-1 (without referencing an antibody) in the second step, plus it adds a fourth step of administering an effective amount of anti-TNF antibodies to the diagnosed patient. This last treatment step was regarded as known, but sufficed to provide the requisite something significantly more than the judicial exception because the judicial exception is integrated into the diagnostic and treatment process.

The last claim simply recites a method of treating a patient with julitis (no mention of detection or diagnosis), comprising administering an effective amount of anti-TNF antibodies to a patient suffering from julitis. This claim is treated as not directed to a judicial exception, and therefore eligible.

The remaining examples included with the May 2016 guidance provide either a further look at nature-based products (Example 3 dealing with artificial sweetener) or closely track claims that were addressed by the courts (see especially Example 4 dealing with screening for genetic alterations).

What's A Patent Prosecutor to Do? Or, How to Squeeze Blood from A Turnip

The examples provided by the USPTO in the May 2016 provide far more useful guidance than had been available for the last several years, as those in the biotechnology patent community waited for more clarification from the courts as to how one might extrapolate the holdings in *Mayo* and *Myriad* to more typical diagnostic claims. Although these examples provide some clear guideposts for articulating eligible diagnostic claims, those guideposts are only helpful in limited circumstances. For those diagnostic inventions involving novel reagents or very specific assay steps, drafting (or amending) claims to overcome eligibility rejections under Section 101 is fairly straightforward. Unfortunately for those seeking to protect their diagnostic inventions, most typical diagnostic developments can only be eligible for patenting if the claims are awkwardly converted into treatment claims, and even then, adding a treatment step offers a route to eligibility only where the treatment step itself is not routine and conventional.

For example, one may have discovered a wonderfully effective serum biomarker for detecting a disease that previously had been nearly impossible to detect without subjecting patients to costly and invasive procedures. The biomarker may be a true game-changer that opens up valuable new possibilities for saving lives and lowering medical costs, but if the biomarker is a known protein that has already been detected in a different context using routine and conventional methods (e.g., immunoassay, PCR), methods of detecting the marker and/or using that marker to detect or diagnose the disease cannot be patented. Adding a treatment step could make it eligible, but only if the specification discloses a treatment strategy that is specific to that disease and would not have been routine and conventional in the context of other diseases associated with that biomarker.

Of course, adding a treatment step to a diagnostic claim has serious drawbacks for the patentee. Whenever possible, patent claims should be drafted so that all method steps would be performed by a single party. Without a single party performing all steps, direct infringement will not occur. Even indirect infringement, such as inducement, requires that a single party perform all the steps. Practitioners can try to draft the claim so that the detection or diagnosis steps can be attributed to the same physician who administers the treatment (rather than a laboratory technician), but this may not be practical. For example, one might include steps that require ordering a diagnostic test and then administering the treatment, taking care to avoid phrasing that might be construed as mere "mental steps".

To ensure the treatment step suffices to provide the requisite "significantly more" than a judicial exception, the treatment step should be tailored to the condition being diagnosed and treated. Sometimes a simple recitation of "administering a treatment effective for X condition" may be enough, but often it is necessary to be more specific. For example, one can recite administering an inhibitor of X effective to reduce levels of X to below Y threshold. If the treatment is for a specific type of cancer, and the same biomarker is already known to be associated with another

type of cancer, the treatment step would have to be specific to the newly-discovered associated cancer and not overlap with a treatment already known for the other cancer.

Not all eligibility workarounds are disappointing, however. One strategy that has been successful is to employ a group of biomarkers together. If a group of three biomarkers employed together creates a useful diagnostic tool, and the same three markers have not been known to be useful together, then one can claim an assay kit comprising reagents specific to those three markers. This provides protection for a product claim, which is of greater value and easier to enforce. In addition, one can obtain method claims that recite use of the kit. Such a method claim would be in the style of eligible claim 1 of the USPTO's julitis example, and not subject to a rejection under Section 101 because it would not be directed to a judicial exception. Note that any mention of the target patient population or a disease condition is likely to lead to a rejection based on an assertion that the claim is directed to a judicial exception. Assay claims work because they are only directed to the assay itself, and not the purpose of the assay.

Another way to avoid having a claim characterized as directed to a judicial exception is to direct the claim to an unexpected result, such as the improved method of cryopreservation of hepatocytes that was the subject of the *CellzDirect* case.[31] This type of claim structure makes it easier to show that any underlying natural correlation has been integrated into the method steps. In contrast, the claims that recited steps of amplifying fetal DNA in the *Ariosa* case were considered directed to the judicial exception.

The remaining hazard with method claims directed to detection or diagnosis is use of language that is considered directed to an abstract idea. This has been found with "comparing" and "analyzing" assay results, which are regarded as "mental steps". Greater success can be found with method steps that require physical action or interaction between tangible objects or compositions.[32] A few examples of claims that have been recently allowed by the USPTO are provided below.

U.S. Patent No. 9,488,655:

> 1. A method of treating endometrial cancer in a subject comprising:
> (a) measuring binding of antibodies in a serum sample obtained from the subject, wherein the antibodies specifically bind three biomarkers consisting of transthyretin (TTR), apolipoprotein AI (ApoAI) and transferrin (TF) in the serum sample;
> (b) administering radiotherapy or chemotherapeutic drugs for endometrial cancer to the subject when a decrease is found in the measured three biomarkers of in the serum sample compared to the measurement of the three biomarkers in the normal sample.

U.S. Patent No. 9,315,867:

> 1. A method of detecting pancreatic cancer in a biological sample, the method comprising:

[31] *Rapid Litigation Management Ltd. V. Cellzdirect, Inc*. 827 F.3d 1042 (Fed. Cir. 2016).
[32] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d (Fed. Cir. 2015).

(a) contacting a detectably labeled nucleic acid probe with white blood cells in the sample, wherein the sample is blood, and wherein the probe specifically hybridizes with a palladin target nucleic acid; and

(b) detecting the palladin target nucleic acid that is abnormally expressed in a white blood cell in the sample,

wherein a detected level of palladin target nucleic acid that is at least about 0.4 log lower than a control level from normal white blood cells of the palladin target nucleic acid indicates that the sample is from an individual with pancreatic cancer, wherein the palladin target nucleic acid is a palladin mRNA that encodes the 90 kD isoform of palladin encoded by SEQ ID NO: 1, and wherein the probe is selected from SEQ ID NOs: 49-62 and complements thereof.

U.S. Patent No. 9,220,697:

1. A method of detecting a polymorphism in an EFHC1 gene in a human subject, comprising:

(a) providing a biological sample from a human subject, wherein the sample comprises all, or a portion of, an EFHC1 gene;

(b) contacting one or more labeled oligonucleotide probes under stringent hybridization conditions to the EFHC1 gene or the portion thereof, wherein each oligonucleotide probe is capable of hybridizing to a portion of the EFHC1 gene comprising the 330C>A or 763G>A polymorphism under stringent hybridization conditions but incapable of hybridizing to a portion of the EFHC gene that does not comprise the 330C>A and 763G>A polymorphisms under stringent hybridization conditions, wherein the EFHC1 gene comprises at least 85% sequence identity to SEQ ID NO: 3; and

(c) detecting hybridization of the one or more labelled oligonucleotides with the EFHC1 gene or the portion thereof under stringent hybridization conditions; (d) detecting a polymorphism in an EFHC1 gene in the human subject.

U.S. Patent No. 9,110,083:

1. A kit consisting of agents that specifically bind biomarkers, wherein the biomarkers consist of:

(a) transthyretin;

(b) transferrin; and

(c) apolipoprotein AI (ApoAI), and

(d) CA125

wherein the agents are polynucleotides or antibodies, wherein the polynucleotides are labeled with a detectable marker, and wherein the kit optionally further consists of at least one container for housing the agents and/or instructions for use of the agents for determining status of ovarian neoplasia in a test sample.

Markedly Different Materials

When it comes to patent protection for biological molecules and other natural products, patent eligibility requires more than isolation from its natural environment. There must be something markedly different between the product as it exists in nature and the product recited in the claim. This can be achieved by adding something to the molecule (e.g., an affinity tag or a heterologous sequence), altering the molecule (e.g., by mutation or chemical modification), or by requiring a particular level of purity or combining it with another ingredient in a composition. Care should be taken to ensure that a composition claim is requiring a combination of elements that does not exist in nature. Remember that water is considered a pharmaceutically acceptable carrier, and attention should be paid to how "pharmaceutically acceptable carrier" is defined in the specification.

Closing Thoughts

We have witnessed some big changes over the last few years, and there is no reason to expect that we will not continue to see changes in this area of law. Practitioners should keep in mind that what works for our patent filings today may not work for us a few years in the future during prosecution or enforcement. Do not assume that you cannot in the future obtain claims that are more valuable than what can be allowed in the current environment. We must also continue to draft our claims and specifications with the entire globe in mind, not just peculiarities of U.S. patent law. We are always one court decision, one legislative change, or one jurisdiction away from wishing we had written our patent applications differently. Keep it flexible!