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The USPTO Grants Two Patents Claiming Diagnostic Methods Post the Supreme Court's *Mayo v. Prometheus* Decision

AUTHORS

Miguel A. Lopez, Ph.D.

Stefan J. Kirchanski, Ph.D.

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On March 20, 2012 the Supreme Court in its decision of ***Mayo v. Prometheus*** unanimously held that claims directed to a method of administering a drug to a patient, measuring metabolites of that drug, and with a known threshold for efficacy in mind, deciding whether to increase or decrease the dosage of the drug, were not patent eligible subject matter.

Briefly, in its decision of *Mayo v. Prometheus*, the Supreme Court analyzed claim 1 of US patent No. 6,355,623. Claim 1 states:

> *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 8×108 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8×108 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.*

After analyzing the claim, the Supreme Court held that the correlation between the naturally produced metabolites and therapeutic efficacy and toxicity to be an unpatentable "natural law." Although the Supreme Court conceded that the first two steps of the claim were not themselves natural laws, it concluded that they were well understood, routine, conventional activities already engaged in by the scientific community and as such do not add anything of patentable significance.

This decision sparked controversy in the legal and biotechnology communities alike. From the legal perspective, a number of patent practitioners alleged that the Supreme Court displayed a rudimentary knowledge of patent law in this decision based on its perceived misinterpretation of the §101 patent eligibility requirements and the §102 novelty requirements. At the same time, biotechnology entrepreneurs, companies, and investors were left deeply unsure about the validity of issued diagnostic patents and the potential viability of patents for diagnostic assays and similar devices for enabling personalized medicine. Nevertheless, two patents have been recently issued that have claims strikingly similar to those held unpatentable in *Mayo v. Prometheus*.

US Patent No. 8,623,601 (assigned to Duke University and Cognosci, Inc.) claims:

> *A method of predicting or assessing the level of severity of cancer or cancer progression in a patient diagnosed with chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma comprising determining the ratio of SET alpha isoform to SET beta isoform in B lymphocytes isolated from the patient and comparing the ratio of SET alpha isoform to SET beta isoform to the ratio in a control sample or a standard value, wherein an increase in the ratio of SET alpha isoform to SET beta isoform relative to the ratio in the control sample or standard value is indicative of a more severe form of cancer or later stage of cancer progression in the patient.*

Analysis of the prosecution history of this patent reveals that a §101 rejection was never issued (as might have been expected given the Supreme Court ruling in *Mayo v. Prometheus*). Instead, following the Applicant's election of claims in response to a Restriction Requirement, rejections under 35 U.S.C. §112 (pre AIA) first and second paragraphs were issued. Applicants proceeded to amend the claims so as to more satisfactorily enable and distinctly claim the invention and provided arguments describing how the newly amended claims were allowable. A notice of allowance was issued shortly thereafter.

US Patent No. 8,628,920 (assigned to National Tsing University in Taiwan) claims:

> *A method for determining risk of metastatic liver cancer, comprising the steps of:*
>
> *(A) providing a sample obtained from a subject;*
>
> *(B) assessing the RNA expression level of four subtypes of alpha-mannosidase genes consisting of MAN1A1, MAN1A2, MAN1B1 and MAN1C1 in the sample by detecting MAN1A1, MAN1A2, MAN1B1 and MAN1C1 RNA expression levels in the sample;*
>
> *(C) comparing the MAN1A1, MAN1A2, MAN1B1 and MAN1C1 expression levels in the sample with MAN1A1, MAN1A2, MAN1B1 and MAN1C1 expression levels in a normal control; and*
>
> *(D) determining whether the subject has a risk of metastasis of liver cancer in accordance with the result of step (C);*
>
> *wherein a subject with MAN1A1, MAN1A2 and MAN1B1 expression levels in the sample that are higher than those in the normal control, and MAN1C1 expression level in the sample that is lower than that of the normal control has a high risk of metastasis of liver cancer, wherein the sample and the normal control are liver biopsies.*

The prosecution history of this patent reveals that the Examiner issued a rejection of the original claims under 35 U.S.C. §101 in a non-final Office Action. The Examiner held that the claims were non-statutory being drawn to a method having a "natural principle" as a limiting step without reciting additional steps that integrate the natural principle into the claimed invention. The Examiner stated that, according to *Mayo v. Prometheus*, a claim that focuses on use of a natural principle must also include additional elements or steps to show that the inventors have practically applied, and added something significant, to the natural principal itself.

In response to this rejection, the Applicant amended the claims to add limitations of assessing "RNA," detection of "specific markers", and assessing and comparing the expression level by the "specific markers." The Applicant also amended the preamble of the independent claim at issue to read "A method for determining risk of metastatic liver cancer…" as opposed to "A method for diagnosis of liver metastasis…" as was originally claimed. In response to these amendments, the Examiner withdrew the §101 rejection and issued a 35 U.S.C. §112 (pre AIA) second paragraph rejection for the alleged unclear recitation of "specific markers." As a result, the Applicant amended the claim to remove this recitation and a Notice of Allowance issued shortly thereafter.

The Supreme Court's decision of *Mayo v. Prometheus* was a controversial one that shook up the legal and biotechnology communities. Nevertheless, diagnostic method claims remain important in basic research, particularly with respect to work being done in universities and medical schools. The viability of patents claiming diagnostic methods is important to licensing opportunities for these institutions. While the issuance of these two patents might give one hope that diagnostic methods claims remain patentable, there is little specific guidance that can be extracted from these two cases. In the case of the '601 patent, *Mayo v. Prometheus* was never faced because the Examiner neglected to issue a §101 rejection. In the case of the '920 patent, the §101 rejection was overcome by adding steps, which to the present authors seem likely to fall short of the "something more" and limitations on the overall use of a "natural principle" as called for by the Supreme Court. It remains to be seen how the two patents will hold up in the face of litigation. Unfortunately, convenient patent invalidation proceedings such as an *Inter Partes* Review cannot reach a §101 problem. So these patents can be challenged on that ground only through litigation.

Of course, it is impossible (and foolhardy) to predict the results of a future litigation, but it does seem to the present authors that the '601 patent remains vulnerable because the granted claims do not seem to comport with the Supreme Court's *Prometheus* requirements. Similarly, the claims of the '920 might not adequately limit the use of a "natural principle." But it must be kept in mind that the prosecutors involved in these two cases certainly did the best they could when faced with specifications that were written

prior to *Prometheus*. Although one certainly wishes that the Supreme Court would have avoided terms such as “natural principle” because all of science and technology are based on the understanding and use of “natural principles,” it remains clear (but untested) the sorts of approaches one should take in drafting new diagnostic patents. It is important to detail the experiments leading to the discovery of a biological correlation and the specific technical steps (with experimental verification) needed to make practical use (*i.e.*, diagnosis) of the discovered correlation. In this way the discovery will not appear to be a “natural principle” that was just lying around. In addition, the technical steps will inherently limit the overall use of the correlation. It is no longer viable to draft a simple diagnostic claim that essentially says “the use of discovery A to diagnose the existence of condition B.”