Patents and Laboratory Medicine: What Is Required to Turn an Unpatentable Natural Phenomenon or Law of Nature into a Patentable Invention?

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According to the US Patent Act, “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).

The courts have construed this statement as covering “anything under the sun made by man” (2). Although this language is very encompassing, not everything is patentable. The invention must be novel (3) and nonobvious (4). In addition, “laws of nature, natural phenomena, and abstract ideas” are not patentable (5), but novel applications of laws of nature, natural phenomena, and abstract ideas can be patentable.

The courts have been struggling with just how much application is required to turn an unpatentable natural phenomenon or law of nature into a patentable invention. Two current cases involving laboratory medicine illustrate this difficulty. The “Prometheus” case (6), decided recently by the US Supreme Court, relates to the patentability of using a patient’s metabolite concentrations to provide proper drug dosing. The “Myriad” case (7) has been decided by the US Court of Appeals for the Federal Circuit (the US appeals court that handles all patent appeals), but the Supreme Court has asked the appeals court to reconsider its ruling in light of the Prometheus decision. The Myriad case involves the patentability of gene targets. Table 1 shows how the 2 cases have progressed through the courts.

The patents involved in both the Prometheus and Myriad cases certainly describe natural phenomena and laws of nature. The Prometheus patents set forth a specific metabolite concentration above which would cause harm and another metabolite concentration below which would prove ineffective. The Myriad patents involve various aspects of the BRCA1 (breast cancer 1, early onset) and BRCA2 (breast cancer 2, early onset) genes. A large majority of patents, in some form or another, describe and claim natural phenomena or laws of nature. The question in both the Prometheus and Myriad cases is whether the claimed subject matter does substantially more than describe these laws of nature.

In the first case, Prometheus owned several patents on the administration of thiopurine drugs for the treatment of gastrointestinal diseases, more specifically on the correlation between thiopurine metabolite concentrations and the toxicity and efficacy of the thiopurine drugs. At the time of the discoveries that led to the patents, thiopurine drugs were in use. It was known that metabolite concentrations in a patient’s blood were correlated to the likelihood that a dosage of the thiopurine would be high enough to cause harm or low enough to lack efficacy, and it was known that different patients metabolized thiopurines at different rates. The patents covered (a) “administering” the drug and (b) “determining” the concentration of the metabolite, wherein a concentration of 230 pmol per 8 × 10⁸ red blood cells indicates a need to increase the dosage and a concentration of 400 pmol per 8 × 10⁸ red blood cells indicates a need to decrease the dosage. The trial court found that the accused methods infringed the patents but held that the patents were invalid because they essentially claimed unpatentable laws of nature. The appeals court reversed this ruling, finding that the patent claims satisfied the court’s machine-or-transformation test, under which a process is patentable if it is tied to a particular machine or apparatus or if it transforms a particular article into a different state or thing (8). Shortly thereafter, however, the Supreme Court held that the machine-or-transformation test is not the exclusive test of patentable subject matter but only an important clue (9), and the Supreme Court asked the appeals court to reconsider the Prometheus opinion.

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† Human genes: BRCA1, breast cancer 1, early onset; BRCA2, breast cancer 2, early onset.
Again, the appeals court found the Prometheus claims to be patentable subject matter.

On March 20, 2012, the Supreme Court, in a unanimous decision, reversed the appeals court, finding that the Prometheus patents were not patentable subject matter. The Supreme Court reiterated earlier decisions in stating that “to transform an unpatentable law of nature into a patent-eligible application of such a law, one must do more than simply state the law of nature while adding the words ‘apply it.’” The Supreme Court found that the Prometheus claims did not apply the natural laws sufficiently, because the other steps in the patented processes merely apply “well-understood, routine, conventional activity.” Although the appeals court had previously determined that the steps of (a) administering the drug and (b) determining the resultant metabolite concentration sufficiently satisfied the machine-or-transformation test, the Supreme Court disagreed, noting that the administration step merely refers to a preexisting audience—the doctors who have already been using thiopurine drugs—and the determining step tells the doctor to determine the relevant metabolite concentrations in the patient’s blood, a step that was already known in the art. The “wherein” clause tells the doctor about laws of nature (the dosing amounts), with a suggestion to take these into account when treating the patient. Thus, the Supreme Court found that the laws of nature are combined only with conventional activities that existed before the invention.

The Myriad case involves several patents on the breast cancer genes \textit{BRCA1} and \textit{BRCA2}. Three different types of claims are at issue: (a) claims involving cDNA of spliced coding regions or isolated DNA of the \textit{BRCA1} gene, (b) claims to methods of screening potential cancer therapeutics by analyzing growth rates of cells with altered \textit{BRCA} genes in the presence or absence of the therapeutics, and (c) claims to methods of analyzing \textit{BRCA} gene sequences by comparing the cancer-predisposing mutations to normal sequences. Subsequently, although the members of the appeals court disagreed with each other on the patentability of the cDNA and isolated DNA, the majority found these claims to be valid, because neither cDNA nor isolated DNA is something that exists in nature and, accordingly, is not a product of nature. The appeals court found, however, that Myriad’s claims to methods of analyzing \textit{BRCA} gene sequences and comparing those with cancer-predisposing mutations to normal sequences is not patentable subject matter.

The issue regarding patentability of cDNA and isolated DNA has been appealed to the Supreme Court; however, immediately subsequent to the Supreme Court decision in Prometheus, the Supreme Court asked the appeals court to reconsider in light of the Prometheus decision. Because the Prometheus case relates to methods and not objects, it is unclear how the appeals court will apply that decision to claims for DNA sequences that exist in a synthetic or isolated form. It is also unclear whether the appeals court must or will revisit its decisions on the 2 types of method claims, which were not appealed to the Supreme Court. Thus, anything can still happen to the Myriad patents.

| Table 1. Court decisions in the Prometheus and Myriad cases. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Prometheus**                  | **Myriad**      | **Myriad**      | **Myriad**      |
| Methods of optimizing dosage    | cDNA and isolated DNA | Methods of screening | Methods of analyzing sequences |
| **District Court (trial court)** | Invalid—Claims natural phenomena | Invalid—Isolated DNA is a product of nature | Invalid—All transformative steps were preparatory data gathering | Invalid—Required only mental processes without physical transformation |
| **Federal Circuit (appeals court)** | Valid—Sufficient transformation of natural phenomena | Valid—Transformed into something distinct from a product of nature | Valid—Sufficient application of law of nature | Invalid—Natural phenomenon plus a mental step |
| **Supreme Court**               | Remand for reconsideration in light of Bilski | Remand for reconsideration in light of Prometheus | | |
| **Federal Circuit (on remand from Supreme Court)** | Valid—Sufficient transformation of natural phenomena | To be determined | ???—Unclear if court will reconsider | ???—Unclear if court will reconsider |
| **Supreme Court**               | Invalid—Claims natural phenomena with directions to “apply it” | To be determined | | |
What do the invalid claims of Prometheus and Myriad have in common? In both cases, the invalid claims require application of a law of nature without any specific definition on how to apply that law of nature. The Supreme Court found a claim unacceptable if it stated a law of nature with only vague directions to “apply it.” The appeals court described the same issue as unacceptable if the application of the law of nature is done in a way that can be accomplished by “abstract mental steps.” Both sets of claims require a doctor or laboratory technician to perform some actual step that is transformative; however, that transformative step was known and had previously been done. The potentially patentable novel step was written in a way that could be performed solely by thought or with a vague direction to apply it. To be valid, the patented law of nature must be applied in a useful way (the more tangible, the better). If the law of nature can be applied by a mental step or if there is not much guidance on how to apply the law of nature, the subject matter probably falls outside of patentable scope.

The take-home lesson from these cases is that novel and nonobvious items remain patentable subject matter. Laws of nature and natural phenomena are not patentable unless they are applied with specificity. At this point, it is unclear whether cDNA and isolated DNA of novel sequence meet that level of specificity. On the other hand, the Prometheus patents are dead and are likely to remain dead, because Prometheus has very few legal options at this time. Laboratories are cautioned, however, to consult with their legal counsel before using Prometheus’ methods, because other patents may exist that were not part of that litigation.

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8. In re Bilski, 545 F.3d 943, 954 (Fed. Cir. 2008).