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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JACK H. LADENSON, OMAR LATERZA, and VIJAY MODUR

Appeal 2016-002006
Application 13/929,600[1]
Technology Center 1600

Before TAWEN CHANG, RACHEL H. TOWNSEND, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to a method of diagnosing Alzheimer's disease. The Examiner entered final rejections that the claims are directed to patent-ineligible subject matter.

We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

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[1] Appellants identify the Real Party in Interest as Washington University. App. Br. 1.

STATEMENT OF THE CASE

Background

> The diagnosis of Alzheimer's disease (AD), the most common form of dementia in Western countries, is largely based on historical and clinical criteria. Although many studies report a reasonably high degree of diagnostic accuracy (80–90%), often these studies include patients evaluated at specialized centers with advanced disease. At present, post-mortem examination of brain tissue is the only tool for definitive diagnosis. Therefore, the development of a biomarker for AD would aid greatly in the diagnosis of this disease. In addition, such a marker could potentially be utilized to measure efficacy in future therapeutic trials.

Spec. ¶ 3.

"Most studies of AD biomarkers to date have focused on known pathological substrates for the disease." *Id.* ¶ 4.

> Although studies exploring the use of . . . biomarkers in the diagnosis of disease have been carried out, the results have not led to a useful, definitive method. Significant overlap in values for these biomarkers between cases and controls limits their utility as diagnostic biomarkers. In addition, several reports have demonstrated the lack of correlation between amyloid plaque load and the degree of dementia, suggesting that the former may not directly relate to the latter. At present, there is a need for an improved tool more reliable than those currently available for the diagnosis of Alzheimer's disease.

Id. ¶ 5.

"The invention provides methods that include the VLP-1 biomarker to predict the imminence and progression of Alzheimer's disease. When an elevated level of VLP-1 is detected in bodily fluids, *e.g.,* in cerebrospinal fluid or in serum, it is associated with brain injury such as that caused by Alzheimer's disease." *Id.* ¶ 8.

The Claims

Claims 7–9 are on appeal. Sole independent claim 7 is illustrative and reads as follows:

> 7. A method of diagnosing Alzheimer's disease in a subject which method comprises determining the level of visinin-like protein 1 (VLP-1) in a sample of biological fluid of a human subject in combination with determining the presence or absence of an ApoE ϵ4 allele in said subject;
>
> comparing the level of said VLP-1 with the level of VLP-1 in normal controls;
>
> wherein a higher level of VLP-1 in combination with the presence of an ApoE ϵ4 allele in said subject results in a diagnosis for said subject of Alzheimer's disease.

App. Br. 6 (Claims Appendix).

Appellants seek our review of the Examiner's rejection of claims 7–9 under 35 U.S.C. § 101 as directed to patent-ineligible subject matter. The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the claims are directed toward non-statutory subject matter?

Findings of Fact

1. The Specification teaches that

> Visinin-like protein 1 (VLP-1), [is] a calcium sensor protein [biomarker] which is expressed in high abundance in neurons of the central nervous system. VLP-1 is elevated in the CSF of rats following transient focal ischemia, and is detectable in elevated concentrations in the plasma of ischemic stroke patients. The use of VLP-1 as a marker for brain damage and for AD has been described.

Spec. ¶ 7.

2. The Specification states:

> As described in the above-cited PCT publication WO 2006/012351, VLP-1 levels in biological fluids, especially cerebrospinal fluid correlate with the incidence of brain damage associated with Alzheimer's disease. It has now been found that by combining the results of determining VLP-1 levels with at least one alternative marker . . . the accuracy of diagnosis can be improved. The accuracy can also be improved by correlation of VLP-1 levels with an ApoE ϵ4 genotype.
>
> Methods for evaluating the levels of each of these markers are known in the art. Literature references which describe such methods are set forth in the examples below. However, the method of the invention is not limited to employing these precise methods; any method for determining these markers or for assessing the presence of an ApoE ϵ4 allele may be used. Such methods include immunoassays, chromatographic assays and the like.

Id. ¶¶ 15, 16.

Principles of Law

> In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, . . . 132 S.Ct. 1289 . . . (2012), the Supreme Court set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to a patent-ineligible concept. *Id.* at 1297. If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. *Id.* at 1298. The Supreme Court has described the second step of this analysis as a search for an "inventive concept"—i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself." *Id.* at 1294.

Ariosa Diagnostics v. Sequenom, Inc. 788 F.3d 1371, 1375 (Fed. Cir. 2015).

Analysis

We follow the analytical framework set forth by the Supreme Court in *Mayo* and applied by the Federal Circuit in *Ariosa*. Under the first step of this analytic rubric, we agree with the Examiner that claim 7 is directed to a patent-ineligible law of nature, specifically, the relationship between an increased level of VLP-1 protein in combination with the presence of an ApoE ϵ4 allele and the presence of Alzheimer's disease. (Ans. 4).

In *Mayo*, the claim at issue was directed to

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10_8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10_8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Mayo, 132 S.Ct. at 1295. The Supreme Court held that this claim was directed to patent ineligible subject matter because it sought to claim a law of nature. *Id.* at 1305. The Court reasoned "[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 1297. Similar to the optimization of therapeutic

efficacy claim issue in *Mayo*, the diagnostic process claim at issue here is concerned with a correlation that is a consequence of natural processes. That is the level of a particular protein (VLP-1) in a subject's biological fluid and the subject's particular genotype (the presence of an ApoE ϵ4 allele) is determinative of a diagnosis whereas in *Mayo* the level of 6-thioguanine per $8x10_8$ red blood cells was determinative of subsequent dosage administration of the drug to a patient.

We next turn to the second step of the analysis and "consider the elements of [the] claim both individually and 'as an ordered combination' to determine whether additional elements 'transform the nature of the claim' into a patent-eligible application." *Ariosa*, 788 F.3d at 1375 (citation omitted).

In this case, we find none of the additional steps in claim 7 represent more than a drafting effort. The Specification acknowledges that "the use of VLP-1 as a marker for [Alzheimer's Disease] has been described." FF1. The Specification acknowledges that "[m]ethods for evaluating the levels of [markers such as VLP-1] are known in the art" and that an ApoE ϵ4 allele may be identified by routine methods that "include immunoassays, chromatographic assays and the like." FF2. The Specification describes routine measurement and analysis of the VP-1 marker levels and similarly routine ApoE ϵ4 allele identification. *See, e.g.,* Spec. Examples 2–4 (¶¶ 26–32), citing to external references for experimental methodology and statistical evaluation methods applied. The Specification discloses no novel techniques or products used to detect VP-1 marker levels or identify the ApoE ϵ4 allele. Instead, the identification of VP-1 and presence of an ApoE ϵ4 allele in individuals having Alzheimer's disease is an observation of a

natural phenomenon that is not separately patentable under *Mayo*. We, therefore, agree with the Examiner that claim 7 is drawn to patent ineligible subject matter. (*cf.* Ans. 6)

Appellants admit that "the association of elevated levels of VLP-1 with Alzheimer's disease is a 'law of nature' and that association of ApoE ϵ4 alleles in subjects is associated with Alzheimer's disease is a law of nature." App. Br. 3. Appellants argue, however, that because "neither of these laws of nature is tied up by the claim" because the claim is to "the improvement in assays achieved when a combination of these tests is performed," that the claim is statutory. *Id.* *See also* Reply Br. 3–5.

Appellants further submit that the elements of claim 7 "when required in combination do not tie up any law of nature and each element adds significantly to each other. *Id.* at 3–4. Appellants also argue that the absence of a prior art rejection over the claimed subject matter distinguishes Appellants' invention from that in *Mayo*, "where essentially the only test performed was already routinely performed in the art," and also from *University of Utah Research v. Ambry Genetics Corp.,* 774 F.3d 755 (Fed. Cir. 2014) and *Assn. for Molecular Pathology, et al., v. Myriad Genetics, et al.,* 133 S.Ct. 2107 (2013) *(Myriad)*, neither of which claimed "a combination of assays." *Id.* at 4.

We do not find these arguments persuasive. "[T]he absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. "Where 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." *Id.* Furthermore,

a claim does not transform into a patent-eligible application of natural laws merely because it recites a combination of two laws of nature.

Claim 7 comprises the identification of a natural phenomenon, the relationship between an increased level of VLP-1 protein in combination with the presence of an ApoE ϵ4 allele on the one hand, and the presence of Alzheimer's disease on the other. The relationship is demonstrated in Figures 1 and 3 of the Specification: Figure 3 demonstrates that individuals with the ApoE ϵ4 allele had a higher level of VLP-1 protein, and Figure 1 shows that individuals known to have Alzheimer's disease had a higher level of VLP-1 protein compared to controls.

The Specification supports the Examiner's position that the physical steps of the claimed method, regardless of whether the steps are sufficiently narrow in scope, represent routine elements taught in the prior art. Determining the level of VLP-1 in a sample of biological fluid from a human subject is routine, as evidenced by the Specification's teaching that methods for its evaluation are known in the art (FF2) as well as use of the VLP-1 marker to diagnose Alzheimer's disease (FF1). The Specification also describes routine ApoE ϵ4 allele identification. *See, e.g.,* Examples 2–4 (¶¶ 26–32). We are not persuaded by Appellants' argument that "the [claimed] improvement in assays achieved when a combination of these tests is performed," which Appellants note has not drawn a prior art rejection, would render the subject matter patent eligible. Rather, we find this case similar to *Ariosa,* 788 F.3d at 1380, in which the court found a method for detecting paternally inherited cffDNA using a combination of routine elements taught in the prior art (nucleic acid amplification and detection) to be patent ineligible.

As *Mayo* instructs, "[s]imply appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable." *Id.* at 1300 (2012). We conclude that the limitations of claim 7, as in *Ariosa*, comprise the type of "conventional steps, specified at a high level of generality" that the Supreme Court has held cannot confer patentability upon a law of nature.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that claim 7 is directed toward patent-ineligible subject matter. Claims 8 and 9 were not argued separately; their rejection is also affirmed. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the Examiner's rejection of claims 7–9 under 35 U.S.C. §101 as directed to patent-ineligible subject matter.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED