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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* SYLVIE BEAUDENON, LAURA ELIZONDO, MARTINA DOLESHAL, DAVID BROWN, and EMMANUEL LABOURIER

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Appeal 2017-008538
Application 14/051,354[1]
Technology Center 1600

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Before ULRIKE W. JENKS, JOHN E. SCHNEIDER, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for detecting in a patient the presence of cancer cells in a lymph node sample, which have been rejected as failing to comply with the enablement requirement and as being 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 Asuragen, Inc. (Br. 2.)

STATEMENT OF THE CASE

"For many cancers, lymph node involvement, or metastasis to lymph nodes, has become recognized as a strong predictor of disease recurrence and patient survival." (Spec. ¶ 6.) "In general, current methods for assessing lymph node involvement, especially those for evaluating the presence of MMD[, micrometastatic disease], have significant limitations." (*Id.* ¶ 7.) "Only a very small fraction of a lymph node (approximately 0.1-0.2%), is evaluated microscopically for metastatic cancer cells by a pathologist." (*Id.*) "It is believed that a major contributing factor to missed metastases is the presence in the lymph node of occult metastasis (i.e., not readily apparent or hidden) and/or MMD that is not detected by the present state of the art examination." (*Id.*) The invention is directed at overcoming the current limitations for assessing lymph node involvement in the use of novel molecular markers, microRNAs ("miRNAs"). (*Id.*)

Claims 1, 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103[2] are on appeal. Claims 1 and 102 are representative and read as follows:

> 1. A method for detecting in a patient the presence of cancer cells in a lymph node sample associated with cancer or suspected of cancer comprising measuring an elevated level of expression of one or more of the following miRNAs: miR-141, miR-200a, miR-200b, miR-200c, miR-203, or miR-429 compared to the expression level in cells of a non metastatic lymph node and identifying the sample as containing cancer cells.

(Br. 7.)

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[2] Claims 96–101 have been withdrawn from consideration. (Final Action 2.)

> 102. A method for detecting in a patient the presence of cervical or breast cancer cells in a lymph node sample associated with cancer or suspected of cancer comprising
>
> a) measuring an elevated level of expression of at least a first miRNA that is miR-141, miR-200a, miR-200b, miR-200c, miR-203, or miR-429 compared to the expression level in cells of a non metastatic lymph node;
>
> b) measuring an elevated level of expression of at least a second miRNA that is miR-182 or miR-183,
>
> c) identifying the sample as containing cervical or breast cancer cells.

(Br. 8–9.) In response to a species restriction made by the Examiner on November 18, 2014, Appellants elected to pursue examination of the claims with respect to miR-200b and miR-141. (Response dated May 18, 2015.)

The following grounds of rejection by the Examiner are before us on review:

Claims 1, 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

Claims 1, 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

## DISCUSSION

*Lack of Enablement*

The Examiner finds that the broad invention recited by the claims is in a highly unpredictable art. (Final Action 16.) As to the breadth of the claim, the Examiner explains that "the claims are drawn to detecting expression level of any one of these miRNAs[, the elected ones in addition to the other named miRNAs,] or their combinations, in addition to any other miRNAs due to the 'comprising' language." (Ans. 14.) In addition, the Examiner

notes that the "lymph node sample" "can have a few cancer cells, a large percentage of cancer cells or no cancer cells." (*Id.*) Moreover, explains the Examiner, "[t]he claims do not require that the non-metastatic lymph node [to which the expression level of miRNAs is to be compared] be obtained from a patient, therefore it could be obtained from a different individual." (*Id.*) In addition, the Examiner points out that, "[e]xcept for claim 10, the claims do not require any specific method of measuring expression levels of the claimed miRNAs." (*Id.*) And as to claim 10, which requires using RT-PCR or hybridization or both, the claim does not provide for "specific miRNA or their combination to be used for gene expression normalization," which one of ordinary skill in the art usually used "[i]n order to obtain meaningful expression data." (*Id.* at 14–15.) The Examiner further explains that "the claims are drawn to any cancer (claims 1, 3, 4, 6, 7, 10), breast, colon or cervical cancer (claim 11) or cervical or breast cancer (claim[s] 94, 95, 102 and 103)." (*Id.* at 15.)

Regarding the state of the art, based on a review of several published papers, the Examiner finds that "there is a large variability in the miRNA expression profiles, which can be the result of genuine differences in the levels of miRNA expression between primary tumors and metastatic cells, sample heterogeneity, differences in the number of samples used for analysis, differences in technical platform and analysis methods." (Final Action 13.) This conclusion is based on the following findings by the Examiner.

The Examiner finds that in one paper concerning the study of cancer tissue discrimination from normal tissue using levels of miRNA expression, and in which the goal was to determine whether there were universal

miRNAs that were overexpressed in more than one tumor type, a number of miRNAs were found to be overexpressed in more than one tumor type compared to normal tissue samples but the authors noted "a significant discrepancy between their findings and the results obtained" by another author. (*Id.* at 11.) The other author, carrying out a similar study, found all of the miRNAs differentially expressed between cancer and normal tissues were underexpressed relative to normal tissue. (*Id.*) The Examiner notes that the authors suggest that the "differences in results could be caused by differences in sample number . . . and/or the detection technique and different analytical approach." (*Id.*)

Additionally, the Examiner explains that in another paper, published after the filing date of the present invention where microarray hybridization was carried out,

> Mir-200b and mir-141 were found to be downregulated in the lymph node samples as compared to the tumors. However, when the tissue specificity was considered, there was no overlap between the miRNAs differentially expressed in all tumors vs. all lymph nodes as compared to specific pairs of tumors and lymph nodes (Table 2). Further, the specific differentially expressed miRNAs *were both overexpressed and underexpressed in the metastatic lymph nodes as compared to solid tumors*.

(*Id.* at 12 (emphasis added).)

In yet another study examining the possibility of classifying the origin of metastatic tissues based on miRNA expression, it was noted by the authors that

> "For most cancers, such as breast or colon cancer (Supplementary Fig. 4a,b online), we found no significant differences between primary and metastatic tumors (Fig. 2a,b)."

(*Id.* (quoting Rosenfeld[3]).) But in stomach, prostate, or head and neck primary tumors there was some differentiation from solid tumor and metastases to lymph node for three miRNAs. (*Id.*) However, those miRNA were not miR200b or 141 and overexpression for two was found in primary tumors from the stomach not in lymph cells. (*Id.*) Thus, even differentiating primary tumors from metastases, the authors note "that primary tumors can be used in training a classifier for metastases, but must be used with care and with attention to specific markers and to context." (*Id.* at 13.)

Turning to the Specification guidance, the Examiner finds that while the Specification includes working examples where differential expression of sets of miRNAs was detected between normal tissues and cancer-negative lymph nodes or between cancer and/or cancer-positive lymph nodes and cancer-negative lymph nodes, these examples do not determine whether cells of unknown status at the time of testing are cancer-positive. (*Id.* at 8–9.) Moreover, the Examiner finds that differential expression data indicates that the "fold-change of mir-200b and mir-141 expression is of the same magnitude in normal breast cancer and cancer-positive lymph nodes as compared to cancer-negative lymph nodes." (*Id.* at 9.) The Examiner finds also that while there is data concerning differential expression of mir-200b and mir-141 in normal tissue type as compared with normal lymph nodes, (*see* Specification Table 37), the disclosure "does not provide any data which shows that the same miRNAs are overexpressed in all of the 15, 12 and 10 metastatic cells found in the lymph nodes." (*Id.* at 10.)

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[3] Rosenfeld et al., *MicroRNAs accurately identify cancer tissue origin*, 26 Nature Biotech. 462–469, 463 (2008).

The Examiner further finds that in the examples "different miRNAs were used for calibration of results in the different samples. Which miRNA was used depended on its expression level between samples, i.e., the miRNA used for result calibration was determined after the data was collected." (*Id.* at 9.) The Examiner further finds that the data in the Specification demonstrates that "the number of lymph nodes examined influences the results due to the heterogeneity of miRNA expression in cancer-positive lymph nodes." (*Id.* at 11.) In summary the Examiner explains

> [Appellants] data presented in Examples 3–8, 11, 12, 17, 18, 40 and 42–47 for samples of lymph nodes from patients with melanoma, colon, breast and cervical cancers clearly indicates that issues such as the method of detection of the miRNA expression level, normalization factor, amount of cancer cells in the lymph node and sample heterogeneity have a significant effect on the determined levels of miRNAs in the different types of cancerous lymph nodes, indicating unpredictability in the outcome of the measurements.

(Ans. 15.)

The Examiner concludes:

> While the data presented shows that some miRNA expression levels can differentiate between different tissue types or between cancerous and non-cancerous lymph nodes, there is no evidence that expression levels of any single miRNA or any miRNAs combinations can be used to determine a status of an unknown lymph node. Further, even if such status could be determined, i.e., indicating that the lymph node is cancer-positive, it would further require investigation as to which type of tumor cells is present in the lymph node. . . . [A] lot of further research is required before the instant data can be used to assess any disease or condition, including cancer.

(Final Action 10–11.) The Examiner further finds that "years of inventive effort" would be required to determine the usefulness of the elected miRNAs for cancer diagnosis. (*Id.* at 15–16.) In particular, the Examiner notes

> The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to detection of cancer cells in lymph nodes, including, among others, determination of unique, cancer specific miRNA markers which are specific for metastatic cells, development of techniques for miRNA expression determination which produce consistent results among different technical platforms, large-scale clinical trials of the markers to determine their usefulness . . . .

(*Id.* at 15.)

We agree with the Examiner's factual findings and conclusion that the claims are not enabled. Appellants argue that the enablement requirement is met because (a) "[t]he specification shows which miRNAs have differential expression—including miRNAs recited in the claims, and it provides guidance to one skilled in the art how this would be done on a lymph node of unknown cancer status," (Br. 3–4), and (b) "the Action admits that the data in the specification—that is data generated as of the time of filing—provides evidence of differential miRNA expression" (*id.* at 4). We are not persuaded for the reasons explained by the Examiner, which we note above. In particular, we agree with the Examiner that while the Specification includes working examples where differential expression of sets of miRNAs was detected between normal tissues and cancer-negative lymph nodes or between cancer and/or cancer-positive lymph nodes and cancer-negative lymph nodes, these examples do not determine whether cells of unknown status at the time of testing are cancer-positive and the level of expression of a given miRNA depends on the type of cancer examined. Furthermore, we

agree with the Examiner that Appellants' own data indicates that "[t]he level of overexpression (or a lack thereof) of a given miRNA strongly depends on the assay used to determine the level of expression: the levels of expression obtained by microarray hybridization differ from levels obtained using quantitative real-time PCR, and even different microarray-based methods produce different results." (Ans. 24.) As the Examiner explained, despite the differential expression data in the Specification of sets of miRNAs detected between normal tissues and cancer-negative lymph nodes or between cancer and/or cancer-positive lymph nodes and cancer-negative lymph nodes:

> one of ordinary skill in the art at the time of the invention would have to examine cancer-positive lymph nodes for all possible types of cancers to determine which miRNAs provide consistent expression levels for different analysis platforms and analysis parameters. Further, one of ordinary skill in the art at the time of the invention would have to determine what the expression threshold is for each of these miRNAs or their combinations in order to be able to determine whether a given miRNA is overexpressed in the lymph nodes harbouring cancer cells.
>
> Considering the conflicting results presented by Appellant[s] and unpredictability in the art of determining miRNA expression in metastatic cells and lymph nodes, as described in the cited references, this would constitute undue experimentation . . . .

(Ans. 25.) Appellants do not refute the foregoing or that there is unpredictability using miRNA overexpression for cancer tissue discrimination evidenced in the prior art.

Thus, for the foregoing reasons, Appellants do not persuade us that the Examiner erred in rejecting claim 1 for lack of enablement.

Claims 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

II

*Patent-Ineligible Subject Matter*

The Examiner finds that claim 1 is directed to a method of detecting cancer cells in lymph nodes by measuring elevated levels of expression of at least two miRNA's compared to expression levels in cells of non-metastatic lymph nodes. (Final Action 17.) The Examiner finds that the method is, thus, directed to a naturally existing correlation, *i.e.*, the level of expression of particular miRNAs and the presence of cancer cells in a lymph node sample. (*Id.*; *see also id.* at 6.) The Examiner explains that "this type of correlation is a consequence of a natural process[], similar to the naturally occurring correlation found to be a law of nature by the Supreme Court in *Mayo*[ *Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012)]." (Ans. 26.) The Examiner notes that "[t]he only step required by the claims is measuring expression level" in order to determine whether the lymph node contains cancer cells. (*Id.*) The Examiner finds that this step "is recited at a high level of generality such that it amounts to insignificant presolution activity, e.g., a mere data gathering step necessary to use the correlation." (*Id.* at 26–27.)

Appellants argue that the claim is "not attempting to patent a 'law of nature'" because there is "is no evidence that laws of nature involve measuring the levels of expression of certain miRNAs in order to detect the present of cancerous cells among non-cancerous cells. There is nothing natural about measuring these levels of miRNA expression in these cells." (Br. 5) (emphasis omitted.) Appellants further argue that unlike in *Mayo*,

the claimed method "set[s] forth a limitation as a result of the previous [measuring] step[], such as the identification of a sample as containing cancer cells" and unlike in *Mayo*, there is no prior art that indicates the thing that is measured is indicative of the result observed. (*Id.*)

We agree with the Examiner that Appellants claimed methods are patent-ineligible. We analyze this case under the two-step framework described by the Supreme Court in *Mayo* and *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208 (2014) taking into consideration the "2019 Revised Patent Subject Matter Eligibility Guidance" ("Revised Guidance"), issued by the Director of the USPTO on January 7, 2019, and which provides further details regarding how the Patent Office is to analyze patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50–57 (Jan. 7, 2019).

In our analysis, we must still determine whether Appellants claims are directed to a law of nature. We analyze claim 1 as representative. We agree with the Examiner that claim 1 is directed to a law of nature. Claim 1 recites a method in which a law of nature is observed, the presence of an elevated level of expression of specific miRNA that is correlated to whether a lymph node sample contains a cancer cell. The method does not purport to alter the expression levels in any way, it just "sees" the levels. "The correlation exists in nature apart from any human action." *Athena Diagnostics v. Mayo Collaborative Servs.*, appeal no. 2017-2508, slip op. at 10 (Fed. Cir. Feb. 6, 2019). This is similar to the facts of *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 859 F.3d 1352 (Fed. Cir. 2017) in which our reviewing Court found the following claim directed to a law of nature:

> 11. A method of assessing a test subject's risk of having atherosclerotic cardiovascular disease, comprising

> comparing levels of myeloperoxidase in a bodily sample from the test subject with levels of myeloperoxidase in comparable bodily samples from control subjects diagnosed as not having the disease, said bodily sample being blood, serum, plasma, blood leukocytes selected from the group consisting of neutrophils, monocytes, subpopulations of neutrophils, and sub-populations of monocytes, or any combination thereo[f];
>
> wherein the levels of myeloperoxidase in the bodily from the test subject relative to the levels of [m]yeloperoxidase in the comparable bodily samples from control subjects is indicative of the extent of the test subject's risk of having atherosclerotic cardiovascular disease.

859 F.3d 1352, 1356, 1360–61. Similarly in *Mayo*, the Supreme Court found that a claim was directed to a natural law, where the claim required administering a drug and determining the levels of a metabolite following administration, where the level of metabolite was indicative of a need to increase or decrease the dosage of the drug. *Mayo*, 566 U.S. at 74.[4]; *see also Athena*, slip op. at 9–10 (noting that detecting the presence of a label in a method for diagnosing neurotransmission or developmental disorders related

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[4] The claim in *Mayo* recited:

> 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.

*Id.* at 74–75 (quotations omitted).

to MuSK comprising contacting labeled MuSK with a bodily fluid, immunoprecipitating any antibody/MuSK labeled complex, monitoring for the label, and noting the presence of the label is indicative neurotransmission or developmental disorder related to MuSK, involves "the correlation between the presence of naturally-occurring MuSK autoantibodies in bodily fluid and MuSK related neurological diseases" that "exists in nature apart from any human action.").

Under the Revised Guidance, we further determine "whether the claim recites additional elements that integrate the exception into a practical application of that exception." 84 Fed. Reg. at 54. Limitations that are indicative of integration into a practical application include applying the natural law to effect a particular treatment or prophylaxis for a disease or medical condition. *See, e.g.*, *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1134–35 (Fed. Cir. 2018) (holding that claims including a limitation of genotyping to determine if a patient is a CYP2D6 poor metabolizer and then administering a drug in certain amounts depending upon whether the patient is or is not a CYP2D6 poor metabolizer where risk of QTc prolongation is correlated to the amount of drug administered and status as CYP2D6 metabolizer is an application of the relationship between the drug, CYP2D6 metabolism, and QTc prolongation). On the other hand, diagnostic methods that simply measure the concentration of a drug after administration and determine whether a particular dosage of a drug will prove ineffective or cause harm is not a practical application. *Mayo*, 566 U.S. at 77. That is because the method itself does not recite a use of the relationship that is an entirely natural process, it simply provides for an observation based on that relationship. *Id.*;

*see also Athena*, slip op. at 12 (noting that while the claims include certain concrete steps, those steps only apply conventional techniques to detect the natural law, i.e., "observe its operation."), *Cleveland Clinic*, 859 F.3d at 1362. We find, as the Examiner did, that the only steps required by the claims is measuring expression level and once that is done an observation is made as to whether cancer cells are present. The measuring step is not an additional element that integrates the exception into a practical application, nor is the observation. Similar to the "determining" step in *Mayo*, here the measuring step tells the person performing the method to determine the level of miRNAs through whatever process that person wishes to use. *See Mayo*, 566 U.S. at 79.[5] The identification step simply notes that a particular conclusion can be drawn in light of the correlation: "rather like Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant." *Id.* at 78. Moreover, as indicated in Appellants' Specification, the determination of the miRNAs in a sample can be done using "techniques well known to one of ordinary skill in the art." (Spec. ¶¶ 10–11, 49, 177–178, 180–185, 187, 190–191, 195.)

Furthermore, considering the steps of claim 1 together as an ordered combination "adds nothing to the laws of nature that is not already present when the steps are considered separately." *Id.* at 79. We conclude, therefore, that the claims do not recite additional elements that integrate the

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[5] While claim 10 recites the use of a particular detection method, the named methods are conventional techniques. Indeed, Appellants does not purport to have invented these techniques. (*See* Br. 5.) As the Supreme Court stated in *Mayo*: "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." *Mayo*, 566 U.S. 79.

exception into a practical application of that exception. The process steps here merely tell those "interested in the subject about the correlations that the researchers discovered" *id.* at 78, just as our reviewing court found was the case in *Cleveland Clinic*, where the diagnostic method claims had steps paralleling the ones present here, *see supra*. *Cleveland Clinic*, 859 F.3d at 1363; *see also Athena*, slip op. at 13 and 16–17 ("The claims here are directed to a natural law because they recite only the natural law together with standard techniques for observing it. That the routine steps are set forth with some specificity is not enough to change that conclusion.").

Appellants essentially argue that the prior art does not disclose that overexpression of the recited miRNAs could be used to identify cancer cells among non-cancerous lymph cells. (Br. 5.) But the correlation between those miRNAs and the relationship to cancer is a law of nature, and cannot impart patentability to the claims even if it was previously unknown. *Athena*, slip op. at 17–18. The process itself, not merely the recognition of the law of nature, must be new and useful. *See Parker v. Flook*, 437 U.S. 584, 591–95 (1978) ("[R]espondent's claim is, in effect, comparable to a claim that the formula $2\pi r$ can be usefully applied in determining the circumference of a wheel. As the Court of Customs and Patent Appeals has explained, 'if a claim is directed essentially to a method of calculating, using a mathematical formula, even if the solution is for a specific purpose, the claimed method is nonstatutory.' *In re Richman*, 563 F.2d 1026, 1030 (1977)."). That is "to supply an inventive concept the sequence of claimed steps must do more than adapt a conventional assay to a newly discovered natural law; it must represent an inventive application beyond the discovery of the natural law itself." *Athena*, slip op. at 18.

Thus, for the foregoing reasons, Appellants do not persuade us that the Examiner erred in rejecting claim 1 as being directed to patent-ineligible subject matter.

Claims 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

## SUMMARY

We affirm the rejection of claims 1, 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement.

We affirm the rejection of claims 1, 3, 4, 6, 7, 10, 11, 94, 95, 102, and 103 under 35 U.S.C. § 101 as being 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