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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ANTHONY GONCALVES, JEAN-PAUL BORG, ERIC THOMAS FUNG, and XIAO-YING MENG[1]

Appeal 2013-009917
Application 11/917,766
Technology Center 1600

Before DEMETRA J. MILLS, FRANCISCO C. PRATS, and ULRIKE W. JENKS, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims directed to determining the course of breast cancer in a subject based on a correlation of biomarkers. The Examiner rejects the claims as directed to non-statutory subject matter, anticipated, and obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] According to Appellants, the Real Party in Interest is Quest Diagnostics Incorporated. (App. Br. 1.)

STATEMENT OF THE CASE

Claims 1–11, 29, 30, and 36–40 are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claims 1, 11, 29, and 30 are representative of the claims on appeal, and read as follows:

> 1. A method for determining breast cancer status in a subject, comprising:
>
> (a) measuring at least one biomarker in a biological sample from the subject, wherein the at least one biomarker is selected from the group consisting of the biomarkers of Table 2; and
>
> (b) correlating the measurement with breast cancer status according to Table 1,
>
> wherein the biomarker is not Apolipoprotein Al or transferrin.
>
> 11. A method for determining the course of breast cancer in a subject, comprising:
>
> (a) measuring, at a first time, at least one biomarker in a biological sample from the subject, wherein the at least one biomarker is selected from the group consisting of the biomarkers of Table 2;
>
> (b) measuring, at a second time, the at least one biomarker in a biological sample from the subject; and
>
> (c) comparing the first measurement and the second measurement;
>
> wherein the comparative measurements, according to Table 1, determine the course of breast cancer,
>
> wherein the biomarker is not Apolipoprotein Al or transferrin.
>
> 29. A method comprising detecting at least one biomarker of Table 2 by mass spectometry or immunoassay, wherein the biomarker is not Apolipoprotein A1.
>
> 30. A method comprising communicating to a subject a diagnosis relating to breast cancer status determined from a correlation of at least one biomarker in a sample from the subject, wherein the biomarker is selected, for an assay of the

> sample, from the group consisting of the biomarkers of Table 2 but is not Apolipoprotein A or transferrin, wherein the correlation is according to Table 1 and wherein results of the assay are communicated to the subject via a computer-generated medium or by phone.

App. Br. 17, 18, 20 (Claims Appendix).

The Examiner rejects the claims as follows:

I. claims 29 and 30 under 35 U.S.C. § 102(b) as being anticipated by Petricoin[2] (Final Act. 3–4; Ans. 2–3);

II. claims 29 and 30 under 35 U.S.C. § 102(b) as being anticipated by Lamoureux[3] (Final Act. 4–5; Ans. 3–4);

III. claims 11, 36, 38, and 40 under 35 U.S.C. § 102(b) as being anticipated by Baars[4] (Final Act. 5–6; Ans. 4–5);

IV. claims 1, 2, 6, 7, 9, 29, 30, and 39 under 35 U.S.C. § 102(a) being anticipated by Fernandez-Pol[5] (Final Act. 6–7; Ans. 5–6);

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[2] Petricoin et al., WO 02/077176 A2, published Oct. 3, 2002 ("Petricoin").
[3] Lamoureux et al., *Biologic Markers and Breast Cancer: A Multiparametric Study-1. Increased Serum Protein Levels*, 49 Cancer 502–512 (1982)("Lamoureux").
[4] Baars et al., *The activation of polymorphonuclear neutrophils and the complement system during immunotherapy with recombinant Interleukin-2*, 65 B. J. Cancer 96–101 (1992)("Baars").
[5] Fernandez-Pol et al., *Genomics, Proteomics and Cancer: Specific Ribosomal, Mitochondrial, and Tumor Reactive Proteins Can Be Used as Biomarkers for Early Detection of Breast Cancer in Serum*, 2 Canc. Genom. and Prot. 1–24 (2005) ("Fernandez-Pol").

V. claims 1, 2–10, 29, 30, 37, and 39 under 35 U.S.C. § 103(a) as unpatentable over Fernandez-Pol in view of Petricoin and Coombes[6] (Final Act. 7–10; Ans. 7–10); and

VI. claims 1–11, 30, and 36–40 are rejected under 35 U.S.C. § 101 as being patent ineligible because the subject matter is directed to a law of nature or natural principle (Final Act. 10–12; Ans. 10–12 and 18–25).

I. Anticipation by Petricoin

The issue is: Does the preponderance of evidence of record support the Examiner's finding that Petricoin anticipates claims 29 and 30?

Findings of Fact

FF1. Petricoin teaches:

> methods for extracting proteins from samples of micro dissected cells, and applying various analytic processes to the extracted proteins, such as immunoassays, . . . Matrix Assisted Laser Desorption Ionization/Time of Flight (MALDI/TOF), . . . and Surface Enhanced Laser Desorption Ionization Spectroscopy (SELDI). These methods allow for direct comparison of qualitative and quantitative protein content of tumor cells and normal cells from the same tissue sample.

(Petricoin 2:8–14; 8:18 to 9:29).

FF2. Petricoin teaches "the identified proteins can be used as early markers for diagnosis of breast cancer, particularly with metastatic potential, as well as for monitoring the effectiveness of treatment" (Petricoin

[6] Coombes et al., *Quality Control and Peak Finding for Proteomics Data Collected from Nipple Aspirate Fluid by Surface-Enhanced Laser Desorption and Ionization*, 49 Clin. Chem. 1615–1623 (2003) ("Coombes").

34:7–8). "Identification of proteins specifically upregulated early in the disease process (*i.e.*, premalignant or DCIS for breast cancer) provides new biomarkers for early disease (or disease progression) detection, new imaging targets for patient monitoring, and new drug targets for early intervention" (*id.* at 41:6–9).

FF3. The Examiner finds that "[t]able 8 of Petricoin . . . is a computer-generated communication" (Ans. 3). The table includes biomarkers such as apolipoprotein A1 and transferrin (*see* Petricoin 34, Table 8).

FF4. Table 2 of the Specification, reproduced below, provides a list of biomarkers

Marker	Identity	Expected molecular weight
M6433	Apolipoprotein C1 (truncated)	6,432.36
M6647	Apolipoprotein C1	6,630.59
M8936	Complement C3a (C3a anaphylatoxin des-Arg)	8,932.50
M9192	Haptoglobin alpha 1	9,192.21
M10069	Apolipoprotein A1 (fragment)	10,069.46
M28284	Apolipoprotein A1	28,078.62
M81763	Transferrin	77,049.87

(Spec. 11, Table 2.)

Principle of Law

"A single prior art reference that discloses, either expressly or inherently, each limitation of a claim invalidates that claim by anticipation." *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368, 1375 (Fed. Cir. 2005).

Analysis

The Examiner finds that Petricoin "teaches a method of managing treatment based on the course of breast cancer comprising measuring transferrin in a biological sample from a subject and correlating the measurement with breast cancer status" (Final Act. 3; Ans. 2–3).

We agree with the Examiner that Petricoin discloses a method of detecting a biomarker as recited in claim 29. Specifically, Petricoin teaches detecting transferrin in a sample (FF1–FF3). Appellants have not presented any arguments with respect to claim 29, accordingly, we affirm this rejection as to claim 29 (*see* App. Br. 13; Ans. 12 ("Appellants' arguments did not address the rejection of claim 29".)).

The Examiner interprets that "claim 30 is broadly drawn to communicating a diagnosis 'relating to' a status determined by an assay and is not drawn to actually performing any assay" (Ans. 2 (emphasis omitted)).

We do not agree with the Examiner's interpretation of claim 30, specifically, that the claim does not require preforming an assay. Although claim 30 is broadly directed to communicating a diagnosis related to breast cancer status, the claim still requires "a correlation of at least one biomarker in a sample from the subject, wherein the biomarker is selected" from apolipoprotein C1, complement C3a, and haptoglobin alpha 1 as recited in table 2 of the Specification and the "correlation is according to Table 1" (*see* App. Br. 20, Claims Appendix). Accordingly, we interpret claim 30 as requiring that a patient sample is tested for a biomarker, and the test result is compared to the correlation in Table 1, followed by communicating the results.

Appellants contend that "claim 30 does not recite a correlation between transferrin and breast cancer status" (Ans. 14). Specifically, claim 30 provides that the biomarkers *do not* include Apolipoprotein A or transferrin. "[N]either Petricoin nor Lamoureux teach a correlation between the recited biomarkers of Table 2 and breast cancer status" (Ans. 14.)

Petricoin discloses assaying samples, using the proteins to identify patients as well as monitor patient progress (FF1 and FF2). We agree with the Examiner's position that the results presented in Table 8 of Petricoin must have been generated and printed using a computer (FF3). However, what is missing in Petricoin is a teaching to use apolipoprotein C1, complement C3a or haptoglobin alpha1, as disclosed in Table 2 of the Specification (FF4) to measure disease progression. Because Petricoin does not disclose assaying apolipoprotein C1, complement C3a or haptoglobin alpha1 we do not find that the reference anticipates claim 30. Accordingly, we reverse the rejection of claim 30 based on Petricoin.

II. Anticipation by Lamoureux

The issue is: Does the preponderance of evidence of record support the Examiner's finding that Lamoureux anticipates claims 29 and 30?

Findings of Fact

FF5. Lamoureux teaches that the use of serum proteins to monitor disease stage and prognosis of patients with breast cancer. (Lamoureux, Abstract). Specifically, "β_1-transferrin were significantly higher in carcinoma patients than in normal controls" and "[s]erum levels of C3, C4, and C5 were significantly different in breast cancer patients ($P< 0.001$) from those in controls: 165, 43, and 16 compared with 145, 34, and 13 mg/dl" (Lamoureux 504).

FF6. Lamoureux teaches that

> the high level of these serum proteins, reflecting an abnormal biochemical profile, provides valuable information that relates to the stage of the disease and patients' prognosis. Results also suggest that these proteins may aid in differentiating the group with high recurrent risks from that with a more favorable prognosis

> for a given clinical and pathologic stage, illustrating their importance as biologic markers in breast cancer.

(Lamoureux, Abstract.)

Analysis

The Examiner finds that Lamoureux "teaches a method of breast cancer subject management after subject treatment comprising using an immunoassay to detect Transferrin in serum from a subject and correlating, by a software classification algorithm, the measurement with breast cancer status" (Final Act 4–5; Ans. 3–4).

We agree with the Examiner that Lamoureux discloses a method of detecting a biomarker as recited in claim 29. Specifically, Lamoureux teaches detecting transferrin in a sample (FF5 and FF6). Appellants have not presented any arguments with respect to claim 29, accordingly affirm this rejection as to claim 29 (*see* App. Br. 13; Ans. 13 ("Appellant's arguments did not address the rejection of claim 29".)).

Appellants contend that "claim 30 does not recite a correlation between transferrin and breast cancer status. Still further, neither Petricoin nor Lamoureux teach a correlation between the recited biomarkers of Table 2 and breast cancer status" (Ans. 14.) We find that Appellants have the better position; as discussed above we find that the Examiner's interpretation of claim 30 as not requiring any assay component is not reasonable based on the plain claim language. We interpret claim 30 as requiring that a patient sample is tested for a biomarker, and the test result is compared to the correlation in Table 1 of the Specification, followed by communicating the results.

Lamoureux teaches that some serum proteins are elevated in patients with breast cancer (FF5 and FF6). Specifically, Lamoureux finds that the level of complement component C3 is elevated in breast cancer patients (FF5). Table 2 of the Specification recites complement component C3a (FF4). Complement component C3a is not the same as complement component C3. Additionally, we note that Table 1 of the Specification indicated that the complement component C3a has to go down in order to correlate with subsequent metastatic relapse. Even if C3a and C3 were the same marker, Lamoureux notes that the complement component C3 is elevated in breast cancer patients – thus the trend in Lamoureux is for the marker to go up rather than down as required in Table 1 of the Specification. Accordingly, we find that the evidence of record does not support the Examiner's conclusion that Lamoureux anticipates claim 30.

III. Anticipation by Baars

The issue is: Does the preponderance of evidence of record support the Examiner's finding that Baars anticipates claims 11, 36, 38, and 40?

Findings of Fact

FF7. Baars teaches that "[t]wo groups of patients with metastatic malignant melanoma or renal cell carcinoma undergoing IL-2 therapy in the department of medical oncology were studied" (Baars 96). Baars studied "[a]ctivation of the complement system, as assessed by changes in the C3a component, in patients receiving fixed dose IL-2 is illustrated in Figures 2 and 3. C3a levels became significantly elevated by 5 to 6 h after IL-2 [administration] and reached a peak at 12 h" (Baars 96 and 98). "C3a levels were assessed by a radio-immuno assay and expressed as nmol l^{-1}" (Baars 97).

Analysis

The Examiner finds that Baars "teaches a method comprising measuring Complement C3a at two different times from a subject and comparing the first and second measurements" (Final Act. 4; Ans. 14). "As defined by the instant claims, the method of Baars et al *inherently* determines the course of breast cancer in a subject according to instant Table 1" (Ans. 14).

Appellants contend that "Baars does not teach or suggest a correlation between a biomarker and ***breast*** cancer" (App. Br. 13).

The Examiner interprets claim 11 to "broadly encompasses methods wherein biomarker measurements are to be performed on a sample from a subject that does not actually have breast cancer" (Ans. 14). We do not agree with the Examiner's interpretation of claim 11. Here, the preamble of claim 11 recites that the method determines "the course of breast cancer in a subject" and the result of measuring a biomarker over a time course determines if the marker goes up or down which in turn determines the course of breast cancer in the subject. Here, the comparing step reads back on the preamble – thus, this limitation is part of the claim. "[P]reamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise." *Boehringer Ingelheim Vetmedica v. Schering-Plough Corp.,* 320 F.3d 1339, 1345 (Fed. Cir. 2003). Here, the preamble identifies the patient population, this population is referenced again in the body of the claim to identify that the correlation as disclosed in Table 1 of the Specification is limited to the subset of patients that have breast cancer.

Although we recognize that the method steps could be performed on any patient population, the results obtained would only be valuable for the population in which a correlation to the subsequent metastasis is determined. We agree with the Examiner that Baars discloses the method steps of measuring C3a over a period of time (FF7). Appellants, however, have the better position because the claims do require that the correlation is in reference to Table 1 of the Specification that lists whether the particular biomarkers are up or down regulated in breast cancer subjects with subsequent metastatic relapse (*see* Spec. 7–10, Table 1). In other words, performing the steps on a different patient population, for example one without prior breast cancer, would not provide information with respect to the breast cancer status in that tested population. Because Baars applies the method steps to a different patient population, one with metastatic melanoma or renal carcinoma, we find that the evidence of record does not support the Examiner's finding that Baars anticipates claim 11 and any of its dependents.

IV. Anticipation by Fernandez-Pol

The issue is: Does the preponderance of evidence of record support the Examiner's finding that Fernandez-Pol anticipates claims 1, 2, 6, 7, 9, 29, 30, and 39?

Findings of Fact

FF8. Fernandez-Pol teaches that "measurement of anaphylotoxin [(complement C3a)] in heated sera from patients with breast cancer may be useful to detect BC cancer activity" (Fernandez-Pol 21, *see also* 16, Fig. 12.) "Sequence analysis of the protein bands increased

in the sera of cancer patients showed . . . C3 of the complement (anaphylotoxin) of 9,100 Da" (Fernandez-Pol 21).

FF9. Fernandez-Pol teaches that "haptoglobin-hemoglobin complex is degraded by the liver. . . . Since haptoglobin is a protein reactive to hemoglobin release, the increased level of Haptoglobin in BC is most likely due to cancer bleeding. Thus, it is unlikely that haptoglobin will be a useful marker for early detection of BC cancer" (Fernandez-Pol 21).

FF10. The clinical specimens in Fernandez-Pol's experiments came from healthy control females, "women with primary breast cancer (23 % intraductal and 77 % intraductal and infiltrative adenocarcinomas) staged according to TNM classification. Furthermore, 40 women with benign breast disease were also studied" (Fernandez-Pol 3).

Analysis

The Examiner finds that Fernandez-Pol "teaches a method for determining breast cancer status in a subject comprising measuring biomarkers complement C3a and Haptogoblin alpha 1" (Ans. 6). "As Fernandez-Pol et al teaches a correlation between the biomarkers and breast cancer status . . . [the reference] *inherently* determines relapse of breast cancer" (Ans. 6).

Appellants contend:

> Fernandez-Pol does not teach or suggest a method wherein the biomarkers of Table 2 are correlated with breast cancer status according to Table 1. In this regard, Fernandez-Pol teaches that up-regulation of complement c3a is correlated with breast cancer. See Fig. 12. The

> present claims, however, correlate breast cancer status with a ***down-regulation*** **of** complement c3a.

(App. Br. 14.) "Fernandez-Pol teaches that 'it is unlikely that haptoglobin will be a useful marker for early detection of [breast] cancer.' See Fernandez-Pol, p. 21. Hence, Fernandez-Pol does not teach or suggest each and every element of the claimed invention" (App. Br. 14.) "Even were the examiner's assertion accepted at face value, however, appealed dependent claims recite the ability to use the recited biomarkers to determine a likelihood of relapse of breast cancer versus breast cancer free survival" (Reply Br. 5).

On this record, we find that with respect to the complement C3a biomarker Appellants have the better position. Here, claim 1 requires, measuring a biomarker and "correlating the measurement with breast cancer status according to table 1" of the Specification. Table 1 of the Specification shows that down regulation of C3a complement fraction is associated with subsequent metastatic relapse, while upregulation of Haptoglobin is associated with relapse (Spec. 8, Table 1). Fernandez-Pol is interested in finding biomarkers that allow for early detection of breast cancer (*see* Fernandez-Pol Title and Abstract) and in that patient population, both C3a and haptoglobin biomarkers were found to be up regulated (FF8 and FF9). Thus, the results indicate that an up regulation of complement C3a is associated with breast cancer – while the correlation in the claims requires a down regulation of that marker. Thus, for the complement C3a limitation in claim 1 we find that Appellants have the better position.

However, we are not persuaded by Appellants' position with respect to the haptoglobin biomarker. Here, Fernandez-Pol assays biological

samples from the same patient population – subjects with breast cancer – and determines changes in the biological markers compared to controls (FF8–FF10). Fernandez-Pol explains that because "haptoglobin is a protein reactive to hemoglobin release, the increased level of Haptoglobin in BC is most likely due to cancer bleeding" (FF9). We recognize that Fernandez-Pol appears to discount the haptoglobin biomarker as useful (FF9), however, as explained by the Examiner, Fernandez-Pol tells us that the increase in haptoglobin may be due to bleeding of the cancer (FF9). The Examiner explains that "markers for mid- and late-breast cancer are useful. Based on the teachings of Fernandez-Pol . . . that haptoglobin measurement is elevated with advanced breast cancer due to cancer bleeding (see page 21, in particular), [thus,] haptoglobin ***is*** taught by Fernandez-Pol to be a useful marker for breast cancer" (Ans. 18). An elevated haptoglobin biomarker in a patient sample would indicate that the patient has bleeding and as explained by Fernandez-Pol that bleeding is most likely due to cancer (FF9). "[A] reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time." *Abbott Labs. v. Baxter Pharm. Products, Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006).

Accordingly, we find that the preponderance of the evidence of record supports the Examiner's conclusion that Fernandez-Pol anticipates claim 1. Claims 2, 6, 7, 9, 29, 30, and 39 were not separately argued and fall with claim 1. 37 C.F.R. § 41.37(c)(1)(iv).

V. Obviousness over Fernandez-Pol in view of Petricoin and Coombes

The Examiner acknowledges that Fernandez-Pol "does not specifically teach methods of detecting complement C3a and Haptogoblin

alpha 1 by capturing the biomarkers on an adsorbent surface of a SELDI probe and detecting the captured biomarker by laser desorption-ionization mass spectrometry" (Ans. 8). The Examiner looks to Petricoin and Coombes to teach these methods of detecting biomarkers (Ans. 8–9).

Appellants contend that "[t]he present claims, however, correlate breast cancer status with a ***down-regulation*** of complement c3a" and that "Fernandez-Pol's teaching that haptoglobin is unlikely to be a useful breast cancer biomarker, would have been lead away from using haptoglobin as a breast cancer biomarker" (App. Br. 14 and 15).

This argument is unpersuasive for the same reasons discussed above (*IV.*) with respect to the anticipation rejection of claim 1 based on the Fernandez-Pol reference. We are also unpersuaded by Appellants teaching away argument. We agree with the Examiner's position that even if

> Fernandez-Pol et al teaches ". . . it is unlikely that haptoglobin will be a useful marker for early detection of BC cancer". Clearly, markers for mid- and late-breast cancer are useful. Based on the teachings of Fernandez-Pol et al that haptoglobin measurement is elevated with advanced breast cancer due to cancer bleeding (see page 21, in particular), haptoglobin ***is*** taught by Fernandez-Pol to be a useful marker for breast cancer.

(Ans. 17–18.)

Because Appellants have waived the opportunity to present additional arguments directed specifically to the rejections of claims 2–10, 30, 37, and 39, we affirm the rejections of those claims as well for the same reasons discusses above for claim 1 (*see IV.*). *See Hyatt v. Dudas*, 551 F.3d 1307, 1314 (Fed. Cir. 2008)

IV. 35 U.S.C. § 101 Patent Ineligible Subject Matter

The Examiner has rejected claims 1–11, 30, and 36–40 on appeal under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter (Final Act. 10–12; Ans. 10–12 and 18–25). The Examiner finds that the claims are directed to a method that applies "'natural principals' as a limiting element or step without reciting additional elements/steps that integrate the natural principals into the claimed invention such that the natural principals are practically applied, **and** are sufficient to ensure that the claim amounts to significantly more than the naturals principals themselves" (Final Act 10–11; *see* Ans. 11). The Examiner reached this conclusion by applying the test set out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), as directed in a 2012 guidance memo (Final Act 10–11; *see* Ans. 11–12, 18–25), *see Ariosa Diagnostics, Inc. v. Sequenom*, Inc. 788 F. 3d 1371, 1376 (2015)(applying the two step test set out in *Mayo*).

Appellants argue that the claims "recite a practical application of, and impose meaningful limits on, any purported 'law of nature'" (App. Br. 7). That dependent "[c]laim 9 is directed to managing the treatment of a subject," "[c]laims 37 and 38 are directed to performing surgery or adjuvant therapy, both of which are not laws of nature" and that "[c]laims 39 and 40, directed to performing additional diagnostic tests based on breast cancer status, likewise recite practical applications of the newly discovered correlation" (App. Br. 7). Finally, Appellants argue, these "additional elements/steps are significantly more than the natural principle when they '***impose a meaningful limit*** on the claim scope'" (App. Br. 8).

We agree with the Examiner that, under the two-step test of *Mayo*, the claims are not directed to patent-eligible subject matter. The *Mayo* court applied its test to claims that are similar to those of the instant application. In *Mayo*, the claimed invention was a "method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising administering a certain class of drug and then determining the level of 6-thioguanine (6-TG) in a patient, where a level of 6-TG below or above certain amounts indicated a need to increase or decrease, respectively, the drug dosage. *Mayo*, 122 S. Ct. at 1295.

Claim 1 of the instant application is similar, in that it is directed to a method of assaying biomarkers and correlating the measured response with breast cancer status.

The *Mayo* Court concluded that the claims at issue in that case "set forth laws of nature--namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." *Id.* at 1296.

Similarly here, claim 1 on appeal sets forth a law of nature--namely, a relationship between the level of expression of a biomarker of patients with breast cancer and the likelihood of subsequent metastatic relapse based on the up or down regulation of the biomarker. Under the first step of the *Mayo* test, claim 1 on appeal is directed to a law of nature or natural phenomenon.

The *Mayo* Court next turned to the question "[w]hat else is there in the claims before us?" *Id.* at 1297. The claims in *Mayo* included an "administering" step, a "determining" step, and a "wherein" clause. *Id.* The Court concluded that "[t]he upshot is that the three steps simply tell doctors

to gather data from which they may draw an inference in light of the correlations." *Id.* at 1298. In other words,

> the claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.

Id. The Court concluded that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Id.*

Like the steps of the claims in *Mayo*, the manipulative steps of claim 1 on appeal also "consist of well-understood, routine, conventional activity already engaged in by the scientific community." *Id.* Measuring the protein in samples is conventional, as shown by Petricoin:

> [M]ethods for extracting proteins from samples of micro dissected cells, and applying various analytic processes to the extracted proteins, such as immunoassays, . . . Matrix Assisted Laser Desorption Ionization/Time of Flight (MALDI/TOF), . . . and Surface Enhanced Laser Desorption Ionization Spectroscopy (SELDI). These methods allow for direct comparison of qualitative and quantitative protein content of tumor cells and normal cells from the same tissue sample.

(FF1).

The final step of correlating protein levels is also routine, as also shown by Petricoin, which states that "the identified proteins can be used as early markers for diagnosis of breast cancer, particularly with metastatic potential, as well as for monitoring the effectiveness of treatment." (Petricoin 34–41, Table 8 and 9; *see also* FF8 (Fernandez-Pol "measurement

of anaphylotoxin [(complement C3a)] in heated sera from patients with breast cancer may be useful to detect BC cancer activity").)

Thus, when claim 1 is considered as an ordered combination, it informs a relevant audience of certain laws of nature: specifically, that the expression level of a protein biomarker can be used to distinguish between breast cancer patients whose cancer is more likely to experience a metastatic relapse or those whose cancer is less likely to relapse. Any additional steps of claim 1 consist of well-understood, routine, conventional activity already engaged in by the scientific community as shown in Petricoin and Fernandez-Pol.

We conclude that, under the *Mayo* test, claim 1 is directed to patent-ineligible subject matter. The rejection of claim 1 under 35 U.S.C. § 101 is affirmed. Claim 2–11, 30, and 36–40 were not argued separately and therefore fall with claim 1. 37 C.F.R. §41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claim 29 under 35 U.S.C. § 102(b) by Petricoin, but reverse the rejection of claim 30.

We affirm the rejection of claim 29 under 35 U.S.C. § 102(b) by Lamoureux, but reverse the rejection of claim 30.

We reverse the rejection of claims 11, 36, 38, and 40 under 35 U.S.C. § 102(b) by Baars.

We affirm the rejection of claim 1 under 35 U.S.C. § 102(a) as unpatentable over Fernandez-Pol. Claims 2, 6, 7, 9, 29, 30, and 39 were not argued separately and therefore fall with claim 1.

We affirm the rejection of claims 1 under 35 U.S.C. § 103(a)

Fernandez-Pol in view of Petricoin and Coombes. Claims 2–10, 29, 30, 37, and 39 were not argued separately and therefore fall with claim 1.

We affirm the rejection of claim 1 under 35 U.S.C. § 101 as being directed to patent ineligible subject matter. Claim 2–11, 30, and 36–40 were not argued separately and therefore fall with claim 1.

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