Comments of Coalition for 21st Century Medicine on

USPTO's October 2016 Request for Comments Related to Subject Matter Eligibility

January 18, 2017

I. Introduction

The Coalition for 21st Century Medicine (the "Coalition") appreciates the opportunity to present comments in response to the request from the United States Patent and Trademark Office ("USPTO") in the October 2016 "Notice of Roundtables and Request for Comments Related to Subject Matter Eligibility." 81 Fed. Reg. 71485 (Oct. 17, 2016).

The Coalition represents some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists and patient advocacy groups who share a common mission: to develop and commercialize state-of-the-art diagnostics that improve patient health. Diagnostics are increasingly important as the health care industry focuses on improving the delivery of individualized care through personalized medicine. Coalition member companies dedicate significant time, scientific knowledge and financial resources in order to develop and to commercialize cutting edge diagnostic technologies to improve the quality of patient care. Patents play a key role in the ability of Coalition member companies to successfully discover and commercialize new precision medicine diagnostics.

The Coalition respectfully submits these comments to discuss recent case law from the Supreme Court and the Federal Circuit regarding subject matter eligibility under 35 U.S.C. § 101, including how diagnostic claims should be examined for subject matter eligibility. The Coalition previously submitted comments in August 2014,[1] in March 2015,[2] and in October 2015[3] to discuss the appropriate framework for examining subject matter eligibility and to

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[1] See *Coalition for 21st Century Medicine Comments on Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products,* available at https://www.uspto.gov/sites/default/files/patents/law/comments/mm-a-coalitionfor21stcenturymed20140806.pdf (last visited Jan. 16, 2017) ("*August 2014 Comments*").

[2] See *Coalition for 21st Century Medicine Comments on December 2014 Guidance*, available at http://www.uspto.gov/sites/default/files/documents/2014ig_a_21st_2015mar16.pdf (last visited Jan. 16, 2017) ("*March 2015 Comments*").

[3] See *Coalition for 21st Century Medicine Comments on July 2015 Update on Subject Matter Eligibility,* available at https://www.uspto.gov/sites/default/files/documents/2015ig_a_coalition_28oct2015.pdf (last visited Jan. 16, 2017).

comment on recent USPTO guidance. As the Coalition has indicated in its earlier comments, the Coalition believes that recent court cases do not replace the broad statutory framework governing patent eligibility. On the contrary, court decisions have carved out limited, fact-specific exceptions to the broad statutory paradigm of eligibility under § 101. In these comments, the Coalition discusses some exemplary claims to illustrate the applicability of these cases to evolving diagnostic technology and why diagnostic medicine claims remain patent-eligible. The Coalition, as discussed in the cases and examples below, believes that the USPTO can continue to educate patent examiners to comply with the broad paradigm of § 101.

II. Key Subject Matter Eligibility Cases

The Supreme Court and Federal Circuit's recent subject matter eligibility cases beginning with *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[4] are fact-specific and cannot be applied broadly to life sciences claims, including diagnostics claims. Some of these cases involved patents that claimed processes that in every particular were routine in the art at the time of filing. Significantly, many of these cases concern claim strategies and structures and technologies that are now outdated and no longer representative of today's diagnostic fields.

The Coalition is concerned that these cases are being applied far more broadly than their fact-bound holdings. Examiners should guard against treating these decisions, which address overly broad and outdated claims, as sweeping bright-line decisions. Rather, examiners should exercise care in light of evolving technology and, consistent with the governing statutory provision, err on the side of eligible subject matter during the examination phase.

A. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*

In *Mayo*, the claims at issue recited methods of "administering" a drug to a subject, "determining" the level of a metabolite, and "wherein" clauses that correlated specific levels of that metabolite with a need to increase or decrease a thiopurine drug amount.[5] The *Mayo* Court made clear that these claims simply describe the natural relationships between concentrations of certain metabolites in the blood and the need to adjust the dosage of a thiopurine drug accordingly (*i.e.* metabolites above a certain threshold indicate the need to lower the dose and metabolites below a certain threshold indicate a need to increase the dose). This process of administering the drug and measuring metabolite levels was "well-understood, routine, [and] conventional" in the art at the time of filing.[6] Analyzing the art at the time of filing, the *Mayo* Court stated, "scientists already understood that the levels in a patient's blood of certain metabolites, including, in particular, 6-thioguanine and its nucleotides (6-TG) and 6-methylmercaptopurine (6-MMP), were correlated with the likelihood that a particular dosage of a thiopurine drug could cause harm or prove ineffective."[7]

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[4] 566 U.S. 66 (2012).

[5] *Id*. at 74-75.

[6] *Id*. at 74.

[7] *Id.* at 74-75.

Mayo exemplifies a § 101 ineligibility ruling that is focused on the facts underlying the claims at issue: namely, the claim recited a process that was identical in every particular to a well-known pre-existing process, observed a newly-discovered fact about that known process, and did not specify any new or even a modified step, structure or element for the process. *Mayo*'s fact-specific justification for concluding the claims were patent ineligible does not have broad applicability for examiners evaluating modern diagnostic inventions where, as discussed in Section III.B. below, the patents teach and claim processes that are materially different from what was well-known in the art before.

B. *Association for Molecular Pathology v. Myriad*

Association for Molecular Pathology v. Myriad Genetics, Inc.,[8] like Mayo, is a fact-bound decision that analyzes claims to older technology no longer claimed in diagnostic medicine. In *Myriad,* the Supreme Court issued a limited decision: "We ***merely hold*** that genes and the information they ***encode*** are not patent eligible under §101 ***simply because*** they have been isolated from the surrounding genetic material."[9] The court reasoned that the claimed isolated DNAs fell within the law of nature exception because they were structurally identical to the natural genes and did not rely on any chemical changes that result from isolation. Importantly, Myriad had not contributed any new alteration, structure, property or function to its alleged invention. The Court instead emphasized its conclusion that the claims were expressly defined in terms of the genes' natural functions of encoding a natural protein: "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information ***encoded*** *in the BRCA1 and BRCA2 genes*."[10] The Court explicitly left intact many potential claims to *applications* of gene technology, noting that this case "does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes."[11] The Court also held, by contrast, that cDNAs that have been synthetically created are sufficiently different from natural DNA molecules for patent eligibility.

The claims at issue in the Supreme Court's narrow decision in *Myriad* are wholly different from the kinds of claims sought in diagnostic medicine today. Current claims in diagnostic medicine do not, for example, simply recite isolated strands of DNA encoding a protein. It is a mistake to elevate *Myriad*'s importance given that the underlying specific claims bear little to no resemblance to current claims in the diagnostic space. As the Coalition previously stated in its August 2014 comments setting forth a framework for analyzing subject matter eligibility, "A claim does not encompass a natural product simply because the claimed composition shares some or many properties with a natural product. If those properties are put to

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[8] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc*., 133 S. Ct. 2107 (2013).

[9] *Id*. at 2120 (emphasis added).

[10] *Id*. at 2118 (emphasis added).

[11] *Id*. at 2120.

new, different, or enhanced function or use in the particular composition of the claim, then the claim is to a patent eligible human invention."[12]

C. *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp.*

In *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation v. Ambry Genetics Corporation* ("*Ambry*"),[13] the Federal Circuit found ineligible certain composition of matter claims related to primers and certain method claims related to comparisons between the wild-type BRCA sequences with the patient's BRCA sequences. Both the composition and method claims in *Ambry* are fundamentally different from the kinds of method claims typically sought in diagnostic medicine today.

The Federal Circuit concluded in *Ambry* that the method claims at issue were patent ineligible because it was undisputed that many of the elements of claims 7 and 8 "set forth well-understood, routine and conventional activity engaged in by scientists at the time of" the patent applications.[14] But as we explained in a prior comment on the USPTO's guidance:

> Central to the Federal Circuit's holding on the method claims was its finding that 'The district court found, *and Myriad does not challenge*, that the elements of the second paragraphs of claims 7 and 8 "set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications."'[15] Viewed from the perspective of the patentee purportedly admitting the claims recited purely well-understood, routine and conventional activity engaged in by scientists at the time of filing, the Ambry holding is a rather unremarkable application of Mayo and should not be interpreted by the Office as breaking any new ground.[16]

Unless an applicant makes admissions along these lines, *Ambry* should not apply. *Ambry* is therefore so narrow in its factual and procedural context as to preclude its application to virtually any patent claims presented to the Office.

D. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*

In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,[17] the Federal Circuit affirmed a district court decision invalidating certain claims directed to methods for amplifying and detecting

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[12] *See August 2014 Comments* at 6.

[13] 774 F.3d 755 (Fed. Cir. 2014).

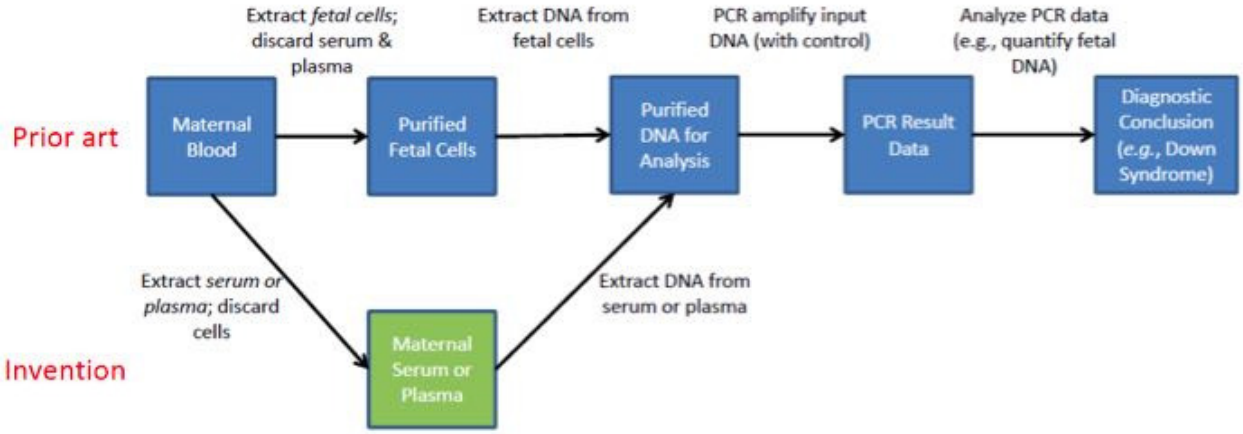
[14] *Id.* at 764.

[15] *Id.* (emphasis added).

[16] *March 2015 Comments* at 19.

[17] 788 F.3d 1371 (Fed. Cir. 2015).

paternally inherited cell-free fetal DNA ("cffDNA"), as well as claims to methods for making diagnoses based on the detected cffDNA. Similar to *Mayo* and *Myriad*, *Sequenom* addresses claims that resemble naturally occurring phenomena far more closely than current claims in diagnostic medicine do. Furthermore, there are reasons to seriously question the robustness and, therefore, the applicability of the *Sequenom* court's analysis beyond the specific facts of the case. For example, the court explained that "the preparation and amplification of DNA sequences in plasma or serum were well-understood, routine, conventional activities performed by doctors" at the time of filing.[18] This statement and others throughout the *Sequenom* decision suggest the court failed to grasp at least one critical and highly technical difference between Sequenom's claimed process and what was routine in the art at the time of filing (as shown below).



As explained in more detail in Section III.B. below, the facts and holding in *Sequenom* are easily distinguished from the kind of novel and complex human-made correlations claimed in diagnostic medicine today.

E. Importance of Examining Claims as a Whole.

The Federal Circuit continues to appropriately caution that each claim must be examined as a whole. As the Federal Circuit recently noted in *Rapid Litigation Management v. Cellz-Direct, Inc.*, "in examining claims under step two, ***we must view them as a whole***, considering their elements both individually and as an ordered combination." (emphasis added).[19] As the Supreme Court explained in *Diamond v. Diehr*, even if many or all of the constituent steps may be well known and in use, the claim as a whole ordered combination may well be novel.[20] If examiners simply tease apart the steps and fail to conduct the analysis of the claim as an entire

[18] 788 F.3d at 1377.

[19] 827 F. 3d 1042, 1051 (Fed. Cir. 2016).

[20] *Diamond v. Diehr*, 450 U.S. 175, 188 (1981) (stating "a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made").

ordered combination, they violate the Supreme Court's command for assessing subject matter eligibility.[21]

III. Applicability of Cases to Diagnostic Medicine

A. Overview of Diagnostic Medicine

The Coalition believes that it is essential for examiners to appreciate how diagnostics work and how the claims typically sought in diagnostic medicine differ from decades-old claims held in court decisions to simply recite a law of nature. Diagnostic medicine seeks to analyze complex statistical correlations to advance patient diagnosis and treatment. Claims that recite a law of nature per se recite a cause and effect, direct biological connection between two phenomena. By contrast, a complex statistical correlation is a human-made connection between two or more phenomena not directly related in any biological/mechanistic way. In diagnostic medicine today, especially where the low-hanging fruit of high penetrance genes such as *BRCA1* has been picked, a particular level of a marker or the presence of a mutation typically does not alone indicate the individual patient has the disease in question. Instead, a diagnosis is made based on a complex statistical correlation invented by humans, involving analysis of multiple different markers. The kind of molecular diagnostic testing claims sought by Coalition member companies today typically integrates an algorithm into the technical process of gathering specific biomarker information (*i.e.*, the information that is relevant to the specific algorithm), applying the algorithm to that to that information, and then diagnosing a disease based at least in part on the results of the algorithm.

B. Example Claim

The Coalition has previously submitted a very detailed framework for analyzing subject matter eligibility and exemplary claims, all completely and painstakingly harmonized with old and new governing case law.[22] We reiterate our call for the Office to adopt this framework or, at the very least, incorporate significant portions of its analytical approach and principles (*e.g.*, difference between properties and functions, careful comparison to a clearly identified next closest natural product or law/process, etc.). These exemplary patent-eligible claims illustrate some of the differences between typical claims sought in diagnostic medicine and the claims at issue in the cases discussed above.

The Coalition previously submitted the following sample claim, including background information about the specification and the state of the art, to discuss how to analyze subject matter eligibility issues for diagnostic claims:

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[21] *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (claim elements must be evaluated "both individually and as an ordered combination")

[22] *See generally August 2014 Comments* at 18-43.

Sample Claim[23]

A method for determining the likelihood a test patient has sepsis, the method comprising:

(a) measuring the concentration of D1 in a blood sample obtained from said test patient;

(b) measuring the concentration of D2 in the blood sample;

(c) measuring the concentration of D3 in the blood sample;

(d) combining the measured concentrations to derive a numerical index score;

(e) comparing said index score with a numerical reference score, wherein said comparison indicates the likelihood said patient has sepsis.

In the above example, by way of background, the hypothetical specification teaches that sepsis is a complex, incompletely understood and often fatal disorder, typically accompanied by porphyria. D1 is 15-amino-acid peptide that, among its multiple effects, induces porphyria. D1 has been shown to be useful as a biomarker in diagnosis of stroke and inflammatory bowel syndrome, as a biomarker of neural transmitter activity in animal health diagnosis, and as a biomarker for identifying a patient susceptible to particular cancer therapies. The specification teaches for the first time that increased plasma concentrations of D1 are associated with sepsis.

The hypothetical specification for this sample claim teaches the development of a multi-biomarker assay, measuring and comparing the relative levels of D1, D2 & D3 to better diagnose sepsis. The specification further refines this multi-biomarker panel by showing that the combination of D1, D2 & D3 level measurements into a single index score yields a test where patients with an index score exceeding a particular reference score are predicted to have sepsis with sensitivity of 95% and specificity of 97%. D1, D2 & D3 are all well-known proteins in the art. The art teaches numerous techniques for measuring these biomarkers in several specimen types. D1, D2 & D3 levels are routinely measured in emergency room patients as part of a comprehensive panel comprising 23 other markers. This panel screens for several critical conditions common to emergency room patients, including anemia, tachycardia and sepsis. Nothing in the art discloses measuring D1 for the purpose of detecting sepsis. D1 is in the routine emergency room panel as a rough screen for acute anemia associated with blood loss. The art teaches measuring D2 independently as a rough screen for sepsis. The art further teaches measuring D3 as part of a 5-marker panel for hypotension, a dangerous condition in its own right and a common sign of sepsis as well as several other critical conditions.

In this example claim, the routine process and the claimed process are identical up to and including the point of measuring these three markers. However, the claimed process adds important elements and steps to the routine process by (1) defining a distinct panel of markers (D1, D2, D3) never taught in the art as being analyzed or having any utility *as a discrete set*, (2) combining the three markers' concentrations to derive a numerical index score and (3) comparing this index score to a reference score. Combining D1, D2 & D3 into a numerical score is new. Because the claimed method recites a new rather than routine process that is a specific statistical application of innumerable known and unknown underlying natural principles, it is not directed to any natural principles per se and is therefore eligible for patenting.

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[23] This sample claim was originally discussed as "Claim 11" at pp. 42-43 of the Coalition's *August 2014 Comments*.

This sample claim illustrates that kind of new non-routine processes sought by applicants in diagnostic medicine, and how the mere presence of claim steps that have some background natural principles are still patentable when the claims recite a process that differs from that which is well-understood, routine, and conventional in the art.

IV. Conclusion

The Coalition believes that a greater appreciation for the narrowness of the holdings in the recent subject matter eligibility cases in the life sciences is warranted. Examiners must better familiarize themselves with the gaps between the subject matter claimed and the specific reasoning applied in cases such as *Mayo*, *Myriad*, *Ambry*, and *Sequenom* on the one hand, and current claims sought in molecular diagnostics on the other. The Coalition hopes that the USPTO will use the framework and the analysis we have submitted here and in our past comments to continue to improve the quality of examination of molecular diagnostic claims.