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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YUK MING DENNIS LO and LIT MAN POON

Appeal 2018-003411
Application 14/599,082
Technology Center 1600

Before DEBORAH KATZ, ULRIKE W. JENKS, and JOHN G. NEW, *Administrative Patent Judges*.

KATZ, *Administrative Patent Judge*.

DECISION ON APPEAL

Introduction

Appellants[1] seek our review, under 35 U.S.C. § 134(a), of the Examiner's decision to reject claims 39–56 (Appeal Brief filed July 27, 2017 ("App. Br.") 5.)

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

The Examiner rejects the claims as follows (Final Office Action mailed February 6, 2017 ("Final Act.") 3–23):

Claims	**Reference**	**Basis**	**Final Rejection**
39–56		35 U.S.C. § 101	3–12
39–41, 48, 49, 54, 55	Lo Coco[2]	35 U.S.C. § 102(b) (pre-AIA)	12–14
39–44, 49, 50, 52, 53	Turhan[3]	35 U.S.C. § 102(b) (pre-AIA)	14–15
39–56	U.S. Pat. No. 8,962,280, Claims 1–14 U.S. Pat. No. 6,927,028, Claims 1, 3, 5–7, 24–26 U.S. Pat. No. 8,431,343, Claims 1–9 U.S. Pat. No. 7,709,197, Claims 1–5 U.S. Pat. No. 7,901,884, Claims 1–27	Obviousness-type Double Patenting	15–24

[1] Appellants report that the real party in interest is The Chinese University of Hong Kong. (App. Br. 3.)

[2] Lo Coco et al., *Polyclonal Hematopoietic Reconstitution in Leukemia Patients at Remission After Suppression of Specific Gene Rearrangements*, 82 Blood 606–612 (1993).

[3] Turhan et al., *Transient Suppression of Clonal Hemopoiesis Associated with Pregnancy in a Patient with a Myeloproliferative Disorder*, 81 Journal of Clinical Investigation 1999–2003 (1988).

	U.S. Pat. No. 8,026,067, Claims 1–22		

Appellants' Specification provides methods for differentiating DNA species originating from different individuals in a biological sample by observing epigenetic differences in DNA methylation. (Specification ("Spec.") ¶ 7.) The Specification explains that "[t]he presence of DNA originating from different individuals in bodily fluids is a well-known biological phenomenon in many clinical and biological scenarios." (Spec. ¶ 2.) The phenomenon may occur following bone marrow transplantation from a donor or during pregnancy. (*See id.* ¶¶ 2–3.) Detection of fetal DNA in maternal plasma and serum has been used for non-invasive prenatal diagnosis. (*Id.* ¶ 3.) However, "[a]ll of these current approaches have utilized the detection of DNA sequences inherited from the father and which are genetically distinguishable from those of the mother . . . [and], the detection of DNA that the fetus has inherited from the mother in maternal plasma or serum has been thought to be impossible." (*Id.*) The Specification argues that "discriminating DNA species originating from different individuals in biological fluids using epigenetic, rather than genetic differences . . . would provide a significant advancement enabling additional screening and diagnostic methods." (*Id.* ¶ 5.)

Appellants' claim 39 recites:

> A method for determining methylation status of a cell-free human DNA species in a biological sample that (1) contains cell-free human DNA originated from two different human individuals and (2) is obtained from one of the two different human individuals, the method comprising the steps of:

> (a) treating the cell-free human DNA from the sample with a reagent that differentially reacts with methylated and unmethylated DNA; and
>
> (b) detecting the presence of a methylated version and/or an unmethylated version of the cell-free human DNA species in the sample, thereby determining methylation status of the human DNA species in the sample.

(Amendment filed January 3, 2017.)[4]

Appellants do not present separate arguments against the rejections of the dependent claims. We focus on claim 39 in our analysis below. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Analysis

35 U.S.C. § 101, Non-Statutory Subject Matter

The Examiner rejects claims 39–56 under 35 U.S.C. § 101 as being directed to non-statutory subject matter. (Final Act. 3.) Although 35 U.S.C. § 101 provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor . . . ," the Supreme Court has determined that there are exceptions to what is patentable. Specifically, "laws of nature, natural phenomena, and abstract ideas" are not eligible subject matter. *See Diamond v. Diehr,* 450 U.S. 175, 185 (1981). To determine if claimed subject matter is statutorily eligible in light of these judicial exceptions the Supreme Court has articulated a two-step framework

[4] Appellants acknowledge that claim 39 listed in the Appeal Brief incorrectly included subject matter submitted in an After-Final Amendment that was not entered (*See* Reply Brief filed February 8, 2018 ("Reply Br.") 5; *see also* Examiner's Answer mailed December 19, 2017 ("Ans.") 3.)

in *Mayo Collaborative Services v. Prometheus Labs., Inc.,* 566 U.S. 66 (2012), and later cases. Specifically,

> [f]irst, we determine whether the claims at issue are directed to one of those patent-ineligible concepts . . . . If so, we then ask, "[w]hat else is there in the claims before us?" . . . To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application.

Alice Corp. Pty. v. CLS Bank Int'l, 573 U.S. 208, 2355 (2014) (quoting *Mayo,* 566 U.S. at 78). Thus, we must determine whether the claim is directed to a judicially determined patent-ineligible concept and, if so, then ask if there is anything in the claim that transforms it into patent-eligible subject matter.

The USPTO recently published revised guidance on the application of § 101. *See 2019 Revised Patent Subject Matter Eligibility Guidance*, 84 Fed. Reg. 50–57 (2019) ("2019 Guidelines"). After determining that claimed subject matter falls within one of the four categories of patentable subject matter identified in 35 U.S.C. § 101, the 2019 Guidelines provides a "revised step 2A." which corresponds to the first step of the *Alice/Mayo* test articulated above, to determine whether a claim is directed to a judicial exception. (*See* 2019 Guidelines, 84 Fed. Reg. 50, 53–54.) In a first prong of revised step 2A, the examiner must determine whether the claim recites a judicial exception. (*See id.* at 54.) If a judicial exception is identified, the second prong requires a determination of whether the judicial exception is integrated into a practical application. (*See id.*) If so, the inquiry ends and the claim is determined to be directed to eligible subject matter under the 2019 Guidelines. (*See id.* at 54 ("When the exception is so integrated [into a

practical application], then the claim is not directed to a judicial exception (Step 2A: NO) and is eligible. This concludes the eligibility analysis.").) If not, the analysis continues to determine if the claim provides an inventive concept. (*See id.* at 56.)

The Examiner finds Appellants' claims are directed to the natural phenomenon of methylated cell-free DNA (cf-DNA) which circulates in the blood stream of pregnant women and transplant patients. (Final Act. 5.) The Examiner finds the claims do not "provide a method which is significantly more from a statement of a natural principle." (*See* Final Act. 6.) In particular, the Examiner finds the "method at issue here amounts to a general instruction to practitioners to apply routine, conventional techniques when seeking to detect [cf-DNA] methylation." (*See* Final Act. 10.) To support the finding that methylation analysis was well-understood, routine and conventional activity in 2001, the Examiner cites Turhan and Lo Coco, addressed in the anticipation discussion below, among other references cited during the prosecution of the application. (*See* Final Act. 6–10.)

In making the rejection, the Examiner relies on *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015). (*See* Final Act. 10.) In *Ariosa*, our reviewing court found Sequenom's claims did not recite patent eligible subject matter, because "[t]he existence and location of cffDNA is a natural phenomenon [and] identifying its presence was merely claiming the natural phenomena itself." *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048 (Fed. Cir. 2016) (citing *Ariosa*, 788 F.3d at 1376). Claim 1, a representative claim, at issue in *Ariosa* recited:

> A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a

> paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1373–74 (Fed. Cir. 2015). Like the claims at issue in *Ariosa*, Appellants' currently pending claims recite a method of detecting nucleic acid originating from a natural source other than the subject providing the sample and characterizing it.

Appellants argue that the Examiner erred in following the Federal Circuit's reasoning in *Ariosa* because "*Ariosa* is inconsistent with *Mayo* and therefore must be disregarded in favor of *Mayo*." (App. Br. 7.) We are not persuaded that the reasoning in *Ariosa* was inconsistent with the reasoning in *Mayo*. The *Ariosa* court expressly followed *Mayo*, stating that "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." (*Ariosa*, 788 F.3d at 1375.) The *Ariosa* court explained that under the first step of the *Mayo* framework, the claimed method falls within an exception to the broad definition of eligible subject matter in 35 U.S.C. § 101 because it is directed to matter that is naturally occurring. *See id.* at 1376 ("The method ends with paternally inherited cffDNA, which is also a natural phenomenon. The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring."). The court continued by determining that under the second step of the *Mayo* framework, "the practice of the method steps does not result in an inventive concept that transforms the natural phenomenon of cffDNA into a patentable invention." (*Id.*)

Thus, the *Ariosa* court followed the two-step framework prescribed in *Mayo* and we disagree that the decision in *Ariosa* must be disregarded. (*See id.* at 1381 (Linn, J., concurring) ("The Supreme Court's blanket dismissal of conventional post-solution steps leaves no room to distinguish *Mayo* from this case, even though here *no one* was amplifying and detecting paternally-inherited cffDNA using the plasma or serum of pregnant mothers.").)

Appellants also argue that their claimed method does not recite a judicial exception to 35 U.S.C. § 101 in light of Example 29 of the May 2016 Subject Matter Eligibility Examples: Life Sciences ("May 2016 Examples"). (App. Br. 6.) According to Appellants, the absence of a step correlating an observed change with a disease indicates it is patentable. (*Id.*, citing *Mayo*, 566 U.S. at 78.) Even if the presence or absence of a correlating step were the sole determiner of eligibility, Appellants' claims include the correlation step of determining methylation status based on the detection of a methylated and/or an unmethylated version of cell-free human DNA in a sample. Thus, claim 1 of Example 29, which includes only the steps of obtaining a sample and detecting whether JUL-1 is present, is not informative for Appellants' pending claims. Example 29 does not indicate that Appellants' claims are directed to eligible subject matter.

We turn to the analysis of eligibility of Appellants' claimed subject matter under the 2019 Guidelines. Under Step 2A, prong one, of Guidelines, we agree with the Examiner that claim 39 recites the judicial exception of a natural phenomenon. (*See* 84 Fed. Reg. at 54.) The Specification acknowledges that cf-DNA from two different individuals can naturally occur in one individual, *e.g.*, a pregnant woman or bone marrow transplant recipient, is a known biological phenomenon. (*See* Spec. ¶ 2.) The

Specification also acknowledges that DNA methylation is a well-known naturally occurring phenomenon. (*See id.* ¶ 5.) Combining the two biological processes, we find the claims recite the natural phenomenon that methylated and unmethylated cf-DNA from two different individuals are present in a sample from a single individual, e.g., a pregnant women or bone marrow transplant recipient. Thus, like the determination in *Ariosa* that claims to detecting paternally inherited nucleic acid of fetal origin from a sample from a pregnant female are directed to a naturally occurring phenomema, Appellants' currently pending claims also recite a naturally-occurring phenomena. (*See Ariosa*, 788 F.3d 1376.)

We next evaluate whether the judicial exception is integrated into a practical application in the second prong of Step 2A. (*See* 84 Fed. Reg. at 54.) For example, a claim element that applies the judicial exception to effect a particular treatment or prophylaxis of disease or medical condition may integrate a natural phenomenon into a practical application. (*See id.* at 55 (citing *Vanda Pharm. Inc. v. West-Ward Pharm. Int'l Ltd.*, 887 F.3d 1117, 1135 (Fed. Cir. 2018)(holding that method of treatment by administering drug at certain dosage ranges based on a patient's genotype was not directed to a natural law)).) Likewise, a claimed advance that harnesses a natural law to produce a technological improvement may be patent eligible. *See Athena Diagnostics, Inc.* v. *Mayo Collaborative Services, LLC*, 915 F.3d 743, 750 (Fed. Cir. 2019). However, steps that merely apply conventional techniques to detect a natural law do not integrate the judicial exception into a practical application. (*Id.* at 751 ("claims that merely recite observing naturally occurring biological correlations 'with no meaningful non-routine steps in between' are directed to a natural law"

(quoting *Cleveland Clinic Found. v. True Health Diagnostics, LLC*, 859 F.3d 1352, 1361)).)

We agree with the Examiner that the claimed method does nothing more than observe and identify the natural phenomenon. (*See* Examiner's Answer issued December 19, 2017 ("Ans.") 16–17.) Claim 39 recites the following steps to determine methylation status: 1) obtain a sample that contains cf-DNA originated from two different individuals; 2) treat the cf-DNA with a methylation specific reagent; 3) detect the presence of reacted or unreacted cf-DNA. As in *Athena*, claim 39 then concludes in a "thereby . . ." clause with a statement of the natural phenomenon, i.e., determining methylation status of the DNA. *See Athena*, 915 F.3d at 751. The steps do not include a practical application of the natural phenomenon. Because the additional elements of the claim do not integrate the natural phenomenon into a practical application, we find that the claim is directed to the judicial exception.

As claim 39 is directed to a judicial exception under the first step of the *Alice/Mayo* test, we must evaluate whether the claim provides an inventive concept, *i.e.*, whether the additional elements amount to significantly more than the exception itself. (*See* 2019 Guidelines, 84 Fed. Reg. at 56.) As discussed above, the Examiner found the additional steps describing the methylation analysis, e.g., treating and detecting, were well-known, routine, and conventional. (*See* Final Act. 6–10.)

Appellants argue that the "established novelty of the claimed method comprising these particular detection steps would support the notion that the claim contains substantially more than merely a judicial exception." (Reply Br. 4.) We are not persuaded. The Specification describes the steps of the

claimed process to observe the natural law as standard techniques applied in a standard way. For example, the treating step, e.g., bisulfite modification, "was performed using a CpGenome DNA Modification Kit (Intergen) as instructed by the manufacturer." (Spec. ¶ 44.) Likewise, the detecting step, e.g., Methylation-specific PCR, was "modified from the protocol as described (Herman *et al.* 1996)." (*Id.* ¶ 45.) The only remaining step of the claim is identifying a sample of cf-DNA that contains methylated and unmethylated DNA. However, "[t]he inventive concept necessary at step two cannot be furnished by the unpatentable law of nature itself." *Athena*, 915 F.3d at 754. We agree with the Examiner that the method at issue in Appellants' claims amounts to general instructions to practitioners to apply routine, conventional techniques when seeking to detect methylated and unmethylated cffDNA and determine its methylation status. (*See* Ans. 10.) Therefore, we find the claim does not provide additional elements that amount to significantly more than the exception itself.

Because we conclude that the natural phenomenon recited in claim 39 is not integrated into a practical application and does not provide an inventive concept, we conclude that the claimed method is not eligible. Thus, we sustain the Examiner's § 101 rejection of claims 39–56 as being drawn to patent-ineligible subject matter.

35 U.S.C. § 102(b), Anticipation

The Examiner rejects claims 39–41, 48, 49, 54, 55 under 35 U.S.C § 102(b) as anticipated by Lo Coco. (Final Act. 12–13.) The Examiner rejects claims 39–44, 49, 50, 52, 53 under 35 U.S.C. § 102(b) as anticipated

by Turhan.[5] (Final Act. 13–14.) Because the same issue applies to both rejections, we discuss the rejections together.

The Examiner finds Lo Coco discloses detecting methylated and unmethylated DNA in bone marrow transplant recipients. (Final Act. 12–13.) Although Lo Coco discloses obtaining DNA species originating from cells of different individuals, the Examiner argues "[o]nce the DNA is extracted it is a cell-free sample." (*Id.*)

The Examiner finds Turhan discloses DNA methylation analysis of a pregnant woman. (Final Act. 14.) Although Turhan discloses analysis of bone marrow and peripheral blood samples, the Examiner argues "Turhan teaches obtaining DNA by extraction, thus, the sample is cell free." (*Id.*)

Appellants argue that "[n]either "Lo Coco nor Turhan teaches the analysis of ***cell-free*** human DNA species." (Reply Br. 5, emphasis in original.) Appellants argue "[t]o construe the term to also mean a human DNA species that is located within cells as it is originally present in a biological sample, *i.e.*, a cellular human DNA species, would equate 'a cell-free human DNA species in a biological sample"' with 'a human DNA species in a biological sample,' thus effectively rendering the claim limitation 'cell-free' completely meaningless. (Reply Br. 6., emphasis in original.)

We are persuaded by Appellants' argument. The broadest reasonable interpretation of a claim must be consistent with the interpretation of one of

[5] Claims 52 and 53 depend from claim 51, which depends from claim 39. The Examiner does not list claim 51 in the anticipation rejection over Turhan. Because both the rejection of claims 52 and 53 and the prior art were presented to Appellants, we find the error to be harmless.

ordinary skill in the art. *See In re Sneed*, 710 F.2d 1544, 1548 (Fed. Cir. 1983). As argued by Appellants, the term "cell-free human DNA" would be interpreted by one of ordinary skill in the art to be distinct from DNA extracted from cells. Applying this interpretation, we find that neither Lo Coco nor Turhan teach obtaining a biological sample containing cell-free human DNA. Therefore, we find the Examiner erred in rejecting the claims as anticipated and we reverse the rejection.

Obviousness-Type Double Patenting

The Examiner rejects claims 39–56 under the doctrine of obviousness-type double patenting. (Final Act. 15–16.) In particular, the Examiner rejects claims 39–56 as being unpatentable over claims 1–14 of U.S. Patent No. 8,962,280; claims 1, 3, 5–7, 24–26 of U.S. Patent No. 6,927,028; claims 1–9 of U.S. Patent No. 8,431,343; claims 1–5 of U.S. Patent No. 7,709,197; claims 1–27 of U.S. Patent No. 7,901,884; and claims 1–22 of U.S. Patent No. 8,026,067. (*See* Final Act. 15–24.)

Appellants do not appeal the double patenting rejection. (*See* App. Br. 5.) We consequently summarily affirm the Examiner's rejections on this ground. (*See* 37 C.F.R. § 41.37(c)(1)(iv) ("[A]ny arguments or authorities not included in the appeal brief will be refused consideration by the Board for purposes of the present appeal")).

Conclusion

Upon consideration of the record and the reasons given, the Examiner's rejection of claims 39–56 under 35 U.S.C. § 101 is sustained;

the Examiner's rejection of claims 39–41, 48, 49, 54, and 55 under 35 U.S.C. § 102(b) over Lo Coco is not sustained;

the Examiner's rejection of claims 39–44, 49, 50, 52, and 53 under 35 U.S.C. § 102(b) over Turhan is not sustained; and

the Examiner's rejections of claims 39–56 under obviousness-type double patenting are sustained.

Therefore, we affirm the decision of the Examiner.

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

AFFIRMED