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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/558,618	12/02/2014	Bruce MACHER	MACH-001	4582

36872 7590 03/04/2020

CENTRAL CALIFORNIA IP GROUP, P.C.
377 W. FALLBROOK AVENUE
#205
FRESNO, CA 93711

EXAMINER
WISE, OLIVIA M.

ART UNIT	PAPER NUMBER
1631	

NOTIFICATION DATE	DELIVERY MODE
03/04/2020	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRUCE MACHER, LESLIE TIMPE, TEN-YANG YEN, and ALEXANDRA PIRYATINSKA[1]

Appeal 2018-003550
Application 14/558,618
Technology Center 1600

Before ERIC B. GRIMES, RICHARD M. LEBOVITZ, and JAMES A. WORTH, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims related to "identifying and using predictive biomarkers for diagnosing and treating cancer." Spec. ¶ 2. The claims have been rejected as indefinite, ineligible for patenting, and obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM the rejections for indefiniteness and patent-ineligibility.

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[1] Appellant identifies the real parties in interest as Bruce Macher, Leslie Timpe, Ten-Yang Yen, and Alexandra Piryatinska. Appeal Br. 3. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

STATEMENT OF THE CASE

The Specification states that "there have been efforts to solve the problem of predicting the responses of cancer cell lines to drugs. Predictor data includes gene mutation, copy number variation, methylation and gene expression data, protein data, and receptor signaling networks." Spec. ¶ 10. The Specification describes "a method of identifying one or more of a plurality of drugs effective to stop or repress proliferation of cancer cells using protein and/or glycoprotein biomarkers, and a system for predicting effectiveness of the drug(s) using the biomarkers." *Id*. ¶ 13.

Claims 1, 4–13, 15, 17–19, 21–24, and 26 are on appeal. Claim 1, reproduced below, is illustrative:

> 1. A method of identifying one or more of a plurality of drugs effective to stop or repress proliferation of cancer cells, comprising:
>
> using a computer having a statistical analysis program recorded in a tangible medium therein, performing a statistical analysis on (i) a first dataset of expression levels of at least 5 glycoproteins in said cancer cells, said expression levels being determined by mass spectrometry, and (ii) a second dataset of responses of said cancer cells to each of at least 5 drugs at a concentration of each drug that causes a 50% reduction in proliferation of the cancer cells;
>
> identifying one or more glycoprotein biomarkers associated with an effective reduction in proliferation of said cancer cells for at least one of said drugs from said statistical analysis; and
>
> using said computer, correlating or associating at least one of said one or more glycoprotein biomarkers with said reduction in proliferation of the cancer cells in response to at least one of said plurality of drugs.

The claims stand rejected as follows:

Claims 1, 4–13, 21, 23, and 26 under 35 U.S.C. § 112(b) as indefinite (Final Action[2] 2);

Claims 1, 4–13, 15, 17–19, 21–24, and 26 under 35 U.S.C. § 101 as directed to patent-ineligible subject matter (Final Action 4);

Claims 1, 5–8, 18, 21, and 23 under 35 U.S.C. § 103 as obvious based on Daemen,[3] Even-Desrumeaux,[4] and Yen[5] (Final Action 9–10[6]);

Claims 1, 4, 18, 19, and 26 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Zucknick[7] (Final Action 14);

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[2] Office Action mailed Feb. 24, 2017.

[3] Anneleen Daemen et al., "Modeling precision treatment of breast cancer," Genome Biology 14:R110, pp. 1–14 (2013) (available at genomebiology.com/2013/14/10/R110).

[4] Klervi Even-Desrumeaux et al., "State of the Art in Tumor Antigen and Biomarker Discovery," Cancers 3:2554–96 (2011).

[5] Ten-Yang Yen et al., "Glycoprotein Profiles of Human Breast Cells Demonstrate a Clear Clustering of Normal/Benign versus Malignant Cell Lines and Basal versus Luminal Cell Lines," Journal of Proteome Research 11:656–67 (2011).

[6] For each of the rejections under 35 U.S.C. § 103(a), the Examiner also cites a "UniProt Entry" for each of fourteen proteins. *See, e.g.*, Final Action 9–10. The UniProt Entries are cited as evidence that certain proteins are glycosylated; i.e., they are glycoproteins as recited in the claims. *See id*. at 10–11. Appellant does not dispute that the proteins in question are glycoproteins. *See, e.g.*, Ans. 23–24 (discussing the UnitProt Entries). Since the UniProt Entries are cited for a point that is undisputed, we will not discuss them further.

[7] Manuela Zucknick et al., "Comparing the Characteristics of Gene Expression Profiles Derived by Univariate and Multivariate Classification Methods," Statistical Applications in Genetics and Molecular Biology, Vol. 7, Iss. 1, Art. 7 (2008).

Claims 1, 7, and 8 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Ford[8] (Final Action 15–16);

Claims 1, 7, and 9 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Di Michele[9] (Final Action 17–18);

Claims 1, 7, and 10 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Serrero[10] (Final Action 19);

Claims 1, 7, and 11 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Herter-Sprie[11] (Final Action 20–21);

Claims 1, 7, 12, and 13 under 35 U.S.C. § 103 as obvious based on Daemen, Even-Desrumeaux, Yen, and Brünner-Kubath[12] (Final Action 22); and

Claims 15, 17, 22, and 24 under 35 U.S.C. § 103 as obvious based on Derr,[13] Daemen, Even-Desrumeaux, and Yen (Final Action 24).

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[8] US 8,129,114 B2, issued March 6, 2012.
[9] Michela Di Michele et al., "A proteomic approach to paclitaxel chemoresistance in ovarian cancer cell lines," Biochimica et Biophysica Acta 1794:225–236 (2009).
[10] US 2008/0114070 A1, published May 15, 2008.
[11] Grit S. Herter-Sprie et al., "Activating mutations in *ERBB2* and their impact on diagnostics and treatment," Frontiers in Oncology 3:1–10 (2013).
[12] Caroline Brünner-Kubath et al., "The PI3 kinase/mTOR blocker NVP-BEZ235 overrides resistance against irreversible ErbB inhibitors in breast cancer cells," Breast Cancer Research & Treatment 129:387–400 (2011).
[13] WO 2013/134649 A1, published September 12, 2013.

OPINION

Indefiniteness

Claim 1, and its dependent claims, stand rejected on the basis that "[t]he nexus between the steps of identifying . . . and correlating or associating . . . is unclear." Final Action 3. The Examiner reasons that

> [t]he identification of the one or more biomarkers based on association with an effective reduction in proliferation of the cancer cells for at least one of the drugs inherently includes determining an association between the glycoprotein biomarkers and an effective reduction in proliferation of the cancer cells for at least one of the drugs.

Id. The Examiner concludes that,

> [t]herefore, it is unclear if the additional correlating or association step is intended to require an additional, second step of correlating or associating the at least one biomarkers with a reduction of proliferation of the cancer cells in response to the at least one of the drugs or if this step is intended to limit the association performed in the identification step.

Id.

We agree with the Examiner that claim 1 is indefinite as written. Claim 1 requires performing a statistical analysis on two datasets, then "from said statistical analysis," "identifying one or more glycoprotein biomarkers associated with an effective reduction in proliferation of said cancer cells for at least one of said drugs," and further "using said computer, correlating or associating at least one of said one or more glycoprotein biomarkers with said reduction in proliferation of the cancer cells in response to at least one of said plurality of drugs."

As the Examiner has pointed out, *identifying* a glycoprotein biomarker *associated with* reduced proliferation in response to a drug inherently

associates that glycoprotein biomarker with reduced proliferation in response to that drug, because what *identifies* the glycoprotein as a biomarker is its *association* with reduced proliferation of the cancer cells in response to the drug. Thus, it is unclear what use of a computer is required by the last step of claim 1: "using said computer, correlating or associating at least one of said one or more glycoprotein biomarkers with said reduction in proliferation of the cancer cells in response to at least one of said plurality of drugs."

Appellant's argument on this issue does not clarify the intended meaning of the claim language. Appellant argues that

> the number of glycoprotein biomarkers correlated or associated with at least one effective drug can be less than the number of glycoprotein biomarkers identified in the identifying step. Such language indicates that the correlating or associating step is in addition[] to the identifying step. . . . Thus, the rejection is in error and should be reversed.

Appeal Br. 103.

Regardless of how many glycoproteins are "identified" and "correlated or associated," however, the claim (and Appellant's argument) implies that two separate actions are taken with regard to the glycoprotein(s). The question therefore remains: after one or more glycoproteins are "identif[ied]" as associated with reduced proliferation in response to a drug, what function(s) must be carried out using a computer to meet the further requirement of "correlating or associating" at least one of the one or more glycoprotein biomarkers with reduced proliferation in response to a drug?

Appellant has not pointed to any description in the Specification that clarifies the meaning of the claim language, and no such description is apparent to us. "Applying the broadest reasonable interpretation of a claim, . . . the Office establishes a prima facie case of indefiniteness with a rejection explaining how the metes and bounds of a pending claim are not clear because the claim contains words or phrases whose meaning is unclear." *Ex parte McAward*, 2017 WL 3669566, at *2 (PTAB 2017) (precedential) (citing *In re Packard*, 751 F.3d 1307, 1310 (Fed. Cir. 2014)). *See also id*. at *5 (*Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898 (2014), did not change the applicability of the *Packard* test by the PTAB.) Claim 1 contains words or phrases whose meaning is unclear, and is therefore indefinite. We affirm the rejection of claims 1, 4–13, 21, 23, and 26 under 35 U.S.C. § 112(b).

Patent Ineligibility

Claims 1, 4–13, 15, 17–19, 21–24, and 26 stand rejected under 35 U.S.C. § 101 as being "directed to a judicial exception (i.e., a law of nature, a natural phenomenon, or an abstract idea) without significantly more." Final Action 4. The Examiner finds that each of the independent claims recites steps of "statistically analyzing," "identifying," and "correlating," and reasons that these steps

> are similar to the concepts of comparing data in knowledge bases in order to identify medical options in *SmartGene, Inc. v Advanced Biological Labs.* (555 Fed. Appx. 950 (Fed. Cir. 2014)) and organizing information through mathematical correlations in *Digitech Image Techs., LLC v Electronics for Imaging, Inc.* (758 F.3d 1344 . . . (Fed. Cir. 2014)).

Id.

The Examiner also finds that the claims recite limitations that are "similar to the concept of determining the relationship between a level of a metabolite of a drug in a patient and correlating that to a specific outcome in *Mayo Collaborative Svcs. v. Prometheus Labs*." *Id*. The Examiner finds that the claims here "recite the judicial exception that is the natural phenomenon of a correlation between a naturally known product and a result based on a correlation of the naturally known product." *Id*. at 5.

With regard to whether the claims amount to significantly more than a judicial exception, the Examiner notes that "the claims do not recite any active, positive limitations for performing the physical assay steps to gather the datasets and instead only require having the data in a dataset." *Id*. The Examiner also notes that the claims require only "generic computer components and functions." *Id*. With regard to claim 15, the Examiner finds that "administering the one or more drugs to the patient in an effective amount . . . equates to conventional post-solution activity." *Id.* The Examiner concludes that "the claims do not amount to significantly more than the judicial exception itself . . . [and] are directed to non-statutory subject matter." *Id*. at 6.

Appellant argues that "Claim 1 recites considerably more than merely comparing new and stored information and using rules to identify options including a mathematical relationship or function," and "[c]learly, . . . is not an abstract idea." Appeal Br. 103–104. Appellant argues that, "[s]imilar to *MCRO* [*McRO, Inc. v. Bandai Namco Games Am. Inc.*, 837 F.3d 1299 (Fed. Cir. 2016)], the present claims use a program in a computer specifically designed to improve on the prior art." *Id*. at 107. Appellant also argues that

the Macher Declaration[14] provides evidence that the method of claim 1 "includes specific and unconventional components and/or limitations that amount to significantly more than the judicial exception." *Id*. at 110–111.

Principles of Law

A. Section 101

An invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101. However, the U.S. Supreme Court has long interpreted 35 U.S.C. § 101 to include implicit exceptions: "[l]aws of nature, natural phenomena, and abstract ideas" are not patentable. *E.g.*, *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014).

In determining whether a claim falls within an excluded category, we are guided by the Court's two-part framework, described in *Mayo* and *Alice*. *Id.* at 217–18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75–77 (2012)). In accordance with that framework, we first determine what concept the claim is "directed to." *See Alice*, 573 U.S. at 219 ("On their face, the claims before us are drawn to the concept of intermediated settlement, *i.e.,* the use of a third party to mitigate settlement risk."); *see also Bilski v. Kappos*, 561 U.S. 593, 611 (2010) ("Claims 1 and 4 in petitioners' application explain the basic concept of hedging, or protecting against risk.").

Concepts determined to be abstract ideas, and thus patent ineligible, include certain methods of organizing human activity, such as fundamental

[14] Declaration under 37 C.F.R. § 1.132 of Bruce Macher, filed August 8, 2016.

economic practices (*Alice*, 573 U.S. at 219–20; *Bilski*, 561 U.S. at 611); mathematical formulas (*Parker v. Flook*, 437 U.S. 584, 594–95 (1978)); and mental processes (*Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). Concepts determined to be patent eligible include physical and chemical processes, such as "molding rubber products" (*Diamond v. Diehr*, 450 U.S. 175, 191 (1981)); "tanning, dyeing, making waterproof cloth, vulcanizing India rubber, smelting ores" (*id.* at 182 n.7 (quoting *Corning v. Burden*, 56 U.S. 252, 267–68 (1853))); and manufacturing flour (*Benson*, 409 U.S. at 69 (citing *Cochrane v. Deener*, 94 U.S. 780, 785 (1876))).

In *Diehr*, the claim at issue recited a mathematical formula, but the Court held that "a claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula." *Diehr*, 450 U.S. at 187; *see also id.* at 191 ("We view respondents' claims as nothing more than a process for molding rubber products and not as an attempt to patent a mathematical formula."). Having said that, the Court also indicated that a claim "seeking patent protection for that formula in the abstract . . . is not accorded the protection of our patent laws, and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment." *Id.* (citation omitted) (citing *Benson* and *Flook*); *see, e.g.*, *id*. at 187 ("It is now commonplace that an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.").

If the claim is "directed to" an abstract idea, we turn to the second step of the *Alice* and *Mayo* framework, where "we must examine the elements of the claim to determine whether it contains an 'inventive

concept' sufficient to 'transform' the claimed abstract idea into a patent-eligible application." *Alice*, 573 U.S. at 221 (quotation marks omitted). "A claim that recites an abstract idea must include 'additional features' to ensure 'that the [claim] is more than a drafting effort designed to monopolize the [abstract idea].'" *Id.* (alterations in original) (quoting *Mayo*, 566 U.S. at 77). "[M]erely requir[ing] generic computer implementation[] fail[s] to transform that abstract idea into a patent-eligible invention." *Id.*

B. USPTO Section 101 Guidance

In January 2019, the U.S. Patent and Trademark Office (USPTO) published revised guidance on the application of § 101. 2019 Revised Patent Subject Matter Eligibility Guidance, 84 Fed. Reg. 50 (Jan. 7, 2019) ("2019 Revised Guidance").[15] "All USPTO personnel are, as a matter of internal agency management, expected to follow the guidance." *Id.* at 51; *see also* October 2019 Update at 1.

Under the 2019 Revised Guidance and the October 2019 Update, we first look to whether the claim recites:

> (1) any judicial exceptions, including certain groupings of abstract ideas (i.e., mathematical concepts, certain methods of organizing human activity such as a fundamental economic practice, or mental processes) ("Step 2A, Prong One"); and

[15] In response to received public comments, the Office issued further guidance on October 17, 2019, clarifying the 2019 Revised Guidance. USPTO, *October 2019 Update: Subject Matter Eligibility* (the "October 2019 Update") (available at https://www.uspto.gov/sites/default/files/documents/peg_oct_2019_update.pdf).

> (2) additional elements that integrate the judicial exception into a practical application (*see* MPEP § 2106.05(a)–(c), (e)–(h) (9th ed. Rev. 08.2017, Jan. 2018)) ("Step 2A, Prong Two").[16]

2019 Revised Guidance, 84 Fed. Reg. at 52–55.

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, do we then look, under Step 2B, to whether the claim:

> (3) adds a specific limitation beyond the judicial exception that is not "well-understood, routine, conventional" in the field (*see* MPEP § 2106.05(d)); or
>
> (4) simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception.

2019 Revised Guidance, 84 Fed. Reg. at 52–56.

[16] This evaluation is performed by (a) identifying whether there are any additional elements recited in the claim beyond the judicial exception, and (b) evaluating those additional elements individually and in combination to determine whether the claim as a whole integrates the exception into a practical application. *See* 2019 Revised Guidance - Section III(A)(2), 84 Fed. Reg. 54–55.

Revised Guidance Step 2(A), Prong 1

Following the Revised Guidance, we first consider whether the claims recite a judicial exception. Claim 1 recites the steps of:

(a) performing a statistical analysis on

(i) a first dataset of expression levels of at least five glycoproteins in cancer cells, said expression levels being determined by mass spectrometry, and

(ii) a second dataset of responses of said cancer cells to each of at least five drugs at a concentration of each drug that causes a 50% reduction in proliferation of the cancer cells,

(b) "identifying one or more glycoprotein biomarkers associated with an effective reduction in proliferation of said cancer cells for at least one of said drugs from said statistical analysis," and

(c) "correlating or associating at least one of said one or more glycoprotein biomarkers with said reduction in proliferation of the cancer cells in response to at least one of said . . . drugs."

The Revised Guidance identifies "[m]athematical concepts—mathematical relationships, mathematical formulas or equations, mathematical calculations"—as abstract ideas. 84 Fed. Reg. at 52. *See also Digitech Image Techs., LLC v. Elecs. for Imaging, Inc.*, 758 F.3d 1344, 1351 (Fed. Cir. 2014) (The "claim recites a process of taking two data sets and combining them into a single data set. . . . Without additional limitations, a process that employs mathematical algorithms to manipulate existing information to generate additional information is not patent eligible.").

Here, the step of "performing a statistical analysis" on two datasets describes mathematical calculations carried out to identify relationships between the data in the datasets; i.e., relationships between glycoproteins in the glycoprotein dataset and drugs in the drug-response dataset. Statistical analysis is a mathematical process. *See* Spec. ¶ 46: "The present method statistically analyzes the database(s) by modeling quantitative drug response data as a function of a number of quantitative predictor variables. In general, the statistical analysis comprises a regression analysis." *See also id*. ¶¶ 48–52 ("Exemplary Statistical Analyses"). Thus, the step of "performing a statistical analysis" recites a mathematical concept, which is a category of abstract ideas. *See, e.g., SAP Am., Inc. v. InvestPic, LLC*, 898 F.3d 1161, 1163–1165 (Fed. Cir. 2018) (claims to a "method of providing statistical analysis of investment data" were found to be patent-ineligible).

The Revised Guidance also identifies "[m]ental processes—concepts performed in the human mind (including an observation, evaluation, judgment, opinion)"—as abstract ideas. 84 Fed. Reg. at 52 (footnote omitted); *see also Mayo*, 566 U.S. at 71 ("[M]ental processes[] and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").

Here, the step of identifying, from the results of a statistical analysis, a glycoprotein biomarker as being associated with an effective reduction in cancer cell proliferation for a drug merely requires observing and evaluating the results of the statistical analysis that was performed on the datasets of glycoprotein expression levels and cancer cell responses to drugs. The same is true for "correlating or associating" a glycoprotein biomarker with

reduced cancer cell proliferation in response to a drug, which—as discussed above—appears to be inherent in the previously recited "identifying" step. Observation and evaluation are mental processes, and therefore abstract ideas. *See* 84 Fed. Reg. at 52.

Although claim 1 states that the "correlating or associating" is carried out "using a computer," no specific computer components or functions are recited, and the claimed step can practically be performed in the mind. *See id*., note 14 ("If a claim, under its broadest reasonable interpretation, covers performance in the mind but for the recitation of generic computer components, then it is still in the mental processes category unless the claim cannot practically be performed in the mind."). The "correlating or associating" step thus reads on a mental process, as does the "identifying" step.

In summary, we agree with the Examiner that claim 1 recites an abstract idea.

Revised Guidance Step 2(A), Prong 2

Although claim 1 recites an abstract idea, it would still be patent-eligible if "the claim as a whole integrates the recited judicial exception into a practical application of the exception." 84 Fed. Reg. at 53. "A claim that integrates a judicial exception into a practical application will apply, rely on, or use the judicial exception in a manner that imposes a meaningful limit on the judicial exception." *Id*. The analysis of whether the claim integrates the judicial exception into a practical application includes "[i]dentifying whether there are any additional elements recited in the claim beyond the judicial exception(s)" and "evaluating those additional elements individually and in

combination to determine whether they integrate the exception into a practical application." *Id.* at 54–55.

The exemplary considerations indicating that an additional element may integrate an exception into a practical application include "[a]n additional element [that] reflects an improvement in the functioning of a computer, or an improvement to other technology or technical field." *Id*. at 55. However, "[a]n additional element . . . [that] merely includes instructions to implement an abstract idea on a computer, or merely uses a computer as a tool to perform an abstract idea" is an indication that "a judicial exception has not been integrated into a practical application." *Id*.

Here, in addition to mathematical calculations (statistical analysis) and mental processes ("identifying," "correlating or associating"), claim 1 also recites "using a computer having a statistical analysis program recorded in a tangible medium therein" to perform the statistical analysis and "using said computer" to carry out the correlating or associating. However, the claim does not require any specific statistical analysis programming, and does not require any specific configuration of the recited computer that might reflect an improvement in computer functioning.

The Specification confirms that Appellant's invention is not in the method of statistical analysis or in the computer system used. For example, the Specification states that "there have been efforts to solve the problem of predicting the responses of cancer cell lines to drugs. . . . Other conventional methods that have been used in attempt to solve the prediction problem of drug effectiveness on cell lines include machine learning and statistical methods." Spec. ¶ 10.

The Specification states that "[s]everal related statistical methods have been employed recently in modeling drug response in cancer cell lines for both mRNA and protein data. Ridge regression has been used as part of an effort to predict patient drug response based on the drug responses of cancer cell lines." *Id*. ¶ 11. "Elastic net regression has also been used recently for predicting drug response. In two cases the predictor variables are proteins, measured by mass spectrometry." *Id*. ¶ 12.

Claim 1 encompasses using any method of statistical analysis, including ridge regression or elastic net regression. The claim thus does not reflect an improvement in identifying biomarkers through statistical analysis.[17]

With regard to the computer recited in claim 1, the Specification describes "a system configured to predict effectiveness of one or more drugs to stop or repress proliferation of cancer cells." Spec. ¶ 118. The system comprises "a memory" storing two datasets, "and a computer configured to statistically analyze the first and second datasets." *Id*. "The computer may be

[17] And, in any event, an improved judicial exception—such as an improved mathematical calculation—is still a judicial exception. *See SAP Am.*, 898 F.3d at 1163 (Fed. Cir. 2018) ("The claims here are ineligible because their innovation is an innovation in ineligible subject matter. . . . [T]he advance lies entirely in the realm of abstract ideas, with no plausibly alleged innovation in the non-abstract application realm. An advance of that nature is ineligible for patenting."); *Trading Techs. Int'l, Inc. v. IBG LLC*, 921 F.3d 1084, 1093 (Fed. Cir. 2019) ("The claims . . . do not improve the functioning of the computer, make it operate more efficiently, or solve any technological problem. Instead, they recite a purportedly new arrangement of generic information that assists traders in processing information more quickly. . . . We conclude that the claims are directed to [an] abstract idea.").

configured to statistically analyze the first and second datasets using lasso regression." *Id*. ¶ 119.

The Specification does not describe any specialized data structure for storing the recited datasets in the memory, nor does it describe any other aspect of the computer that purports to improve on the storage, retrieval, or analysis of the datasets. Rather, the Specification states:

> The present system further includes algorithms, computer program(s), computer-readable media and/or software, implementable and/or executable in a *general purpose* computer or workstation equipped with a *conventional* digital signal processor, and configured to perform one or more of the methods and/or one or more operations of the hardware (e.g., computer) disclosed herein.

Id. ¶ 120 (emphasis added).

We conclude that the method of claim 1 does not reflect an improvement in the functioning of a computer, or an improvement to another technical field. Rather, the generic computer and generic statistical analysis program recited in the claim merely implement the recited mathematical calculations and mental processes on a computer. They therefore do not integrate the recited judicial exceptions into a practical application.

In summary, claim 1 recites an abstract idea and does not integrate it into a practical application. Claim 1 is therefore directed to a judicial exception to patentability.

Revised Guidance Step 2(B)

Finally, the Revised Guidance directs us to consider whether claim 1 includes "additional elements . . . [that] provide[] 'significantly more' than

the recited judicial exception." 84 Fed. Reg. at 56. The Revised Guidance states that an additional element that "simply appends well-understood, routine, conventional activities previously known to the industry, specified at a high level of generality, to the judicial exception, . . . is indicative that an inventive concept may not be present." *Id*.

Here, the only elements recited in claim 1, other than the mathematical calculations and mental processes themselves, are a generic computer and a generic statistical analysis program. As discussed above, however, claim 1 does not require any unconventional computer configuration or statistical analysis software, nor does the Specification describe any unconventional hardware or software as being necessary for the claimed method.

Therefore, claim 1 requires using only a generic computer system to carry out the recited statistical analysis, and "the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention." *Alice*, 573 U.S. at 223. The combination of elements recited in the method of claim 1 does not amount to significantly more than the judicial exception itself, and under 35 U.S.C. § 101 the claimed method is ineligible for patenting.

Appellant's Arguments

Appellant argues that the instant appeal is similar to *McRO, Inc. v. Bandai Namco Games Am., Inc.*, 837 F.3d 1299 (Fed. Cir. 2016), because "the present claims use a program in a computer specifically designed to improve on the prior art." Appeal Br. 107. That is, "[t]he present Claim 1 uses a program recorded in a tangible medium in a computer" to statistically

analyze data and to "correlate or associate" glycoprotein biomarkers with reduction in proliferation in response to a drug and, "[a]s a result, the present claim is eligible for patentability." *Id*. at 108.

We do not agree that the invention claimed in *McRO* is analogous to instant claim 1. In *McRO*, "the claimed improvement . . . [was] allowing computers to produce 'accurate and realistic lip synchronization and facial expressions in animated characters' that previously could only be produced by human animators." *McRO*, 837 F.3d at 1313. "[T]his computer automation [was] realized by improving the prior art through 'the use of rules, rather than artists, to set the morph weights and transitions between phonemes.'" *Id*. Thus, the claim "focused on a specific asserted improvement in computer animation, i.e., the automatic use of rules of a particular type." *Id*. at 1314. The court concluded that, "[w]hen looked at as a whole, claim 1 is directed to a patentable, technological improvement over the existing, manual 3–D animation techniques." *Id*. at 1316.

Appellant's claimed method, by contrast, does not include specific rules or other limitations that allow computerization of an activity that previously could only be done by humans. Rather, claim 1 requires nothing more than using a conventional computer to analyze preexisting datasets with a conventional statistical software program. The claimed method therefore does not reflect an improvement in computer technology or another technical field, and *McRO* does not support the patent eligibility of Appellant's claims.

Appellant also argues "the Declaration of Bruce Macher filed on August 8, 2016 (hereinafter referred to as 'the Macher Declaration')

provides sufficient evidence that" the claimed method "includes specific and unconventional components and/or limitations that amount to significantly more than the judicial exception." Appeal Br. 110–111. "For example, the present claims recite determining expression levels of glycoproteins by mass spectrometry (MS), which enables the claimed methods and system to efficiently and effectively determine which drug(s) may be effective in stopping or repressing proliferation of cancer cells over conventional methods." *Id*. at 111 (citing Macher Decl. ¶ 40). "As a result, the Macher Declaration provides specific and unconventional components and/or limitations that amount to significantly more than the judicial exception." *Id*.

This argument is unpersuasive, because claim 1 does not, in fact, "recite determining expression levels of glycoproteins by mass spectrometry." Appeal Br. 111. As the Examiner has pointed out, the "claims do not recite ***active, positive*** steps" of determining glycoprotein expression levels using mass spectrometry; "[r]ather, this limitation only serves to further limit the type of data" used for the statistical analysis. Ans. 24. That is, claim 1 does not include a step of using mass spectrometry to determine the expression levels of glycoproteins in cancer cells. Instead, it recites using a computer to access a preexisting dataset that consists of glycoprotein expression levels, which were determined using mass spectrometry.

We therefore affirm the rejection of claim 1 under 35 U.S.C. § 101. Claims 5–7, 21, and 23 were argued as a group with claim 1. Appeal Br. 103. We therefore affirm the rejection of claims 5–7, 21, and 23 as well.

With regard to claims 4, 8–13, and 26, Appellant relies on the same arguments presented with regard to claim 1. *See* Appeal Br. 110–118. These arguments are unpersuasive for the reasons discussed above, and we therefore affirm the rejection under 35 U.S.C. § 101 of claims 4, 8–13, and 26.

With regard to claim 15, Appellant again argues that "[s]imilar to *M*[*c*]*RO*, the present claims use a program in a computer specifically designed to improve on the prior art." Appeal Br. 123. Appellant also argues again that the Macher Declaration "provides evidence that" the claimed method "includes specific and unconventional components and/or limitations that amount to significantly more than the judicial exception." *Id*. at 125–126. These arguments are adequately addressed above.

Appellant also argues that claim 15's step of administering one or more drugs in a pharmaceutically acceptable carrier or excipient to a patient having the cancer cells in an amount effective to stop or repress the proliferation of the cancer cells, constitutes an additional element that amounts to significantly more than the judicial exception. Appeal Br. 125.

This argument is also unpersuasive. It is true that "an additional element that applies or uses a judicial exception to effect a *particular treatment* or prophylaxis for a disease or medical condition" may indicate that a judicial exception has been integrated into a practical application. 84 Fed. Reg. at 55 (emphasis added). Claim 15, however, does not recite a *particular* treatment. Rather, it recites using a patent-ineligible process to identify a correlation between a generic glycoprotein biomarker and the effectiveness of a generic drug, and then applying that correlation by

administering the drug to a patient having cancer cells that express the glycoprotein.

Claim 15 therefore is distinguishable from a "method of treating schizophrenia patients with iloperidone wherein the dosage range is based on the patient's genotype," as in *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1121 (Fed. Cir. 2018). In *Vanda*, "[t]he inventors recognized the relationships between iloperidone, CYP2D6 metabolism, and QTc prolongation, . . . [and] claimed an application of that relationship." *Id*. at 1135. "Thus, the . . . claims are 'a new way of using an existing drug' that is safer for patients because it reduces the risk of QTc prolongation." *Id*.

Appellant's claim 15, by contrast, does not recite using a specific drug, at a specific dosage, to treat a cancer cell expressing a specific glycoprotein biomarker. It simply recites using the recited patent-ineligible method of statistical analysis to identify a correlation, and then treating a patient in accordance with whatever correlation is identified. Claim 15 is not directed to a new way of using an existing drug in the same way the *Vanda* claims were.

We therefore affirm the rejection of claim 15 under 35 U.S.C. § 101. Claims 17, 22, and 24 were argued as a group with claim 15. Appeal Br. 119. We therefore affirm the rejection of claims 17, 22, and 24 as well.

With regard to claim 18, Appellant again argues that "[s]imilar to *M*[*c*]*RO*, the present claims use a program in a computer specifically designed to improve on the prior art." Appeal Br. 130. Appellant also argues again that the Macher Declaration "provides evidence that a computer including" a processor and instructions to perform the recited method

"includes specific and unconventional components and/or limitations that amount to significantly more than the judicial exception." *Id*. at 133. These arguments are adequately addressed above.

With regard to claim 19, Appellant relies on the same arguments as presented for claim 18, which are unpersuasive for the reasons previously discussed. We therefore affirm the rejection of claims 18 and 19 under 35 U.S.C. § 101.

In summary, we affirm the rejection of claims 1, 4–13, 15, 17–19, 21–24, and 26 under 35 U.S.C. § 101.

Obviousness: Daemen, Even-Desrumeaux, and Yen

Claims 1, 5–8, 18, 21, 23 stand rejected under 35 U.S.C. § 103 based on Daemen, Even-Desrumeaux, and Yen. The Examiner finds that Daemen teaches "a software package to predict compound efficacy in individual tumors in breast cancer utilizing correlative analysis between molecular features, including protein expression, and drug response, as well as identifying molecular features associated with responses of cell cance[r] lines to therapeutic agents." Final Action 10.

The Examiner finds that Daemen used a dataset of "the concentration of each drug required to inhibit growth by 50%" for a number of different drugs and cancer cell lines. *Id*. The Examiner also finds that Daemen used "seven pretreatment molecular profiling data sets that include protein abundance measurements from a Reverse Phase Protein Lysate Array (RPPA) . . . [which] measured the abundance of 146 proteins." *Id*. The Examiner finds that fourteen of these proteins are glycoproteins. *Id*. at 10–11 (citing UniProt entries).

The Examiner finds that Daemen is "silent to the expression levels of at least 5 glycoproteins being determined by mass spectrometry." *Id*. at 12. The Examiner finds, however, that "Even-Desrumeaux et al. teach that mass spectrometric methods of protein identification and quantitative measurement are at the center of new technologies and methods for biomarker discovery." *Id*. "Even-Desrumeaux et al. further teach that different modes of mass spectrometry can be utilized for *de novo* discovery of biomarker candidates from tumor tissues." *Id*.

The Examiner also finds that Yen teaches "utilizing liquid chromatography/electrospray ionization-tandem mass spectrometry in order to identify and quantify glycoproteins in breast cancer cell lines." *Id*. "Yen et al. teach that the mass spectrometric method identifies and quantifies almost 500 different glycoproteins." *Id*. at 13.

The Examiner concludes that, because Daemen teaches that "the full combination of all data sets, which includes protein expression for at least 5 glycoproteins obtained from RPPA . . . yields a higher AUC value than any dataset by itself," it would have been obvious to "add in protein abundance data to the software to predict the efficacy of compounds in individual patients in order to gain the advantage of more robust candidate signatures for classification and prediction of the most effective treatment." *Id*. at 13.

The Examiner also concludes that, because Even-Desrumeaux teaches that "mass spectrometric methods are better suited to . . . identification of novel biomarkers than RPPA" and Yen teaches "a mass spectrometric method that is able to identify and quantify nearly 500 different glycoproteins for biomarker discovery in breast cancer cells," it would have

been obvious "to substitute the mass spectrometric methods to measure protein abundance taught by Yen et al. for the RPPA assay in the candidate signature development method taught by Daemen et al., in order to utilize a better suited method for novel biomarker identification, as taught by Even-Desrumeaux et al." *Id*. at 13–14.

Appellant argues that "Daemen is silent with regard to using mass spectrometry to identify and measure protein abundance. . . . As a result, Daemen cannot disclose or suggest performing a statistical analysis on a dataset of expression levels of at least 5 glycoproteins in cancer cells as determined by mass spectrometry." Appeal Br. 23.

Appellant argues that, "although Even-Desrumeaux discusses glycoproteins and mass spectrometry, Even-Desrumeaux merely discusses the use of glycoproteins as antigens for immunotherapies. Even-Desrumeaux does not discuss modeling drug response with quantitative measurements of glycoprotein expression. Even-Desrumeaux therefore fails to cure the deficiencies of Daemen." *Id*. at 25.

Appellant also argues that,

> [a]lthough Yen discloses using glycoproteins as biomarkers for classifying tumors, Yen does not disclose their use for predicting a response to cancer cell proliferation-reducing drugs by determining expression levels of glycoproteins by mass spectrometry, or identifying one or more glycoprotein biomarkers associated with an effective reduction in proliferation of the cancer cells for at least one of the drugs from the statistical analysis.

Id. at 26. "Thus, Yen fails to cure the deficiencies of Daemen, the UniProt entries, and Even-Desrumeaux." *Id*. at 27. Appellant concludes that, "[a]s a

result, ***the combination of*** Daemen, the UniProt entries, Even-Desrumeaux, and Yen fails to disclose or make obvious all the limitations of Claim 1." *Id*.

We agree with Appellant that the Examiner has not persuasively shown that a person of ordinary skill in the art would have had sufficient reason to modify Daemen's method to include the glycoprotein expression dataset disclosed by Yen. As the Examiner accurately summarized (Final Action 10), Daemen analyzed correlations "between molecular features, including protein expression, and drug response" in breast cancer cells. Specifically, Daemen

> used least squares-support vector machines and random forest algorithms to identify molecular features associated with responses of a collection of 70 breast cancer cell lines to 90 experimental or approved therapeutic agents. The datasets analyzed included measurements of copy number aberrations, mutations, gene and isoform expression, promoter methylation and protein expression.

Daemen 1, abstract.

Least squares-support vector machines and random forest algorithms are machine learning-based methods. *Id*. at 2, left col. Daemen's protein expression (protein abundance) dataset was based on "Reverse Protein Lysate Array" or "Reverse Phase Protein Array (RPPA)." *Id*. at 2, right col.

There is no dispute that Daemen's machine learning methods meet the claim limitation of "statistical analysis," or that some of the proteins included in Daemen's RPPA dataset were glycosylated, and therefore glycoproteins. *See* Appeal Br. 22–24 (discussing Daemen's disclosure). However, as the Examiner has conceded, Daemen is "silent [as] to the expression levels of at least 5 glycoproteins being determined by mass

spectrometry." Final Action 12. The Examiner relies on Even-Desrumeax and Yen to make up for this deficiency in Daemen.

Even-Desrumeaux is a "review aim[ed] at describing recent advances in biomarkers and tumor antigen discovery in terms of antigen nature and localization, and . . . highlighting the most recent approaches used for their discovery." Even-Desrumeaux 2554, abstract. "A biomarker . . . is a biological molecule found in blood, another body fluid or in tissues that is a sign of a normal or abnormal process." *Id*. at 2563. Specifically, the biomarkers addressed by Even-Desrumeaux are those that are useful in identifying cancer cells. *See id*. Thus, Even-Desrumeaux's statement that "MS-based protein identification combined with quantitative measurements is at the center of development of new technologies and methods," *id*. at 2569, is in the context of identifying biomarkers that can be used to diagnose cancer or as potential targets in developing new drugs. *Id*. at 2564. The Examiner has not pointed to any suggestion in Even-Desrumeaux that its biomarkers would be correlated with cancer cells' responsiveness to a particular drug.

Yen states that "[b]iomarkers detectable in the blood have the potential either to provide information about a tumor before surgery or to be used to monitor for recurrence. Proteins found in the blood . . . are likely to be glycoproteins." Yen 657, left col. Yen describes "a shotgun proteomics approach to identify candidate biomarkers for breast cancer," in which "[g]lycoproteins from the cells were captured . . . and subjected to electrospray ionization/tandem mass spectrometry to identify their protein components." *Id*. "A total of 486 glycoproteins . . . were identified among

the 14 cell lines." *Id*. at 660, left col. Yen thus discloses a dataset comprising at least five glycoproteins in cancer cells.

Yen states that the "results demonstrate that the glycoprotein patterns of normal breast cancer cells and breast cancer cell lines vary significantly. In addition, glycoproteins are differentially expressed in benign versus malignant cells, in cell lines of basal versus luminal origin, and in cell lines of basal A and B subtypes." *Id*. at 663, right col. That is, the "results show that these various breast cell types can be distinguished by cluster analysis of their glycoproteins." *Id*. at 657, left col.

However, Yen does not disclose that the glycoproteins in its dataset are useful in distinguishing between cancer cells that respond differently to particular drugs. Yen states that "[a]n important research *goal* is to identify mRNA or protein biomarkers that provide clinically useful information about the diagnosis, prognosis, or *response to treatment* of breast cancer." *Id*. at 656, left col. (emphasis added). Yen does not, however, describe its glycoprotein biomarkers as actually useful in providing information about response to drug treatment.

The Examiner does not rely on any express suggestion in Yen to use its glycoprotein expression dataset in a method like Daemen's, reasoning instead that a skilled artisan "would have been motivated to add in protein abundance data . . . in order to gain the advantage of more robust candidate signatures for classification and prediction of the most effective treatment." Final Action 13. The cited references, however, do not provide adequate evidence that a skilled artisan would have expected that adding Yen's

glycoprotein dataset to those used by Daemen would have provided "more robust candidate signatures" for predicting drug-responsiveness.

The Examiner also reasons that it would have been obvious "to substitute the mass spectrometric methods to measure protein abundance taught by Yen et al. for the RPPA assay in the candidate signature development method taught by Daemen et al., in order to utilize a better suited method for novel biomarker identification, as taught by Even-Desrumeaux et al." Final Action 14. This reasoning, however, does not account for the different goals of Daemen and Even-Desrumeaux: predicting the response of specific cancer cells to specific drugs in Daemen, versus distinguishing between cancer cells and normal cells in Even-Desrumeaux. The Examiner has not persuasively explained why Even-Desrumeaux's discussion of using mass spectrometry to discover cancer biomarkers would have led to an expectation that it would also be useful in Daemen's method.

In summary, we conclude that the cited references do not provide a person of ordinary skill in the art an adequate reason to combine their teachings, without the benefit of hindsight. We therefore reverse the rejection of claims 1, 5–8, 18, 21, and 23 under 35 U.S.C. § 103 based on Daemen, Even-Desrumeaux, and Yen.

Obviousness: Daemen, Even-Desrumeaux, Yen, and other references

Claims 1, 4, 7–13, 15, 17–19, 22, 24, and 26 stand rejected under 35 U.S.C. § 103 based on Daemen, Even-Desrumeaux, Yen, and one of Zucknick, Ford, Di Michele, Serrero, Herter-Sprie, Brünner-Kubath, or Derr.

With regard to claims 1, 4, 7–13, 18, 19, and 26, the Examiner concludes that Daemen, Even-Desrumeaux, and Yen would have made

obvious the inventions of independent claims 1 and 18, and cites one of Zucknick, Ford, Di Michele, Serrero, Herter-Sprie, or Brünner-Kubath for the limitation(s) of the dependent claims. *See* Final Action 14–23.

With regard to claims 15, 17, 22, and 24, the Examiner relies on the same findings and reasoning discussed above with respect to claim 1 (*id*. at 25–28), and relies on Derr for disclosing "a method of identifying cancer patients likely to respond positively to drugs" based on "the level of gene expression for each of a plurality of genes," and "treating the patient with the preselected drug." *Id*. at 24–25.

Thus, all of the remaining § 103 rejections depend on the same reasoning discussed, and found inadequate, above with regard to combining Yen's glycoprotein expression dataset with Daemen's method of predicting cancer cell responses to drugs. We therefore reverse the rejections under 35 U.S.C. § 103 based on Daemen, Even-Desrumeaux, Yen, and one of Zucknick, Ford, Di Michele, Serrero, Herter-Sprie, Brünner-Kubath, or Derr, for the reasons discussed above.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 4–13, 21, 23, 26	112(b)	Indefiniteness	1, 4–13, 21, 23, 26	
1, 4–13, 15, 17–19, 21–24, 26	101	Eligibility	1, 4–13, 15, 17–19, 21–24, 26	
1, 5–8, 18, 21, 23	103	Daemen, Even-Desrumeaux, Yen		1, 5–8, 18, 21, 23

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 4, 18, 19, 26	103	Daemen, Even-Desrumeaux, Yen, Zucknick		1, 4, 18, 19, 26
1, 7, 8	103	Daemen, Even-Desrumeaux, Yen, Ford		1, 7, 8
1, 7, 9	103	Daemen, Even-Desrumeaux, Yen, Di Michele		1, 7, 9
1, 7, 10	103	Daemen, Even-Desrumeaux, Yen, Serrero		1, 7, 10
1, 7, 11	103	Daemen, Even-Desrumeaux, Yen, Herter-Sprie		1, 7, 11
1, 7, 12, 13	103	Daemen, Even-Desrumeaux, Yen, Brünner -Kubath		1, 7, 12, 13
15, 17, 22, 24	103	Derr, Daemen, Even-Desrumeaux, Yen		15, 17, 22, 24
Overall Outcome			1, 4–13, 15, 17–19, 21–24, 26	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED