LEGAL GENOME

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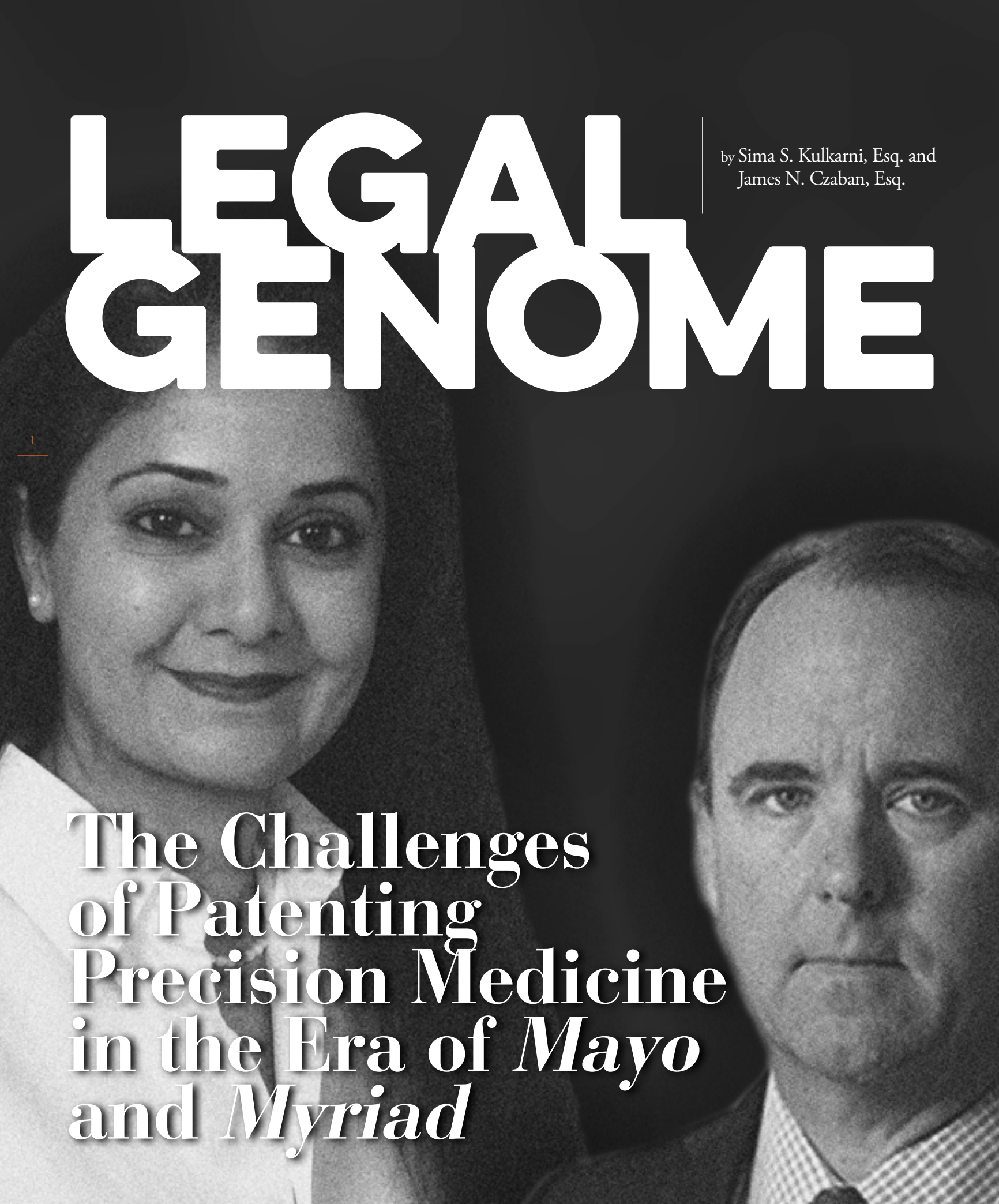

The Challenges of Patenting Precision Medicine in the Era of *Mayo* and *Myriad*

Breakthroughs in Precision Medicine do not grow on trees, although to read recent patent case decisions involving Precision Medicine, one might wonder whether the courts necessarily agree. Specifically, several landmark decisions of the U.S. Supreme Court and the U.S. Court of Appeals for the Federal Circuit have invalidated patents covering subject matter fundamental to developments in Precision Medicine, such as relationships between genetic variations and disease diagnoses or treatment. Like the protective function of bark on a tree or the seasonal cycle of leaves dropping in autumn, the identified clinical relationships have been characterized by courts as simply "laws of nature" or "products of nature" and therefore ineligible for patent protection. Of course, research in Precision Medicine has continued, at great cost in time, money, and effort, and the "laws of nature" analyses employed in some cases have not wholly prevented innovators from enjoying the benefits of patents on their discoveries. But the nuanced judicial application of the patent laws to Precision Medicine illustrates the importance of sophisticated crafting and positioning of Precision Medicine innovations to optimize their potential patent protection and commercial viability.

This article provides an overview of key recent patent law decisions and trends, and provides practical considerations for patenting strategies designed to avoid legal pitfalls in order to align the patentability of Precision Medicine discoveries with their most marketable elements.

I. THE ORIGINS OF PATENT RIGHTS AND THEIR IMPORTANCE TO PRECISION MEDICINE

The right to obtain patent protection for scientific inventions is deeply rooted in the U.S. Constitution, but is expressed in broad terms that leave implementation of the patent system and patentability standards to Congress, the United States Patent and Trademark Office ("USPTO"), and the courts. Article One, Section 8 of the Constitution provides that "Congress shall have power...[t]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." As a reward and incentive for inventors to develop and share the products of their intellectual endeavors, U.S. law provides inventors with a limited monopoly on their technology in the form of patents, which permit the inventor the "right to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States" for a term of 20 years from the date the patent application was filed. 35 U.S.C. § 154(a).

As is readily apparent to readers of the Journal, advances in technology, particularly in biotechnology, are occurring at an unprecedented rate. From drug design, to dosing regimens and cancer treatment, medicine and health care has become increasingly sophisticated transitioning from a macro to micro level of customization. As scientists and inventors continue to make significant progress, can we be sure that they are being provided with the appropriate incentives? Is current patent law adequately providing protection to their innovations, in a dependable and predictable way such that investors are willing to support commercialization efforts so that new products and therapies can successfully be delivered to those people that need them?

When it comes to Precision Medicine and intellectual property protection, many patent practitioners and industry members today will shake their heads and sigh with concern. In recent years, multiple significant court rulings have limited the scope of protection available to biotech and life science inventions, notably in the diagnostic and therapeutic space. From correlating genetic profiles with disease states, to customizing drug dosing regimens based on patient metabolite spectrums, courts have been unwilling to endorse the validity of patents claiming such subject matter, dismissing them as unpatentable and categorizing such inventions simply as natural phenomenon.

Proponents of these decisions applaud the results claiming that they allow health care providers to more freely practice their professions. Critics however, caution that such restrictions on patent eligible subject matter will ultimately result in diminished innovation and a reduction in investments, enabling fewer new products and slowing and weakening technological advancement. The field of biotechnology however is increasingly more refined and complex, and is progressing at a rapid pace with the potential to significantly and positively impact human life: it is imperative therefore, to ensure that an appropriate balance is struck whereby innovators are justly incentivized and rewarded, and patients can reap the benefits of today's medical advancements.

To illustrate where the Precision Medicine-patent law balance currently lies, and where it may be heading, in section II below we summarize the more noteworthy court decision from the past six years and their impacts on Precision Medicine. In section III we briefly discuss one of the most promising new areas of medical therapy, CAR-T, and its potential to avoid some of the pitfalls of the recent court decisions. And in section IV we offer some practical patenting strategies for Precision Medicine innovators and patent practitioners hoping to optimize the legal protection and commercial viability of their inventions.

II. INTO THE WOODS OF "LAW OF NATURE" PATENTABILITY DECISIONS – *MAYO v. PROMETHEUS* AND ITS OFFSHOOTS

Starting in 2012, with the landmark Supreme Court decision in Mayo v. Prometheus, innovators in biotechnology have been forced to navigate a confusing and treacherous path to both defend existing patents and to secure viable patent rights in newer inventions. Below we map out the key court decisions and the scientific contexts in which they were decided.

2012: Correlating Metabolites and Drug Dosing Regimens

In 2012 the Supreme Court decided a case that on its face, appeared to be a direct affront to the progress of Precision Medicine with regard to patent concerns. Specifically, the Court in *Mayo v. Prometheus*, 566 U.S. 66 (2012) (hereafter '*Mayo*') unanimously held that claims directed to a method of giving a drug to a patient, measuring metabolites of that drug, and then deciding to modify the dosage of the drug to meet parameters of a predetermined efficacy standard, did not constitute patent-eligible subject matter.

The two patents at issue, U.S. Patents No. 6,355,623 and No. 6,680,302, contained claims that recited methods of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of the drug in said subject, wherein the level of the drug below a certain threshold indicated the need to increase the amount of the drug and wherein the level of the drug above a certain threshold indicated the need to decrease the amount of the drug.

In arriving at the determination that the subject matter was patent ineligible, the Court categorized the correlation between the naturally-produced metabolites and therapeutic efficacy, as falling within the scope of natural law. The Court maintained that the act of isolating a metabolite and connecting it to the efficacy of a drug was not sufficiently transformative to move the activity away from simply being an observation of a law of nature. Furthermore, the Court stated that a process reciting a law of nature is patentable only if it recites "additional features that provide practical assurance that the process is more than a drafting effort to monopolise the law of nature itself". From the ruling in *Mayo* emerged a two-prong analysis for determining patentable subject matter: (1) are the claims at issue directed to patent-ineligible concepts (laws of nature); and (2) if yes, is there something "significantly more" in the claim to ensure that the claim is not merely covering just the ineligible concept.

The *Mayo* ruling has formed the foundation for many of the discouraging rulings that have followed. Not only has *Mayo* influenced (negatively) examination of patent applications subsequently filed, it has also resulted in the challenge of previously issued patents. Numerous issued patents have been invalidated as a result of rejections based on assertions of lack of patentable subject matter.

Though difficult to objectively quantify, the number of patent applications claiming subject matter related to inventions involving diagnostic discoveries seems to be declining, and if so, it is important to consider whether *Mayo* is undermining the goal of Article One, Section 8, and does it in fact diminish inventors' motivation to create, to pursue intellectual endeavors, and contribute to the advancement of Precision Medicine?

2013: Isolated DNA Sequences and Cancer Diagnosis

Within just one year of the *Mayo* decision, the Supreme Court again ventured into the world of patents, and in addressing patentable subject matter again, dealt yet another blow to the field of biotechnology and consequently Precision Medicine. In *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013) (hereafter '*Myriad*'), the Court ruled that claims directed to isolated DNA coding for a polypeptide associated with breast cancer, wherein the polypeptide has a specific (previously unidentified) amino acid sequence was not considered patent eligible subject matter because it was a product of nature. The fact that it had been isolated was insufficient to overcome the 'product of nature' hurdle.

In arriving at the *Myriad* ruling, the Supreme Court did not invalidate all the claims of the patents at issue, and Myriad Genetics attempted to continue to enforce the remaining claims, initiating infringement actions against several competitors. Ultimately however, a district court in Utah ruled that the remaining claims were also ineligible for patent protection, and Myriad finally decided to settle the pending lawsuits.

At issue in the Myriad case were the claims of seven patents, including U.S. Patent No. 5,747,282 ('282 patent). The main independent claim of the '282 patent was directed to an isolated DNA coding for a BRCA1 polypeptide, wherein the polypeptide was defined as having a specifically identified amino acid. Until this point, the USPTO had granted hundreds of patents on claims wherein the subject matter consisted of isolated biological components including DNA, amino acid sequences and proteins. Following *Myriad*, many such patents came under attack on invalidity grounds and again, inventors in this field were faced with a conundrum: should they continue their efforts, often built on decades of relentless pursuit of breakthrough scientific discovery, and if so to what end?

2015: Selective Detection of Fetal DNA for Predictive Analysis

The ability to patent isolated DNA was again dealt a serious blow in an important decision by the Federal Circuit in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). In this case, the invention consisted of a detection method performed on a maternal serum or plasma sample from a pregnant female, the method comprising the detection of a nucleic acid of fetal origin in the sample. An important and valuable aspect of the invention was that it enabled non-invasive prenatal diagnosis including for example sex determination, blood typing and other genotyping, and detection of pre-eclampsia in the mother. This testing methodology alleviated the risks of previously-available testing that was predominantly limited to amniocentesis, a methodology that could result in a miscarriage.

In arriving at its decision, the court relied on principles established in the *Mayo* ruling. Namely, the court found that the subject matter of the claim was not eligible for patent protection because the invention consisted of simply detecting a natural phenomenon. Furthermore, the court maintained that the invention did not demonstrate anything that was "significantly more" than the natural phenomenon and thus that the subject matter did not deserve patent protection.

The *Ariosa* decision highlights another risk with respect to highly innovative and highly disruptive new technologies such as Precision Medicine, namely, the fact that protection of inventive work can be undone years after the fact, and can disrupt settled commercial expectations. In this case, the patent application was originally filed in November 1999 and issued in July 2001 (prior to the rulings in both *Mayo* and *Myriad*), yet the Federal Circuit ruling invalidating a majority of the key claims did not occur until 16 years after the filing date, and 14 years after the USPTO had issued the patent.

2017: Genetic Profile and Treatment Determination

The *Mayo* decision has continued to have an impact in the Precision Medicine space, including more recently, when last year the USPTO's Patent Trial and Appeal Board (PTAB) affirmed an Examiner's decision rejecting the claims of application Serial No. 13/269,365 for lack patentable subject matter in *Ex Parte Timothy*. The claims of this application recited a method for identifying the presence of a genetic signature (the presence of a genotype comprising a homozygous genotype for the T allele at rs11960832 and either a homozygous or heterozygous genotype for the T allele at rs7975477), and treating a subject having that genetic signature with an antipsychotic treatment other than clozapine or quetiapine.

In arriving at its decision, the PTAB relied on *Mayo*, stating that in *Mayo* doctors were required to apply the law of nature (detection of drug metabolite) and then determine drug dosage, and this case, doctors were also required to apply the law of nature (determination of genetic signature) and then determine resistance to two specific drugs: as the court reasoned, "anyone who wants to make use of the natural law – the relationship between the OPRP genetic signature and the lack of efficacy of clozapine or quetiapine must first determine whether a given patient hasthe OPRP genetic signature before

determining which antipsychotic medication to treat them with. Thus, claim 1 amounts to nothing significantly more than an instruction to doctors to apply the applicable law [of nature] when treating their patients". This rejected application, like the invalidated patents in *Ariosa*, was filed prior to the *Mayo* decision which proved to be its undoing.

One noteworthy aspect of this case is that the correlation of the specifically claimed genetic profile with resistance to clozapine or quetiapine, was not known in the art prior to the invention. This correlation was not conventional, hence arguably outside of the scope of *Mayo*. In hindsight, and as a going-forward strategy, had the Applicant argued that the claims demonstrated that the invention was "significantly more" than just a natural phenomenon, the result might have been different.

Perhaps the strategic question to pose in similar circumstances should be: "is the correlation of natural phenomenon with a particular treatment something that is known, or something that is newly discovered?" Given the uncertainty with which these challenges are addressed, it is not possible to predict how the PTAB may have ruled. Going forward, however, applicants should keep in mind the totality of their discoveries, especially in the context of the second prong of analysis under *Mayo* wherein it may be possible to demonstrate that the invention is significantly more than simply a natural phenomenon.

2018: Is the Edge of the Forest in Sight?

In 2018, we see signs that the Federal Circuit may be softening its stance somewhat with regard to patent eligibility and the "law of nature" construct. Earlier this year, in *Exergen Corp. v. Kaz USA, Inc.*, Appeal No. 2016-2315, 2016-2341 (Fed. Cir., March 8, 2018), the Federal Circuit made a determination of patent eligible subject matter that may foreshadow a positive trend for Precision Medicine innovations going forward.

In this case, which did not involve Precision Medicine *per se*, the claims were directed to detectors and methods of using detectors to calculate a person's body temperature "by detecting the temperature of the forehead directly above the superficial temporal artery." The claims recited a radiation detector; and electronics that measure radiation from at least three readings per second of the radiation detector as a target skin surface over an artery is viewed, the artery having a relatively constant blood flow, and that process the measured radiation to provide a body temperature approximation, distinct from skin surface temperature, based on detected radiation. The device calculated the body temperature by applying a "constant coefficient" to skin and ambient temperature readings.

In making its determination, the Federal Circuit followed the two-part analysis established by *Mayo*. With regard to the first part, whether or not the claims are "directed to" a law of nature, it was determined that measuring temperature does indeed fall within the law of nature consideration. But, with regard to the second part of the analysis – whether there is "something more" amounting to an "inventive concept" that is not merely "routine, conventional, and well-understood" in the prior art – the court determined that it did indeed surpass the threshold of being merely routine: "Following years and millions of dollars of testing and development, the inventor determined for the first time the coefficient representing the relationship between temporal-arterial temperature and core body temperature and incorporated that discovery into an unconventional method of temperature measurement. As a result, the method is patent eligible…." The opinion further distinguishes both *Mayo* and *Ariosa* on the basis that the methods recited in those claims were routine, conventional and well understood.

Just a month after the *Exergen* decision, the Federal Circuit decided *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals Int'l Ltd.*, F.3d, 2018 WL 1770273 (Fed. Cir. April 13, 2018). In this case, the court considered claims directed to a method of treating schizophrenia with iloperidone, wherein the drug dosage administered is determined by the patient's genotype, and found the claims to contain patentable subject matter, unlike the claims in *Mayo*, because according to the court, Vanda's claims were specifically directed to the application of a drug to treat a particular disease. The opinion of the court described how method of treatment claims like Vanda's, unlike the claims in *Mayo*, "[were] of confined reach that limited preemption concerns and did more than simply tell engineers to apply a known natural relationship or to apply an abstract idea with computers."

Even more recently, on September 23, 2018 in a speech at the Intellectual Property Owners Association's meeting, U.S. Patent and Trademark Office Director Andrei Iancu announced that the Office is developing guidance for patent examiners aimed at providing "significantly more clarity" on when inventions are eligible for patenting. More specifically, he stated that the Office is "contemplating revised guidance" on what may be considered patent-eligible under Section 101 of the Patent Act. While he noted that any new proposal would take time to finalize, he also acknowledged that the current state of affairs concerning patent-eligibility is confusing and muddled. There is hope on the horizon, therefore, for improved direction in this area, and hope also for improved predictability in identifying patentable subject matter as it pertains to Precision Medicine.

In light of *Vanda* and *Exergen*, and the USPTO's guidance announcement, perhaps there is a reason to be optimistic: that given careful crafting of claim language and the evolving interpretation of *Mayo* by the Federal Circuit,

applicants seeking patent protection for their Precision Medicine inventions may have new strategies and renewed hopes for successfully navigating patentable subject matter eligibility challenges.

III. CAN IMMUNOTHERAPY ESCAPE THE WRATH OF MAYO?

A promising and rapidly developing branch of biotechnology involves immunotherapy methodologies using an approach called adoptive cell transfer (ACT). In essence, the technology comprises collecting and using patients' own immune cells to treat their cancer. There are several types of ACT approaches but thus far, CAR-T (chimeric antigen receptor T-cell therapy), has advanced the furthest in clinical development, including two FDA-approved therapies, Kymriah® (tisagenleceucel) for the treatment of both B-cell non-Hodgkin lymphoma (NHL) and B-cell acute lymphoblastic leukemia, and Yescarta® (axicabtagene ciloleucel) for treatment of diffuse large B-cell lymphoma (DLBCL).

CAR-T uses modified T-cell receptors consisting of binding factors such as antibodies located on the outside of a cell that are customized to bind to particular components (including ligands and antigens) on tumors. The process of treatment involves obtaining T-cells from a patient, customizing those T-cells to contain and display the desired receptor, and then infusing the modified T-cells back into the patient where they will multiply and attack the tumor. Preliminary anecdotal analysis suggests that CAR-T technology may not have the same types of "law of nature" patentability barriers as other Precision Medicine innovations have faced.

Patent applications related to many aspects of CAR-T immunotherapy have been filed, and several have been granted, including U.S. Patent No. 9,540,445 (composition comprising an anti-tumor effective amount of a population of human T cells); and U.S. Patent No. 9,855,298

(methods of increasing the efficacy of a T cell therapy in a patient involving preconditioning the patient by administering a combination of cyclophosphamide and fludarabine) Given the nature of these inventions, there appear to be few if any patent applications being challenged based on subject matter eligibility. For example, with regard to the first prong of the *Mayo* analysis, in the context of therapeutic methods based on the infusion of T-cells to a patient, though such cells are derived from a patient and are naturally occurring, the surfaces of the cells are altered by the modification and/or addition of receptors, and therefore typically meet the requirements of the "significantly more" or second prong of *Mayo*.

Perhaps certain aspects of innovation in this space may be more challenging to qualify for patent protection-for example, claims to a method of altering cell surface receptors, wherein the method is a regular molecular biology process, may be categorized as merely "routine and conventional" and therefore ineligible for protection. For many of the inventions being developed in this area however, there is likely to be a sufficient amount of innovation involved such that the inventions meet the threshold for subject matter eligibility.

IV. PRACTICAL PATENT STRATEGIES FOR PRECISION MEDICINE

Under current law discussed above, patent claims based on subject matter that may be categorized as "laws/phenomenon of nature" likely will face continued headwinds under the *Mayo/Myriad/Ariosa* line of cases despite decades of intellectual pursuit and significant financial investments that have already been expended to make such discoveries. In order to optimize the chances of successfully prosecuting patent applications in Precision Medicine, patent applicants would be well-served by focusing on the second prong of the *Mayo* subject matter eligibility test. Increased emphasis on the "significantly more" aspect of the invention should assist in addressing the eligibility requirements, and help to demonstrate how the invention is the result of actual and methodical discovery.

Specifically, when drafting a patent application, applicants should include as much information as possible beyond the

"law of nature" relationship aspect of the discovery to support the claims. Typically, as examination of a patent application progresses, claims are narrowed from broad embodiments to narrower embodiments, and in order for the USPTO to accept claim amendments, there must be support in the specification. (This is true in the United States and in most other international jurisdictions). Amongst other details, highlighting the dearth of comparable data and corresponding findings, may be especially useful. If possible, practitioners may want to have on hand access to similar studies conducted by other experts in the field that failed to yield similar results. Often times during patent prosecution, it is helpful to provide such comparative studies to the patent examiner to show how the applicant has succeeded, where others have failed.

In addition, wherever possible, it is advisable to describe the invention in terms that remove it from being classified as "merely routine" or "conventional." In the "Example" section of the patent application it is important to include explanations of successful methods and protocols that enabled the discovery of the claimed invention. Often times, inventors will gloss over the exact details of how certain protocols or methods were implemented, and often times patent practitioners may not request such information from inventors or include it in an application; however, it is vital to make sure that as many details as possible are in fact incorporated into the application.

The patent application drafting process is dynamic, and requires meaningful communication between the patent practitioner and the inventor. What may be considered 'routine' by the inventor, may not actually be 'routine' from a patentability perspective, and a skillful practitioner can facilitate the identification of such details. For example: it is possible that the temperature range at which a certain step was carried out was adjusted for a particular invention; it may be that PCR techniques were employed to facilitate the detection of particular peptide but that those techniques had to be modified in order to carry out the process; it may be that a certain biomarker is associated with a particular diagnosis, however, when several biomarkers are used in a panel in a particular combination under specific conditions, the rates and accuracy of detection are significantly improved. The range of potentially helpful experimental details is as varied as the inventions in Precision Medicine itself. It is important to capture as many details, and as many changes, no matter how subtle, that are made to conventional techniques.

In summary it is crucial to obtain as much detailed information from the inventor(s) regarding the method of discovery, the implications of the discovery and even comparative efforts by others in the field. It is important to incorporate as much relevant information as possible into the application so as have sufficient support for claims that can capture the nuances of the invention and thereby optimize the chances of overcoming subject matter eligibility challenges.

Conclusion

Over the past decade, courts and the USPTO have made it increasingly challenging for many inventions in the field of Precision Medicine to overcome the fundamental threshold of satisfying patent eligible subject matter requirements. In light of recent case law, as Precision Medicine technology continues to evolve, patenting strategies should as well, and in combination, these may further influence the courts' jurisprudence in ways that mitigate the barriers erected by *Mayo*, *Myriad* and related cases. ■

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