2017-2508

United States Court Of Appeals for the Federal Circuit

ATHENA DIAGNOSTICS, INC.; OXFORD UNIVERSITY INNOVATION LTD.; MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.,

Plaintiffs/Appellants,

v.

MAYO COLLABORATIVE SERVICES, LLC, d/b/a Mayo Medical Laboratories; MAYO CLINIC,

Defendants/Appellees,

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF MASSACHUSETTS, CASE NO. 1:15-CV-40075-IT. THE HONORABLE INDIRA TALWANI, JUDGE PRESIDING

DEFENDANTS-APPELLEES' RESPONSIVE OPENING BRIEF

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January 30, 2018

CERTIFICATE OF INTEREST

Counsel for Appellees, Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic, certifies the following:

1. The full name of every party represented by me is: Mayo Collaborative Services LLC d/b/a Mayo Medical Laboratories and Mayo Clinic

2. The name of the real party in interest (please only include any real party in interest NOT identified in Question 3) represented by me is: Mayo Collaborative Services, LLC

3. Parent corporations and publicly held companies that own 10% or more of the stock in the party: N/A

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

Fish & Richardson, P.C.: Adam J. Kessel, Kelly Allenspach Del Dotto

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. *See* Fed.

Cir. R. 47.4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary). None.

Dated: January 30, 2018

/s/ *Jonathan E. Singer*

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STATEMENT OF RELATED CASES

Defendants-Appellees Mayo Collaborative Services, LLC, d/b/a Mayo Medical Laboratories, and Mayo Clinic (collectively "Mayo") agree with the statement of Plaintiffs-Appellants. There are no related cases as defined by the applicable rules.

STATEMENT OF JURISDICTION

The district court had subject matter jurisdiction over this patent infringement case under 28 U.S.C. §§ 1331 and 1338. This Court has jurisdiction over the appeal from the district court's final judgment under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the asserted claims are patent ineligible where those claims are directed to methods of diagnosing disease by detecting in a human fluid sample naturally occurring autoantibodies that correlate to the presence of disease, and where the claimed method uses only conventional laboratory techniques admitted by the patent as "standard" and "known per se in the art."

2. Whether the district court properly granted Mayo's Rule 12(b)(6) motion to dismiss based on the pleadings, the plain language of the claims, statements in the patent, and counsels' admissions.

STATEMENT OF THE CASE

Asserted claims 6-9 of the '820 patent cover patent ineligible subject matter under this Court's and the Supreme Court's *Mayo* and *Alice* authorities. The district court's decision consistent with those authorities should be affirmed.

As properly found by the district court, the asserted claims are directed to the diagnosis of the neuromuscular disorder *myasthenia gravis* through the detection of naturally occurring autoantibodies to the MuSK protein. Standing alone, this purpose is a patent ineligible law of nature: the correlation between naturally occurring substances on the one hand, autoantibodies to MuSK, and a disease on the other hand, *myasthenia gravis*. Whatever value the inventors' asserted discovery of this natural correlation may have to the medical field, it is by now settled that this discovery alone does not confer patent eligibility. Something more is required—namely, the application of that correlation in non-conventional, non-routine ways not well understood in the art at the time of the invention.

The asserted claims plainly do not meet this standard of eligibility, as the district court properly held. Each applies the inventors' asserted discovery in a routine and conventional way, which the '820 patent itself admits. The patent describes the immunological assay techniques used in the asserted claims as "known per se in the art" and as "standard techniques in the art," citing as exemplary aged references employing the same techniques to diagnose the same disease. Appellants

do not and cannot dispute this. In fact, they admitted it to the district court. Given these statements in the patent, the claims plainly fail the *Alice* and *Mayo* tests.

Appellants' attempts to recast their claims as first-in-kind laboratory methods offer no sanctuary. Applying conventional techniques to a newfound discovery of a natural correlation does not confer eligibility as a "new" laboratory method. Nor does the mere use of man-made reagents or the recitation of "concrete steps" in a method confer eligibility. Rather, what is required is implementation of the natural law in a non-conventional way to yield something more than just an observation of that law. The asserted claims fail to achieve this end, and are thus ineligible for patent protection.

The district court found the asserted claims invalid for lack of subject matter eligibility at the proper stage of this case, its beginning. Everything needed to find the asserted claims invalid under § 101 is spelled out in the '820 patent's specification, and was not contested by Appellants. Invalidity is clear-cut. This Court should affirm.

STATEMENT OF THE FACTS

I. THE '820 PATENT-IN-SUIT

A. The '820 Patent Arose Out of the Discovery that Certain Antibodies Cause *Myasthenia Gravis*

Myasthenia gravis, or MG, is a neuromuscular disorder characterized by the weakness and rapid fatigue of skeletal muscles. (Appx43 (1:13-23).) In the 1960s, decades before the '820 patent inventors filed their first patent application in 2000,

researchers found that a type of naturally-occurring antibody caused about 80% of MG cases. (Appx36; Appx43 (1:24-36).) Instead of targeting foreign substances as antibodies normally do, those antibodies targeted and bound to a receptor in the body called the acetyl choline receptor (AChR). (Appx43 (1:24-36).) Thus, MG was identified as autoimmune in origin. That means that the body's immune system generates antibodies that target a natural bodily substance, which leads to the destruction of healthy tissue. (Appx43 (1:42-48).) These types of antibodies, which attack naturally occurring bodily substances as foreign antigens, are known as autoantibodies. (*Id.*)

Pinpointing the cause of the remaining 20% of MG cases was the research interest of the named inventors of the '820 patent. According to the patent, the inventors' research found that many patients with MG who do not generate autoantibodies to AChR instead generate autoantibodies against another known protein in the body called MuSK (muscle specific tyrosine kinase).[1] (Appx43 (2:49-61).) Taking the patent at its word, the inventors thus discovered a pre-existing natural relationship between a naturally occurring bodily substance—autoantibodies to MuSK—and the incidence of MG and related disorders.

[1] According to the '820 patent, MuSK had been identified as a "receptor tyrosine kinase" associated with muscle cells in the mid-1990's. (Appx43 (1:62-2:5).)

B. The '820 Patent Discloses Only the Use of "Known" Techniques to Detect the Presence of Autoantibodies to MuSK to Diagnose MG

After describing their alleged discovery of this natural correlation between autoantibodies to MuSK and the incidence of MG in a patient, the '820 patent's inventors describe how that correlation can be used to diagnose MG by detecting autoantibodies to MuSK in a bodily fluid. (Appx43-44 (2:61-3:3).) The patent teaches using only routine biological techniques to do so, explaining that "[t]he actual steps of detecting autoantibodies in a sample of bodily fluids may be performed in accordance with immunological assay techniques ***known per se in the art***. Examples of suitable techniques include ELISA,[2] radioimmunoassays and the like." (Appx44 (3:33-35) (emphasis added).)

The patent describes two of these techniques that were "known per se in the art"—one radioimmunoassay technique and one ELISA technique. On a general level, each technique involves the conventional steps of (1) introducing the antigen into a bodily fluid sample, and (2) detecting any autoantibody-antigen complexes that subsequently form. (Appx44 (3:38-47).)

The radioimmunoassay technique "known per se in the art" is implicated by asserted claims 7 through 9. In this "known" and "standard" technique, a labeled antigen is used. (Appx44 (3:3-35, 3:66-4:12).) The labeled antigen (here, MuSK) is

[2] ELISA stands for enzyme-linked immunosorbent assay.

put into contact with a bodily fluid to facilitate formation of autoantibody-antigen complexes. According to the patent, antibodies (including autoantibodies) are precipitated from the fluid. This typically first involves addition of a second "anti-human" antibody to generate complexes of labeled MuSK/autoantibody/secondary antibody that will then precipitate. (Appx44 (3:43-47); *see also* Appx47 (10:48-67).) As was previously well-known, anti-human antibodies recognize features common to all human antibodies, including autoantibodies. (Appx44 (3:43-47).) Finally, after immunoprecipitation of the formed complexes, the assay detects the label associated with the antigen. (Appx44 (4:2-9).)

Because the label is on the MuSK antigen, the assay only detects the label if the labeled antigen has bound to an autoantibody to MuSK. Thus, detecting the MuSK antigen's label after precipitation is the same as detecting autoantibodies to MuSK, which, in turn, indicates that the patient is suffering from a MuSK-related disorder. (Appx44 (3:66-4:9); *see also* Appx47 (10:48-61).)

The patent identifies as a preferred label radioactive labels such as ^{125}I (*i.e.*, radioactive iodine): "Preferably, the label is a radioactive label which may be ^{125}I, or the like." (Appx44 (4:9-10).) Appellants admitted before the district court that "[c]ertainly I-125 was known" at the time of the inventors' law-of-nature discovery. (Appx314 (13:8); *see generally* Appx313-314.)

The '820 patent describes implementation of this known immunoprecipitation assay technique to the inventors' asserted discovery of the connection between MuSK

and MG in a straightforward manner. (Appx47 (10:48-67).) (*See* Opening Br. at 5). Notably, the patent describes the preparation of ^{125}I-MuSK without reference to any of the complexities that Appellants now seek to ascribe to it. (Appx47 (10:50-53).) (*See* Opening Br. at 13-15.)

The '820 patent teaches that the use of immunoprecipitation assays, as well as iodination of antigens (i.e., adding an iodine label) are "standard techniques in the art, the details of which can be found in [prior art] references (4 and 6)." (Appx44 (4:10-12); *see also* Appx47 (10:50-53).) Reference 4 pre-dates the '820 patent's filing date by fifteen years, Reference 6 by twenty-five. (Appx48 (11:19-22, 26-29); Appx140-147; Appx148-155.) Reference 4 is entitled "Acetylcholine receptor antibody as a diagnostic test for myasthenia gravis: results in 153 validated cases and 2967 diagnostic assays." (Appx48 (11:19-21).) Reference 6 is entitled "Antibody to acetylcholine receptor in myasthenia gravis: prevalence, clinical correlates and diagnostic values." (*Id.* at 11:26-28.)

The patent's reliance on these publications to explain the claimed techniques demonstrate what the patent readily admits: immunoprecipitation methods were routine and well understood in the field. (Appx44 (4:10-12); Appx48 (11:19-22, 26-29); *see also* Appx47 (10:50-53); Appx317-321.) As their titles evince, the methods described in these articles are premised upon the natural law underlying the other 80% of MG cases—the presence of autoantibodies to AChR. (Appx141; Appx149.) The patent then applies these same techniques to the inventors' alleged discovery.

The patent's lone working example relies heavily on the previously understood nature of these techniques. The example describes the prior art method involving the use of radiolabeled AChR to diagnose MG in reference 4 as the "***standard*** radioimmunoprecipitation assay for anti-AChR antibodies." (Appx46 (7:37-41) (emphasis added); *see also* Appx43 (1:33-35).) Reference 4 is one of the two references the patent earlier associates with the preferred methods of iodination and immunoprecipitation at Column 4. (Appx 44 (4:10-12).) The example further concedes that the immunoprecipitation performed in the example has been "described previously," citing two more prior art references (12 and 13). (Appx46 (8:24-27), Appx48 (11:50-57).)

Simply put, the only difference between the prior art immunoprecipitation methods and the immunoprecipitation methods described and claimed in the '820 patent is the identity of the labeled antigen: AChR vs. MuSK. (*Compare* Appx142, Appx150, Appx43 (1:33-26), and Appx46 (7:37-41), *with* Appx47 (10:48-67) (describing immunoprecipitation method using ^{125}I-labeled MuSK).) The '820 patent and these publications teach that an antigen can be iodinated using standard techniques, and commercial reagents, and then used in a conventional diagnostic immunoprecipitation method.

The other example given in the '820 patent of a technique "known per se in the art" is the ELISA example implicated by claim 6. This technique also involves creating an autoantibody-MuSK complex, but differs in terms of what part of the

complex is labeled. (Appx44 (3:33-35, 3:66-4:12); Appx46 (8:32-47).) In the "known" ELISA technique, a labeled secondary anti-human antibody is used to detect autoantibody-MuSK complexes. (Appx44 (3:33-53).) In the ELISA technique, a labeled, secondary anti-human antibody will bind to autoantibodies, creating a complex of the autoantibody/antigen/labeled secondary antibody. (Appx44 (3:47-56).) The label on the anti-human secondary antibody can be used to detect autoantibodies to MuSK in the sample since they are bound together as a complex, thereby indicating that the patient is suffering from a MuSK-related disorder. (Appx44 (3:57-65).)

The patent identifies various types of standard, well-known tags and labels for use with the ELISA technique. These tags and labels include enzymatic and radioactive tags, heavy metals, and fluorescent or luminescent molecules. (Appx44 (3:47-53, 3:57-65); Appx46 (8:41-43).) Each of these tags and labels provides a detectable signal indicating the presence of the autoantibody/antigen/labeled secondary antibody complex, and thus the autoantibody of interest. (Appx44 (3:33-65).)

C. Asserted Claims 6-9 Recite Diagnostic Methods Based on the Detection of Naturally-Occurring Autoantibodies Using "Standard" Techniques

The asserted claims, all of which depend from claim 1, recite methods of diagnosing neurotransmission or development disorders related to MuSK based on the presence of autoantibodies to MuSK in a bodily fluid sample. Claim 1 reads:

> 1. A method for diagnosing neurotransmission or developmental disorders related to muscle specific tyrosine kinase (MuSK) in a mammal comprising the step of detecting in a bodily fluid of said mammal autoantibodies to an epitope of muscle specific tyrosine kinase (MuSK).

(Appx48 (12:31-35).) Claim 1 thus covers any possible way of observing the natural law allegedly discovered by the inventors.

Dependent claims 7-9 narrow claim 1 to specify use of the radioimmunoassay technique that the specification identifies as "known per se in the art." Claim 7 describes the conventional steps required to precipitate an antibody from a fluid sample using a labeled antigen, in this case MuSK, and then to monitor for the label associated with the resulting autoantibody/MuSK complex. (Appx48-49 (12:62-13:5).) The label indicates the presence of the autoantibody, and thus the disease. (*Id.*) Claims 8 and 9 then narrow the type of label on the MuSK antigen to the "preferred" standard label—namely, a radioactive label like ^{125}I. (Appx49 (13:6-9).) These claims parrot the specification's description of how to apply the "standard technique" of radioimmunoprecipitation to the inventors' newfound natural law. (*Compare* Appx44 (4:2-12) *with* Appx48-49 (12:62-13:9).)

Claim 6 involves the ELISA example "known per se in the art" that uses a labeled, secondary anti-IgG antibody, as described in Claim 3 from which it depends. (Appx48 (12:47-49).) Claim 6 adds only the conventional idea of comparing the intensity of the sample's signal to the signal of both positive and negative controls to indicate the relative amount of the autoantibody in the sample. (Appx48 (12:57-61).)

II. THE DISTRICT COURT PROPERLY INVALIDATED THE ASSERTED CLAIMS

A. The District Court First Finds the Asserted Claims Are Directed to a Natural Law and Violate *Alice* Step One

Mayo offers medical diagnostic testing for Mayo Clinic and others through Mayo Medical Laboratories, a global reference laboratory that provides diagnostic tests across a wide range of health care subspecialties. Two of those tests relate to the diagnosis of MG. In their complaint, Appellants accused these tests of infringing the '820 patent.

In response to the complaint, Mayo moved to dismiss, raising the § 101 issue. Mayo argued then, as it does now, that the '820 patented methods fail the two-step test for patent eligibility outlined in *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014). Mayo made specific arguments for each of the patent's claims. (Appx105-106; Appx113-118.) In response, Appellants limited the claims at issue to "claims 7-9, and to a lesser extent claim 6," primarily arguing that the claims' recited use and detection of man-made molecules, including ^{125}I-MuSK, made them patent eligible. (Appx162-63, Appx165-179.) They also stated that, while claim 6 "does not require radioactive MuSK or complexes, many other arguments relating to claims 7-9 apply to claim 6." (Appx180.)

At oral argument on Mayo's motion, the district court suggested it would find the asserted claims directed to a law of nature under *Alice* step one. (Appx227-229, Appx244-248, Appx273.) The district court, however, questioned whether it could

resolve *Alice* step two based on the patent's statements that immunoprecipitation and iodination were "standard techniques in the art" and that the claimed methods involved "immunological assay techniques known per se in the art," since those technical matters were "beyond [its] expertise." (Appx230-236; Appx44 (4:10-12 (citing references 4 and 6)); Appx48 (11:19-22, 26-29 (citations for references 4 and 6)); *see also* Appx47 (10:50-53).) The district court sought guidance on whether it could, as a procedural matter, properly hold Appellants to the patent's statements on a motion to dismiss or whether some limited discovery might be necessary. (Appx262, Appx271 (1-9).) Mayo explained that it was within the Court's power to do so, (Appx236), while Appellants suggested that expert and full-blown fact discovery was necessary. (*E.g.*, Appx261 (8-24), Appx262.)

In a well-reasoned 11-page order, the district court then found the asserted claims violated *Alice* step one because they are directed to a patent ineligible law of nature. (Appx280-284.) The district court found that "[t]he focus of the [asserted] claims of the invention is the interaction of the ^{125}I-MuSK and the bodily fluid, an interaction which is naturally occurring. The purpose of the patent is to detect whether any antibody-antigen complexes are formed between the ^{125}I-MuSK receptor and the antibodies 'present in said bodily fluid.'" (Appx282.) In finding the claims directed to patent ineligible subject matter, the district court rejected Appellants' contention that the claims did not violate *Alice* step one due to the presence of man-

made compounds within the claimed methods, properly finding that the claims are directed to methods of diagnosing disease. (Appx281-283.)

The district court drew proper parallels between the asserted claims and controlling case law in deciding *Alice* step one. The district court correctly observed that the asserted claims of the '820 patent resemble those in *Mayo Collaborative Services v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012), where "a man-made substance was administered to a person, and the by-product of the metabolization of that man-made substance was observed." (Appx283.) It also compared the discovery here "that some patients with MG have MuSK autoantibodies in their bodily fluid" with that in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015), where "[t]he only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum." (Appx283.) And it correctly distinguished the asserted claims from those in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016) on the basis that the end result of Appellants' claimed methods is an observation of a natural law, whereas the end result of the *CellzDirect* claims was not the observation of the newly found ability of hepatocytes to survive multiple freeze-thaw cycles, but rather a useful laboratory tool. (Appx283.)

The district court nonetheless denied Mayo's motion to dismiss at that point because, on *Alice* step two, it could not "determine at this juncture whether Plaintiffs' patented methods uses standard techniques in the art, or whether it is sufficiently

inventive to be patentable." (Appx285.) The outcome of *Alice* step two was thus left an open question.

B. After Appellants Admitted that They Did Not Contest the Patent's Description of the Claimed Techniques as "Standard," the District Court Finds the Asserted Claims Lack an Inventive Concept, and Are Thus Invalid Under § 101

The parties next appeared before the district court in the context of a status conference on how much discovery, if any, was necessary to resolve Mayo's § 101 motion. (Appx287; Appx30 (Dkt. 112).) Having already resolved *Alice* step one, the district court focused on step two, seeking to flesh out whether Appellants "used a standard technique that was known in the art" merely to observe their law-of-nature discovery. (Appx305-306.)

At the hearing, the district court commented that, if Appellants agreed with the statements in the patent and the disclosures of its cited references that iodination and immunoprecipitation are standard techniques in the art, then judgment for Mayo was warranted. (Appx306-307(5:18-6:2); Appx318-320.) In response, Appellants admitted that the claimed techniques were, in fact, standard, just as the patent says. Appellants conceded that "[u]sing labels was known in the art," and, as a radioactive label, "[c]ertainly I-125 was known." (Appx313 (12:18-21); Appx314 (13:8).) Appellants also affirmed as correct the '820 patent's statements about the conventional nature of the claimed techniques and their description in the prior art:

> THE COURT: Let me ask plaintiffs' counsel, recognizing your disagreement about the import of this point, **is there any disagreement**

> **as to the truth of this statement, "iodination and immunoprecipitation are standard techniques in the art, the details of which may be found in references (4 and 6)" of the patent?** Because I wasn't willing to take, even though it was in the patent and asserted in the patent and they argued, therefore, an admission, I took the position that that was beyond the motion to dismiss and something to be determined on summary judgment. **So the question is, is there a dispute of fact as to that statement?**
>
> MR. McMAHON: **That statement isolated I can't dispute**, but --
>
> THE COURT: Okay. So then where we are is if that statement isolated is not in dispute, then I should be granting their motion either as a motion to dismiss or as a motion for summary judgment, and you should appeal my decision. Because that is the basis on which they did not get the motion to dismiss, was on the basis of my understanding your opposition being that I could not make that determination on a motion to dismiss.

(Appx318-319 (emphases added).)

After Appellants made these concessions, the district court invited Mayo to renew its motion to dismiss. (Appx343, Appx358-361.) That was warranted—the district court's only stated reason for denying Mayo's initial motion to dismiss was because it questioned whether the patent's admissions were "beyond the motion to dismiss and something to be determined on summary judgment." (Appx319, *see also* Appx304, Appx320, Appx302-361.) By conceding that they did not dispute those statements, Appellants removed the district court's perceived procedural hurdle to granting Mayo's motion. (Appx319-320, Appx360, *see generally* Appx302-361.) As the district court noted, "I just don't think this is a factual dispute case at this point." (Appx352.)

Mayo then renewed its motion, emphasizing the patent's undisputed statements about the conventional nature of the claimed techniques recited in asserted claims 6-9, and substantively addressing each of those claims. (Appx372-377, Appx381-387.) In response, Appellants addressed the claims as a group (*see generally,* Appx541-578) and failed to address specifically claim 6 at all, as they acknowledge in their brief here. (Opening Br. at 15; *see* Appx554.) Substantively, Appellants sought to walk back their prior admissions by submitting an expert declaration and a hodgepodge of statements designed to suggest the existence of one or more disputes of fact. (Appx574-581.)

The district court then granted Mayo's renewed motion to dismiss, concluding that the asserted claims were invalid under § 101 and specifically referencing asserted claims 6-9. (Appx3, Appx5-12.) Relying on its initial ruling, the district court reiterated that the asserted claims of the '820 patent fail *Alice* step one because they are directed to a patent ineligible law of nature. (Appx5-10.) On *Alice* step two, the district court took as undisputed the '820 patent's statement that "immunoprecipitation and iodination are standard techniques in the art" given Appellants' admission. (Appx1-2.) Based on those undisputed facts, it found that the asserted claims employ methods commonly used by researchers in the field and lack an inventive concept, rejecting each of Appellants' attempts to sidestep this conclusion. (Appx10-12.)

In particular, the district court rejected Appellants' arguments that the techniques of iodination and immunoprecipitation are not standard when applied to

proteins because proteins are complex, noting this alleged complexity is not reflected in the patent. (Appx11.) The court found that Appellants' complexity argument "directly contradicts the language in the specification," which "simply state[s] that the 'suitable label' is ^{125}I or the like, and that iodination of the label is a standard technique in the art." (Appx11-12.) And, finally, the district court rejected Appellants' arguments that "the use of a man-made molecule necessarily makes the claims patent eligible," citing the Supreme Court's *Myriad* decision, and noting that the claims do not cover a process for making a man-made molecule. (Appx12.) *See also generally Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013).

STANDARD OF REVIEW

This Court "review[s] a grant of a motion to dismiss according to the law of the regional circuit." *Cleveland Clinic Found. v. True Health Diagnostics LLC*, 859 F.3d 1352, 1359 (Fed. Cir. 2017). The First Circuit reviews *de novo* a district court's dismissal of a complaint for failure to state a claim, "accept[ing] as true all well-pleaded facts alleged in the complaint and drawing all reasonable inferences therefrom in the pleader's favor." *Butler v. Balolia*, 736 F.3d 609, 611 (1st Cir. 2013). In the First Circuit, a district court has broad discretion to convert a Rule 12 motion to one for summary judgment. *Trans-Spec Truck Serv., Inc. v. Caterpillar, Inc.*, 524 F.3d 315, 321-22 (1st Cir. 2008); *see also* Fed. R. Civ. P. 12(d).

Whether the claims of a patent recite patent-eligible subject matter under 35 U.S.C. § 101 is a question of law, reviewed *de novo*. *Cleveland Clinic*, 859 F.3d at 1359.

SUMMARY OF THE ARGUMENT

To determine whether a claim is invalid under § 101, this Court employs the now familiar two-step *Alice* framework. Step one asks whether the claims are directed to ineligible subject matter, like a law of nature. *Alice*, 134 S. Ct. at 2355. If the answer is yes, step two asks whether, considered both individually and as an ordered combination, "the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78). The step two analysis looks for an "inventive concept," or some claim element or elements "'sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Id.* (quoting *Mayo*, 566 U.S. at 72-73) (alteration in original).

Asserted claims 6-9 of the '820 patent are invalid under a straightforward application of the *Alice* framework. Each of those claims is directed to a method of diagnosis by observing a law of nature—the relationship between autoantibodies to MuSK, and MuSK-related disorders. They are thus directed to ineligible subject matter and violate *Alice* step one. Further, each element, or step, in the claimed methods employs assay techniques that were undisputedly "standard" and "known" techniques when the inventors filed their patent application. Viewed alone, and as an ordered combination, those claim elements lack an inventive concept. The claims apply a law of nature with conventional techniques to yield an observation of that law of nature, and thus violate *Alice* step two.

None of Appellants' efforts to liken their claims to those upheld under § 101, or to distinguish them from those invalidated under § 101, have merit.

First, Appellants did not invent a new laboratory technique. Instead, they applied well-known and standard techniques to observe their law-of-nature discovery in a method of diagnosis. That is not patentable, and contrary to Appellants' arguments, *CellzDirect* does not say it is. The asserted claims do not involve a new and useful combination of steps that amounts to more than claiming a natural property itself, as in *CellzDirect*. Rather, they follow the same steps to detect autoantibodies that were "known per se in the art," except with a different antigen, MuSK. Those steps lead merely to the observation of a natural law, and the corresponding diagnosis based on it.

Second, that the inventors may have been the *first* to describe a method involving the correlation between anti-MuSK autoantibodies and MuSK-related disorders says nothing about patent eligibility. The asserted novelty of that law-of-nature discovery cannot supply the inventive concept under the *Alice* framework. *Cleveland Clinic*, 818 F.3d at 1361-63.

Third, the mere use of a man-made reagent in the claimed methods does not confer patent eligibility. That argument has already been rejected in the context of screening with a man-made material, a DNA probe. *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 761, 764 (Fed. Cir. 2014); *see also Ariosa*, 788 F.3d at 1374, 1378. No different outcome is warranted here.

The district court correctly invalidated the asserted claims in the face of all these same arguments, and Appellants' procedural objections to that ruling do not salvage their claims. Appellants' admission that the patent accurately states that the assay methods recited in the asserted claims are standard dispensed of any possible factual dispute on *Alice* step two. The outcome of the § 101 inquiry was and remains plain on the face of the uncontroverted pleadings.

ARGUMENT

I. *ALICE* STEP ONE: THE ASSERTED CLAIMS ARE DIRECTED TO INELIGIBLE SUBJECT MATTER

A. The Asserted Claims Are Directed to a Law of Nature: The Correlation Between the Presence of Autoantibodies to MuSK and MuSK-Related Disorders

Asserted claims 6-9 are directed to patent ineligible subject matter—a law of nature. The claims cover methods for observing the presence of a naturally occurring autoantibody in a human fluid sample, which correlates to the existence of MuSK-related disorders. Each asserted claim depends from claim 1, which recites a method of diagnosis by detecting in a human fluid sample the presence of a naturally-occurring autoantibody directed against MuSK. (Appx48-49 (12:31-35, 12:47-49, 12:57-13:9).) Each asserted claim provides some additional, admittedly known and standard detail about how, or with what, to detect the autoantibody, and that is where each claim stops. (*Id.*) Each asserted claim is thus directed to a patent-ineligible law

of nature: the relationship between (1) the presence of autoantibodies to MuSK in bodily fluid, and (2) the disease.

The specification demonstrates that the asserted claims are directed to a law of nature. *Cleveland Clinic*, 859 F.3d at 1360-61 (consulting specification to support conclusion that claims are directed to patent ineligible subject matter); *Ariosa*, 788 F.3d at 1376 (same). It states that the inventors were the first to uncover the correlation between anti-MuSK autoantibodies and certain neurotransmission disorders:

> The present inventors surprisingly found that many of the 20% of MG patients which do not exhibit any autoantibodies to AChR, instead have IgG antibodies directed against the extracellular N-terminal domains of MuSK, a receptor tyrosine kinase located on the cell surface of neuromuscular junctions, indicating that they are afflicted with a form of MG which has a different etiology from MG characterized by circulating autoantibodies to AChR. (Appx43 (1:54-61).)

> The present inventors have therefore now shown that anti-MuSK antibodies have functional effects on agrin-induced AChR clustering in vivo, and direct interference with this agrin/MuSK/AChR pathway may be an important disease mechanism in vivo. (Appx43 (2:46-50).)

The specification also explains the diagnostic aspect of the "invention is particularly advantageous because the identification of this new subclass or subtype of MG patients will allow for more accurate and speedy diagnosis of individuals by medical practitioners." (Appx44 (3:4-7).) The inventors' descriptions of their finding, and diagnostic "invention," are based on the relationship between anti-MuSK antibodies and disease. That is a law of nature.

This Court and the Supreme Court's § 101 case law compels the conclusion that the asserted '820 patent claims are directed to a law of nature. In *Mayo*, the Supreme Court concluded that claims directed to "relationships between concentrations of certain metabolites [of a thiopurine drug] in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm" were based on "entirely natural processes" and were therefore drawn to a law of nature. *Mayo*, 566 U.S. at 77. The same is true of the relationship set out in the '820 patent's claims: the presence of a MuSK-related disease correlates to the existence of the MuSK autoantibodies, both of which are naturally occurring.

Similarly, this Court found claims "directed to multistep methods for observing the law of nature that MPO [myeloperoxidase] correlates to cardiovascular disease" as directed to a law of nature because the "invention . . . involves 'seeing' MPO already present in a bodily sample and correlating that to cardiovascular disease." *Cleveland Clinic*, 859 F.3d at 1361; *see also PerkinElmer, Inc. v. Intema Ltd.*, 496 F. App'x 65, 70-71 (Fed. Cir. 2012) (claims describing the relationship between biological marker levels from a pregnant woman's first and second trimesters and the risk of fetal Down's syndrome directed to a natural law). Here, too, the claimed '820 invention involves "seeing" "already present" autoantibodies to MuSK in the bodily fluid sample, and correlating that to a MuSK-related disease.

That the only advance over the prior art described by the '820 patent is the correlation between autoantibodies to MuSK and MuSK-related diseases also counsels

that the asserted '820 patent claims are directed to a law of nature. In *Genetic Technologies Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1371-72 (Fed. Cir. 2016), the patent focused on a newfound concept called "linkage disequilibrium," by which coding regions of DNA are correlated with a non-coding region of DNA. While the claim required analysis of a biological sample, the "claim focuse[d] on a newly discovered fact about human biology," and was thus directed to ineligible subject matter. *Id.* at 1375-77.

Appellants' attempt to distinguish *Mayo*, *Cleveland Clinic*, and also *Ariosa*, on the basis that the claims in those cases "gave no specific direction for performing the method," and "recite[] no specific concrete steps" whereas asserted claims 6-9 do is unavailing. (Opening Br. at 35-38.) The level of direction (generic vs. specific) or type of step (concrete vs. mental) recited in a claim to carry out its method is not the concern of *Alice* step one. The pertinent concern is whether a claim is "directed to" merely observing or detecting a natural law, or something more. *Alice*, 134 S. Ct. at 2355.[3]

[3] Amici's professed concern regarding standards for determining *Alice* step one is not relevant to this case. There can be no reasonable dispute in this case that the claims are designed to observe or detect the association between the naturally occurring autoantibodies to MuSK and the MuSK-related disease. That is a natural relationship. While a future case may present itself to elucidate further the standard for *Alice* step one in the life sciences arts, this case does not require such elaboration.

Here, just as in *Mayo, Cleveland Clinic*, and *Ariosa*, the asserted claims are directed to ineligible subject matter, and the level of detail in the claimed methods does not change this. The asserted claims are premised on observing the relationship between autoantibodies to MuSK and certain disorders, a *natural* relationship lacking any human ingenuity. In this regard, Appellants ignore that many of the claims invalidated in *Ariosa* and *Mayo* included specific, concrete, steps for carrying out the claimed methods, including performing PCR and using a probe in *Ariosa*, 788 F.3d at 1374, 1378, and high-performance liquid chromatography in *Mayo*, but were still directed to ineligible subject matter. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1351, 1357 (Fed. Cir. 2010), *rev'd* 566 U.S. 66 (2012). Simply put, the law provides no support for Appellants' assertion that just because their claims are directed to methods that incorporate a natural law they are somehow *per se* patent eligible. (Opening Br. at 32.)

Appellants' suggestion that the asserted claims' use of ^{125}I-MuSK gets them past *Alice* step one also fails, and the district court was manifestly not "flat out wrong" to call the interaction between ^{125}I-labeled MuSK and the autoantibodies of interest in the bodily fluid naturally occurring. (Opening Br. at 29-30, 36, 38.) Those materials bind together according to a law of nature, and the use of the label does not change the nature of their binding nor of the relationship between them. The district court was correct to characterize this as a "natural occurrence." (Appx282.)

This Court has repeatedly held that the mere use of a man-made material in a method claims will not save a claim under § 101. Claims directed to screening a patient's DNA using a man-made material—a labeled DNA probe—failed to satisfy § 101 in *In re BRCA1*, 774 F.3d at 761, 764. Likewise, this Court invalidated a claim involving the use of a man-made probe to detect a naturally-occurring substance in *Ariosa*, 788 F.3d at 1374, 1378. *See also Genetic Techs.*, 818 F.3d at 1378 n.3 ("We are not persuaded by GTG's arguments that claim 1 is inventive because it involves analysis of *man-made* amplified DNA." (emphasis in original)). And the *Mayo* claims involved administering a man-made drug, but were not patent eligible because they were directed to the natural correlations between the drug's metabolites and toxicity. *Mayo*, 566 U.S. at 72, 77-80.

Appellants' arguments about the cDNA claims upheld by the Supreme Court fall flat. The sequence of cDNA does not exist in nature, and thus can be said to be "markedly different" than anything naturally occurring. *Myriad*, 569 U.S. at 594-95 (2013); *see id.* at 590-91. Here, there is nothing "markedly different" between labeled MuSK and non-labeled MuSK—there simply is an attached, conventional label. Extending patent protection to conventionally labeled natural materials would gut the Supreme Court's *Myriad* decision. Indeed, the "isolated DNA" of that case also did not exist in nature, but the difference between that and the intact DNA was considered too routine to warrant patent protection. *Id.* at 594-95. The same is true

here. Thus, the mere fact some asserted claims use labeled MuSK does not make them patent eligible under *Alice* step one.

B. The Asserted Claims Are Unlike Those Upheld in *CellzDirect*

Appellants' primary strategy on *Alice* step one—namely, attempting to draw parallels to the claims this Court found patent eligible in *CellzDirect*—is of no avail. The claims in *CellzDirect* were not directed to observing the natural property the inventors discovered: the ability of hepatocytes to survive multiple freeze/thaw cycles. Instead, the claims utilized that newly-discovered property in a new laboratory technique. By contrast, the asserted '820 patent claims plainly are directed to observing the natural law the inventors allegedly discovered: the correlation between autoantibodies to MuSK and MuSK-related diseases.

The claims in *CellzDirect* recited a "method of producing a desired preparation of multi-cryopreserved hepatocytes" and set out steps required to produce such a preparation. 827 F.3d at 1046. Although the claims included a newfound natural property of hepatocytes discovered by the inventors—"said hepatocytes being capable of being frozen and thawed at least two times"—the "end result" of the claims was "not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles." *Id.* at 1046-48. Rather, the claims are directed to a "new and useful" method of preserving hepatocyte cells. *Id.* at 1048.

The *CellzDirect* claims appropriately *applied* the discovery of a natural property of hepatocytes "to create a new and improved way of preserving hepatocyte cells for

later use." *Id.* ("The inventors certainly discovered the cells' ability to survive multiple freeze-thaw cycles, but that is not where they stopped, nor is it what they patented."). The claimed methods resulted in a preparation of cells with much higher viability than could be achieved with prior art methods. *Id.* at 1045, 1047. That result was due to the particular steps the inventors designed based on applying the natural property they uncovered, and which are recited in the claimed process. *Id.* at 1047-48.

This Court distinguished the claims in *CellzDirect* from claims that "amounted to nothing more than observing or identifying [an] ineligible concept itself." *Id.* at 1048. The distinguished and ineligible claims referenced by the Court in *CellzDirect* included those in *Genetic Technologies*, which "recited methods for ***detecting*** a coding region of DNA based on its relationship to non-coding regions," as well as those in *Ariosa*, which "recited methods for ***detecting*** paternally inherited cffDNA in the blood or serum of a pregnant female." *Id.* (emphases added). Critically, "[a]lthough the claims in each of these cases employed method steps, the end result of the process, the essence of the whole, was a patent-ineligible concept." *Id.* The same was true in *Cleveland Clinic*, where, after *CellzDirect*, this Court found claims reciting methods of assessing a patient's risk for disease by ***detecting*** the levels of a naturally occurring molecule in a patient sample and comparing them to controls were directed to ineligible concepts. *Cleveland Clinic*, 859 F.3d at 1361.

Just like those ineligible claims, Appellants' claimed methods are for diagnosing certain diseases by ***detecting*** naturally occurring antibodies that correlate with those

diseases. This is nothing more than the observation of a natural law, which is ineligible subject matter. The asserted claims are not, as Appellants imply, directed to some new way of detecting antibodies. (Opening Br. at 28, 32-33.) Rather, the asserted claims are methods for diagnosis of a disease by detecting antibodies produced in the human body associated with that disease using conventional techniques. That "in form" they add various steps to carry out that detection does not change that to which they are directed. (*See id.* at 31.)

Appellants also erroneously assert that *CellzDirect* stands for the proposition that "[m]ethod claims that recite specific steps to be performed in a laboratory are and have always been patent eligible, even when the method involves a law of nature." (*Id.* at 22; *see also id.* at 23.) This asserted view of the law runs counter to numerous precedents holding claims patent ineligible that involved concrete steps performed in a laboratory setting. *See, e.g.*, *Cleveland Clinic*, 859 F.3d at 1356-57 (measuring molecules in blood, serum, plasma or urine), *Genetic Techs.*, 818 F.3d at 1372 (DNA amplification); *Ariosa*, 788 F.3d at 1373-74 (manipulating blood samples; DNA amplification; detection with probe; nucleic acid analysis); *In re BRCA1*, 774 F.3d at 1245 (isolating DNA from sample; probe hybridization). Indeed, *Mayo* itself belies this supposed rule, as it found ineligible claims reciting the laboratory steps of administering a drug and determining a metabolite level. *Mayo*, 566 U.S. at 74-75, 78-79.

Appellants make much of the alleged novelty of the correlation they discovered and, if true, the concomitant fact that they were therefore the first to perform the claimed method. That is irrelevant to *Alice* step one. Patent eligibility does not concern itself with who was the first to carry out a claimed method. *See Ariosa*, 788 F.3d at 1379-80 (declining to find eligibility because "no one" was using a pregnant mother's plasma to amplify paternally inherited cffDNA before the inventors' discovery). Rather, what matters is whether that claimed method is directed to a natural law. As properly found by the district court, Appellants' claimed methods are so directed under *Alice* step one.

II. *ALICE* STEP TWO: ASSERTED CLAIMS 6-9 LACK AN INVENTIVE CONCEPT BECAUSE THEY EMPLOY STANDARD, WELL-KNOWN TECHNIQUES TO YIELD ONLY THE OBSERVATION OF THE NATURAL LAW

A. The Method Steps Were Admittedly Well-Understood, Conventional and Routine

Because they are directed to a law of nature, the asserted claims are only patent eligible if they include an inventive concept, as required by *Alice* step two. They do not. The additional process steps claimed for detecting autoantibodies to MuSK are, as described in the '820 patent and admitted by Appellants, "known per se in the art" and "standard techniques in the art." (Appx44 (3:33-35, 3:66-4:12); Appx318-319.) The claims thus lack an "inventive concept" and are invalid. *See Mayo*, 566 U.S. at 73 (invalidating claims where "the steps in the claimed processes (apart from the natural

laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field").

As described above, the additional process steps in claims 7-9 specify that autoantibodies to MuSK are detected through the use of a labeled antigen. The steps in claim 7 include (1) contacting a labeled MuSK antigen with a patient's bodily fluid sample to generate complexes of the autoantibody and labeled MuSK, (2) immunoprecipitating those complexes, and (3) monitoring for the label. These are the same "actual steps of detecting autoantibodies in a fluid sample" the patent lists and explains are "known per se in the art." (Appx44 (3:33-35, 3:66-4:12).) Neither claim 8 nor claim 9 adds any additional steps to claim 7. Claim 8 refines claim 7 by requiring the use of a radioactive label, and claim 9 further refines that label to ^{125}I. As Appellants had to acknowledge, "[u]sing labels was known in the art," and, as a radioactive label, "[c]ertainly I-125 was known." (Appx313 (12:18-21); Appx314 (13:8).)

The '820 patent itself describes the previous use of each step of these claimed methods, only with a different ^{125}I-labeled antigen. The patent explains that immunoprecipitation with radiolabeled AChR as the antigen had been used to diagnose MG in the majority of patients. (Appx43 (1:33-35).) It calls that particular radioimmunoprecipitation method to diagnose MG "standard." (Appx46 (7:35-41).) The patent also directs the reader to two decades-old scientific publications that describe previous use of radioimmunoassays to detect autoantibodies, again using

radiolabeled AChR. (Appx44 (4:9-12); Appx48 (11:19-22, 26-29); *see also* Appx46 (7:35-41); Appx47 (10:50-53).)

Based on the '820 patent itself, anyone wishing to detect the presence of autoantibodies that target a specific antigen would have known that it could be done by (1) contacting a bodily fluid sample with the labeled antigen, (2) precipitating the antibodies in the sample, and (3) monitoring for the label. Each of these individual steps is present in claims 7-9 and, viewed as a whole, the order of the claimed steps mirrors the order of steps used in the standard assays. By tracking standard immunoassay techniques, claims 7-9 "do nothing more than spell out what practitioners already knew"—how to detect autoantibodies in a bodily fluid sample by using a radiolabeled antigen that would complex with the autoantibody, precipitate along with it, and signal its presence. *See In re BRCA1*, 774 F.3d at 764. The claims thus lack an inventive concept. *Id.*; *see also Mayo*, 566 U.S. at 79 ("Purely 'conventional or obvious' '[pre]-solution activity' is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." (alteration in original)).

Claim 6 also recites admittedly standard techniques and lacks an inventive concept. Claim 6 depends from claim 3 and specifies the use of a tagged or labeled anti-IgG antibody to detect any MuSK/autoantibody complexes that form during the assay. (Appx48 (12:31-35, 47-49, 57-61).) This is the ELISA antibody detection

technique the specification identifies as "known per se in the art." (Appx44 (3:33-65).) These steps cannot supply an inventive concept. *See Mayo*, 566 U.S. at 79-80.

Beyond this admittedly known technique, claim 6 recites a patent-ineligible mental process of comparing data to determine relative amounts of antibodies. Claim 6 tells one that the strength of the sample's signal can indicate the relative amount of antibody present by comparison to the signals of positive and negative controls. (Appx48 (12:57-61).) The claim does not require that one make the comparison or do anything with it. This mental step does not supply an inventive concept to claim 6. *See Mayo*, 566 U.S. at 78-79; *In re BRCA1*, 774 F.3d at 763 (explaining that "an abstract mental process of 'comparing' and 'analyzing' two gene sequences" is a patent ineligible abstract idea).

Claims 6-9 are analogous to many others this Court has found lacked an inventive concept. In *Cleveland Clinic*, this Court found claims directed to a law of nature and reciting steps of measuring a natural by-product involved in that natural law as lacking an inventive concept where known measuring techniques, and known statistical models, could be employed. 859 F.3d at 1362. This Court pointed out that Cleveland Clinic had not invented or claimed any new assay technique. *Id.* Nor have Appellants. And in *Ariosa*, claims directed to a natural phenomenon and reciting the steps of DNA amplification and probe-based detection lacked an inventive concept where the patent expressly described those steps as "standard," just like the '820 patent does. 788 F.3d at 1377-78. (Appx44 (3:33-4:12).)

Similarly, in *Genetic Technologies*, claims directed to a law of nature and reciting the physical steps of DNA amplification and analysis lacked an inventive concept because the specification confirmed those were "standard experimental techniques." 818 F.3d at 1375-77. There, as here, it was undisputed the claimed techniques were well known, routine and conventional when the patent application was filed. *Id.* at 1377-78. The patentee, like Appellants, admitted so, including that the techniques were already being practiced in the field and described in the prior art. *Id.*

The *Genetic Technologies* claims also recited a mental process step, like claim 6 here, but that step did not supply an inventive concept because "it merely sets forth a routine comparison that can be performed by the human mind." *Id.* at 1378. Other cases similarly hold that methods involving only mental comparisons and routine and conventional activities are not patent eligible. *In re BRCA1*, 774 F.3d at 763-65 (finding mental comparisons ineligible, and steps of hybridizing a gene probe, detecting the hybridization product, amplification, and sequencing were "well-understood, routine, and conventional," and thus insufficient to supply an inventive concept); *see also PerkinElmer*, 496 F. App'x at 70 (finding the steps of "measuring a screening marker" and "determining risk" by making comparisons lacks an inventive concept where the patent stated measurements could be undertaken with "known methods" and "known statistical techniques").

Although they largely ignore it in their briefing, Appellants have admitted that their patent correctly states that detecting autoantibodies using ELISA,

immunoprecipitation, and iodinated antigens were standard techniques when they filed their patent applications. Those standard techniques are the only ones recited in the steps of claims 6-9. And those steps are arranged in the claims in the same manner scientists had long employed to achieve the same end—detecting autoantibodies including those directed against AChR. Claims 6-9 therefore lack an inventive concept and fail *Alice* step two. *See Mayo*, 566 U.S. at 72-73, 79-80.

B. Appellants' Asserted "Inventive Concepts" Are Not Supported

As they do with *Alice* step one, Appellants try but fail to recast their claims to avoid invalidity. But the '820 patent claims say what they say, reciting admittedly well-known, oft-used, and standard methods. They lack an inventive concept, and the district court did not err in so finding.

1. Claims 6-9 Do Not Set Out a New Combination of Steps

The steps of claims 6-9, whether taken individually or as an ordered combination, track standard antibody detection techniques and lack an inventive concept. Appellants' argument that their asserted claims describe an "innovative, new combination of steps" belies their admissions and their patent's teachings. (Opening Br. at 42-43.) It also runs afoul of the black letter law that an inventive concept cannot rest upon the purported novelty of ineligible subject matter. *Cleveland Clinic*, 859 F.3d at 1361-63; *see also Myriad*, 569 U.S. at 591 ("Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.").

Appellants now describe asserted claims 7-9 as involving four steps: "(1) labeling MuSK or specific MuSK fragment, (2) combining the labeled-MuSK fragments with a patient sample to form a labeled-MuSK/autoantibody complex (if anti-MuSK autoantibodies are present in the patient's sample), (3) adding a "second" antibody which binds to the MuSK autoantibody to precipitate the entire labeled-MuSK/autoantibody/ "second" antibody complex, and (4) detecting the presence of autoantibodies by the label." (Opening Br. at 42-43.) Those are not the steps claimed, as even Appellants recognize earlier in their brief. (Opening Br. at 7.) Claims 7-9 do not include the step of "labeling MuSK or specific MuSK fragments." (Appx48-49.) Even so, absent some claimed details of how to label MuSK or its fragments that differ from conventional techniques, the mere labeling of MuSK, were it claimed, would also fail to supply an inventive concept. *In re BRCA1*, 774 F.3d at 761, 764; *see also Esoterix Genetic Labs. LLC v. Quiagen, Inc.*, No. 14-cv-13228-ADB, 2016 U.S. Dist. LEXIS 117447, at *28-31 (D. Mass. 2016).

The steps actually recited in claims 7-9 are the same steps required of any radioimmunoassay used to detect autoantibodies, which Appellants admit are "standard." Those steps are listed in the specification just as ordered in the claims: contacting labeled MuSK with bodily fluid; immunoprecipitation; and monitoring for the label, and the specification directs the skilled artisans to publications for further information about those steps. (Appx44 (4:2-12); Appx48 (11:19-22, 26-29); Appx142; Appx150.) Appellants' current approach, to use different words to describe

these steps, does not change what the steps are and how they operate (combining vs. contacting; adding a secondary antibody . . . to precipitate vs. immunoprecipitating; detecting vs. monitoring). They are the same and operate in the same way as had already been done, and lack an inventive concept. *Mayo*, 566 U.S. at 78-81; *Ariosa*, 788 F.3d at 1377-78; *In re BRCA1*, 774 F.3d at 764 (finding claims ineligible where they "do nothing more than spell out what practitioners already knew—how to compare gene sequences using routine, ordinary techniques"); *see also CellzDirect*, 827 F.2d at 1051.

Claim 6 also uses the same steps, in the same order, as the admittedly "standard" prior art techniques. It requires detecting antigen-autoantibody complexes with a labeled secondary antibody. This is just what the inventors admitted in the specification was "known per se in the art." (*Compare* Appx48 (12:31-35, 47-49, 57-61) *with* Appx44 (3:33-65).)

Appellants' claims therefore are not like those in *Bascom Global Internet Services, Inc. v. AT&T Mobility LLC*, 827 F.3d 1341, 1350 (Fed. Cir. 2016), where a conventional piece, a filtering tool, had a different function than it normally would because of where it was positioned in the claimed system. Unlike that software system, the steps of the immunoassay described in the '820 patent occur in exactly the order and perform the same functions as one would expect. This also distinguishes Appellants' claims from those in *CellzDirect*, which, although they included known

"individual steps," recited them in a new order and combination. *CellzDirect*, 827 F.3d at 1051.

Lacking any new individual steps, or new arrangement of known steps, Appellants rely on the fact that the claims were supposedly the first to recite a test for detecting autoantibodies to MuSK—a natural product—in an effort to drum up an inventive concept. (*See* Opening Br. at 43 ("Before the '820 patent there was no description of a method comprising these steps, and no test *at all* to detect MuSK autoantibodies.").) That ploy fails. The purported novelty of a law of nature cannot supply an inventive concept; "instead, the application must provide something inventive, beyond mere 'well-understood, routine and conventional activity.'" *Genetic Techs.*, 818 F.3d at 1376 (quoting *Mayo*, 566 U.S. at 73). Thus, even if Appellants' claimed methods were the first to detect MuSK autoantibodies, or use labeled MuSK to do so, that does not change the outcome of *Alice* step two, just as in *In re BRCA1* the fact that Myriad may have been the first to test for the BRCA1 gene "d[id] not add 'enough' to make the claims as a whole patent-eligible." *In re BRCA1*, 774 F.3d at 764.

In analyzing *Alice* step two and finding the claims invalid, the district court relied on these exact points—that the claim elements individually and as a whole simply match the details in the admittedly "standard" techniques discussed in the specification and cited art. (Appx10-12.) The district court did not improperly substitute a § 112 written description analysis in finding no inventive concept, as

Appellants suggest. (*See* Opening Br. at 46-47.) The district court did not do a written description analysis at all. Appellants had argued that the supposed "complexity" in applying the "standard techniques" of immunoprecipitation and iodination to proteins gave rise to an inventive concept. So the district court properly referred to the written description requirement to demonstrate that this "complexity" argument contradicted both what the inventors taught in the specification and claimed. (Appx11-12 ("None of the complexity to which Plaintiffs cite is described or claimed in the patent").)

The court thus referred to the written description in the patent in a manner this Court has sanctioned, namely to check whether the patentee's asserted inventive concepts in litigation are consistent with the initially described invention. *See In re TLI Commc'ns LLC Patent Litig.*, 823 F.3d 607, 611-15 (Fed. Cir. 2016) (alleged inventive concept concerning a telephone unit lacked merit where the patent described the telephone unit as "behav[ing] as expected"). Finding Appellants' complexity assertions inconsistent with the specification, the district court properly held Appellants to what they admitted long before this case began: that the claimed methods use only standard techniques.

2. The Use of Man-Made Reagents in the Claimed Methods Is Not a Sufficient Inventive Concept to Confer Eligibility

Appellants also assert an inventive concept in the claims merely because a man-made reagent—in claims 7-9, labeled MuSK, which they call a "novel probe"—is used

in them, but this Court's precedent holds otherwise. (*See* Opening Br. at 44-46.) The claims found invalid in *In re BRCA1* covered methods for detecting variations from a normal DNA sequence that required (1) the use of a man-made probe that "hybridized" (or complexed) with the patient's DNA, and (2) the subsequent detection of the resulting hybridization product (a complex). *In re BRCA1*, 774 F.3d at 761-62, 764. Claim 4 found invalid in *Ariosa* also involved the use of a man-made probe to detect a naturally-occurring substance. 788 F.3d at 1373-74, 1378.

The probes used in those cases, while consisting of man-made pieces of labeled DNA, did not result in anything patentably different from that which was found in nature; accordingly, they did not render the claims patent eligible. Utilizing conventional technology like probes or radioactive iodine labels to alter an otherwise natural material does not change the underlying nature of the material sufficiently to render that altered material patentable. *See discussion supra* at Argument Section I.A. In this regard, as already argued above, Appellants' analogy to the patent-eligible cDNA is inapt. *Id.* The Supreme Court held cDNA patent eligible not simply because it was man-made, but because it was markedly different from that which was found in nature. *Myriad*, 569 U.S. at 594-95; *see also Esoterix Genetic Labs. LLC v. Quiagen, Inc.*, No. 14-cv-13228-ADB, 2016 U.S. Dist. LEXIS 117447, at *29-30 (D. Mass. 2016) (finding "there is nothing inventive about adding a detectable label to the probe, in order to identify when hybridization has occurred" where the patent states "[t]hose skilled in the art are familiar with the preparation of probes with particular

specificities," "[s]uitable assay labels are known in the art," and "[a] number of exemplary labels are known in the art and . . . may be employed in connection with the present invention").

Appellants' sweeping statement that "[a] claim that *requires* the use of a man-made molecule includes an 'inventive concept' because it 'ensure[s] that the patent in practice amounts to significantly more than a patent upon the natural law itself," is thus wrong. (Opening Br. at 45.) *See also Mayo*, 566 U.S at 77-80 (holding invalid claims that require administration of a man-made drug). The question on *Alice* step two is not whether man-made components are present in the claims, but rather, whether the claims include an inventive concept so as to result in something more than the observation of the natural law at issue. As admitted by Appellants, the man-made materials in their claims arise out of nothing more than "standard" labels already used in the art. They do not add patentable weight to their claims.

C. Appellants' Preemption Argument Is Both Moot and Wrong.

Because the asserted claims fail both *Alice* steps one and two, they are invalid. Appellants' plea that the asserted claims are valid because they do not completely preempt the use of a natural law cannot change this. (Opening Br. at 39-40.) As this Court has explained, "[w]here a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, as they are in this case, preemption concerns are fully addressed and made moot." *Ariosa*, 788 F.3d at 1379; *id.* ("[Q]uestions on preemption are inherent in and resolved by the § 101 analysis.").

Preemption is not the test for patent eligibility, as even Appellants confess. (Opening Br. at 40.) Rather, the two-step *Alice* test is, and the asserted claims fail it.

Besides being moot, Appellants' preemption arguments carry no weight. While Appellants encourage a conclusion of eligibility because the asserted claims allegedly do not completely preempt the field, unlike, say, unasserted claim 1, the asserted claims taken together do, in fact, preempt diagnosis of MG through the detection of MuSK autoantibodies using "standard" techniques "known per se in the art." (Appx44.) The asserted claims thus raise the very preemption concern that underlies § 101—preempting the use of known technology to observe an unpatentable natural correlation. *See Mayo*, 566 U.S. at 85-86.

Second, Appellants' preemption argument is based on a misreading of *McRo Inc. v. Bandai Namco Games America Inc.*, 837 F.3d 1299 (Fed. Cir. 2016). That case did not reverse a finding of ineligibility "in part" because the claimed method was not broadly preemptive, as Appellants assert. (Opening Br. at 39.) Rather, this Court found that the claims in *McRo* did not violate *Alice* step one because they were not directed to patent ineligible subject matter. *McRo*, 837 F.3d at 1316. While this Court in *McRo* considered preemption, it nonetheless recognized that "'the absence of complete preemption does not demonstrate patent eligibility.'" *Id.* at 1315 (quoting *Ariosa*, 788 F.3d at 1379). As the Supreme Court has consistently recognized, the prohibition against patent-ineligible subject matter "cannot be circumvented" by limiting the claimed use "to a particular technological environment." *See Bilski v.*

Kappos, 561 U.S. 593, 610-11 (2010) (quoting *Diamond v. Diehr*, 450 U.S. 175, 191-92 (1981)). Precedent thus soundly rejects Appellants' suggestion that eligibility follows because they limited their claims to particular known tests to apply a natural law.

III. THE DISTRICT COURT PROPERLY INVALIDATED CLAIMS 6-9 ON THE RECORD BEFORE IT

A. The District Court Properly Invalidated the Asserted Claims on Mayo's 12(b)(6) Motion Because No Dispute of Fact Existed to Prevent Judgment

This Court has "repeatedly recognized that in many cases it is possible and proper to determine patent eligibility under 35 U.S.C. § 101 on a Rule 12(b)(6) motion." *Genetic Techs.*, 818 F.3d at 1373–74; *Cleveland Clinic*, 859 F.3d at 1360 (collecting cases). This is just such a case.

Complaints that do not "contain sufficient factual matter, accepted as true, to 'state a claim to relief that is plausible on its face'" should be dismissed under Rule 12(b)(6). *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (citing *Bell Atl. Corp. v. Twombly*, 550 U.S. 544, 570 (2007)). In considering § 101 at the pleading stage, a court must take as true the facts as alleged in the complaint and accompanying papers. *Rodi v. S. New England Sch. Of Law*, 389 F.3d 5, 9 (1st Cir. 2004). This includes the patent and statements made in it concerning the state of the prior art. *See Cleveland Clinic*, 859 F.3d at 1362 (relying on statements in specification describing known statistical methods described in a prior art article in affirming grant of § 101 motion to dismiss); *Genetic Techs.*, 818 F.3d at 1377 (relying on patent's statements in Background section

as prior art in affirming grant of § 101 motion to dismiss). *Cf. PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362–63 (Fed. Cir. 2007) ("Admissions in the specification regarding the prior art are binding on the patentee for purposes of obviousness.").

Here, the '820 patent states, and thus admits, that the techniques recited in claims 6-9 were "known per se in the art" and "standard techniques in the art." (Appx44 (3:33-35, 4:10-12).) Even though the district court could have invalidated claims 6-9 under Rule 12(b)(6) based on those admissions without more, it instead gave Appellants the benefit of the doubt, doing so only after Appellants conceded the truth of the patent's admissions on the record. (Appx318-319; Appx321.) Appellants' admissions on the record dispelled any possible factual dispute, even though, in this case, the patent already had. (Appx352 ("I just don't think this is a factual dispute case at this point.").)

The district court's ruling was in line with numerous § 101 decisions finding patents ineligible by holding patentees to statements of conventionality within a patent's specification. *E.g.*, *Cleveland Clinic*, 859 F.3d at 1362-63; *Genetic Techs.*, 818 F.3d at 1377-78; *Esoterix Genetic Labs. LLC v. Qiagen Inc.*, 133 F. Supp. 3d 349, 359-60 (D. Mass. 2015) (holding no inventive concept when the patent conceded that methods for discerning the presence of a genetic mutation were well-known in the art); *see also Ariosa*, 788 F.3d at 1377 ("The specification . . . confirms that the

preparation and amplification of DNA sequences in plasma or serum were well-understood, routine, conventional activities . . . .").

The district court's ruling was proper even in the face of Appellants' submitted supplemental materials in opposition to Mayo's renewed motion to dismiss. A district court has broad discretion not to consider materials outside the pleadings in ruling on a motion to dismiss, and not to convert a motion to dismiss into a motion for summary judgment. Fed. R. Civ. P. 12(d) (explaining permissive, not mandatory, nature of conversion); *Trans-Spec Truck Serv.*, 524 F.3d at 321-22 (affirming district court's decision to refuse to consider materials attached to plaintiff's opposition to the motion to dismiss). Conversion of a motion to dismiss into one for summary judgment is thus not automatic merely because a party submits supplemental materials. *Garita Hotel Ltd. P'ship v. Ponce Fed. Bank*, 958 F.2d 15, 19 (1st Cir. 1992) ("In other words, the test is not whether supplementary materials were filed, but whether the court actually took cognizance of them, or invoked Rule 56, in arriving at its decision.").

Given these rules, Appellants have not shown that the district court abused its discretion in declining to consider their supplemental evidence. Conceding this, Appellants instead argue that their supplemental expert declaration should have been considered as a consistent elaboration on the factual allegations in their complaint, citing out-of-circuit cases in support. (Opening Br. at 55.) Those cases offer no refuge because, to the extent the declaration alleges that creating labeled MuSK or a

fragment thereof is complex, the declaration—just like the argument the district court rejected (Appx11-12)—takes positions *inconsistent* with and contrary to the '820 patent. The '820 patent describes—nor claims[4]—none of that complexity; instead, it states that labeling by iodination is a "standard technique in the art," and describes a straightforward iodination of "the purified extracellular domain of MuSK." (Appx44 (4:9-12); Appx47 (10:50-53).)

Appellants' other case, *Watterson v. Page*, 987 F.2d 1 (1st Cir. 1993), also does not support their position that the district court was required to consider their expert declaration in ruling on Mayo's motion to dismiss. (Opening Br. at 21.) Appellants' expert declaration does not qualify for any of the "narrow exceptions" to the rule that documents outside pleadings may not be consulted on a motion to dismiss. *Watterson*, 987 F.2d at 3. It is not an official public record, was not referred to in the complaint (it was created well after the complaint was filed), and is not a document central to Appellants' claim, that being the patent here.

The undisputed record here, which included the '820 patents' admissions of conventionality, contained no factual disputes that support the § 101 eligibility of Appellants' claims. Accordingly, the district court properly rendered judgment on that record.

[4] Appellants had previously acknowledged in the motion to dismiss proceedings that there were no claim construction issues that needed to be resolved. (Appx254-255 (32:15-33:1).)

B. Claim 6 Is Invalid for the Same Reasons as Claims 7-9, and Appellants Waived Any Contrary Argument

Raising a separate procedural issue, Appellants wrongly argue that this Court should remand as to claim 6 because the district court did not rule on it, or at least did not provide sufficient reason for invalidating it. (Opening Br. at 51-52.) First, the district court did rule on claim 6, identifying it as at issue, including it in the list of contested claims, and granting Mayo's motion in full, which specifically addressed claim 6. (Appx2-3, Appx6, Appx12.) The district court did this, not on its own, but because Appellants had placed claim 6 at issue. (Appx163.)

In opposing Mayo's motion, Appellants did not distinguish between any asserted claim, but consistently treated them all together. At the time, Appellants identified "the principal focus of the claims at issue [as] whether it was standard or routine to contact a patient's bodily fluids *with* 'MuSK or an epitope or antigenetic determinant thereof having a suitable label thereon' to create an 'antibody/MuSK complex or antibody/MuSK epitope or antigenetic determinant complex' as part of a method of diagnosing neurotransmission disorders like MG." (Appx553-554 (emphasis in original).) Appellants' briefing before the district court consistently grouped the claims together and, in fact, failed to address claim 6 at all, as they concede. (Opening Br. at 15; *e.g.*, Appx547-548, Appx550-551; *see also* Appx585 (¶ 15).)

Given the procedural posture and the arguments of Appellants before the district court, it was proper for the district court to treat all claims together. This Court has repeatedly sanctioned the use of representative claims in the *Alice/Mayo* analysis. *See, e.g.*, *Mayo*, 566 U.S. at 74-75 (taking as typical claim 1); *Intellectual Ventures I LLC v. Erie Indem. Co.*, 850 F.3d 1315, 1332 & n.7 (Fed. Cir. 2017) ("Although we only address representative claim 40, we have reviewed the remaining claims and conclude nothing in addition to the elements recited in claim 40 transforms the abstract idea into patentable subject matter."); *In re TLI Commc'ns*, 823 F.3d at 611 (same); *Content Extraction & Transmission LLC v. Wells Fargo Bank, Nat. Ass'n*, 776 F.3d 1343, 1346 (Fed. Cir. 2014) (same).

Especially where "the claims are substantially similar and linked to the same law of nature, analyzing representative claims is proper." *Cleveland Clinic*, 859 F.3d at 1360. That is the case here, as demonstrated above. Claims 6-9 are all directed to the same law of nature, and both recite no more than admittedly "standard" techniques for detecting autoantibodies. It was therefore proper for the district court to find claim 6 invalid under § 101 for the same reasons as claims 7-9. *See id.* ("Although Cleveland Clinic argues that the unexamined dependent claims provide sufficient inventive concepts over the representative claims, our examination reveals the opposite."). None of the cases Appellants cite (Opening Br. at 51-52) are to the contrary. Although the cases find error where a district court did not provide sufficient analysis in ruling on a particular issue, all involve situations where the parties had presented

competing evidence on the issue. Here, by contrast, Appellants presented ***no*** evidence on claim 6 to the district court.

Further, Appellants' failure before the district court to address Mayo's arguments as to claim 6 results in a waiver of any separate argument as to the validity of that claim. In the First Circuit, "[o]n appeal, absent extraordinary circumstances counseling for exception, we routinely deem waived arguments not timely presented before the district court." *Butler v. Deutsche Bank Tr. Co. Ams.*, 748 F.3d 28, 36-37 (1st Cir. 2014) (finding argument in opposition to motion to dismiss waived where it was not presented to the district court and only raised, albeit incompletely, in an appellate reply brief); *see also Snyder v. Collura*, 812 F.3d 46, 49, 51 (1st Cir. 2016) (deeming waived theories presented for the first time on appeal); *Rocafort v. IBM Corp.*, 334 F.3d 115, 121 (1st Cir. 2003) (finding waiver where party failed to meet duty to "to incorporate all relevant legal arguments in the papers that directly address a pending motion" (internal quotation marks omitted)).

This Court has similarly held that failing to separately address the validity of claims in the § 101 analysis can result in waiver. *SmartGene, Inc. v. Advanced Biological Labs., SA*, 555 F. App'x 950, 952-54 (Fed. Cir. 2014) ("In its summary-judgment filings, SmartGene expressly asserted that claim 1 was representative and that any differences between the claims are immaterial under section 101 . . . and ABL did not dispute that characterization in its briefing. It is well established that arguments that are not appropriately developed in a party's briefing may be deemed waived." (citing

SmithKline Beecham Corp. v. Apotex Corp., 439 F.3d 1312, 1320 (Fed. Cir. 2006) (collecting cases) (internal citation omitted).).

For all these reasons, the district court properly ruled claim 6 invalid under Section 101, and there is no basis for remand.

CONCLUSION

This Court should affirm the district court's judgment that asserted claims 6-9 of the '820 patent improperly claim patent ineligible subject matter and are thus invalid.

Dated: January 30, 2018 Respectfully submitted,

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CERTIFICATE OF SERVICE AND FILING

I hereby certify that I electronically filed the foregoing document with the Clerk of the Court of the United States Court of Appeal for the Federal Circuit by using the Court's CM/ECF filing system.

I certify that all participants in the case are registered CM/ECF users and that all counsel were served via CM/ECF on January 30, 2018.

/s/ Jonathan E. Singer
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CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that the response and opening brief for Mayo Collaborative Services, LLC d/b/a Mayo Medical Laboratories and Mayo Clinic complies with the type-volume limitation set forth in Fed. R. App. P. 32(a)(7)(B). The relevant portions of the brief, including all footnotes, contain 11,739 words as determined by Microsoft Word.

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