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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTOPHER STROH
and ANJA VON HEYDEBRECK

Appeal 2017-011373[1]
Application 14/668,268
Technology Center 1600

Before RICHARD M. LEBOVITZ, TAWEN CHANG, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to methods for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer will respond therapeutically to treatment with an anti-EGFR antibody. The Examiner rejected the claims under 35 U.S.C. § 101 as patent-ineligible because they are directed to a natural law or a natural phenomenon. Pursuant to 35 U.S.C. § 134, Appellants appeal the Examiner's determination that the claims are unpatentable. We have

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[1] The Appeal Brief ("Appeal Br.") identified Merck Patent Gesellschaft mit beschränkter Haftung as the real party in interest.

jurisdiction for this appeal under 35 U.S.C. § 6(b). The Examiner's decision is AFFIRMED.

STATEMENT OF THE CASE

Claims 17–25 stand rejected by the Examiner under 35 U.S.C. § 101 as directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea). Final Act. 4. The Examiner states that the claims "are directed to the natural correlation between expression levels of EREG before and after exposure to the EGFR antibody and responsiveness to treatment with EGFR antibody" without reciting "additional elements that amount to significantly more" than the correlation. *Id.*

Claim 17, the only independent claim on appeal, is reproduced below. All Appellants' arguments are focused on this claim. Consequently, dependent claims 18–25 stand or fall with claim 17.

> 17. An *in vitro* method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer (mCRC) will respond therapeutically to the treatment with an anti-EGFR antibody, comprising:
>
> (a) measuring by diagnostic means and/or diagnostic apparatus in a KRAS wild type EGFR expressing metastatic colorectal cancer (mCRC) biopsy tissue sample from tumor tissue or plasma of said patient the expression level of EREG
>
> (b) exposing ex-vivo said tissue sample from tumor or plasma of said patient to said anti-EGFR antibody,
>
> (c) following exposure to said anti-EGFR antibody, measuring in said exposed tissue sample of step (b) the expression level of EREG, and

(d) calculating the differences in expression levels measured in steps (b) and (c),[2]

wherein an increase in the expression level of EREG obtained in step (c) compared to step (a) indicates an increased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody, and wherein a decrease in the expression level of EREG obtained in step (c) compared to step (a) indicates a decreased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody; and

wherein said anti-EGFR antibody is administered to said patient upon a finding in step (d) of an increased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody.

CLAIM 17

The claims are directed to predicting the likelihood that a patient suffering from KRAS wild type EGFR (epidermal growth factor receptor) expressing metastatic colorectal cancer (mCRC) will respond therapeutically to treatment with an anti-EGFR antibody.

KRAS is a gene which makes the k-ras protein, a signaling protein involved in signaling pathways in human cells.[3] KRAS is involved in the EGFR signaling cascade. Spec. 14:8–10. Mutated KRAS has been

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[2] Step (d) of the claim calculates a difference in expression levels between steps (b) and (c). Expression levels are not measured in step (b). They are measured in steps (a) and (c). While the Examiner did not raise an objection to the claim, we do not understand how a difference in expression levels between (b) and (c) can be calculated when expression levels are not measured in (b). From the subsequent "wherein" clause of the claim, Appellants may have intended the claim to calculate the difference between (a) and (c).

[3] *See* https://ghr.nlm.nih.gov/gene/KRAS (last visited November 16, 2018).

identified in several different cancers.[4] The claims, however, are drawn to the class of patients having colorectal cancer expressing the "wild-type" or normal form of the KRAS gene and EGFR on the cell surface.

Cetuximab is an example of an "anti-EGFR antibody," as claimed, which had been used prior to the invention to treat cancer tumors which express EGFR. Spec. 2:25–27.

EGFR expression on cancer cells, however, "has proved to be a disappointing biomarker for the efficacy of EGFR-targeted treatment in CRC." *Id.* at 14:5–7. A cancer tumor may express EGFR on its surface, but not respond to anti-EGFR antibody therapy. As a result, scientists have looked for other biomarkers which predict the response to anti-EGFR antibody therapy.[5] The Specification discloses that the "mutation status of KRAS" has been found "to be a powerful predictive biomarker for cetuximab activity in CRC, allowing the exclusion from treatment of a subpopulation unlikely to derive a significant benefit." Spec. 14:17–19.

Tumors in which KRAS is wild-type also do not always respond to cetuximab. Spec. 14:20–23. The Specification states that therefore "there is a need for the identification and use of further biomarkers that can be used in addition to the KRAS mutation status to better predict the clinical outcome of cetuximab treatment in CRC patients." *Id.* at 14:24–26. The inventors found that the expression of a biomarker called EREG can be used to predict the response to anti-EGFR antibodies in patients with colorectal cancer

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[4] *See* https://www.cancer.gov/publications/dictionaries/cancer-terms/def/kras-gene (last visited November 16, 2018).

[5] Khambata-Ford et al., 2007, *J. Clin. Oncol.*, 25(22):3230-3237 (listed on IDS provided by Appellants on Jan. 25, 2016).

expressing wild-type KRAS. EREG is the abbreviation for epiregulin. Epiregulin is a ligand for EGFR.[6]

Claim 17 comprises step (a) of measuring the expression level of EREG in a biopsy sample from a KRAS wild type EGFR expressing mCRC patient. The claim further comprises exposing the biopsy sample to anti-EGFR antibody (step (b)) and then measuring the expression of EREG (step (c)) after exposure to the antibody. The differences in EREG expression levels before and after exposure to the anti-EGFR antibody are determined in step (d).

Increased EREG expression as compared to expression before exposure to the antibody "indicates an increased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody." App. Br. 13, Claims App.

Decreased EREG expression as compared to expression before exposure to the antibody "indicates a decreased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody." *Id.*

The claim further requires that anti-EGFR antibody is administered when an increased likelihood of patient therapeutic response is found. Thus, the claim does not require anti-EGFR antibody administration in all cases in which EREG levels are measured. Furthermore, it does not require treatment of the patient with a therapeutic amount of anti-EGFR antibody even if an increased likelihood of a patient therapeutic response is determined based on EREG levels.

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[6] *Id.* at 3233.

ISSUE

The Examiner rejected all of the claims in this appeal on the basis of the claims being directed to a law of nature or natural phenomenon, which are judicial exceptions to eligibility for patenting under 35 U.S.C. § 101. Final Act. 4. The Examiner found that the claims "are directed to the . . . correlation between (1) expression levels of EREG before and after exposure to the EGFR antibody" and (2) the cancer's "responsiveness to treatment with an EGFR antibody," which the Examiner characterized as natural law or natural phenomenon. *Id.* The Examiner further found that the claim does not include additional elements that are significantly more than the judicial exception. *Id.* Rather, the Examiner found that the additional steps in the claims were routine and conventional at the time of the invention. As evidence of this, the Examiner cited the patent publication by Ford,[7] for its disclosure of the recited steps of exposing a biological sample *ex vivo* to an anti-EGFR antibody and measuring the levels of a biomarker as an indicator of whether the cancer will respond to the antibody. *See* Ford 5:11–2; *see also* Final Act. 6–7 (referring to steps (b)–(d) of claim 17).

Appellants argue that "the additional elements amount to a claim *as a whole* that adds meaningful limits on the use of the exception (the correlation and critical thinking step)." Appeal Br. 4. Appellants contend that the rejected claims "do not foreclose the public from taking advantage of the correlation between ex-vivo EREG expression levels following exposure of a KRAS wild-type EGFR expressing CRC or mCRC tumor to

[7] Ford et al., WO 2007/025044 A2; published March 1, 2007 (hereinafter "Ford").

an anti-EGFR antibody and the responsiveness to treatment of the tumor with that anti-EGFR antibody." *Id.* at 5. Appellants state that the claims require a "a particular technique for measuring the expression of EREG" and "a very specific therapy targeted to the individual subpopulation of patients with KRAS wild-type expressing CRC or mCRC tumors." *Id.*

DISCUSSION

We have considered Appellants arguments, but are not persuaded that the Examiner erred in concluding that, under the two-step test of *Alice Corp. Pty. Ltd. v. CLS Bank Int'l,* 134 S.Ct. 2347 (2014), claim 17 is directed to patent-ineligible subject matter.

The *Alice* Court stated that "[i]n *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, [132 S.Ct 1289 (2012)] . . . we 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." *Alice Corp.,* 134 S.Ct. at 2355. The *Alice* Court described the *Mayo* test as follows:

> First, 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. We have described step two of this analysis as a search for an "'inventive concept'" — *i.e.*, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Id. (citations omitted).

The *Mayo* Court applied its test to claims that are similar to the rejected claims in this appeal. In *Mayo,* the claimed invention was a "method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder" comprising administering a thiopurine drug to a patient and then determining the subsequent level of 6–thioguanine (6-TG). *Mayo,* 132 S.Ct at 1295. 6-TG was a known metabolite of the drug. *Mayo*, *Id.* at 1295. The claim recited that the level of 6-TG below or above certain amounts indicated a need to increase or decrease the drug dosage.

Rejected claim 17 is similar to the *Mayo* claim in that an administered anti-EGFR antibody modulates EREG production through a natural process in the patient's biopsied tissue, in the same way that administering the thiopurine drug naturally elicits the 6-TG metabolite. Claim 17 uses the level of EREG, as modulated by the antibody drug, to determine whether to administer the drug to a patient. Thus, the level of a biomarker — 6-TG in *Mayo* and EREG in claim 17 — is used similarly to tell the doctor about the effect of administering a drug to the patient.

For this reason, the *Mayo* Court's conclusion 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" are applicable here. *Mayo*, 132 S.Ct. at 1296. That is, rejected claim 17 sets forth a law of nature, namely, a natural relationship or natural correlation between the levels of a biomarker in a patient after anti-EGFR antibody administration and the "likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody." The fact that the rejected claims involve *ex vivo* modulation of biomarker expression outside the body,

while the *Mayo* claims involved the *in vivo* production of the biomarker inside the body, does not change the analysis because in both cases a biomarker is being used for the same diagnostic purpose to determine parameters of drug administration to a patient. For this reason, we conclude that under the first step of the *Alice/Mayo* test, claim 17 on appeal is directed to a law of nature or natural phenomenon.

The *Mayo* Court next turned to the question of "[w]hat else is there in the claims before us?" *Mayo*, 132 S.Ct. at 1297. The claims in *Mayo* included an "administering" step, a "determining" step, and a "wherein" clause. *Id.* The Court found that "the 'determining' step tells the doctor" to determine the level of the relevant metabolites in the blood, through whatever process the doctor or the laboratory wishes to use, which the Court determined in their case to be "well-understood, routine, conventional activity previously engaged in by scientists who work in the field." *Id.* at 1297–1298. Relying on earlier case law, the Court stated that "conventional or obvious" activity "is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Id.* at 1298.

The Court considered all three steps as "an ordered combination" and found that "the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients." *Mayo*, 132 S.Ct. at 1298. The Court stated:

> The upshot is that the three steps simply tell doctors to gather data from which they may draw an inference in light of the correlations. To put the matter more succinctly, 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. at 1298. The Court concluded that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications of those regularities." *Id.*

The rejected claims in this appeal stand on similar footing. Steps (a) through (d) of claim 17 involve measuring the amount of the EREG biomarker in a tissue sample from a patient before and after exposure to the anti-EGFR antibody and then calculating the difference. These steps are analogous to the "determining the level of 6-TG" step of the *Mayo* claim, because both are directed to measuring a biomarker modulated by a drug for the same purpose of informing the doctor of the appropriate therapy to administer to the patient. As in *Mayo*, the steps "simply tell doctors to gather data from which they may draw an inference in light of the correlations," which in this case is whether or not to administer the anti-EGFR antibody. *See Mayo*, 132 S.Ct. at 1298.[8]

The method by which the EREG levels were determined in the patient's tissue was found by the Examiner to be the same as those in Ford,

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[8] We note that claim 17 is not directed to a method of treatment. The claim preamble does not recite a method of treatment. Moreover, the wherein clause concerning administration of anti-EGFR after determining the expression levels of EREG does not recite that a therapeutically effective amount of anti-EGFR is administered, nor does it recite administration of a particular amount or dosage range of anti-EGFR to administer. Thus, we do not find claim 17 to be like the claims found patent eligible in *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals*, 887 F.3d 1117 (Fed. Cir. 2018).

providing evidence that the activity was "well-understood, routine, conventional activity already engaged in by the scientific community." *Mayo*, 132 S.Ct. at 1297–1298; *see also* Final Act. 6–7. Thus, the Examiner had basis to conclude that they added "nothing significant beyond the sum of their parts taken separately." *Mayo*, 132 S.Ct. at 1298.

Appellants contend that "when viewed 'as a combination' it is clear that the claims are not 'directed to' the natural correlation, but integrate the correlations into a method of measuring and treatment that adds significantly more to the natural correlation." Appeal Br. 4. Appellants argue that the "significantly more" test in *Mayo* "aims to ensure that patent claims recite meaningful limitations such that the public is not foreclosed *(i.e.,* preempted) from taking advantage of what exists in nature." *Id.* at 5. Appellants state that the "instant claims do not foreclose the public from taking advantage of the correlation between ex-vivo EREG expression levels following exposure of a KRAS wild-type EGFR expressing" colorectal cancer tumor "to an anti-EGFR antibody and the responsiveness to treatment of the tumor with that anti-EGFR antibody." *Id.* The reason, Appellants explain, is that they use a specific technique to measure the EREG and a narrowly tailored therapy. *Id.* at 5–6. Specifically, Appellants refer to the order of the steps involving ex vivo exposure to the anti-EGFR antibody. *Id.* at 5.[9]

This argument does not persuade us that the Examiner erred.

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[9] Notably absent from Appellants' argument regarding "a narrowly tailored therapy" is any assertion that the claims require a therapeutically effective amount of the specific anti-EGFR antibody be administered or that a particular dosage range of the specific anti-EGFR antibody be administered to treat the cancer.

First, claim 17 does not recite a specific technique to measure EREG levels in the biopsy sample. Thus, Appellants' argument that the claim utilizes a particular technique to measure EREG is unavailing.

Second, the order of the steps involving ex vivo exposure to the anti-EGFR antibody is also not new. The Ford publication cited by the Examiner shows that one of ordinary skill in the art had used the same steps as claimed to determine the differences in EREG levels before and after antibody administration. Ford discloses:

> In one aspect, the invention provides a method for predicting the likelihood a mammal will respond therapeutically to a method of treating cancer comprising administering an EGFR modulator, wherein the method comprises: (a) measuring in the mammal the level of at least one biomarker selected from epiregulin [EREG] and amphiregulin; (b) exposing a biological sample from the mammal to the EGFR modulator; (c) following the exposing of step (b), measuring in the biological sample the level of the at least one biomarker, wherein an increase in the level of the at least one biomarker measured in step (c) compared to the level of the at least one biomarker measured in step (a) indicates an increased likelihood that the mammal will respond therapeutically to the method of treating cancer.

Ford 5:11–20 (emphasis added).

Thus, these steps, as in *Mayo*, "consist of well-understood, routine, conventional activity already engaged in by the scientific community." *Mayo*, 566 U.S. at 79–80.

Despite this explicit disclosure, Appellants contend that the "Office has not provided any evidence that it was routine in the art to measure the EREG expression of EGFR-expressing CRC or mCRC tumors ex-vivo following exposure to an anti-EGFR antibody in order to determine responsiveness to treatment with the anti-EGFR antibody." Appeal Br. 9.

However, the above-reproduced disclosure shows that Ford disclosed measuring EREG in a cancer following exposure to an EGFR modulator. Ford also discloses that an EGFR modulator can be an anti-EGFR antibody ("EGFR binding monoclonal antibodies"). Ford 5:7–10. Ford further discloses that in one embodiment "the EGFR modulator is cetuximab [an anti-EGFR antibody] and the cancer is colorectal cancer." *Id.* at 5:30–31. Thus, as in rejected claim 17, EREG expression elicited by an anti-EGFR antibody is disclosed by Ford to determine "increased likelihood that the mammal will respond therapeutically to the method of treating cancer." With regard to whether the colorectal cancer expresses EGFR as required by claim 17, Ford teaches the EGFR expression is detected in colorectal cancer. Ford 3:15–27.

While Appellants state that "the use of markers for predicting treatment responsiveness was *not actually routinely or conventionally used* by clinicians," (Appeal Br. 9), clearly the same technique as claimed of exposing a sample from a patient to an EGFR modulator, such as an EGFR antibody, and then measuring EREG levels, is described in Ford. We do not see how adopting a technique described in the prior art for determining a sample's responsiveness to an anti-EGFR antibody and using that responsiveness (an increase in the levels of EREG) to determine whether to administer anti-EGFR to a patient could transform the natural correlation between EREG levels and responsiveness to a drug into a patent-eligible application of the natural correlation.

Appellants contend that Ford's technique, described in one patent publication, is not sufficient to establish it as "conventional activity already

engaged in by the scientific community," citing guidance materials provided by the USPTO. Appeal Br. 9–10.

Claim 17 uses Ford's technique in exactly the same way as does Ford, namely to predict a response to an anti-EGFR antibody by modulating the production of EREG in a sample from the patient and assessing the expression levels of the EREG before and after administration of the antibody. Ford 5:11–20 (reproduced above). Appellants did not adequately distinguish the steps in claim 17 from those described by Ford. The point is that claim 17 has not added anything significantly more than what was already available in the prior art to one who sought to utilize EREG levels as an indicator of responsiveness to anti-EGFR antibody. *Mayo* did not strictly limit what is "significantly more" to transform an ineligible claim to anything that is not *conventional* or *routine*, but rather considered factual scenarios where steps that were "obvious" or "already in use" could be insufficient, as well. *Mayo*, 132 S.Ct. at 1299. As explained in *Mayo*, a process of using a mathematical equation was found to be patent eligible in *Diamond v. Diehr*, 450 U.S. 175 (1981), because it "nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional." *Mayo*, 132 S.Ct. at 1299.

We considered Appellants' argument that "the use of gene expression markers for tumor diagnosis was still gaining acceptance and approval, both in the medical community and within government agencies at the time the application was filed," but are not persuaded by it. Appeal Br. 9.

First, Appellants did not direct us to evidence that government approval is necessary to establish that a technique is conventional. Second, Appellants have not provided evidence that measuring biomarkers as

described in Ford had not gained acceptance in the industry as a useful tool to predict a response to a drug. Indeed, the Specification discloses that one such marker, HER2, had been used clinically to select patients for antibody treatment. Spec. 2:3–4. An argument made by counsel in a brief does not substitute for evidence lacking in the record. *Estee Lauder, Inc. v. L'Oréal, S.A.*, 129 F.3d 588, 595 (Fed. Cir. 1997).

Ford specifically teaches using the same EREG biomarker and the same steps as claimed to determine a cancer's response to an anti-EGFR antibody. The same gene expression technology which is claimed was "already in use" to measure levels of a biomarker in cancerous tumors and thus does not add "significantly more" to the claimed natural correlation. *Mayo*, 132 S.Ct. at 1298–1299. Appellants have not provided evidence that actual clinical use is necessary to establish that the steps in a claim do not add significantly more to an otherwise ineligible natural law.

Appellants also attempt to distinguish claim 17 on the basis of the anti-EGFR antibody administration. Appellants argue:

> Ford *et al.* does not demonstrate routine administration of an anti-EGFR antibody to a subpopulation of CRC or mCRC tumors having increased expression of EREG following ex-vivo exposure of the tumor sample to the anti-EGFR antibody. In fact, Ford *et al.* does not teach administration of an anti-EGFR antibody at all. Instead, the reference is directed solely to predicting the likelihood of response to any EGFR modulator.

Appeal Br. 10.

Appellants also contend that the market approval in 2004[10] does not provide an indication for KRAS wild type colorectal tumors and thus cannot be evidence of routine use. Reply Br. 3. Appellants provided an FDA label from 2012 in which they assert establishes this fact. *Id.*

Claim 17 does not require that an antibody be administered to a patient. The claims specifies that the anti-EGFR antibody is administered "upon a finding in step (d) of an increased likelihood that said patient responds therapeutically to the treatment with said anti-EGFR antibody." The claim, however, does not require administering antibody when the recited "decreased likelihood" of a response to therapeutic treatment of the antibody is determined. Appellants' attempt to distinguish the claim based on antibody administration is not persuasive because the claim as a whole does not require an antibody to be administered. Consistently, the claim preamble recites that it is "[a]n *in vitro* method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer (mCRC) will respond therapeutically to the treatment with an anti-EGFR antibody." The "likelihood" of a response is a reflection of the natural levels of the EREG biomarker in the specific cancer type and therefore the claim as a whole is directed to natural law. For this reason, while we reviewed Appellants' arguments regarding antibody administration, we do not find it necessary to address them.

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[10] Appellants do not explain the inconsistency with statement in the Specification that approval was obtained in 2003.

Appellants' contention that Ford does not teach anti-EGFR antibody administration to CRC tumors (Appeal Br. 10) is not persuasive because, as discussed above, claim 17 does not require antibody administration, but rather is a method of predicting the likelihood of a response to the anti-EGFR antibody. When certain biomarker parameters are not met, the antibody is not administered.

Because the claim is neither directed to administration of a therapeutic amount of antibody nor requires such administration, the issue before us is whether the claim is directed to a natural law, namely, the natural correlation between EREG levels and anti-EGFR response and its predictive value in determining whether to administer the antibody to a patient suffering from KRAS wild type EGFR expressing mCRC. The additional steps of determining the levels of the EREG are not significantly more than the natural law, itself, because these steps merely inform the doctor to apply the correlation to the patient when determining whether to administer antibody. The *Mayo* claim held to be patent ineligible also measured the metabolite biomarker after exposure to the drug, which along with Ford, show the conventionality of using measuring biomarker levels after exposure to a drug to gauge how much of it to administer, if any.

Appellants cite *Rapid Litigation Management Ltd and In Vitro, Inc. v. CellzDirect, Inc.* as holding that claims which "merely 'involved' a natural phenomenon" are patent eligible. Appeal Br. 6. Appellants argue that such analysis applies here since claim 17 does not just measure a metabolite, but utilizes a particular procedure with several manipulative steps. *Id.* at 7.

This argument does not persuade us that the Examiner erred. In *CellzDirect*, the claims were directed to a method of producing

cryopreserved hepatocytes comprising steps of subjecting the cells to density gradient fractionation, recovering the viable cells, and cryopreserving them. *CellzDirect*, 827 F.3d at 1046. In contrast, rejected claim 17 is directed to a "method for predicting the likelihood that a patient suffering from KRAS wild type EGFR expressing metastatic colorectal cancer (mCRC) will respond therapeutically to the treatment with an anti-EGFR antibody"; no cell based product is produced.

In *CellzDirect*, the claims were found eligible for a patent because the "end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells." *CellzDirect*, 827 F.3d at 1048. In claim 17, the so-called manipulative steps recited in the claim are carried out to measure the EREG levels which are used to determine whether to administer the antibody. The end result is an "observation" about the levels of EREG before and after antibody exposure. Claim 17 does not even require antibody administration if the expression levels of EREG do not increase in comparison to expression prior to exposure to the antibody. Rather, the claim is an in vitro method for predicting the likelihood of a therapeutic response to anti-EGFR antibody.

For the foregoing reasons, the rejection of claim 17 under 35 U.S.C. § 101 is affirmed. Claims 18–25 were not argued separately and fall with claim 17.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED