United States Court of Appeals for the Federal Circuit

2008-1403

PROMETHEUS LABORATORIES, INC.,

Plaintiff-Appellant,

v.

MAYO COLLABORATIVE SERVICES (doing business as Mayo Medical Laboratories) and MAYO CLINIC ROCHESTER,

Defendants-Appellees.

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Appealed from: United States District Court for the Southern District of California

Judge John A. Houston

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v.

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Defendants-Appellees.

Appeal from the United States District Court for the Southern District of California in Case No. 04-CV-1200, Judge John A. Houston.

DECIDED: September 16, 2009

Before MICHEL, Chief Judge, LOURIE, Circuit Judge, and CLARK, District Judge.[*]

LOURIE, Circuit Judge.

Prometheus Laboratories, Inc. ("Prometheus") appeals from the final judgment of the United States District Court for the Southern District of California granting summary judgment of invalidity of U.S. Patents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent") under 35 U.S.C. § 101. Prometheus Labs., Inc. v. Mayo Collaborative Servs., No. 04-CV-1200, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008) ("Invalidity Opinion"). Because the district court erred as a matter of law in finding the asserted claims to be drawn to non-statutory subject matter, we reverse.

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[*] Honorable Ron Clark, District Judge, United States District Court for the Eastern District of Texas, sitting by designation.

BACKGROUND

Prometheus is the sole and exclusive licensee of the ’623 patent and the ’302 patent. The patents claim methods for calibrating the proper dosage of thiopurine drugs, which are used for treating both gastrointestinal and non-gastrointestinal autoimmune diseases. These drugs include 6-mercaptopurine (“6-MP”) and azathiopurine (“AZA”), a pro-drug that upon administration to a patient converts to 6-MP, which are used to treat inflammatory bowel diseases (“IBD”) such as Crohn’s disease and ulcerative colitis. 6-MP is broken down by the body into various 6-MP metabolites, including 6-methyl-mercaptopurine (“6-MMP”) and 6-thioguanine (“6-TG”) and their nucleotides.[1] The patents involve measurements of these two metabolites. Drugs that deliver 6-TG are widely used for their cytotoxic and immunosuppressive properties.

Although drugs such as 6-MP and AZA have been used for years to treat autoimmune diseases, non-responsiveness and drug toxicity may complicate treatment in some patients. To that end, the patents claim methods that seek to optimize therapeutic efficacy while minimizing toxic side effects. As written, the methods typically include two separately lettered steps: (a) “administering” a drug that provides 6-TG to a subject and (b) “determining” the levels of the drug’s metabolites, 6-TG and/or 6-MMP, in the subject. See, e.g., ’623 patent claim 1. The measured metabolite levels are then compared to pre-determined metabolite levels, “wherein” the measured metabolite levels “indicate a need” to increase or decrease the level of drug to be administered so as to minimize toxicity and maximize efficacy of treatment. See, e.g., id. In particular,

[1] For the purposes of this opinion, “6-TG” encompasses 6-thioguanine nucleotides.

according to the patents, a 6-TG level greater than about 400 picomole ("pmol") per 800 million red blood cells or a 6-MMP level greater than about 7000 pmol per 800 million red blood cells indicates that a downward adjustment in drug dosage may be required in order to avoid toxic side effects. See id. col.20 ll.22, 54. Conversely, according to the patents, a 6-TG level of less than about 230 pmol per 800 million red blood cells indicates a need to increase the dosage to ensure therapeutic efficacy. See id. col.20 ll.18-19.

Claim 1 of the '623 patent is representative of the independent claims asserted by Prometheus in this case:

> 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.

Claim 1 of the '302 patent is substantially the same, with the inclusion of determining 6-MMP levels in addition to 6-TG.

Prometheus marketed a PROMETHEUS Thiopurine Metabolites test (formerly known as the PRO-PredictRx® Metabolites test) that used the technology covered by the patents in suit. Mayo Collaborative Services and Mayo Clinic Rochester (together, "Mayo") formerly purchased and used Prometheus's test, but in 2004, Mayo announced that it intended to begin using internally at its clinics and selling to other hospitals its

own test. Mayo's test measured the same metabolites as Prometheus's test, but Mayo's test used different levels to determine toxicity of 6-TG and 6-MMP.

On June 15, 2004, Prometheus sued Mayo for infringement of the patents. Prometheus asserted independent claims 1, 7, 22, 25, and 46 of the '623 patent and independent claim 1 of the '302 patent. Most of these claims cover a "method for optimizing therapeutic efficacy" and/or "reducing toxicity" in patients taking a drug such as AZA or 6-MP in the treatment of an immune-mediated gastrointestinal disease. See '623 patent claims 1, 7, 25, & 46; '302 patent claim 1. One independent claim was for treatment of a non-IBD autoimmune disease. See '623 patent claim 22. Prometheus also asserted several dependent claims that require either that the measurement of the metabolites is done using high pressure liquid chromatography, see '623 patent claims 6, 14, 24, 30, and 53, or that the thiopurine drug used is one of four specified drugs, see '623 patent claims 32, 33, 35, and 36. Mayo rescinded its announcement shortly after the lawsuit was filed and still has not launched its test.

On November 22, 2005, the district court held on cross-motions for summary judgment that Mayo's test literally infringed claim 7 of the '623 patent. Prometheus Labs., Inc. v. Mayo Collaborative Servs., No. 04-CV-1200, slip op. at 23 (S.D. Cal. Nov. 22, 2005) (Dkt. No. 227). In its opinion, the court construed "indicates a need" to mean "a warning that an adjustment in dosage may be required." Id. at 18. This construction did not require doctors to adjust drug dosage if the metabolite level reached the specified levels; rather, the court found the wherein phrases to mean "that when the identified metabolites reach the specified level, the doctor is warned or notified that a

dosage adjustment may be required, if the doctor believes that is the proper procedure." Id. at 17-18.

On January 29, 2007, Mayo filed a motion for summary judgment of invalidity, arguing that the patents in suit are invalid because they claim unpatentable subject matter under 35 U.S.C. § 101. Specifically, Mayo contended that the patents impermissibly claim natural phenomena—the correlations between, on the one hand, thiopurine drug metabolite levels and, on the other hand, efficacy and toxicity—and that the claims wholly preempt use of the natural phenomena.

On March 28, 2008, the district court granted Mayo's motion for summary judgment of invalidity under § 101. First, the court found that the patents claimed the correlations between certain thiopurine drug metabolite levels and therapeutic efficacy and toxicity. The court reasoned that, as construed in the November 2005 summary judgment order, the claims have three steps: (1) administer the drug to a subject; (2) determine metabolite levels; and (3) be warned that an adjustment in dosage may be required. The court stated that the fact that inventors framed the claims as treatment methods does not render the claims patentable. Rather, the court found that the "'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations" and that "as construed, the final step—the 'warning' step (i.e. the 'wherein' clause)—is only a mental step." Invalidity Opinion, 2008 WL 878910, at *6. The court noted that the warning step does not require any actual change in dosage and that "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." Id. With this understanding of the claims, the court concluded that the claims recited the correlations between particular

concentrations of 6-TG and 6-MMP and therapeutic efficacy or toxicity in patients taking AZA drugs.

Second, the district court found that those correlations were natural phenomena and not patentable inventions because the correlations resulted from a natural body process. The court stated that the inventors did not "invent" the claimed correlation; rather, "6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity." Invalidity Opinion, 2008 WL 878910, at *7. Finally, the court determined that "[b]ecause the claims cover the correlations themselves, it follows that the claims 'wholly pre-empt' the correlations." Id. at *11. Thus, the court concluded that there was no genuine issue of material fact to be resolved as to whether the patents in suit were directed to statutory subject matter and found by clear and convincing evidence that the claims were invalid under § 101.

On May 16, 2008, the district court entered final judgment, disposing of all the parties' claims and counterclaims. On May 30, 2008, Prometheus timely appealed the district court's grant of summary judgment of invalidity under § 101. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

We review the district court's grant of summary judgment de novo. AT&T Corp. v. Excel Commc'ns, 172 F.3d 1352, 1355 (Fed. Cir. 1999). Summary judgment is appropriate if there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Id.; Fed. R. Civ. P. 56(c). Whether a patent

claim is directed to statutory subject matter is a question of law that we review de novo. AT&T, 172 F.3d at 1355.

B. Section 101

The issue before us is whether the claims meet the requirements of § 101, so we begin with the text of the statute. Section 101 provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title.

35 U.S.C. § 101. According to § 100(b), "[t]he term 'process' means process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or materials." 35 U.S.C. § 100(b). But, as noted in In re Bilski, this definition of process is "unhelpful" because the definition itself uses the term "process." 545 F.3d 943, 951 n.3 (Fed. Cir. 2008) (en banc), cert. granted, 129 S. Ct. 2735 (June 1, 2009). Thus, we turn to the case law to guide our understanding of what constitutes statutory subject matter under § 101.

The Supreme Court has construed § 101 broadly, noting that Congress intended statutory subject matter to "include anything under the sun that is made by man." Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980). It is well-established, however, that this sweeping statement does not indicate that § 101 is unlimited and embraces every discovery:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Id. (quoting Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)). More specifically, the Court has held that a claim to a process is not patent-eligible if it claims "laws of nature, natural phenomena, and abstract ideas." Diamond v. Diehr, 450 U.S. 175, 185 (1981); see also Gottschalk v. Benson, 409 U.S. 63, 67 (1972) ("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.").

At the same time, it has also been established that "while a claim drawn to a fundamental principle"—i.e., a law of nature, natural phenomenon, or abstract idea—"is unpatentable, 'an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" Bilski, 545 F.3d at 953 (quoting Diehr, 450 U.S. at 187). The key issue for patentability, then, at least on the present facts, is whether a claim is drawn to a fundamental principle or an application of a fundamental principle. Although this inquiry is hardly straightforward, following the Supreme Court, we articulated in Bilski a "definitive test" for determining whether a process is patent-eligible under § 101: "A claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." Id. The machine-or-transformation test is a "two-branched inquiry," i.e., the patentee "may show that a process claim satisfies § 101 either by showing that his claim is tied to a particular machine, or by showing that his claim transforms an article." Id. at 961.

The machine-or-transformation test has two further aspects: "the use of a specific machine or transformation of an article must impose meaningful limits on the

claim's scope to impart patent-eligibility," and "the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity." Bilski, 545 F.3d at 961-62 (citations omitted). "This transformation must be central to the purpose of the claimed process." Id. at 962. Thus, in most cases, one cannot ground the transformative nature of a process in a step that is "insignificant extra-solution activity" or merely a "data-gathering step." See id. at 963 ("Further, the inherent step of gathering data can also fairly be characterized as insignificant extra-solution activity."). In other words, if steps of a method are included for the purpose of data-gathering rather than being "central" to the purpose of the process, the patentee likely cannot rely on the data-gathering steps to prove that the claimed process is transformative and thus drawn to patentable subject matter. See id. at 963 (stating that mere data-gathering will not, "at least in most cases, . . . constitute a transformation of any article").

The Supreme Court has also made clear that the patent eligibility of a claim as a whole should not be based on whether selected limitations constitute patent-eligible subject matter. See Bilski, 545 F.3d at 958 (citing Diehr, 450 U.S. at 188; Parker v. Flook, 437 U.S. 584, 594 (1978)). As noted in Diehr, the Court has specifically stated that it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." 450 U.S. at 188. Moreover, it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements set forth in 35 U.S.C. §§ 102 and 103, respectively. Bilski, 545 F.3d at 958 (citing Diehr, 450 U.S. at 188-91).

With this understanding of the present state of the law, we now turn to the parties' arguments in the instant action.

C. Analysis

On appeal, Prometheus argues that the claimed processes satisfy § 101 because they meet both prongs of the machine-or-transformation test articulated in Bilski. With respect to the machine prong, Prometheus argues that the patents inextricably rely on numerous machines to process the bodily sample, determine the metabolite levels, and thereby calibrate the proper dose. Prometheus asserts that the district court erred by failing to consider separately the asserted dependent claims, some of which specify measurement through high pressure liquid chromatography, which clearly requires the use of machines. In addition, Prometheus contends that Bilski's use of "machine" in its machine-or-transformation test must be read as shorthand for all patentable subject matter, including compositions of matter. To that end, Prometheus argues that the synthetic drugs used in its treatment methods are compositions of matter, and the claims' central reliance on those drugs is enough to meet the machine-or-transformation test. Alternatively, Prometheus asserts that we should recognize that Bilski does not apply where, as here, the treatment methods use synthetic drugs and thus do not recite or wholly preempt any natural phenomenon.

With respect to the transformation prong, Prometheus points to three "transformations" within its claimed process: (1) the first step of administering a synthetic drug transforms the biochemical makeup of the patient's body for the purpose of treating disease; (2) the second step requires the transformation of a bodily sample to determine the created metabolites' concentration levels; and (3) the metabolite levels

are transformed into a warning for a doctor to alter the dosage. Regarding the first asserted transformation, Prometheus argues that physical transformations, such as the human body's metabolic reaction to drugs, initiated by human actions and artificial chemical compounds, such as the administration of a thiopurine drug into the body, cannot be unpatentable under Bilski simply because they proceed according to natural laws or occur within the human body. Prometheus contends that everything proceeds according to natural laws. Regarding the second asserted transformation, Prometheus argues that all of the several methods available to determine the metabolite levels in a bodily sample require a physical transformation of blood or human tissue in order to extract the metabolite and determine its concentration. Finally, regarding the third asserted transformation, Prometheus posits that the ultimate end of the processes is to transform—and improve—the patient's treatment regime while avoiding deadly side effects by transforming the metabolite levels into a warning regarding dosage.

Prometheus then argues that these machines and transformations are central to the invention's purpose of improving a process of treatment and are not confined to extra-solution activity. Prometheus asserts that the district court erred by parsing the steps of the treatment method rather than looking at the method as a whole, which applies the correlations in concrete physical processes—that Prometheus argues are patentable absent the correlation—to generate useful information. Prometheus contends that adoption of the district court's reasoning would have the effect of eliminating all medical treatment and diagnostic patents, when future medical advances will depend on optimizing treatment based on genetic or other testing.

Mayo responds that the district court properly examined the claims as a whole and correctly determined that they recite the correlations themselves, which are natural phenomena. With respect to the machine prong, Mayo argues that any involvement of machines is insignificant extra-solution activity. Mayo asserts that the step of determining the metabolite levels via an unspecified machine is merely gathering data that is necessary to correlate information. Mayo argues that Bilski requires the use of a "particular machine or apparatus" and that no particular machine is involved in Prometheus's process. Mayo contends that Prometheus's reliance on the dependent claims reciting the use of high pressure liquid chromatography is misplaced because choosing to limit the claims to one possible method for performing one of the steps is not sufficient to impart patentability over a natural phenomenon.

Similarly, with respect to the transformation prong, Mayo argues that there is no patentable transformation in the claimed processes. First, Mayo asserts that the administering step is merely a data-gathering step. Mayo points out that the asserted claims do not all include the administering step and thus argues that the administration of the drug cannot be central to the claim. Mayo also contends that although the thiopurine drugs used in the claims are synthetic, the body's reaction to them is natural, and the drugs themselves were well known. Second, Mayo argues that the determining step is also data-gathering necessary to make any use of the correlations, and the presence of the physical step of transforming clinical samples does not impart patentability to claims to natural correlations. Third, Mayo argues that there is no transformation of data into a warning because the claims do not require any action to be taken to adjust dosage. Under the claim construction argued by Prometheus and

adopted by the district court, the final step is a mental step and thus, Mayo argues, the data undergoes no transformation at all.

Furthermore, Mayo asserts that the district court properly determined not only that the claims were to the correlations themselves but that the claims preempt all practical use of the correlations. Post-Bilski, Mayo argues that Supreme Court precedent invalidating a claim that wholly preempts a natural phenomenon such that the practical effect is a patent on the phenomenon itself still stands. Mayo contends that because nothing is done with the naturally occurring correlation, the claims cover all implementations resulting from that natural phenomenon and are thus unpatentable. Finally, Mayo argues that invalidating Prometheus's claims will not affect medical treatment methods because infringement of the asserted claims requires no act by a physician at all and no treatment of any disease or condition in a patient. Furthermore, Mayo asserts that upholding the claims under § 101 is dangerous because infringement would occur any time the natural correlation was even considered by a physician.

A number of amici curiae filed helpful briefs on both sides. Those supporting Prometheus argued that the transformation that flows from the use of thiopurine drugs in the patented processes is not "insignificant" post-solution activity but rather a specific and practical application of the correlations in medical treatment. They also argue that the future of personalized medicine will involve knowledge of the physiological or biological significance of biomarkers and how to use them in diagnostic or therapeutic procedures and that patents on those biomarkers should be granted. Those supporting Mayo argue that the district court properly found that the claims impermissibly preempt a natural statistical correlation by asserting exclusive rights over the mere recognition by

a treating physician of those correlations. They argue that finding Prometheus's claim to cover patentable subject matter would be granting exclusive rights over mere knowledge of the correlations and would thus interfere with the provision of medical care and with research and quality control in clinical chemistry.

1. The administering and determining steps are transformative

We agree with Prometheus that the asserted claims are drawn to statutory subject matter and thus reverse the district court's grant of Mayo's motion for summary judgment of invalidity. As an initial matter, we note that the only issue before us is whether the claims meet the requirements of § 101. This appeal does not raise any questions about lack of novelty, obviousness, or overbreadth, since those are separate statutory requirements for patentability under §§ 102, 103, and 112, respectively. See Bilski, 545 F.3d at 958 (citing Diehr, 450 U.S. at 188-91). The proper inquiry under § 101 is whether these methods meet the Supreme Court's machine or transformation test articulated in Benson and Diehr, and applied in Bilski, and, if so, whether the machine or the transformation is central to the purpose of the claims.[2]

We conclude that the methods of treatment claimed in the patents in suit squarely fall within the realm of patentable subject matter because they "transform an article into a different state or thing," and this transformation is "central to the purpose of the claimed process." See Bilski, 545 F.3d at 962. The transformation is of the human body following administration of a drug and the various chemical and physical changes

[2] We note that the district court did not have the benefit of our Bilski decision when deciding the § 101 issue. However, we believe that even prior to Bilski, the asserted claims should have been found to be patentable subject matter under the Supreme Court's decisions in Benson and Diehr and our cases such as In re Grams, 888 F.2d 835 (Fed. Cir. 1989), and In re Abele, 684 F.2d 902 (CCPA 1982).

of the drug's metabolites that enable their concentrations to be determined. Because the claimed methods meet the transformation prong under Bilski, we do not consider whether they also meet the machine prong.

Contrary to the district court, we do not view the disputed claims as merely claiming natural correlations and data-gathering steps.[3] The asserted claims are in effect claims to methods of treatment, which are always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition. More specifically, Prometheus here claimed methods for optimizing efficacy and reducing toxicity of treatment regimes for gastrointestinal and non-gastrointestinal autoimmune diseases that utilize drugs providing 6-TG by administering a drug to a subject. The invention's purpose to treat the human body is made clear in the specification and the preambles of the asserted claims. See '623 patent col.2 ll.16-19 ("The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder."); see, e.g., id. claim 1 ("A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); id. claim 7 ("A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); id. claim 22 ("A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising . . .").

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[3] In reaching its conclusion, the district court relied heavily on the opinion of three justices dissenting from the dismissal of the grant of certiorari in Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc., 548 U.S. 124 (2006) (Breyer, J., dissenting). See Invalidity Opinion, 2008 WL 878910, at *8 (discussing the dissent in Laboratory Corp. at length and stating that although the dissent "does not have precedential value, the Court finds Justice Breyer's reasoning persuasive"). That dissent is not controlling law and also involved different claims from the ones at issue here.

When administering a drug such as AZA or 6-MP, the human body necessarily undergoes a transformation. The drugs do not pass through the body untouched without affecting it. In fact, the transformation that occurs, viz., the effect on the body after metabolizing the artificially administered drugs, is the entire purpose of administering these drugs: the drugs are administered to provide 6-TG, which is thought to be the drugs' active metabolite in the treatment of disease, to a subject. See '623 patent col.1 ll.49-51. The fact that the change of the administered drug into its metabolites relies on natural processes does not disqualify the administering step from the realm of patentability. As Prometheus points out, quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law. Transformations operate by natural principles. The transformation here, however, is the result of the physical administration of a drug to a subject to transform—i.e., treat—the subject, which is itself not a natural process. "It is virtually self-evident that a process for a chemical or physical transformation of physical objects or substances is patent-eligible subject matter." See Bilski, 545 F.3d at 962. The administering step, therefore, is not merely data-gathering but a significant transformative element of Prometheus's claimed methods of treatment that is "sufficiently definite to confine the patent monopoly within rather definite bounds." Id. (quoting Benson, 409 U.S. at 70).

Mayo is correct that not all of the asserted claims contain the administering step. That omission, which occurs in claims 46 and 53 of the '623 patent, does not diminish the patentability of the claimed methods because the determining step, which is present in each of the asserted claims, is also transformative and central to the claimed

methods. Determining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration. As stated by Prometheus's expert, "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue." Decl. of Dr. Yves Théorêt ¶ 6, Prometheus Labs., Inc. v. Mayo Collaborative Servs., No. 04-CV-1200 (S.D. Cal. Mar. 29, 2007) (Dkt. No. 528-3). That is clearly a transformation. In fact, Mayo does not dispute that determining metabolite levels in the clinical samples taken from patients is transformative, but argues that this transformation is merely a necessary data-gathering step for use of the correlations. Appellees' Br. 37 ("The 'transformation' of the patient's sample is merely a necessary data-gathering step. . . . [T]he presence of the physical step of transforming clinical samples taken from patients does not impart patentability to Prometheus' claims to the natural correlations."). On the contrary, this transformation is central to the purpose of the claims, since the determining step is, like the administering step, a significant part of the claimed method of treatment. Measuring the levels of 6-TG and 6-MMP is what enables possible adjustments to thiopurine drug dosage to be detected for optimizing efficacy or reducing toxicity during a course of treatment. The determining step, by working a chemical and physical transformation on physical substances, likewise sufficiently confines the patent monopoly, as required by Bilski.

2. The administering and determining steps are not merely data-gathering

A further requirement for patent-eligibility is ensuring that the involvement of the transformation in Prometheus's claimed process is "not merely insignificant extra-solution activity." Bilski, 545 F.3d at 962 (citing Flook, 437 U.S. at 590). As made clear from the discussion above, the administering and determining steps are transformative and are central to the claims rather than merely insignificant extra-solution activity.

The crucial error the district court made in reaching the opposite conclusion was failing to recognize that the first two steps of the asserted claims are not merely data-gathering steps. See Invalidity Opinion, 2008 WL 878910, at *6 (finding that "the 'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations"). While it is true that the administering and determining steps gather useful data, it is also clear that the presence of those two steps in the claimed processes is not "merely" for the purpose of gathering data. Instead, the administering and determining steps are part of a treatment protocol, and they are transformative. As explained above, the administering step provides thiopurine drugs for the purpose of treating disease, and the determining step measures the drugs' metabolite levels for the purpose of assessing the drugs' dosage during the course of treatment.

Given the integral involvement of the administering and determining steps in Prometheus's therapeutic methods, this case is easily distinguishable from prior cases that found asserted method claims to be unpatentable for claiming data-gathering steps and a fundamental principle. Perhaps the case that offers the closest comparison is In re Grams, 888 F.2d 835 (Fed. Cir. 1989), but the asserted claims found unpatentable in

that case are readily distinguished from those in the instant action. In Grams, the applicant claimed a process that involved (1) performing a clinical test on individuals and (2) based on the data from that test, determining if an abnormality existed and determining possible causes of any abnormality by using an algorithm. We found that this process was not drawn to patentable subject matter because the essence of the claimed process was the mathematical algorithm, rather than any transformation of the tested individuals. 888 F.2d at 839-41. More specifically, the Grams process was unpatentable because "it was merely an algorithm combined with a data-gathering step," i.e., performing a clinical test. Bilski, 545 F.3d at 963. The claims did not require the performing of clinical tests on individuals that were transformative—and thus rendering the entire process patentable subject matter—because the tests were just to "obtain data." Grams, 888 F.2d at 840. The patent and thus the court focused only on the algorithm rather than the clinical tests purported to be covered by the claims.

Here, unlike the clinical test recited in Grams, the administering and determining steps in Prometheus's claimed methods are not "merely" data-gathering steps or "insignificant extra-solution activity"; they are part of treatment regimes for various diseases using thiopurine drugs. See Bilski, 545 F.3d at 963 (discussing Grams). As a result, the administering and determining steps are not insignificant extra-solution activity, and the claims are therefore not drawn merely to correlations between metabolite levels and toxicity or efficacy.

3. The presence of a mental step does not detract from patentability

We agree with the district court that the final "wherein" clauses are mental steps and thus not patent-eligible per se. However, although they alone are not patent-

eligible, the claims are not simply to the mental steps. A subsequent mental step does not, by itself, negate the transformative nature of prior steps. Thus, when viewed in the proper context, the final step of providing a warning based on the results of the prior steps does not detract from the patentability of Prometheus's claimed methods as a whole. The data that the administering and determining steps provide for use in the mental steps is obtained by steps well within the realm of patentable subject matter. The addition of the mental steps to the claimed methods thus does not remove the prior two steps from that realm.

This analysis is consistent with In re Abele, 684 F.2d 902 (CCPA 1982).[4] In Abele, a method claim called for the use of X-ray attenuation data, which necessarily involved production, detection, and display with a CAT scan. The method also called for use of an algorithm. We found that the claim was patentable because removal of the algorithm still left all the steps of a CAT scan in the claim; thus, the production and detection could not be considered "mere antecedent steps to obtain values for solving the algorithm. . . . We view the production, detection, and display steps as manifestly statutory subject matter, and are not swayed from this conclusion by the presence of an algorithm in the claimed method." Id. at 908. In the instant case, the presence of the mental steps similarly does not detract from the patentability of the administering and determining steps.

As we explained in Bilski,

[4] Although Bilski reiterated that the Freeman-Walter-Abele test is "inadequate" for determining patent-eligibility, Bilski spoke approvingly of the analysis regarding the patent-eligible method in Abele. See Bilski, 545 F.3d at 962-63. Thus, the determination that claim 6 of Abele's patent was patent-eligible subject matter is still good law post-Bilski.

> [I]t is inappropriate to determine the patent eligibility of a claim as a whole based on whether selected limitations constitute patent-eligible subject matter. After all, even though a fundamental principle itself is not patent-eligible, processes incorporating a fundamental principle may be patent-eligible. Thus, it is irrelevant that any individual step or limitation of such processes by itself would be unpatentable under § 101.

545 F.3d at 958 (citations omitted). Such is the case here. Although the wherein clauses describe the mental processes used to determine the need to change the dosage levels of the drugs, each asserted claim as a whole is drawn to patentable subject matter. Although a physician is not required to make any upward or downward adjustment in dosage during the "warning" step, the prior steps provide useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject. When viewing the treatment methods as a whole, Prometheus has claimed therapeutic methods that determine the optimal dosage level for a course of treatment. In other words, when asked the critical question of "What did the applicant invent?," Grams, 888 F.2d at 839 (citation omitted), the answer is a series of transformative steps that optimizes efficacy and reduces toxicity of a method of treatment for particular diseases using particular drugs.

Furthermore, the district court erred in finding that the claims wholly preempt use of correlations between metabolite levels and efficacy or toxicity. The court reached this conclusion because "the claims cover the correlations themselves." Invalidity Opinion, 2008 WL 878910, at *11. As discussed above, the claims are to transformative methods of treatment, not correlations. The claims cover a particular application of natural processes to treat various diseases, but transformative steps utilizing natural processes are not unpatentable subject matter. Moreover, the claims do not preempt natural processes; they utilize them in a series of specific steps. See Diehr, 450 U.S. at

187 ("Their process admittedly employs a well-known mathematical equation, but they do not seek to preempt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process."). Regardless, because the claims meet the machine-or-transformation test, they do not preempt a fundamental principle. See Bilski, 545 F.3d at 954 (characterizing the machine-or-transformation test as "a definitive test to determine whether a process is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself"). The inventive nature of the claimed methods stems not from preemption of all use of these natural processes, but from the application of a natural phenomenon in a series of transformative steps comprising particular methods of treatment. See id. ("[A] claimed process that transforms a particular article to a specified different state or thing by applying a fundamental principle would not pre-empt the use of the principle to transform any other article, to transform the same article but in a manner not covered by the claim, or to do anything other than transform the specified article."). It is clear that these methods of treatment are § 101 patentable subject matter.

Thus, the claimed methods satisfy all of the requirements under Bilski's transformation prong for patent-eligible subject matter under § 101.

CONCLUSION

For the foregoing reasons, we reverse the judgment of the district court and remand to the court with instructions to deny Mayo's motion for summary judgment that the asserted claims are invalid under § 101.

REVERSED and REMANDED