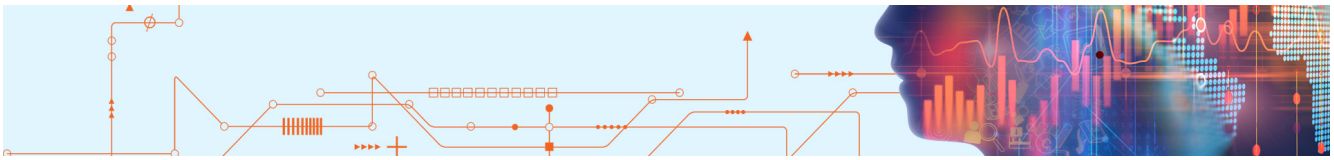

Between a Rock and a Hard Place: Patent Protection in the United States for the Analysis of Biomarker Data Using Artificial Intelligence

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Twenty years ago, the human genome project started producing data that radically improved our understanding of biology. However, identifying clinically relevant biomarkers and using them to improve health care remains a significant challenge. The development of sophisticated computer-based techniques for the analysis of large, noisy data sets is critical for advancing research and realizing the promise of personalized medicine. Artificial intelligence (AI) and machine learning have emerged as powerful tools with the potential to profoundly impact both R&D in the life sciences and clinical decision-making.

Patent protection provides a key competitive advantage for innovators seeking to get new technology into the market. However, navigating the patent system can be difficult – in particular for inventions related to biomarkers or diagnostic methods. To be patentable, a claimed invention must be new and inventive over the prior art, and must be directed to patent eligible subject matter. What is considered 'patent eligible subject matter' differs in each jurisdiction. The last few years have seen significant changes to the framework for determining patent eligible subject matter in the United States. The impact of those changes has been profound and led to the demise of many otherwise-worthy inventions.

In the United States, patent eligibility is determined using a test based on the court decisions in *Mayo*[i] and *Alice*[ii]. First, a claim must be directed to a statutory category of invention, namely a "process machine, manufacture or compositions of matter" (Step 1). This is a relatively easy hurdle to overcome. Next, if a claim is *not* directed to a "law of nature, natural phenomenon, or an abstract idea" (the so-called "judicial exceptions"), it is considered patent eligible (Step 2A). Otherwise, the claim must recite additional elements that amount to "significantly more" than the judicial exception in order to be patent eligible (Step 2B).

In January 2019, the US Patent and Trademark Office released new Guidelines clarifying Step 2A and that a claim is *not* directed to a judicial exception (and therefore patent eligible) if the judicial exception "is integrated into a practical application". While the Guidelines provide examples of additional elements that are considered to impose meaningful limits and have "integrated the exception into a practical application" much remains unclear. For example, limiting a claim to include a data-gathering step or measuring the metabolites of a drug administered to a patient have been identified as examples of insignificant extra-solution activity that are insufficient to render a claim patent eligible. Diagnostic claims that may appear to be "practical applications", such as using cell-free fetal DNA to diagnose fetal abnormalities, have nevertheless been held to be patent ineligible[iii].

Otherwise, a claim must recite something "significantly more" than the judicial exception to be patent eligible (Step 2B). "Significantly more" is considered to include a specific limitation other than what is "well-understood, routine, conventional activity" (WRCA) in the field. The Court of Appeal for the Federal Circuit in the U.S. has affirmed that the mere fact that something is disclosed in the prior art does not mean it is well-understood, routine, or conventional[iv]. However, elements such as the amplification and detection of nucleic acid sequences and/or comparing the level of a biomarker to a control are likely to be considered routine making it difficult to render claims to diagnostic methods patent eligible.

Following the *Alice* decision, US practice now also severely restricts the patentability of computer-based methods.

Inventions directed to fundamental AI technologies that provide a “technical solution” to a “technical problem” in the realm of computing appear to be patent eligible. However, the eligibility of technologies that apply existing AI techniques for the analysis of data is less clear. Claim elements that are considered to merely use a computer to apply a judicial exception are unlikely to be found patent eligible. Computer-implemented diagnostics therefore appear to be stuck between a rock and a hard place, suffering from blows against patentability on both sides.

How does one best pursue claims to diagnostics that include elements based on AI or machine learning? In practice, each case will depend on the facts and the particular technologies involved. Recent granted US patents with claims that refer to the use of AI for the analysis of biomarker data provide some concrete examples of patent eligible methods.

Claim 1 of US Patent No. 9,952,220 is directed to a method of determining the existence of non-small cell lung cancer early in disease progression by measuring expression levels of a set of biomarkers and classifying the subject using “*a machine learning system comprising classification and regression trees selected from the group consisting of Random Forest and AdaBoost or an ensemble thereof*”.

During prosecution the Applicants successfully argued that prior to the filing date of the application the use of a machine learning classification system was not routinely or conventionally used to analyze biomarker data for non-small cell lung cancer. While this approach may not work as the use of machine learning classification systems becomes more widespread, it highlights that novel or unconventional approaches to the analysis of diagnostic biomarker data using AI may be considered something “significantly more” and patent eligible.

Another strategy is to frame the invention within the context of a medical treatment. For example, claim 1 of US Patent No. 9,791,446 refers to a method comprising “*(a) measuring the level of MX dynamin-like GTPase 1 (MX1) and the level of C-reactive protein (CRP) in a sample of the subject; (b) classifying whether the subject has a bacterial infection using a hyperplane having been calculated by combining the measurements of said CRP and said MX1 of a training population; and (c) treating the subject classified as having said bacterial infection with an antibiotic agent, thereby treating the subject*” Dependent claims further define that the hyperplane may be calculated using a statistical classification algorithm such as a support vector machine or neural network.

Under the new Guidelines, the incorporation of a particular treatment step (such as treating with an antibiotic agent) is an additional element that “integrates the exception into a practical application”. While it may not always be possible or desirable to claim a treatment step in combination with a computer-implemented diagnostic, it is prudent to include support in a patent application for particular treatments that may be of use for the relevant disease or condition.

The best strategy for claiming a particular diagnostic invention that uses AI will depend on the nature of the technology, commercial plans as well as the jurisdictions where patent protection is sought. When filing in the United States, inventors should work with their patent agent to identify a number of additional elements that may be used support patent eligibility without necessarily sacrificing commercially relevant claim scope. For some inventions, it may be necessary to file one or more continuation patent applications in order to obtain claims that incorporate different elements in order to obtain the broadest possible protection.

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[i] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* 566 U.S. 66 (2012)

[ii] *Alice Corp. v. CLS Bank International* 573 U.S. 208 (2014)

[iii] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015)

[iv] *Berkheimer v. HP Inc.*, No. 17-1437 (Fed. Cir. 2018)

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