UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/696,109	11/05/2012	Ariel E. Feldstein	CCF-019778 US PCT	7002

26294 7590 11/27/2017

TAROLLI, SUNDHEIM, COVELL & TUMMINO L.L.P.
1300 EAST NINTH STREET, SUITE 1700
CLEVELAND, OH 44114

EXAMINER
MARCSISIN, ELLEN JEAN

ART UNIT	PAPER NUMBER
1678	

NOTIFICATION DATE	DELIVERY MODE
11/27/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

rkline@tarolli.com
docketing@tarolli.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte ARIEL E. FELDSTEIN and STANLEY L. HAZEN

Appeal 2017-001287
Application 13/696,109
Technology Center 1600

Before JEFFREY N. FREDMAN, ROBERT A. POLLOCK, and TIMOTHY G. MAJORS, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal[1] under 35 U.S.C. § 134 involving claims to a method of predicting, detecting, or monitoring nonalcoholic steatohepatitis in a subject with or suspected of having nonalcoholic fatty liver disease. The Examiner rejected the claims as directed to non-statutory subject matter and as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

Statement of the Case

Background

"Nonalcoholic steatohepatitis (NASH) is defined as lipid accumulation with evidence of cellular damage, inflammation, and different

---

[1] Appellants identify the Real Party in Interest as The Cleveland Clinic Foundation (*see* Br. 3).

degrees of scarring or fibrosis. NASH is a serious condition as approximately 25% of these patients progress to cirrhosis and its feared complications of portal hypertension, liver failure and hepatocellular carcinoma" (Spec. ¶ 4). "[T]he available non-invasive markers for NAFLD include a set of clinical signs and symptoms, non-specific laboratory, and radiological imaging tests . . . [but] they lack specificity and sensitivity to distinguish NAFLD from NASH and determine the presence and stage of fibrosis" (Spec. ¶ 5). "To date, liver biopsy, an invasive procedure, remains the gold standard for NAFLD diagnosis. Therefore, there is a great need for development of noninvasive methods that can reliably identify patients with NASH and stage the magnitude of fibrosis present" (*id.*).

The Claims

Claims 38, 43–47, 49, 52, 54–56, 61–67, 70, 72, and 99–104 are on appeal. Independent claim 38 is representative and read as follows:

> 38. A method of predicting, detecting, or monitoring nonalcoholic steatohepatitis in a subject with or suspected of having nonalcoholic fatty liver disease, the method comprising:
>
> obtaining a bodily sample from the subject, the sample including at least one oxidized fatty acid product, wherein the bodily sample is selected from the group consisting of blood, plasma, and serum;
>
> determining a level of the at least one oxidized fatty acid product of linoleic acid in the sample, wherein the at least one oxidized fatty acid product is selected from the group consisting of 13-hydroxyoctadecadienoic acid (13-HODE), 9-hydroxyoctadecadienoic acid (9-HODE), 9-oxo-octadecadienoic acid (9-oxoODE), 9-oxo-octadecadienoic acid (13-oxoODE);

> deriving a risk score using the determined level, wherein an increased risk score compared to a control is indicative of an increased severity or risk of nonalcoholic steatohepatitis, wherein the risk score is derived using an analytical process, wherein the analytical process for determining the risk score comprises the algorithm: risk score = [-10.051+0.0463*Age (years) + 0.147*Body Mass Index (BMI)(kg/m^2) + 0.0293*(aspartate aminotransferase (AST) or alanine aminotransferase (ALT))(IU/L) + 2.658*(Oxidized fatty acid product of linoleic acid:Oxidized fatty acid product of linoleic acid precursor Ratio(mmol/mol)] * 10.

The Issues

A. The Examiner rejected claims 38, 43–47, 49, 52, 54–56, 61–67, 70, 72, and 99–104 under 35 U.S.C. § 101, as being directed to non-statutory subject matter (Final Act. 2–5).

B. The Examiner rejected claims 38, 43–47, 52, 54, 56, 61–67, 70, 72, and 101–104 under 35 U.S.C. § 103(a) as obvious over Watkins[2] and Poynard[3] (Final Act. 6–14).

C. The Examiner rejected claim 49 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, and Altmann[4] (Final Act. 14–16).

D. The Examiner rejected claim 55 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, and Suovaniemi[5] (Final Act. 16–18).

E. The Examiner rejected claims 99 and 100 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, Barnhill,[6] and Sureka[7] (Final Act. 18–21).

---

[2] Watkins et al., WO 2008/021192 A2, published Feb. 21, 2008.
[3] Poynard, T., US 2006/0173629 A1, published Aug. 3, 2006.
[4] Altmann et al., *13-Oxo-ODE is an endogenous ligand for PPARγ in human colonic epithelial cells*, 74 Biochemical Pharmacology 612–22 (2007).
[5] Suovaniemi et al., US 7,358,062 B2, issued Apr. 15, 2008.

A. 35 U.S.C. § 101

The Examiner rejected all of the claims on appeal under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter. The Examiner finds the "claims recite that the natural principle is used to predict, detect or monitor NASH or fibrosis in a subject with or suspected of having NAFLD, which amounts to nothing more than a general instruction to apply it" (Final Act. 4). The Examiner reached this conclusion by applying the test set out in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66 (2012) (Ans. 18–23) and based on the two-step *Alice* framework. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014).

Appellants contend the claims

> [A]pply a law of nature to a new and useful end and do not attempt to merely claim the law itself. The present application is based upon the discovery of the law of nature that specific oxidized fatty acid products are increased in the blood of patients with NASH and that the amounts or levels of these oxidation products, in addition to other clinical indicia, can be used to derive a risk score that correlates with pathologies of NASH and the severity of liver disease.

(Br. 13). Appellants contend "a risk score derived using the recited algorithm was not known and has utility in treating subjects with or suspected of having NAFLD or fibrosis of the liver" (Br. 14–15). Appellants contend the claims recite a risk score so that "the law of nature is practically applied and the steps include activity that goes beyond what was

---

[6] Barnhill et al., US 6,306,087 B1, issued Oct. 23, 2001.
[7] Sureka, A., US 2008/0077544 A1, published Mar. 27, 2008.

well-understood, routine or conventional activity for researchers in the field" (Br. 18).

To determine whether a claim is invalid under § 101, we employ the two-step *Alice* framework. In step one, we ask whether the claims are directed to ineligible subject matter, such as a law of nature, abstract idea, or natural phenomena. *Alice*, 134 S. Ct. at 2355; *Mayo*, 566 U.S. at 75–77; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1375 (Fed. Cir. 2015). Method claims that are directed only to a law of nature, without significantly more, are ineligible subject matter. *Ariosa*, 788 F.3d at 1376.

Alice Step One

Claims 38 and 56 of the instant application are directed to the law of nature that levels of specific oxidized fatty acid products increased in the blood of patients with NASH are associated with fibrosis risk. The Specification teaches:

> The method includes obtaining a bodily sample from the subject. The sample includes at least one oxidized fatty acid product. The level of the at least one oxidized fatty acid product in the sample is then determined. An increased level of the at least one oxidized fatty acid product in the subject compared to a control is indicative of an increase in severity of nonalcoholic fatty liver disease and potentially nonalcoholic steatohepatitis and liver fibrosis.

(Spec. ¶ 6). The Specification teaches "the level of at least one OxFA and/or at least one corresponding precursor molecule in a sample can be quantified using liquid chromatography online electrospray ionization tandem mass spectrometry (LC/ESI/MS/MS)" (Spec. ¶ 76). The Specification teaches that in

> an exemplary embodiment, 50µl of plasma is hydrolyzed . . . and then the released fatty acids are extracted into the hexane layer . . . the lipid extract is then injected onto an HPLC *(e.g.,* Waters 2690 Separations Module, Franklin MA) . . . and then OxFAs and their precursors are separated through a C18 column (Phenomenex[)] . . . . The OxFAs and their precursors are then quantified on a triple quadrupole mass spectrometer *(e.g.,* Quattro Ultima, Micromass., Manchester, UK).

(Spec. ¶ 76).

The claimed invention therefore is drawn to measuring oxidized fatty acid levels using standard, prior art, purification and separation devices and correlating the results to severity of liver disease and liver fibrosis, a relationship that is a patent-ineligible law of nature. *Mayo*, 566 U.S. at 77.

This case is similar to *Ariosa*, where the ineligible claims were directed to a method of detecting paternally inherited cell-free fetal DNA, which is naturally occurring in maternal blood. *Ariosa*, 788 F.3d at 1376. The inventors there did not create or alter any of the genetic information encoded in that DNA. *Id.* Likewise, here, the claims test oxidized fatty acid levels that are a naturally occurring phenomenon. The method then employs the natural relationship between those oxidized fatty acid levels to predict a patient's risk of developing or having liver disease and/or liver fibrosis. Thus, just like *Ariosa*, the method starts and ends with naturally occurring phenomena with only routine steps in between—the presence of particular oxidized fatty acid levels is correlated, using a particular mathematical relationship recited in claims 38 and 56, to liver disease and/or liver fibrosis. The claims are therefore directed to a natural law. *Id.*

Because the claims are directed to a natural law, we turn to the second step of the *Alice* framework.

Alice Step Two

In *Alice* step two, we examine the elements of the claims to determine whether they contain an inventive concept sufficient to transform the claimed naturally occurring phenomena into a patent-eligible application. *Mayo*, 566 U.S. at 71–72 (quoting *Alice*, 134 S.Ct. at 2355). We must consider the elements of the claims both individually and as an ordered combination to determine whether additional elements transform the natural law of the claims into a patent-eligible concept. *Ariosa*, 788 F.3d at 1375.

We conclude that the practice of the method claims does not result in an inventive concept that transforms the natural phenomena of oxidized fatty acid levels being associated with liver disease and/or liver fibrosis into a patentable invention. *Mayo* and *Ariosa* make clear that transforming claims that are directed to a law of nature requires more than simply stating the law of nature while adding the words "'apply it.'" *Mayo*, 566 U.S. at 72; *Ariosa*, 788 F.3d at 1377.

In *Ariosa*, the challenged claims involved a method that was a general instruction to doctors to apply routine, conventional techniques when seeking to detect paternally inherited cell-free fetal DNA in the blood serum of a pregnant woman. *Ariosa*, 788 F.3d at 1377. The same analysis applies here. The claims contain "obtaining" and "measuring" steps that require analyzing bodily samples for levels of oxidized fatty acid levels. Appellants do not purport to have invented blood sample collection methods, oxidized fatty acid purification methods, or the mass spectroscopy methods used to

measure the levels of oxidized fatty acids. The only element identified as inventive in the Specification is the mathematical risk score recited in claims 38 and 56 (*see, e.g.*, Spec. ¶ 15).

> However, the Specification teaches the risk score is generated by
>
> obtaining a dataset associated with a sample, where the dataset includes quantitative data (typically oxidized fatty acid product levels) about oxidized fatty acid products about which have been found to be predictive of severity of NASH and/or liver fibrosis with a statistical significance less than 0.2 *(e.g.,* p value less than about 0.05), and inputting the dataset into an analytical process that uses the dataset to generate a result useful in diagnosing and monitoring NAFLD, NASH, and/or liver fibrosis.

(Spec. ¶ 86). The Specification recognizes the "analytical process may be any type of learning algorithm with defined parameters, or in other words, a predictive model" (Spec. ¶ 87). The Specification further explains that "the analytical process is based on a regression model, preferably a logistic regression model. . . . In such embodiments, the coefficients for the regression model are computed using, for example, a maximum likelihood approach" (Spec. ¶ 97).

Therefore, as in *Cleveland Clinic*, the claims obtain oxidized fatty acid values using conventional methods and "compare those values to predetermined or control values derived from conventional statistical methods." *Cleveland Clinic Foundation v. True Health Diagnostics LLC*, 859 F.3d 1352, 1362 (Fed. Cir. 2017).

We recognize, but find unpersuasive, Appellants' argument that:

> Prior to the present application, researchers did not routinely derive risk scores using a dataset that includes the determined

> level of at least one oxidized fatty acid product in a bodily sample obtained from the blood, serum or plasma of a subject and quantitative data from one or more clinical indicia in order to predict, detect, or monitor nonalcoholic steatohepatitis or fibrosis of the liver in a subject with or suspected of having nonalcoholic fatty liver disease, let alone using the recited algorithm to derive such a risk score.

(Br. 19).

The risk score limitation simply represents an abstract idea embodied by a law of nature that is further defined by the recited mathematical formula in claims 38 and 56. However, a "claim directed to an abstract idea does not automatically become eligible merely by adding a mathematical formula." *RecogniCorp, LLC v. Nintendo Co., Ltd.*, 855 F.3d 1322, 1328 (Fed. Cir. 2017). The addition of the mathematical formula determined using standard regression techniques based on a natural correlation and changing raw data levels into calculated data levels "simply changes the data into other forms of data [that] cannot save [the claims]." *Id.* Similarly, even if the mathematical formula or relationship was new, that would not necessarily transform the claim into eligible subject matter. Indeed, in *Flook*, the Supreme Court "assume[d] that respondent's [mathematical] formula [was] novel and useful and that he discovered it," yet still held the claim was drawn to a patent-ineligible abstraction. *Parker v. Flook*, 437 U.S. 584, 588 (1978).

The claims, whether considered limitation-by-limitation or as a whole, do not sufficiently transform the natural existence of oxidized fatty acid levels and their correlation to risk of liver disease and/or liver fibrosis into a patentable invention. The process steps here merely tell those "interested in

the subject about the correlations that the researchers discovered." *Mayo*, 566 U.S. at 78.

We recognize, but find unpersuasive, Appellants' contention that claims 101–104 "include steps that particularly transform the obtained bodily sample through the process of lipid extraction" (Br. 21; *cf.* Br. 22). As the Specification notes "[t]hose skilled in the art will further understand and appreciate other appropriate solvents that can be employed to extract lipids from the bodily sample" (Spec. ¶ 58). Thus, the step of lipid extraction is recognized by the Specification itself as routine, and adds nothing to the law of nature found unpatentable here.

We therefore conclude that, applying Supreme Court and Federal Circuit precedent, all of the claims on appeal are directed to patent-ineligible subject matter.

B. 35 U.S.C. § 103(a) over Watkins and Poynard

The Examiner finds Watkins teaches "a method for assessing the level of accumulation of triglycerides in the liver" that encompasses monitoring for "non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH)" by measurement of "lipid metabolites, such as *fatty acids and/or eicosanoids*, in a bodily fluid" (Final Act. 6–7). The Examiner finds Watkins specifically includes linoleic acid (*id.* at 7). The Examiner finds Watkins teaches "that serum aminotransferase elevations and hepatic imaging studies show changes suggestive of fatty liver condition" (*id.* at 8). The Examiner finds Watkins teaches "using various mathematical formulas or models to quantify the effect" (*id.* at 7).

The Examiner acknowledges that Watkins "does not specifically teach wherein clinical indicia include at least age, body mass index, or concentration of aminotransferases that are specifically aspartate or alanine transferase and does not teach specific algorithm as recited" (Final Act. 9).

> The Examiner finds Poynard teaches
>
> measuring 5 biomarkers with respect to concentration, one marker being aspartate aminotransferase), another being triglycerides, and studying one clinical marker, such as body mass index, combining the values via logistic functions to obtain an end value (i.e. risk score) and using the risk score to determine the presence of hepatic steatosis.

(Final Act. 9). The Examiner finds it obvious "to arrive at the claimed invention out of the course of routine optimization, by adjusting coefficients of the logistic function as taught by the combination of Watkins et al. in view of Poynard based on said teaching of Poynard regarding variables specific to different markers" (*id.* at 11).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that Watkins and Poynard render the claims obvious?

Findings of Fact

1. Watkins teaches:

> methods of assessing the level of accumulation of triglycerides in the liver of a subject (e.g., a human) and/or monitoring, diagnosing, classifying, assessing the severity, and/or assessing the progression or regression of a liver disorder in the subject. In some embodiments, the liver disorder is hepatic impairment, hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), steatohepatitis, or non-alcoholic steatohepatitis (NASH).

(Watkins ¶ 8).

2. Watkins teaches "determining the amount of one or more lipid metabolites (e.g., fatty acids and/or eicosanoids) in a body fluid from the subject" (Watkins ¶ 8).

3. Watkins teaches "the abbreviation 'PC18:2n6' indicates the percentage of plasma or serum phosphatidylcholine comprised of linoleic acid (18:2n6)" (Watkins ¶ 35).

4. Table 2 of Watkins is reproduced, in part, below:

Table 2. List of Eicosanoids

8-iso-PGF2a	9-HODE	13-HODE
5-HETE	8-HETE	9-HETE

"Non-limiting, exemplary eicosanoids are provided in Table 2" (Watkins ¶ 67).

5. Watkins teaches a "formula containing the levels of one or more lipid metabolites as variables includes any mathematical formula, model, equation, or expression established based on mathematic or statistical

principles or methods using the values of one or more lipid metabolites as variables" (Watkins ¶ 45).

6. Watkins teaches:

> Additional biomarkers and examinations may be used in the methods of diagnosing, monitoring, assessing severity, and for assessing progression or regression of the liver disorder. . . . In some embodiments, the method further comprises the step of (a) performing a physical examination of the subject; (b) measuring the level of an aminotransferase in the blood of the subject; or (c) obtaining an image of the liver of the subject.

(Watkins ¶ 23).

7. Watkins teaches the "relative amount may be compared to a reference . . . as the relative amount becomes increasingly less than the reference, increasing severity of disease is indicated. Exemplary references may be based on the amount(s) of a lipid metabolite(s) from . . . individuals with fibrosis" (Watkins ¶ 84).

8. Poynard teaches "a new diagnosis method for detecting the extent of hepatic steatosis in a patient . . . by using the serum concentration of easily detectable biological markers" (Poynard ¶ 1).

9. Poynard teaches "the best index ('Steatosis score') in term of discrimination was the logistic regression function combining the independent factors" (Poynard ¶ 25).

10. Poynard teaches:

> The logistic function may further comprise other clinical or biochemical markers. In a preferred embodiment, the logistic function also comprises the age and gender of the patient. In another embodiment, the logistic function may also comprise other biochemical markers, such as total bilirubin,

haptoglobin, AST (aspartate aminotransferase), glucose, and (cholesterol or HDL-cholesterol).

(Poynard ¶ 29).

11. Poynard teaches the "numerical definitions for the coefficients in the different functions can vary depending on the number and characteristics of the patients studied. Therefore, the value given for the coefficients of the different markers have to be interpreted as capable to being slightly different" (Poynard ¶ 34).

12. Poynard discloses an exemplary function, reproduced below:

f=6.68805−1.55337E-02.[Age (years)]+1.161531.[*ApoA*1 (g/L)]−0.11 889.[Body Mass Index (Weight/Height^2)]+1.74791.Log[.alpha.2-macroglobulin (g/L)]−0.96453.Log[*ALT* (alanine aminotransferase) (IU/L)]−0.1 1958.Log[total bilirubin (µmol/L)]−0.68125.Log[cholesterol (mmol/L)]−1.17922.Log[*GGT* (gammaglutamyl transpeptidase) (IU/L)]−1.46963.Log[glucose (mmol/L)]−0.34512.Log[Haptoglobin (g/L)]−1.17926.Log[triglycerides (mmol/L)]+0.35052.[Gender (female=0, male=1)].

"A specific usable function, when x is equal to zero" (Poynard ¶ 35).

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

Analysis

We adopt the Examiner's findings of fact and reasoning regarding the scope and content of the prior art (Final Act. 6–14; FF 1–12) and agree that

the claims are obvious over Watkins and Poynard. We address Appellants' arguments below.

Claim 38

Appellants contend

> Watkins fails to teach a correlation between the level of at least one oxidized fatty acid product of linoleic acid and NASH in a subject especially in a subject with or suspected of having NAFLD. While eicosanoids include oxidized fatty acid products of arachidonic acid such as the HETEs, it is well known to the ordinary skilled artisan that oxidized fatty acid products of linoleic acid are not equivalent to or even referred to as eicosanoid oxidized fatty acid products.

(Br. 27).

We find this argument unpersuasive because, as the Examiner notes, "Table 2 of Watkins (page 31) clearly discloses 9-HODE and 13-HODE . . . two of the alternate species specifically recited in the claim by Appellant" (Ans. 31; *cf.* FF 4). These two species, 9-HODE and 13-HODE, are specific hydroxyl-octadecadienoic acid chemical entities (*see, e.g.*, Spec. ¶ 49). Appellants provide no reason why the 9-HODE and 13-HODE compounds disclosed in Watkins would differ in structure in any way from the exact same compounds disclosed in claim 38. "Products of identical chemical composition can not have mutually exclusive properties." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

Appellants contend:

> Poynard et al. does not teach the step of determining the level of an oxidized fatty acid product of linoleic acid in a sample for a method of predicting, detecting, or monitoring NASH in a subject with or suspected of having NAFLD nor does Poynard et al. teach a correlation between the level of at least one

> oxidized fatty acid product of linoleic acid and NASH in a subject.

(Br. 28).

We find this argument unpersuasive because it fails to address the teachings of Watkins and Poynard in combination. The Examiner relies upon Watkins for the disclosure that levels of oxidized fatty acids are associated with steatohepatitis (FF 1–7) and relies upon Poynard to combine additional parameters including age, body mass index, and aminotransferase activity that are associated with steatohepatitis into a specific equation (FF 8–12). "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). In determining obviousness, furthermore, a reference "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *Id.*

Appellants contend:

> Neither Watkins et al. or Poynard et al. teach the analytical process for determining the risk score includes the specific algorithm: risk score = [-10.051 + 0.0463*Age(years) + 0.147*Body Mass Index (BMl)(kg/m^2) + 0.0293*(aspartate aminotransferase (AST) or alanine aminotransferase (ALT))(IU/L) + 2.658*(Oxidized fatty acid product of linoleic acid:Oxidized fatty acid product of linoleic acid precursor Ratio(mmol/mol)] * 10.

(Br. 28).

We find this argument unpersuasive because Poynard specifically teaches "numerical definitions for the coefficients in the different functions

can vary depending on the number and characteristics of the patients studied" (FF 11), thereby recognizing that the equation coefficients may be optimized for specific patient populations. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Here, Appellants provide no evidence that the specific coefficients selected in claim 38 represent anything other than routine optimization for a particular patient population. No evidence of secondary considerations such as unexpected results is presented by Appellants.

Appellants contend "there was no reasonable expectation of success that a risk score derived using the algorithm of claim 38 could be included in an effective method of predicting, detecting, or monitoring NASH in a subject with or suspected of having nonalcoholic fatty liver disease" (Br. 29).

We find this argument unpersuasive because Poynard specifically teaches that a risk score for hepatic steatosis can be generated (FF 9–11) and Watkins teaches that fatty acid levels may be used for assessing steatohepatitis and NASH (FF 1–2). Therefore, the references themselves provide a reasonable expectation of success that the risk score of Poynard could be used with the fatty acid biomarkers of Watkins. "Obviousness does not require absolute predictability of success . . . *all that is required is a reasonable expectation of success*." *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) (citation omitted).

Claim 54

Appellants reiterate arguments already found unpersuasive above, and further contend regarding claim 54 that

> Watkins and Poynard, alone and in combination, fail to teach or suggest incorporation of the level of an oxidized fatty acid product of linoleic acid into predictive models for NASH, let alone that the determined level of the specific oxidized fatty acid product of linoleic acid, HODE-13, can be used in addition to quantitative data from one or more clinical indicia to derive a risk score from the formula recited in claim 54 correlating to NASH in a subject with or suspected of having NAFLD.

(Br. 32).

We find this argument unpersuasive for the same reasons already discussed. In particular, Watkins teaches that fatty acid levels may be used to assess NASH and NAFLD (FF 1) and specifically identifies 13-HODE as a lipid metabolite that may be measured (FF 4). Watkins suggests the use of these lipid metabolite levels in mathematical formula (FF 5) along with additional biomarkers (FF 6). Poynard teaches the use of specific risk scores, along with additional biomarkers including age and aminotransferase activity, for diagnosis of hepatitis steatosis (FF 8, 11). We therefore find the combination of these teachings reasonably renders the specific risk score of claim 54 obvious as a routinely optimized algorithm in the absence of any evidence of secondary considerations.

Claim 56

Appellants contend

> outside of mentioning that NASH is a cause of fibrosis, Watkins does not specifically discuss fibrosis, let alone a correlation of lipid metabolites with fibrosis severity. The fact

> that fibrosis and NASH are both liver conditions does not necessarily mean that lipid metabolite levels can be used in formulas to directly calculate fibrosis severity.

(Br. 34). Appellants also contend

> one of ordinary skill in art would not find it predictable and/or have a reasonable expectation of success in view of Watkins and Poynard for including the level of at least one oxidized fatty acid product in the formula recited in claim 56 to derive a risk score, wherein an increased risk score compared to a control is indicative of an increased severity or risk of fibrosis of the liver.

(Br. 35).

We find these arguments unpersuasive because, as the Examiner points out, "there was a recognized link between NASH and fibrosis" (Ans. 37, *cf.* Watkins ¶ 2) and Watkins specifically teaches that to assess disease severity the relative amounts of fatty acids may be compared to a reference from "individuals with fibrosis" (FF 7). This specific correlation between "individuals with fibrosis" and fatty acid levels would have reasonably suggested the method of claim 56 to at least the method of "monitoring fibrosis of the liver" based on the disclosed correlation that amounts of fatty acids are associated with disease severity and fibrosis, known sequelae of nonalcoholic fatty liver disease and steatohepatitis (Watkins ¶ 2; FF 7).

We have already addressed the issue of a reasonable expectation of success above, and find that the recognition by Watkins that individuals with fibrosis may serve as reference points for the fatty acid analysis (FF 7) provides a reasonable expectation of success in the use of these compounds for monitoring fibrosis of the liver. *Kubin*, 561 F.3d at 1360.

Appellants contend

> one of ordinary skill in the art would not find it predictable and/or have a reasonable expectation of success in view of Watkins and Poynard in practicing a method of predicting, detecting, or monitoring fibrosis of the liver in a subject with or suspected of having nonalcoholic fatty liver disease recited in claim 56 without improper hindsight.

(Br. 36).

We are not persuaded. The obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418. As also noted by the Court, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.* at 421.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that Watkins and Poynard render the claims obvious.

C. 35 U.S.C. § 103(a) over Watkins, Poynard, and Altmann

Appellants contend

> Watkins and Poynard do not teach that the fatty acid metabolite can be 9-oxoODE or 13-oxoODE (Office Action, pg 20).
>
> In addition, Altmann fails to make up for the deficiencies of Watkins and Poynard. While Altmann may teach that 13-oxoODE is an endogenous ligan[]d for PPARγ in human colonic epithelial cel[l]s, Appellants note that Altmann et al. do not teach that 13-oxo-ODE can be measured in the blood, plasma or serum and that the measured amount can be input in an algorithm recited in present claim 38 to produce a risk score that is indicative of an increased severity or risk of nonalcoholic

> steatohepatitis in a subject having or suspected of already having NAFLD.

(Br. 38).

The Examiner responds "one of ordinary skill, considering the teachings of Altmann at the time of the invention, would have reasonably expected to also observe 13-oxoODE in samples wherein one already observes 13-HODE, since 13-HODE dehydrogenase activity leads to 13-oxoODE" (Ans. 39). The Examiner points to the rejection, which finds

> Altmann et al. taught that 13-HODE dehydrogenase activity leads to 13-oxoODE, and that 13-HODE dehydrogenase activity has been highly observed in colon and *liver*, relative to other tissue; therefore it would be obvious to the ordinarily skilled artisan that 13-oxoODE would be a likely indicator of a condition where 13-HODE is also an indicator, especially in a condition that involves the liver, since the liver has been previously reported to show high 13-HODE dehydrogenase activity leading to 13-oxoODE.

(Ans. 16).

We find the Examiner has the better position. Altmann teaches the "enzymatic oxidation of linoleic acid leads to the production of 13-hydroxyoctadecadienoic acid (13-HODE) . . . . Subsequent dehydrogenation of 13-HODE by the NAD^+-dependent 13-HODE dehydrogenase results in the formation of the 2,4-dienone 13-oxooctadecadienoic acid (13-Oxo-ODE)" (Altmann 613, col. 1; citations and references omitted). Altmann also teaches the "highest levels of 13-HODE dehydrogenase activity were observed in the colon and liver relative to other tissues" (Altmann 613, col. 2). Thus, Altmann evidences that 13-Oxo-ODE is a natural intermediate

metabolite of 13-HODE generated by the 13-HODE dehydrogenase enzyme, particularly in the liver where liver fibrosis occurs.

We therefore agree with the Examiner that the ordinary artisan would have reasonably recognized that measurement of a liver metabolite of 13-HODE, 13-Oxo-ODE, would have been expected to have similar correlations with the parent compound because its levels are entirely dependent upon the starting amounts of 13-HODE in the patient.

D. 35 U.S.C. § 103(a) over Watkins, Poynard, and Suovaniemi

Appellants contend

> Suovaniemi et al. fails to make up for the deficiencies of Watkins and Poynard. Suovaniemi et al. merely teach that the concept of cut-off values in assay involving the determination of an analyte concentration is well known and that it generally means a value or set of values chosen as a limit between the reference values and the abnormal values for the test in question.

(Br. 39).

The Examiner responds the ordinary artisan

> would have found it obvious to include [Suovaniemi's] measurements with the data and the algorithm as taught by the prior art . . . in order to derive a risk score because including additional variables known to predict hepatic steatosis, and combining them with the oxidized fatty acid products shown by Watkins et al. to be predictive of NASH in patients with or suspected of having NAFLD, would make the method of Watkins stronger, adding to its predictive value.

(Ans. 39).

We find the Examiner has the better position. Claim 55 is drawn to a specific risk score, or cutoff value, to provide guidance for whether a patient

has, or is at increased risk, of NASH. As already discussed above, Watkins and Poynard render the analysis method of claim 54 obvious, and Poynard provides equations for use in the analysis (FF 11). The Examiner does not find a teaching of a cutoff value in Watkins or Poynard and therefore relies upon Suovaniemi's teaching that:

> The concept of cut-off values in assays involving the determination of analyte concentrations is well known to the person skilled in the art, and it generally means a value or a set of values chosen as a limit between the reference values (normal values) and the abnormal values for the test in question. Such cut-off values are method-specific and depend on the specifi[ci]ty and sensitivity chosen for the test method.

(Suovaniemi 6:4–11). We agree with the Examiner that including a routinely optimized risk score or cutoff value for determining patients at risk of NASH as suggested by Watkins (FF 1) would have been well known and obvious to the ordinary artisan as evidenced by Suovaniemi, and that any specific values for this risk score represent routine optimization in the absence of evidence of a secondary consideration. Here, no such evidence has been provided.

E. 35 U.S.C. § 103(a) over Watkins, Poynard, Barnhill, and Sureka

Appellants contend

> one having skill in the art would not look to combine the teaching of Barnhill and Sureka with Watkins and Poynard to arrive at the methods of claims 99 and 100 without a reasonable expectation of success in view of Watkins and Poynard for including the level of at least one oxidized fatty acid product in the formula recited in claims 38 and 56 used to derive a risk score, wherein an increased risk score compared to a control is indicative of an increased severity or risk of NASH and/or

> fibrosis of the liver in a subject having or suspected of having NAFLD.

(Br. 42).

The Examiner responds "by allowing a computer to perform the derivation, one would be improving a method rather than changing a method" (Ans. 40).

We find that the Examiner has the better position. We have already found claims 38 and 56, the claims from which claims 99 and 100 depend, obvious for the reasons given above. Claims 99 and 100 simply require performance of the analysis method on a computer. The Examiner cites Barnhill and Sureka to demonstrate that computer diagnostic methods have been performed on a computer (*see* Ans. 19–20) and it would have been obvious to employ a computer "in order to gain the commonly understood benefits of such adaptation, such as . . . increased reliability, simplified operation, and reduced cost." *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

SUMMARY

In summary, we affirm the rejection of claims 38, 43–47, 49, 52, 54–56, 61–67, 70, 72, and 99–104 under 35 U.S.C. § 101, as being directed to non-statutory subject matter.

We affirm the rejection of claims 38, 54, and 56 under 35 U.S.C. § 103(a) as obvious over Watkins and Poynard. Claims 43–47, 52, 61–67, 70, 72, and 101–104 fall with claims 38, 54, and 56.

We affirm the rejection of claim 49 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, and Altmann.

We affirm the rejection of claim 55 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, and Suovaniemi.

We affirm the rejection of claims 99 and 100 under 35 U.S.C. § 103(a) as obvious over Watkins, Poynard, Barnhill, and Sureka.

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