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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte NANCY M LEE and PETER L LEE[1]

Appeal 2017-011014
Application 12/601,763
Technology Center 1600

Before JEFFREY N. FREDMAN, RYAN H. FLAX, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to a method of determining an increased risk of colorectal cancer or Crohn's disease in an asymptomatic human subject. Claims 1, 12, 14, 16, 18, and 36–39 are on appeal as rejected under 35 U.S.C. § 101. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] Appellants identify the Real Parties in Interest to be the named inventors. Appeal Br. 2.

STATEMENT OF THE CASE

Claim 1 is representative and is reproduced below:

1. A method of determining an increased risk of colorectal cancer or Crohn's disease in an asymptomatic human subject, comprising:

(i) collecting mucosal epithelial cells from the buccal area of the subject by swabbing the buccal area, and extracting RNA from the swab;

(ii) producing cDNA from the extracted RNA;

(iii) measuring the level of cDNA for a panel of polynucleotides comprising at least three cDNA sequences comprising SEQ ID NO: 1, 21 and 23 from the cDNA produced from the extracted RNA;

(iv) applying each of the measured cDNA levels of the panel of polynucleotides against a database of Mahalanobis-distance (M-dist) values created by analyzing measured cDNA levels of a control panel of polynucleotides from control subjects with no polyps and no family or self-history of cancer or known upper GI problems, wherein the control panel of polynucleotides and the panel of polynucleotides comprise the at least three cDNA sequences, and wherein the applying compares the same polynucleotides expression levels for each of the at least three cDNA sequences using global multivariate analysis of variance (ANOVA) and Mahalanobis-distance (M-dist), wherein the M-dist has chi-square distribution with degrees of freedom equal to the number of polynucleotides in the panel, and wherein the database comprises M-dist values for at least three cDNA sequences comprising SEQ ID NO: 1, 21 and 23, and wherein the database is stored on a computer system;

(v) determining the M-dist values for each of the at least three polynucleotides comprising SEQ ID NO: 1, 21, and 23 of the panel of polynucleotides from the asymptomatic human subject; and

> (vi) indicating that the asymptomatic human subject has an increased risk of colorectal cancer or Crohn's disease if each of the M-dist values for the cDNA levels for the at least three cDNA sequences of SEQ ID NO: 1, 21 and 23 are greater than the 95% percentile of the database's M-dist values.

Appeal Br. 19 (Claims Appendix). Independent claim 14 is similar, but requires contacting the cDNA with a chip having probes for the nucleotides of SEQ ID NO: 1, 21, and 23, and using fluorescence to quantify respective hybridization. *Id.* at 21.

The following rejection is appealed:

Claims 1, 12, 14, 16, 18, and 36–39 stand rejected under 35 U.S.C. § 101 as directed to a law of nature without significantly more. Final Action 2.

DISCUSSION

"[T]he examiner bears the initial burden, on review of the prior art ***or on any other ground***, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) (emphasis added).

"Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 71 (2012) (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). Claims directed to *nothing more* than abstract ideas (such as mathematical algorithms), natural phenomena, and laws of nature are not eligible for patent protection. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *accord* MPEP § 2106 (II) (discussing *Diehr*); *see also*

Parker v. Flook, 437 U.S. 584, 592–94 (1978) (if, once the mathematical algorithm is removed from consideration, nothing patentable remains, the claims are not patent-eligible).

In analyzing patent-eligibility questions under 35 U.S.C. § 101, the Supreme Court instructs us to "first determine whether the claims at issue are directed to a patent-ineligible concept." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014). If the claims are so directed, we then move to a second step and "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." *Id.* (quoting *Mayo*, 566 U.S. at 78–79).

Here, under *Alice's* step one, the Examiner determined that the claims are directed to "the judicial exception of a law of nature / natural principle. That is, the claims are based on a naturally occurring correlation between the naturally occurring expressions of SEQ ID NO. 1, 21, and 23 and risk of colorectal cancer or Crohn's disease." Final Action 3. Under *Alice's* step two, the Examiner determined that:

> the steps of collecting mucosal epithelial cells from the buccal area of an asymptomatic human subject by swabbing and extracting RNA, producing cDNA and measuring the level of cDNA for a panel of polynucleotides comprising at least 3 cDNA sequences comprising SEQ ID NO. 1, 21, and 23 are routine steps in the prior art. Spira et al (Biotechniques 2004 VOl [*sic*] 36 p. 484, previously cited) teaches isolating RNA from buccal samples to be used in expression analysis (p. 484). As such the step of "collecting mucosal epithelial cells from the buccal area by swabbing the buccal area and extracting RNA from the swab" is well understood, routine and conventional. Hao et al. (Clinical Cancer Research 2005 Vol. 11 published online March 2, 2005

> p. 1400 as cited on PTO 892) teaches measuring the expression profile which includes IL8, COX1, and COX2 (p. 1401 last paragraph). As evidenced by NM_000584, NM_000962, and NM_000963 (previously cited on PTO 892), SEQ ID NO 1, 21 and 23 are the genetic sequences of the three genes which Hao et al. measures. Therefore Hao et al. teaches the required steps of measuring expression level and comparing the expression level of IL8, COX1, and COX2 (e.g. SEQ ID NO. 1, 21, and 23) and detecti[ng] a change in the level as compared to a control. Further it would be routine to determine expression in a human subject including those that are asymptomatic in risk determinations. Although the prior art does not teach these steps in combination, when viewed as a whole the determination would be considered routine. In particular it would be routine to determine expression in any sample, including the routine buccal samples taught by Spria [*sic*]. The recited polynucleotides are not specific but rather encompass naturally occurring fragments of genes in which the art teaches that one can determine expression.

Id. at 3–4.[2] Regarding claim 14, the Examiner further cited Fodor as evidence that the claimed measuring fluorescence of polynucleotides using a spectrofluorometer was routine for detecting hybridization of naturally occurring targets, as was using chips (solid supports) with attached nucleic acid sequences.[3] *Id.* at 5.

It is without question that "[t]he line between a patentable 'process' and an unpatentable 'principle' is not always clear." *Flook*, 437 U.S. at 589;

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[2] Avrum Spira et al., *Noninvasive method for obtaining RNA from buccal mucosa epithelial cells for gene expression profiling*, 36 BIOTECHNIQUES 484–87 (2004) ("Spira"); Chun-Yi Hao et al., *Alteration of Gene Expression in Macroscopically Normal Colonic Mucosa from Individuals with a Family History of Sporadic Colon Cancer*, 11 CLIN. CANCER RES. 1400–07 (2005) ("Hao").

[3] US 2001/0053519 A1 (published Dec. 20, 2001) ("Fodor").

see also Synopsys, Inc. v. Mentor Graphics Corp., 839 F.3d 1138, 1150 (Fed. Cir. 2016) ("defining the precise abstract idea of patent claims in many cases is far from a 'straightforward' exercise") (quoting *DDR Holdings, LLC v. Hotels.com, L.P.*, 773 F.3d 1245, 1257 (Fed. Cir. 2014)). Here, a reasonable case could be made that the Examiner's determination under *Alice's* step one is without error on the basis that the claims are, at some level, directed to gene expression's relationship to disease or the risk thereof. *See, e.g., Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013). As noted by the Supreme Court, however, "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas" and "a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm." *Mayo*, 566 U.S. at 71 (quoting *Diehr*, 450 U.S. at 187).

Regarding the Examiner's *Alice* step two determination, Appellants argue that (in the context of the invention) buccal swabbing is not common or routine and that the Examiner erred in determining that the additionally-claimed subject matter, other than the natural phenomenon, considered as an ordered combination, does amount to an inventive concept and is not shown to be merely routine and conventional steps. Appeal Br. 7–8, 11–18; *see also* Reply Br. 4–13. Appellants present other points, but this argument is persuasive.

Even if the claims on appeal were "directed to" a natural phenomenon under the first step of the *Alice* framework as determined by the Examiner, we conclude that the Examiner has not *established* that the additional elements recited in the claims, considered individually and, particularly, as

an ordered combination, were well-understood, routine, and conventional. Regarding a determination that "additional" claim elements are merely routine and conventional, the Federal Circuit has explained that:

> Whether something is well-understood, routine, and conventional to a skilled artisan at the time of the patent is a factual determination. Whether a particular technology is well-understood, routine, and conventional goes beyond what was simply known in the prior art. The mere fact that something is disclosed in a piece of prior art, for example, does not mean it was well-understood, routine, and conventional.

Berkheimer v. HP Inc., 881 F.3d 1360, 1369 (Fed. Cir. 2018).

Here, after we strip away the limitations to the alleged law of nature (a natural correlation between the expressions of SEQ ID NO. 1, 21, and 23 and a risk of colorectal cancer or Crohn's disease, as indicated by the Examiner), we are left with the claims' required coordinated elements of, *inter alia*, collecting mucosal epithelial cells by buccal swabbing and extracting their RNA, and producing cDNA therefrom, in a process for determining risk of colorectal cancer or Crohn's disease in an asymptomatic patient. The Examiner concluded that the cited references, noted *supra*, evidenced that such additional subject matter, as an ordered combination was no more than routine and conventional. Although we agree with the Examiner that the cited prior art references may *disclose*, individually or even in some relevant combination, buccal swabbing, genetic testing, or other individually claimed steps, we conclude that the references cited by the Examiner do not indicate that the claimed individual steps, much less the ordered combination thereof, were necessarily *routine* and/or *conventional*

in the art. To the contrary, the cited references describe the relevant techniques as inventive or unconventional.

For example, Spira, cited by the Examiner as evidencing the routineness and conventionality of buccal swabbing, discloses that its research team was the first to extract RNA from buccal swab samples because, previously, ribonucleases in saliva rapidly degraded epithelial cell RNA during collection. Spira 484. This does not evidence that the claimed step (i) in which mucosal epithelial cells are collected from the buccal swab and RNA is extracted from those cells was routine, much less that it was routine in the claimed ordered combination of steps. To the contrary, it suggests just the opposite; it suggests it was unconventional and previously believed unachievable. Furthermore, Hao may disclose detecting certain gene expression to determine whether asymptomatic individuals are at risk of colon cancer, but it does not disclose that doing so was merely routine or customary for assessing that risk, and it relies on sampling cells from the colon rather than the mouth and specifically states that there are many cell types in colonic mucosa and it was "not know[n] which cell type is responsible for the observed altered gene expression." Hao 1400, 1406. Swabbing and measuring RNA/produced-cDNA levels from buccal epithelial cells, rather than in colon cells, places the invention recited in claim 1 outside the category of well-understood, routine, and conventional inventions. This integrated invention represents an unobvious practical application of two technologies, buccal swabbing and measurement of RNA levels (based on cDNA produced from the extracted RNA) in buccal epithelial cells.

Although the prior art articles cited by the Examiner may be relevant in analyzing obviousness, where routineness and conventionality are not critical determinations, there is no obviousness rejection on appeal and the cited art does not establish the routineness or conventionality of the claimed subject matter for purposes of determining patent eligibility. *See Diehr*, 450 U.S. at 189–90 (novelty and patent eligibility are wholly separate considerations); *Classen Immunotherapies, Inc. v. Biogen IDEC*, 659 F.3d 1057, 1064–65 (Fed. Cir. 2011) (quoting *Diehr*: "rejection on either of [§ 102 or 103] does not affect the determination that respondents' claims recited subject matter which was eligible for patent protection under § 101"); *see also MySpace, Inc. v. GraphOn Corp.*, 672 F.3d 1250, 1261 (Fed. Cir. 2012) ("Following the Supreme Court's lead, [we] should avoid reaching for interpretations of broad provisions, such as § 101, when more specific statutes, such as §§ 102, 103, and 112, can decide the case.").

Thus, while the claims may be directed to a natural phenomenon or law of nature, on some level, and the prior art might teach or suggest individual steps recited by the appealed claims, the evidence on appeal does not support a conclusion that the claimed steps, as an ordered combination, constitute mere routine and customary actions that do not provide the "something more" than the natural law upon which they may rely so as to provide an inventive concept.

For these reasons, we find the rejection insufficiently supported on the record before us. We reverse the rejection.

SUMMARY

The rejection of the claims as directed to patent-ineligible subject matter is reversed.

REVERSED