Procuring Personalized Medicine Patents In US Vs. Europe

Law360, New York (July 20, 2015, 9:56 AM ET) -- Personalized medicine has been interchangeably called precision, tailored, targeted or genomic medicine. Broadly speaking, personalized medicine is individualized medicine that customizes medical treatment to a patient’s genetic characteristics, previous treatment history, lifestyle, environment and/or preferences. Simply put, it provides the right patient with the right drug, at the right dose, at the right time.

For example, in cancer treatments, “personalized oncology” includes known cancer treatments like pharmacogenomics (the prediction of a drug response by studying variations of DNA and RNA characteristics in response to the drug) and tumor biomarker tests. Biomarkers and molecular individualized medicine provide “targeted therapies” to replace the traditional “one size fits all” treatment. In cancer treatment, there is a specific, unique genetic makeup that provides each tumor a unique character with unique responses and outcomes to treatment. Various cancer drugs such as Kalydeco (ivacaftor), Xalkori (crizotinib), and Mekinist (trametinib) that have been recently approved by the U.S. Food and Drug Administration, for example, are personalized drugs that target tumors with a specific genetic characteristic or mutation that are identified by a companion diagnostic test.

With the completion of the sequencing of the human genome and identification of new biomarkers, personalized medicine has entered a new era. New therapies and protocols that take into account the patient’s personal genetic information have emerged. By taking into account individual differences in disease diagnostic and treatment response, selective therapies for given individuals provide significant life extension, treatment efficiency by maximizing the effectiveness of the drug and minimizing side effects, and major cost reductions.

How the United States and Europe Have Addressed Personalized Medicine Patent Claims in Patent Applications

Advancements in personalized medicine center around targeted treatment of patients by the absence or presence of specific biomarkers, and on diagnostic methods for identifying patients with the biomarkers (i.e., the subpopulation group) by companion diagnostic tests. While these advancements are incredibly promising and provide great opportunities for patients, they pose some challenges to the inventors and their patent attorneys.

Generally, patent claims in personalized medicine applications may be directed to medical diagnostic methods (methods of diagnosing a specific disease or affliction), methods of using a specific drug on a patient or on a defined sub-population/sub-group of patients, and methods of dosage of a particular drug. Related claims may include methods of identifying the specific sub-population of patients, to the biomarker per se, or to primers for identifying the biomarker.
For example, a simplified, personalized medicine claim reads as follows:

Compound X for use in treating disease Y in a patient with biomarker Z.

Patent practitioners in the United States and Europe writing and prosecuting such patent claims face various issues regarding whether the claims qualify as patentable subject matter. For example, a question may arise as to whether treatment of a subgroup of patients (subpopulation) having biomarker Z will be patentable (and have novelty in Europe) if (1) the prior art is silent about patients having biomarker Z; (2) biomarker Z was previously unidentified but nonetheless present in some of the sub-group of patients that have disease Y; and (3) treatment of at least one patient having biomarker Z appears inevitable. Is a claim patentable and novel if it specifically limits medical treatment to a sub-group that is within a group (or overlaps with the group) that is known in the prior art?

As discussed below, current U.S. and European patent laws do not provide a uniform platform when addressing personalized medicine claims. In the United States, many patent claims related to personalized medicine are being challenged based on patentable subject matter, whereas in Europe, most claims are questioned based on novelty and inventive step.

**United States**

In the United States, two landmark decisions, Mayo Collaborative Services v. Prometheus Laboratories Inc., 132 S. Ct. 1289 (2012) (Prometheus) and Association for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 2107 (2013) (Myriad), addressing patentable subject matter for therapeutic treatments, personalized medicine diagnostic tools, and DNA sequencing, have resulted in new strategies for procuring patent coverage for inventions relating to diagnostic methods, biomarkers, and personalized medicine in general.

In Prometheus, the claims at issue were directed to methods of optimizing a patient’s dosage level of thiopurine drugs used to treat certain autoimmune diseases like Crohn’s disease.

Specifically, the Prometheus claims were directed to a method of optimizing therapeutic efficacy for treatment by administering a drug to a patient who has an immune-mediated gastrointestinal disorder, and determining the level of drug metabolites in the patient’s body, wherein, with a known threshold for efficacy in mind, the amount of drug metabolite detected indicated whether the dosage should be increased or decreased.

In a unanimous opinion, the U.S. Supreme Court found that these metabolic diagnostic claims for detecting a correlation between a metabolite and the likelihood of responding to a drug are unpatentable laws of nature. The court held that the first two of the claimed steps — administering a drug and analyzing a blood sample — were “well understood, routine, conventional activity already engaged in by the scientific community” at the time of the filing of the patent application.
Myriad addressed claims directed to (1) isolated DNA sequences including genes (e.g., BRCA1 and BRCA2 genes) and sequence-specific nucleic acid probes for detecting breast and ovarian cancer; (2) methods to diagnose propensity to cancer by looking for mutated DNA sequences; and (3) methods to identify drugs using isolated DNA sequences.

In Myriad, the Federal Circuit held that “isolated” DNA such as BRCA1 and BRCA2 genes were patentable subject matter, reasoning that these isolated molecules were “markedly different” new chemical structures that did not occur in nature.

With respect to Myriad’s diagnostic claims directed to comparing and analyzing DNA sequences for genetic diagnosis, the Federal Circuit found these claims noneligible subject matter as being directed to an abstract mental process that did not include any transformative step. If the claims were to recite specific transformative steps such as isolating, extracting, transferring, or sequencing of various samples, for example, then the claims would have had a better chance of being found patent-eligible claims. The Federal Circuit found, however, that screening claims for identifying potential anticancer therapeutics were patent-eligible as these claims recited active transformative steps, such as growing and determining, which amounted to more than an abstract mental step of comparing data.

In a unanimous decision, the Supreme Court invalidated Myriad’s claims to isolated genes and found that isolated DNA (molecules of isolated genomic DNA) was not eligible for patent protection, but that cDNA (“cloned” or “complementary DNA”) could be patented. The majority opinion written by Justice Thomas explained that “a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring.” Justice Clarence Thomas further reasoned that “separating that gene from its surrounding genetic material is not an act of invention” but that, in contrast, Myriad’s cDNA claims were eligible for patent protection because the “non-coding regions have been removed,” creating a new molecular structure not found in nature.

Following Myriad, the Federal Circuit concluded in In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation, 774 F.3d 755 (Fed. Cir. 2014) that claims directed to DNA primers used to bind the chromosomal section of the BRCA1 gene during PCR (the DNA-amplification process) are “likely drawn to ineligible subject matter.” In reviewing these claims, the Federal Circuit found that the “primers before us are not distinguishable from the isolated DNA found patent-ineligible in Myriad and are not similar to the cDNA found to be patent-eligible.”

Although the primers appeared to have been synthetically created through a laboratory process, the Federal Circuit explained that “it makes no difference that the identified gene sequences are synthetically replicated.”

With respect to the method of screening claims, the Federal Circuit held that claims directed to a particular method of screening for BRCA1 mutation by comparing a patient’s gene sequence with a germline BRCA sequence are also not patentable.
In reaching its decision, the Federal Circuit applied the two-step test from Mayo and Alice: (1) whether the asserted claims are directed to an abstract idea (methods directed to identification of alterations of the gene require a simple step of comparing a patient’s gene with the wild-type and identifying the differences which amounts to an abstract idea); and (2) whether there are any “non-patent-ineligible elements” sufficient to “transform the nature of the claim into a patent-eligible application.” Although the claims require various physical transformative steps such as hybridizing the gene probe; amplification of the gene; and sequencing the gene, the Federal Circuit held that these transformative steps are insufficient to transform the claim to patent-eligible application, because those steps “set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad’s patent applications” and a scientist would have relied upon these activities when comparing two gene sequences.

Subsequent to the Prometheus and Myriad decisions, the U.S. Patent and Trademark Office has implemented various examination guidelines for method claims directed to metabolic diagnostic. For example, the document titled “2014 Interim Guidance on Patent Subject Matter Eligibility” includes a flowchart that illustrates the subject matter eligibility analysis for all claims (including composition of matter, manufacture and process claims) and sets forth three distinct steps for determining patent eligibility under 35 U.S.C. § 101: (1) determining whether the subject matter is directed to a method; (2) determining whether the subject matter focuses on a natural principle (laws of nature, natural phenomena, and abstract ideas); and (3) determining whether the subject matter includes additional elements that integrate the natural principle into the claimed invention such that the natural principle is practically applied. Thus, under the USPTO guidelines, the analysis used during examination for evaluating whether a claim is drawn to patent-eligible subject matter appears to rest upon identifying adequate “additional elements.”

**Europe**

According to Article 53(c) EPC, methods of treatment by surgery, therapy and diagnostic methods practiced on human or animal body are specifically barred from patentability. Nevertheless, Article 53(c) EPC has carved out certain exceptions allowing for use-limited product claims (for example, use of a composition or drug in medical treatment methods) as well as for claims to second medical uses.

Early on, the patentability of second medical uses has been addressed by the Technical Board of Appeal in decision T233/96 that imposed a strict two-part test for novelty. According to T233/96, in order for use of a known treatment in a patient subgroup to be novel, (1) the patient groups (i.e., the new group claimed or subgroup and the prior art group) must be nonoverlapping; and (2) the new patient group must be nonarbitrary, i.e., the subgroup must be distinguishable from the prior population by its physiological or pathological status, and there must be a functional relationship between this physiological or pathological status and the therapeutic effect observed.
Subsequent decisions of the board such as T1399/04 and T0734/12, for example, took a more lenient approach allowing claimed subject matter even in instances where patient groups overlapped with the prior art group. For example, in T1399/04, the board concluded that, although there was a clear overlap between the subgroup and prior art groups of treated patients, the claimed use was novel because the claimed subgroup was defined by a previously undisclosed pathological and physiological status as to the prior art group (and the improved effect of the claimed treatment), and the subgroup selection was not arbitrary.

The approach of the European Patent Office to claims relating to treatment of subpopulations is more limited than that of the board. Pharmacogenomics inventions in which a new patient subgroup is defined by a biomarker are typically non-patent-eligible as they lack novelty and are anticipated (as the EPO assumes that one patient with the identified generic marker will inevitably have been treated, even if the prior art does not explicitly say so). As such, the use of a known treatment (drug or composition) in a subgroup characterized by a newly identified biomarker (if it can be established that the biomarker is present in a significant proportion of patients) will most likely be rejected by the EPO as not novel.

When analyzing dosing or dosing method claims, the EPO has aligned with the United States and allows patenting of dosage regimen as medical methods. Dosage or dosing regimen are timetables by which drugs are administered to a patient, taking into account the characteristics of the drug, the number of doses of the drug, and the time between each dosage.

With respect to biomarker claims per se, the EPO may consider as novel claims drafted as diagnostic-style “identify and treat” claims, i.e., directed to a specific step of determining whether or not a patient has a particular genetic marker, and treating such patient. In this instance, a nexus must be established between the presence or absence of the biomarker and an improvement in the patient’s treatment to establish novelty.

**Tips for Patent Practitioners in Drafting and Prosecuting Personalized Medicine Claims in the USPTO and EPO**

In the United States, patent practitioners should ensure that claims directed to personalized medicine methods such as diagnostic methods include active transformative steps which amount to more than an abstract mental step of comparing two sets of data, for example. These active transformative steps could recite, for example, steps such as isolating, extracting, incubating, washing, removing or sequencing, among many others.

Claim recitations that include a chemical transformation of material(s) also confer patent eligibility.

Under U.S. patent law, medical use patents are granted to dosage inventions. Dosage inventions are patentable as a process under 35 USC 101 if they satisfy the patentability requirements of novelty and nonobviousness. Dosage regimen inventions are not patentable as product patents and they should be claimed as medical methods.
In Europe, an important consideration for the patent practitioner is the inclusion of supporting data in an application, to establish that any identified and selected subgroup (subpopulation) was not arbitrary but rather a result of a functional relationship between the claimed feature and an improved effect of the claimed treatment.

Drafting diagnostic method claims according to EPO practice requires the patent practitioner to (1) avoid method of treatment claims directed to treatment on a patient; (2) avoid interventional steps such as “drawing blood from a patient” and instead recite “providing a blood sample” or “analyzing a blood sample”; (3) avoid any surgical steps (for example, use “providing a cut mammal” in lieu of “cutting a mammal”) to avoid Art 53(c) EPC objections; (4) include multiple claims directed to use-limited product claims, as set forth in Art 54(5) EPC; and (5) include experimental data establishing a nexus between the presence or absence of the biomarker and the improvement (efficacy or safety) in the treatment and that the presence/absence of the biomarker distinguishes the patient population with respect to the physiological or pathological status.

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