Intellectual property associated with laboratory-developed tests (LDTs) and *in vitro* diagnostic (IVD) tests

Learning objectives

- Describe the options for protecting intellectual property associated with IVD tests and LDTs, including those that rely on existing technology or known biomarkers
- Describe potential avenues for biomarker patent protection under current patent law
- Describe the steps that an organization can take to understand the patent landscape for a particular test

Introduction

Multiple legal frameworks pertain directly to the development and commercialization of all diagnostic tests, including LDTs and IVD tests. As discussed in previous sections, the FDA and other government agencies have important roles in regulating the development, marketing, and usage of diagnostic tests. Patent law is also a key consideration during the test lifecycle, and there has been a seismic shift in the patenting process for diagnostic tests over the last decade.

An invention must satisfy several criteria to be granted a patent by the United States Patent and Trademark Office (USPTO). First, the patent applicant or inventor must establish that the claimed invention is novel [1]. Establishing patentability also requires that the invention be non-obvious [2], and that it be adequately described in the patent application [3]. Finally, the subject matter must be useful and eligible according to the statutory requirements set forth in 35 U.S. Code (U.S.C.) § 101 [4]. Satisfying the last criterion–subject matter eligibility–has become a significant hurdle to patenting diagnostics and other biotechnologies.

Most of the concepts discussed in this paper pertain to both LDTs and IVD tests. The information herein is presented in the context of LDT intellectual property (IP). Although LDTs and IVD tests differ in some respects, the same IP laws and regulations apply equally to *in vitro* diagnostics.

Protectability of LDTs and IVD tests

Conventional platforms and biomarkers

Patenting and protection of an LDT or IVD test depends in part on the innovation itself. Many diagnostic assays are performed using conventional platforms, such as next-generation sequencing (NGS) systems, polymerase chain reaction (PCR) instruments, or saliva collection kits, and the assays are used to test for one or more biomarkers. Even if the subject matter satisfies 35 U.S.C. § 101 eligibility criteria, it can still be difficult to establish that an innovation is novel and non-obvious. If a significant innovation involves a conventional platform that is commercially available, the platform itself may not be protectable. Depending on the extent to which an assay biomarker has been validated and reported on in the primary literature, the biomarker may not be patentable. If a biomarker is

already in the public domain because it has been reported in a publication, the USPTO will not consider it novel.

Novel platforms and biomarkers

An assay that involves a novel biomarker or platform is more likely to be granted patent protection. If a diagnostic test requires significant alteration of a conventional platform or implementation of an entirely new platform, then the developer may be entitled to a patent on that specific innovation. Such innovations include changes to platform hardware, software, operation, or methodology; changes to sample preparation kits; changes to sample preparation methodology; and the creation of any previously unreported version thereof. For example, if a laboratory creates a new method for preparing samples for whole genome sequencing, the methodology may be protectable. Similarly, creating new reagents or using existing reagents in new combinations or ways may also be protectable.

A diagnostic laboratory may have a research and development (R&D) group that performs discovery experiments to identify new biomarkers for diseases or conditions. If the R&D team identifies a new biomarker or a biomarker that has not been previously associated with a disease or condition, the potential for patent protection should be investigated.

Filing a patent application does not require the quantity and quality of validation data that the FDA and the Clinical Laboratory Improvement Amendments (CLIA) Program do. Since the US patent system prioritizes applications on a first-to-file basis, it is important to file a patent application as quickly as possible.

Biomarker protection in the age of Mayo and Myriad

A significant shift in patent subject matter eligibility occurred in the early 2010s. Prior to this shift, filing a patent application for a biomarker was relatively straightforward as long as the biomarker was demonstrably novel and had a non-obvious relationship with a disease or condition. It was common to see two types of claims in a patent application. These included (i) claims directed to a partial or complete DNA, RNA, or amino acid sequence for a biomarker and (ii) claims directed to a general relationship between a biomarker and one or more diseases or conditions. Making such claims was no longer permitted after two important US Supreme Court decisions, Myriad and Mayo, that significantly changed the subject matter eligibility landscape.

Mayo Collaborative Services vs. Prometheus Laboratories, Inc. [5]

Before this case reached the Supreme Court, Prometheus sued Mayo for infringing two of its patents concerning methods of optimizing thiopurine drug dosages for patients with certain autoimmune conditions. The patent claims included an “administering” step, which instructed doctors on how to administer thiopurine drugs to patients, and a “determining” step to measure thiopurine metabolite concentrations in the bloodstream.

Writing for a unanimous court, Justice Breyer held that Prometheus’s claims encompassed

unpatentable “laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that the dosage … will prove ineffective or cause harm [6].” Justice Breyer elaborated that claims to well-understood, routine, and conventional activities of scientists in the field did not warrant protection because they only recited those activities [7].

Association for Molecular Pathology vs. Myriad Genetics, Inc. [8]

Prior to the Myriad case, the US was one of only a few countries that allowed patent protection of naturally occurring genes. Claims on peptides and naturally occurring DNA, RNA, and amino acid sequences were permitted, but only if the biomolecules were present in an *in vitro* or *ex vivo* environment. Biomolecules in living organisms were not considered eligible for protection. Myriad Genetics had invested heavily in developing and commercializing a *BRCA* assay that was used to gauge susceptibility to breast and ovarian cancer. At issue was whether a naturally occurring sequence, isolated or not, was eligible subject matter for a patent [9].

The Supreme Court decided that, as a matter of law, naturally occurring genetic sequences could not be considered eligible subject matter for patents [10]. The decision invalidated thousands of existing sequence-based patents. Many diagnostics companies anticipated the rejection of sequence-based patent claims in the 2000s and began to move from making claims on sequences to making claims on methods involving potential biomarkers.

Lingering issues affecting patent claims

The diagnostics field was thrown into turmoil by the Mayo decision. It rendered many existing patents invalid on the grounds that the applicants made claims on simple and obvious correlations between biomarkers and diseases without providing additional material evidence of novelty or usefulness. However, the Supreme Court did not specify what level of detail a court of competent jurisdiction should require to consider subject matter eligible for USPTO patent protection. It is important to note that many USPTO examiners who review patent applications are not attorneys. It can be incredibly difficult to dissect US Supreme Court and Federal Circuit rulings sufficiently to enable technical specialists who lack legal expertise to assess the eligibility of a given patent application.

The USPTO has issued guidance for patent practice since the Mayo decision [11], and the Federal Circuit has decided many cases related to 35 U.S.C. § 101. While much remains unclear about what qualifies for a patent, the USPTO and Federal Circuit view the following as eligible subject matter: claims that recite a biomarker, diagnostic, or prognostic aspect and a method of treatment[1]; claims that recite detection of a biomarker with a specific reagent; and claims

[1] This strategy is not always effective, because case law related to divided infringement can be challenging to apply when different healthcare providers run a test and administer treatment.

that recite a multi-biomarker signature.[2] It may also be possible to broadly claim a novel detection method to afford a patent owner potentially commercially valuable protection.[3]

The USPTO is inclined to allow diagnostic claims that are highly detailed and specific. A detailed claim might include a list of specific biomarkers, a specific reagent, a particular type of disease, or a treatment for disease. However, applicants often try to maximize the scope of their claims by providing as little detail as possible. The divergent priorities of the USPTO and patent applicants is a source of ongoing tension, so it is important to strike a balance between detail and scope when making a patent claim.

Trade secret protection

President Barack Obama signed the Defend Trade Secrets Act (DTSA) in 2016 [12], which provided civil recourse for trade secret theft for the first time. Under the DTSA and various state laws, a laboratory may be able to claim an LDT as a trade secret if the LDT satisfies the requirements[4] for protection.[5] Protection of LDTs as trade secrets has an important caveat, which is that key details about trade secrets cannot be made available to the public. If public disclosure of such information is required for regulatory review of an LDT, protection under the DTSA may not be possible. If key details about an LDT are available to the public, an alternate means of seeking IP protection should be pursued.

Another caveat is that trade secret law applies only to theft and misappropriation. In other words, if an innocent party independently recreates an LDT that is protected under the DTSA, there is no grounds for recourse. Reverse engineering an LDT protected as a trade secret is perfectly permissible as long as it is done without theft or misappropriation.

Enforcement of the DTSA and state trade secret laws can be challenging when an applicant seeks trade secret protection for

[2] It is not clear how many biomarkers this strategy would require, but the author of this educational paper has pursued patents with diagnostic claims involving as few as three biomarkers.

[3] This may be applicable when a biomarker has not previously been observed in a body fluid, such as cerebrospinal fluid. However, these claims must still meet the standards for novelty and non-obviousness.

[4] The subject matter criteria for trade secret protection requires the information to have actual or potential economic value of its own that derives from not being generally known to, and not being readily ascertainable through proper means by, other persons who can obtain economic value from its disclosure or use.

[5] One of the benefits of trade secret protection is that there is no formal application process to obtain it. As long as statutory requirements are met, subject matter can be considered a trade secret.

innovations associated with an IVD. This is because regulatory submission is required for premarket approval or clearance of IVDs. The FDA often requires a detailed description of the mechanism behind an IVD. Since this documentation is submitted to the federal government, it may be made public. Consequently, seeking trade secret protection for assays that require premarket approval or clearance may not be productive.

Commercialization of LDTs

Regardless of the strategy a laboratory chooses to pursue IP protection for an LDT, performing a freedom to operate (FTO) competitive IP analysis before developing or commercializing the test will be beneficial. An FTO analysis for an LDT generally involves a detailed breakdown of the technological elements of the test. This will often reveal one or more pending or issued patents that the LDT could infringe upon, which gives the developer some idea of how many potential patent infringement issues to consider.

Depending on the technology and scope of the analysis, an FTO search can cost $100,000 or more.[6] Including both domestic and foreign patent databases in an FTO search can be even more expensive and reveal additional complications. Even though performing an FTO analysis can be costly, discovering existing and relevant patents early in the development process can enable a laboratory to make important strategic decisions. For example, a laboratory could decide whether to develop a test for biomarker X to detect non-small cell lung cancer and potentially face an infringement lawsuit or move in another direction, such as selecting an alternative biomarker to develop a different LDT.

Investigating the patent landscape early can also give a test manufacturer solid business and legal footing if it commercializes an LDT and is later sued for patent infringement. An LDT manufacturer could be required to pay damages and attorney fees if a patent owner is able to establish that the manufacturer knew about the patent before infringing. The LDT manufacturer can seek legal counsel and prepare an invalidity opinion for a patent discovered in its FTO search, although doing so requires a detailed analysis to determine whether the discovered patent is in fact invalid.

It is important to note that the USPTO does not always consider prior art before issuing a patent. If prior art is not considered before a patent is granted, outside counsel can prepare a written legal opinion that makes a reasonable case for invalidating the patent. Having an invalidity opinion prepared in advance of potential litigation can thus give a powerful strategic advantage to a laboratory that is preparing to launch an LDT.

Performing an FTO search may be even more important for an IVD manufacturer. IVDs are usually tangible goods that are marketed to healthcare stakeholders and individual patients, whereas an LDT is generally marketed as a service. A patent owner who seeks to enforce patent rights through an infringement action may find it

[6] Organizations with significantly limited resources may be able to obtain patent infringement insurance to address potential downstream infringement issues.

easier to identify a potentially infringing IVD. Information about IVDs is publicly available, while not all information about LDTs is in the public domain. It is thus wise for an IVD manufacturer to investigate the patent landscape before it commits significant resources to IVD development and any associated regulatory submission.

It is important to remember that an FTO analysis does not guarantee patent eligibility. An LDT may be patentable, but it could also infringe existing patents. Whether a laboratory is designing an LDT or considering IVD development, evaluating intellectual property and potential avenues of protection are important aspects of the planning process. Legal review of patent infringements, analysis of freedom to operate, and strategic consideration of trade secrets should be completed prior to validation and commercialization of an LDT or IVD test.

Conclusion

Patent law directly pertains to the development and commercialization of all diagnostic tests, including LDTs and IVD tests. Patent law should be a key consideration during the test lifecycle, because rulings issued by the United States Supreme Court in the last decade have caused a seismic shift in the patenting process for diagnostic tests. Although LDTs and IVD tests differ in some respects, the same IP laws and regulations apply equally to all *in vitro* diagnostics.

IP law must be considered throughout the development of a diagnostic assay. It is particularly important to understand the patent landscape in the early stages of test design to avoid potential infringement issues later. After reviewing the patent landscape, the research and development team should work with a patent attorney to determine how best to protect any potentially patentable innovations related to the new diagnostic assay.

References

[1] 35 U.S.C. § 102.
[2] 35 U.S.C. § 103.
[3] 35 U.S.C. § 112.
[4] 35 U.S.C. § 101.
[5] 569 U.S. 576 (2013).
[6] *Id.*
[7] *Id.*
[8] 566 U.S. 66 (2012).
[9] *Id.*
[10] *Id.*
[11] See https://www.uspto.gov/patents/laws/examination-policy/subject-matter-eligibility.
[12] 18 U.S.C. § 1830 et seq.

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