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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte GARRY P. NOLAN, OMAR D. PEREZ, KAREN SACHS, and DOUGLAS ALAN LAUFFENBURGER[1]

Appeal 2016-000569
Application 11/338,957
Technology Center 1600

Before JOHN G. NEW, RICHARD J. SMITH, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims directed to a method for characterizing (or diagnosing/prognosing) a disease state. Claims 13, 14, 43–45, 52, 53, 60, 63, 67, 69, 72, 73, and 78–87 are on appeal as rejected under 35 U.S.C. § 101. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

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[1] Appellants identify the Real Parties in Interest as "The Board of Trustees of The Leland Stanford Junior University" and "Massachusetts Institute of Technology." App. Br. 3.

STATEMENT OF THE CASE

The Specification states, as background: "[e]xtracellular and/intracellular cues trigger a cascade of information flow, in which signaling molecules become chemically, physically or locationally modified, gain new functional capabilities, and affect subsequent molecules in the cascade, culminating in a phenotypic cellular response." Spec. ¶ 4. The Specification further states, "Bayesian networks, a form of graphical models, have been proffered as a promising framework for modeling complex systems such as cell signaling cascades by representing probabilistic dependence relationships among multiple interacting components." Spec. ¶ 5 (citing, *inter alia*, Friedman, Pe'er, and Sachs, as identified, *infra* at n.3).

The Specification further states, "[t]he present disclosure discloses experimental and computational methods for constructing cell signaling networks." Spec. ¶ 3. To do so, the Specification explains, "[m]ethods of developing and using models of cellular networks by applying a probabilistic graphical model are provided," where "cellular components can be detected using any of a number of techniques. For example, the cellular components can be detected by flow cytometry or confocal microscopy" and, upon this detection, "[a]ny probabilistic graphical model algorithm can be used. . . . In certain embodiments, the probabilistic graphical model algorithm is a Bayesian network structure inference algorithm." Spec. ¶¶ 6, 10.

Claims 13, 14, and 80 are the independent claims. We find claims 13 and 14 are representative; they are reproduced below:

13. A method of characterizing a disease state comprising:

a) measuring a plurality of cellular components in individual cells exhibiting said disease state to generate a first data set, wherein said measuring comprises:

(i) contacting said cells exhibiting said disease state with a set of distinguishably detectable probes that bind to said cellular components, and

(ii) detecting the binding of said probes to said cellular components in each individual cell of said cells exhibiting said disease state to generate said first data set comprising a plurality of individual cell data sets from said cells exhibiting said disease state;

b) providing a first set of arcs for said cellular components in cells exhibiting said disease state from said first data set, wherein the arcs are obtained by the probabilistic analysis of causal connections between said cellular components in each individual cell in said first data set;

c) measuring a plurality of cellular components in individual cells not exhibiting said disease state to generate a second data set, wherein said measuring comprises:

(i) contacting said cells not exhibiting said disease state with said set of distinguishably detectable probes that bind to said cellular components, and

(ii) detecting the binding of said probes to said cellular components in each individual cell of said cells not exhibiting said disease state to generate a second data set comprising a plurality of individual cell data sets from said cells not exhibiting said disease state;

d) providing a second set of arcs for said cellular components in cells that do not exhibit said disease state from said second data

set, wherein the arcs are obtained by the probabilistic analysis of causal connections between said cellular components in each individual cell in said second data set; and

e) comparing the presence, absence or change of one or more arcs from said first set of arcs as compared to said second set of arcs to determine one or more decisional arcs, wherein said decisional arc is indicative of said disease state.

14. A method of diagnosing or prognosing a disease state in a subject comprising:

a) providing a set of decisional arcs, wherein said set of decisional arcs are indicative of causal connections between cellular components and wherein said decisional arcs are also indicative of the presence, absence or prognosis of said disease state;

b) obtaining a first set of cells from said subject;

c) providing a set of probes that bind to said cellular components in said first set of cells, wherein each probe is labeled with a distinguishable label;

d) detecting the binding of said probes to said cellular components in each individual cell of said first set of cells to generate a first data set associated with cellular components in each of said first cells, wherein the first data set comprises a plurality of individual cell data sets from said individual cells; and

e) applying a probabilistic graphical model algorithm to said first data set to identify a set of arcs between said cellular components in each said individual cell, wherein the results of the detecting of probe binding in each individual cell is treated as an independent observation in said probabilistic analysis, and wherein the set of arcs are indicative of causal connections between said cellular components; and

f) comparing said set of arcs for said cellular components to said set of decisional arcs for said cellular components, wherein

> the presence, absence or change of one or more arcs as compared to one or more decisional arcs is used to diagnose or prognose said disease state in said subject.

App. Br. 25–26 (Claims App'x.).

The following rejection is appealed:

Claims 13, 14, 43–45, 52, 53, 60, 63, 67, 69, 72, 73, and 78–87 stand rejected under 35 U.S.C. § 101 as patent-ineligible. Final Action 3.

CLAIM INTERPRETATION

When analyzing claims, the Patent Office applies the broadest reasonable construction standard in proceedings. *Cuozzo Speed Tech., LLC v. Lee*, 136 S. Ct. 2131, 2145 (2016). "[T]he words of a claim 'are generally given their ordinary and customary meaning.'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005). "[W]hile it is true that claims are to be interpreted *in light of* the specification . . . , it does not follow that limitations from the specification may be read into the claims . . . . [T]he claims define the invention." *Sjolund v. Musland*, 847 F.2d 1573, 1581–82 (Fed. Cir. 1988). "When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term." *Multiform Dessicants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed Cir. 1998).

Here, several of the terms recited by the claims are specifically explained and defined by the Specification. The claim term "arc," as it relates to cellular components, is explained in the Specification to mean something, e.g., a graphical representation or recognized link, which "show[s] statistical dependence of [a] downstream ('second') cellular

component on [an] upstream ('first') cellular component," or a "causal influence[] from the upstream cellular component upon the downstream cellular component." Spec. ¶ 39. With this understanding of "arc," the Specification then explains that the claim term "'decisional arcs' refer[s] to arcs used for comparison to other arcs. Decisional arcs can have a value and/or a directionality." *Id.* ¶ 47. The Specification explains that "[t]he [claim] term 'cellular component' refers to a molecule regardless of molecular weight found within an organism or cell." *Id.* ¶ 52. Regarding the claim term "probe," the Specification states "[v]irtually any molecule can be used as [a] probe to detect one or more of the cellular component described herein." *Id.* ¶ 89. Further, regarding the claim term "distinguishable," the Specification states "[b]y 'distinguishable' we mean that the [probe] labels should be spectrally resolvable from one another." *Id.* ¶ 95.

We interpret the relevant claim language consistent with the Specification, as discussed above.

DISCUSSION

Unless otherwise indicated herein, we adopt the Examiner's findings of fact, reasoning on scope and content of the claims and prior art, and conclusions set out in the Final Action and Answer.[2] Only those arguments made by Appellants in the Appeal Brief and properly presented in the Reply Brief have been considered in this Decision. Arguments not so presented in

[2] Final Office Action, mailed Nov. 12, 2014 ("Final Action"); Examiner's Answer, mailed Aug. 13, 2015 ("Answer").

the Briefs are waived. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2015); *see also Ex parte Borden*, 2010 WL 191083 at *2 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

Further, while separately argued claims are to be separately considered when determining patentability, "[a] statement which merely points out what a claim recites will not be considered an argument for separate patentability of the claim." 37 C.F.R. § 41.37(c)(1)(vii). "[T]he Board [has] reasonably interpreted Rule 41.37 to require more substantive arguments in an appeal brief than a mere recitation of the claim elements and a naked assertion that the corresponding elements [create points of patentability]." *In re Lovin*, 652 F.3d 1349, 1357 (Fed. Cir. 2011).

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

In analyzing patent-eligibility questions under 35 U.S.C. § 101, the Supreme Court instructs us to "first determine whether the claims at issue are directed to a patent-ineligible concept." *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014). If the initial threshold is met, we then move to a second step and "consider the elements of each claim both

individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo*, 566 U.S. at 78–79).

In their brief, Appellants argue the appealed claims under thirteen separate headings. *See generally* App. Br. "The Examiner [did] not agree with said 'Grouping[s]'," but determined "that Independent claims 13 and 80 and those claims dependent therefrom (claims 43, 44, 45, 52, 53, 69, 72, 73, 78, 81, 82, 84, 85 and 87) are drawn to the recitations of claim[s] 13 and 80 which are 'characterizing a disease state' and Claim 14 and those claims dependent therefrom (claims 44, 45, 52, 53, 60, 63, 67, 79, 83, and 86) are drawn to a method of diagnosing or prognosing." Answer 6. However, the Examiner went on to address the claims in the groupings of Appellants' brief. *Id.* at 6–17. Therefore, we address the claims similarly below.

Group I – Claims 13 and 80

Following the two-step patent eligibility analysis dictated by *Alice* and *Mayo*, the Examiner determined that "[t]he claims are directed to the natural occurring correlation between diseased cells versus normal cells (normal state versus disease state)" and "[c]omparisons of changes in 'arcs' (edges) which represent cellular components are made to determine a disease state." Final Action 3–4. The Examiner added "the claims are directed to a natural phenomenon, as well as an abstract idea," and "it is noted that more than one judicial exception is present in the instant claims, i.e. abstract idea recited as providing a first and second set of arcs which entails probabilistic statistical analyses of causal connections." Answer 7.

Having determined that this subject matter was directed to a judicial exception to patent-eligibility, the Examiner moved to step-two of the analysis to ascertain whether the claims, each as a whole, considering individual elements and their ordered combination, recited "something significantly different than the judicial exception," so as to transform the nature of the claim' into a patent-eligible application. Final Action 3. The Examiner determined, *inter alia*, that:

1.

> the instant claims do not provide a direct manipulation of the natural correlation other than assessment of changes between one cell-type (diseased) versus another (normal/not diseased). This is a well-known and routine procedure in the art of molecular biology and statistical analysis (using Bayesian analysis to represent states). *Id.* at 5.

2.

> the steps of comparing profiles (a cell that is diseased to cell that is not) is well-understood in the art. *Id.*

3.

> The instant claims recite nothing more than the application of a statistic to assess differences between cell set A (disease) and cell set B (not diseased) and add nothing specific to the natural principle that would render it patent eligible. *Id.* at 7.

4.

> the claims recite well-known steps of detecting probe binding to generate data sets amongst diseased versus normal cells. Such steps are well-known in the art of molecular biology and bioinformatics. *Id.*

5.

> Generation of "arcs" (edges in a Bayesian network) is routine procedure for such an analysis, as it is a statistical analysis of the natural phenomenon, which is conventional. *Id.* at 8.

6.

> The additional elements recited in the claims 13, 14, and 80, as already established, are:
>
> -measuring a plurality of cellular components in individual cells exhibiting said disease state . . . by contacting said cells exhibiting said disease state with a set of distinguishably detectable probes . . . and detecting binding of said probes . . .
>
> -measuring a plurality of cellular components in individual cells not exhibiting said disease state . . . by contacting said cells not exhibiting said disease state with a set of distinguishably detectable probes . . . and detecting binding of said probes . . .
>
> Those additional steps, when viewed both individually and as a whole, do not provide "significantly more". Answer 8.

We conclude the Examiner has established that the claims are not patent-eligible because they are directed to an abstract idea and natural phenomenon and do not claim more than routine and conventional additional elements. We address Appellants' arguments below.

Appellants argue the "claims include a combination of physical and analytical steps that was in no way routine or conventional at the time of filing. In addition, the claimed method is not drawn to any natural correlation itself, but instead to a method of *identifying a correlation*." App. Br. 10. The physical and analytical steps to which Appellants refer include measuring by contacting cells with detectable probes, which bind to cellular components, followed by detection of that binding. *Id.* Appellants contend

that it is important that these steps are performed on individual cells and that related probabilistic analysis of causal connections relate to cellular components in each such individual cell. *Id.* Appellants argue the Examiner failed to consider the claimed steps as a combined whole. *Id.* at 11. Appellants also contend the Examiner failed to provide evidence that the claimed steps were routine and conventional, arguing that the Examiner's withdrawal of an obviousness rejection over a prior art combination is evidence that these steps are not routine or conventional, but are both novel and non-obvious.[3] *Id.* Appellants argue the claimed invention does not fall under the holding of the Supreme Court in *Mayo*. *Id*. at 11–12.

These arguments are not persuasive. They amount to little more than mere attorney argument. Appellants do not reasonably call into question the Examiner's determination that the claims are *directed to* patent-ineligible subject matter (an abstract idea and a natural phenomenon) and do not establish that any of the additional claim elements amount to *anything*

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[3] *See* Final Office Action dated March 3, 2010, wherein the Examiner rejected the claims under 35 U.S.C. § 103 (and § 102) over combinations of:

US 2003/0232364 Al (pub. Dec. 18, 2003) ("Shaughnessy");

Dana Pe'er et al., *Inferring Subnetworks from Perturbed Expression Profiles*, 17 BIOINFORMATICS S215–24 (2001) ("Pe'er");

Nir Friedman, *Bayesian Network Classifiers*, 29 MACHINE LEARNING 131–63 (1997) ("Friedman");

Stephen P. Perfetto et al., *Seventeen-colour Flow Cytometry: Unravelling the Immune System*, 4 INNOVATION 648–55 (2004) ("Perfetto");

Karen Sachs et al., *Bayesian Network Approach to Cell Signaling Pathway Modeling*, SCIENCE'S STKE 1–5 (Sept. 3, 2002) ("Sachs"); and

Amy Norris, University of Waterloo, *Thesis: Multivariate Analysis and Reverse Engineering of Signal Transduction Pathways* (2002) ("Norris").

significantly more than the natural phenomena and abstract idea identified by the Examiner. Appellants' arguments seeking to distinguish their claims from those in *Mayo* are also not persuasive because, whether or not the appealed claims involve physical and/or analytical steps for identifying a naturally occurring correlation (or relate to individual cells), they nevertheless are directed to merely determining the presence of molecules in samples of normal and diseased cells and applying a mathematical algorithm to illustrate a biological correlation, which, as the examiner determined, is not patent-eligible as being directed to both a natural phenomenon and abstract idea.

Furthermore, having reviewed the prior art references of the withdrawn obviousness rejection(s) of record in this appeal and identified by Appellants (*see supra*, n.3), we note that the prior art evidences that the claim elements in addition to the patent-ineligible subject matter amount to mere well-known, routine, and conventional concepts and processes. For example, the prior art reference Shaughnessy teaches that the use of molecular probes was known in the prior art for correlating genes with disease states, that flow cytometry was a known analysis tool for detecting molecular markers, that it was known that gene expression could be altered to discriminate between normal and malignant (diseased) cells, that Bayesian networks and arcs between nodes could be used as a probabilistic analysis tool to identify genes (cellular components) whose over/under expression is apparent in the comparison of healthy samples and diseased samples of cells. Shaughnessy ¶¶ 22, 78, 179, 201–15. Further, Pe'er teaches that it was known to use Bayesian networking to identify direct

interactions between genes (cellular components) regulating one another. Pe'er S215, S217, S222. Friedman teaches that Bayesian classifiers were known as one of the most effective predictive tools, useful in analyzing biological processes. Friedman 131, 140. Further, Perfetto also teaches that flow cytometry was a known technique to measure multiple fluorescent markers/probes in molecular-cell-analysis. Perfetto 648. Sachs teaches that it was known to use Bayesian networks to analyze cell signaling and model multivariate probabilistic relationships for cellular component pathways (e.g., relating to phosphorylated receptors, activated enzymes, and other biomolecules), and to use flow cytometry in association with such mathematical processes. Sachs 1, 4. Finally, Norris teaches that it was known to use Bayesian networks to recreate biological connections between molecules or genes (cellular components). Norris 59. Thus, the evidence of record supports the Examiner's determination that the claims do not recite elements beyond the patent-ineligible concepts that amount to more than well-known, routine, and conventional steps or techniques.

Claim 1 of U.S. Patent No. 6,355,623, at issue in *Mayo*, reads as follows:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6–thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6–thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6–thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

> wherein the level of 6–thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Mayo, 566 U.S. at 74–75. This is analogous to the claims on appeal, if even less overtly directed to an abstract idea than the appealed claims, and is potentially more specific and narrow than the broadest claims on appeal. It is directed to, but does not expressly claim, the natural phenomenon that an administered compound correlates to predictable levels of metabolites and that understanding this allows doctors to determine this correlation *in vivo* to better treat patients with the compound. The Supreme Court held that determining the results of a natural correlation using well-understood, routine, conventional steps, as per the appealed claims here, amounted to simply telling doctors to apply the natural law, identifying that "a scientific truth, or the mathematical expression of it, is not a patentable invention." *Id.* at 71 (quoting *Mackay Radio & Telegraph Co. v. Radio Corp. of Am.*, 306 U.S. 86, 188 (1939)), 79.

Also relevant is *Parker v. Flook*, 437 U.S. 584 (1978), where the Supreme Court held that a claimed invention amounting to a mathematical process for setting (or adjusting) alarm limits relating to the chemical processes involved in catalytic conversion of hydrocarbons was not patent eligible as directed to an abstract idea. In *Flook*, the Court found the claimed method, in essence, consisted of measuring a value of a variable (e.g., temperature), using an algorithm to calculate an alarm-limit value, and adjusting the alarm limit to an adjusted value, where the difference between the conventional methods of changing alarm limits and the invention resided in the mathematical algorithm. Here, as in *Flook*, the basic methodologies

of the claimed invention are well-known, conventional things (e.g., applying a detectable probe to molecules of separate samples, comparing measurements of those probes between samples). The manipulation of data obtained by such conventional techniques using probability mathematics, which may illustrate a biological correlation between molecules and disease state, is not patent-eligible.

Further, in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1374 (Fed. Cir. 2015), the Federal Circuit held that the following claim was not patent-eligible:

> 25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises obtaining a non-cellular fraction of the blood sample amplifying a paternally inherited nucleic acid from the non-cellular fraction and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

The court held that this claim was directed to a natural phenomenon: the existence of cffDNA in maternal blood, which could be advantageously used for genotyping from this blood. *Id.* at 1376. The court found that the otherwise claimed methodology, e.g., using PCR to amplify and detect cffDNA, was merely well-understood, routine, and conventional, specified at a high level of generality, and, so, the claims were not patent-eligible. Here the claims are directed to a natural phenomenon, i.e., a correlation between cell disease and associated cellular components and the abstract idea that one may apply a probabilistic mathematical algorithm to illustrate such a correlation and the steps and processes used to analyze such cells were well-known, routine, and conventional. The claims on appeal are more general and broader than those in *Ariosa*.

In view of the above-discussed precedent, we must agree with the Examiner that the claims are directed to the patent-ineligible concepts of characterizing a disease state based on a correlation between the disease and cellular components and using a mathematical algorithm to illustrate this correlation and further agree that the other claimed subject matter amounts to no more than known, routine, conventional steps and techniques. Therefore, we affirm the rejection.

Group II – Claim 43

Appellants quote the claim language "applying a probabilistic graphical model algorithm to said first data set and said second data set to identify a set of arcs between individual cellular components in each said cells," and argue the recited step is not routine or conventional and that the Examiner has not provided evidence to the contrary. App. Br. 12.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claim 13, we find that applying a mathematical algorithm to identify a relationship between analyzed cellular components is an abstract idea, as well as something that was known, routine, and conventional in the prior art, as discussed above. The Specification states that "[a]ny probabilistic graphical model algorithm can be used." Spec. ¶ 10. It also lists several well-known techniques, including Bayesian, factor graph, Markov, and conditional random field models. *Id*. Further, the use of Bayesian networks to illustrate biological relationships were disclosed in several of the prior art references discussed above and are understood to

have been routine and conventional. For these reasons, Appellants' argument is not persuasive.

Group III – Claims 69, 73, and 73

Appellants quote the claim language "contacting said cells exhibiting said disease state with an agent that modulates one or more of the plurality of cellular components in said cells prior to contacting said cells exhibiting said disease state with a set of probes," and argue this step is physical, and that the Examiner has not provided evidence that this step in combination with the others claimed is/are routine or conventional. App. Br. 13.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claim 13, we find that using a cellular activity modulator, e.g., altering gene expression, activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. The Specification identifies that the cellular components analyzed can be any molecule found in an organism or cell, which expands the universe of things that are potentially modulated to almost any biological substance. Spec. ¶ 52. The Specification further explains that "[b]y 'modulate' [it means] that the agent interacts with the cellular component such that the cellular component switches from one state or form to another," which includes virtually any change effected on any cellular component. Spec. ¶ 79. No inventive concept is added by including these claim elements. For these reasons, Appellants' argument is not persuasive.

Group IV – Claims 78 and 81

Appellants quote the claim language "'the cellular components are activatable elements, and the probes used are activation state-specific probes'" and argue the claims "represent a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 14.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claim 13, we find that analyzing activatable cellular components, e.g., altering gene expression, activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. The Specification explains that a cellular component is not activatable if it does not switch from one form to another, thus, a cellular component that can change is activatable. Spec. ¶ 75. Some common examples of such activatable cellular components are identified as PKA, calcium, mevalonate, thymidine, glucose, kinases, proteins, enzymes, and nucleotides. *Id.* ¶ 76. Detecting such cellular components was indisputably routine and conventional. For these reasons, Appellants' argument is not persuasive.

Group V – Claims 82 and 84

Appellants quote the claim language "'one or more of the activatable elements is a protein and one or more of the activation state-specific probes is an antibody,'" and argue the claims "represent a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 14.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13 (and 80), we find that analyzing activatable protein cellular components, e.g., activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. As to the argument that the claims are not preemptive, "[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. Appellants' argument does not change the conclusion that the claims are directed to patent-ineligible subject matter. For these reasons, Appellants' argument is not persuasive.

Group VI – Claims 85 and 87

Appellants quote the claim language "'detecting comprises a detection technique selected from the group consisting of: flow cytometry and confocal microscopy,'" and argue the claims "represent a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 15.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claim 13, we find that using, e.g., flow cytometry, was known, routine, and conventional in the prior art, as discussed above. *See supra*, discussion of Shaughnessy and Perfetto. As to the argument that the claims are not preemptive, "[w]hile preemption may

signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. Appellants' argument does not change the conclusion that the claims are directed to patent-ineligible subject matter. For these reasons, Appellants' argument is not persuasive.

Group VII – Claim 14

Similar to their arguments over claims 13 and 80, Appellants argue the claim "a combination of physical and analytical steps that was in no way routine or conventional at the time of filing. In addition, the claimed method is not drawn to any natural correlation itself, but instead to a useful *application* of a correlation." App. Br. 15. Appellants identify the step of detecting the binding of probes to cellular components as a physical step and, again, contend that it is relevant that the probabilistic algorithm method and collected data relate to individual cells. *Id.* at 16. Again, as with their arguments in relation to claim 13, Appellants contend the Examiner has not provided evidence that the claimed combination of steps was routine or conventional and point to the aforementioned withdrawn obviousness rejection as evidence that they were novel and non-obvious and, so, not routine or conventional. *Id.* Appellants again argue that this claim does not fall under the holding of *Mayo*, contending that, here, the wherein clauses indicating that the method steps are practically applied are integrated into the claim and that the lack of similar integration in the claims at issue in *Mayo* was the cause of their patent-ineligibility. *Id.* at 17.

Appellants' arguments over claim 14 essentially restate those made regarding claim 13, which we found unpersuasive, as discussed above.

While the language of claims 13 and 14 is not identical, we agree with the Examiner that these claims are directed to the same natural phenomenon and abstract idea, that is, identifying the natural relationships between cellular components in diseased cells and illustrating the same using a mathematical algorithm, and recite additional elements that are merely known, routine, and conventional, that is, using decisional arcs, using probes, etc., as exemplified by the prior art of record. Therefore, for the same reasons discussed above regarding claim 13, we affirm the rejection as to claim 14.

Group VIII – Claims 60, 63, and 67

Appellants quote the claim language "'contacting said first set of cells with an agent that modulates one or more of the plurality of cellular components in said cells prior to providing a set of probes that bind to the set of cellular components,'" and argue that this is an additional physical step and that the Examiner has not provided evidence that it was routine or conventional. App. Br. 18.

As was the argument relating to Group III, this argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13 and 14, we find that using a cellular activity modulator, e.g., altering gene expression, activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. As discussed above, the Specification identifies that the cellular components can be any molecule found in an organism or cell, i.e., almost any biomolecule. Spec. ¶ 52. As also discussed above, the Specification further explains that "[b]y

'modulate' [it means] that the agent interacts with the cellular component such that the cellular component switches from one state or form to another," which includes virtually any change. Spec. ¶ 79. No inventive concept is added by including these claim elements. For these reasons, Appellants' argument is not persuasive.

Group IX – Claim 79

Appellants quote the claim language "'the cellular components are activatable elements, and the probes used are activation state-specific probes,'" and argue the claim "represents a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 19.

As was the argument relating to Group IV, this argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13 and 14, we find that analyzing activatable cellular components, e.g., altering gene expression, activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. As discussed above, the Specification explains that a cellular component is not activatable if it does not switch from one form to another, thus, a cellular component that can change is activatable, and the Specification also provides a list of several common examples of activatable components. Spec. ¶¶ 75–76. Detecting such cellular components was routine and conventional. For these reasons, Appellants' argument is not persuasive.

Group X – Claim 83

Appellants quote the claim language "'one or more of the activatable elements is a protein and one or more of the activation state-specific probes is an antibody,'" and argue the claim "represents a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 19.

As was the argument relating to Group V, this argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13, 80, and 14, we find that analyzing activatable protein cellular components, e.g., activated enzymes, etc., was known, routine, and conventional in the prior art, as discussed above. As to the argument that the claims are not preemptive, "[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. Appellants' argument does not change the conclusion that the claims are directed to patent-ineligible subject matter. For these reasons, Appellants' argument is not persuasive.

Group XI – Claim 86

Appellants quote the claim language "'detecting comprises a detection technique selected from the group consisting of: flow cytometry and confocal microscopy,'" and argue the claim "represents a way to limit the claimed method in such a way to further ensure that others are not foreclosed from using any alleged judicial exception." App. Br. 20.

As with the argument relating to Group VI, this argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13 and 14, we find that using, e.g., flow cytometry, was known, routine, and conventional in the prior art, as discussed above. *See supra*, discussion of Shaughnessy and Perfetto. As to the argument that the claims are not preemptive, "[w]hile preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility." *Ariosa*, 788 F.3d at 1379. Appellants' argument does not change the conclusion that the claims are directed to patent-ineligible subject matter. For these reasons, Appellants' argument is not persuasive.

Group XII – Claims 44 and 45

Appellants quote the claim language "wherein the probabilistic graphical model algorithm is selected from the group consisting of a Bayesian network structure inference algorithm, a factor graph, a Markov random fields model, and a conditional random fields model," and argue this is an additional limitation to an analytical step and that the Examiner has not provided evidence that it was routine or conventional. App. Br. 20.

As with the argument relating to Group II, this argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as with claims 13 and 14, we find that applying a mathematical algorithm to illustrate a relationship between analyzed cellular components is an abstract

idea as well as something that was known, routine, and conventional in the prior art, as discussed above. As discussed above, the Specification states that "[a]ny probabilistic graphical model algorithm can be used," and lists several well-known techniques, including those of the claims here. Spec. ¶ 10. Further, the use of Bayesian networks to illustrate biological relationships was disclosed in several of the prior art references discussed above and are understood to have been routine and conventional. For these reasons, Appellants' argument is not persuasive.

Group XIII – Claims 52 and 53

Appellants quote the claim language "wherein one or more of said arcs is identified between one of said cellular components bound by one of said probes and a cellular components not bound by one of said probes" and "wherein one or more of said arcs is identified between at least two of said cellular components bound by said probes" of claims 52 and 53, respectively, and argue these are additional limitations to an analytical step and that the Examiner has not provided evidence they were routine or conventional. App. Br. 22.

This argument amounts to no more than quoting the claim language and stating that it renders the claim patentable; more is required of an appeal argument. *See* 37 C.F.R. § 41.37(c)(1)(vii); and *In re Lovin*, 652 F.3d at 1357. In any event, as discussed above, marking molecules of different samples using probes was routine and conventional. Using a mathematical algorithm to analyze such samples is not patent-eligible. We are not persuaded by Appellants' argument.

SUMMARY

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

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