United States Court of Appeals for the Federal Circuit

PROMETHEUS LABORATORIES, INC.,
Plaintiff-Appellant,

v.

MAYO COLLABORATIVE SERVICES (DOING BUSINESS AS MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Defendants-Appellees.

2008-1403

On Remand from the Supreme Court of the United States.

Decided: December 17, 2010

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Before RADER, *Chief Judge*, LOURIE and BRYSON, *Circuit Judges*.

LOURIE, *Circuit Judge*.

This case returns to this court on remand from the Supreme Court for further consideration in light of the Court's decision in *Bilski v. Kappos*, 561 U.S. -- , 130 S. Ct. 3218 (2010). In *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 581 F.3d 1336 (Fed. Cir. 2009), we decided an appeal by Prometheus Laboratories, Inc. ("Prometheus") from a 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. We held that the district court erred as a matter of law in finding Prometheus's asserted medical treatment claims to be drawn to non-statutory subject matter under this court's machine-or-transformation test, which we had held in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), to be the definitive test for determining the patentability of a process under § 101. Following our decision in this case, the Supreme Court held that the machine-or-transformation test, although "a useful and important clue," was not the sole test for determining the patent eligibility of process claims. *Bilski*, 130 S. Ct. at 3226-27. Based on that decision, the Court vacated and remanded our *Prometheus* decision. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 130 S. Ct. 3543 (2010) ("*GVR Order*"). On remand, we again hold that Prometheus's asserted method claims are drawn

to statutory subject matter, and we again reverse the district court's grant of summary judgment of invalidity under § 101.

BACKGROUND

Prometheus is the sole and exclusive licensee of the '623 and '302 patents, which claim methods for determining the optimal dosage of thiopurine drugs used to treat 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, both of 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-methylmercaptopurine ("6-MMP") and 6-thioguanine ("6-TG") and their nucleotides.[1]

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. Accordingly, the patents claim methods that seek to optimize therapeutic efficacy while minimizing toxic side effects. As written, the claimed 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 treatment efficacy. *See, e.g.*, *id.* In particular, according to the patents, a 6-TG

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

level greater than about 400 picomole ("pmol") per 800 million red blood cells or a 6-MMP level greater than about 7,000 pmol per 800 million red blood cells indicates that a downward adjustment in drug dosage may be required 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:

> 1. 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.

'623 patent claim 1 (emphases added). Claim 1 of the '302 patent is substantially the same, with the addition of

determining 6-MMP levels in addition to 6-TG levels. Claim 46 of the '623 patent dispenses with the "administering" step and claims only the "determining" step:

> 46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) *determining* the level of 6-thioguanine or 6-methylmercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathiop[u]rine, 6-thioguanine, and 6-methyl-mercaptoriboside, 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 or a level of 6-methylmercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

'623 patent claim 46 (emphases added).

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 (collectively, "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 '623 and '302 patents. Prometheus asserted independent claims 1, 7, 22, 25, and 46 of the '623 patent and independent claim 1 of the '302 patent. Prometheus also asserted several dependent claims that require either that the measurement of the metabolites be performed using high pressure liquid chromatography, *see* '623 patent claims 6, 14, 24, 30, and 53, or that the thiopurine drug used be one of four specified drugs, *see id.* claims 32, 33, 35, and 36. Mayo rescinded its announcement shortly after Prometheus filed suit, and has yet to launch 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 two "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 subject matter unpatentable 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. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008) ("*Invalidity Opinion*"). First, the court found that the patents only 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) administering the drug to a subject, (2) determining metabolite levels, and (3) being warned that an adjustment in dosage may be required. The court stated that the fact that the inventors framed the claims as treatment methods does not render the claims patent-eligible subject matter. 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." 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 concen-

trations of 6-TG and 6-MMP and therapeutic efficacy or toxicity in patients taking AZA drugs. *Id.* at *6.

Second, the district court found that those correlations were natural phenomena, not patent-eligible 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." *Id.* 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. *Id.* at *14. On May 16, 2008, the district court entered final judgment, and Prometheus timely appealed.

On appeal, we reversed and upheld the asserted claims' validity under what was at the time this court's "definitive test" for determining whether a process is patentable subject matter under § 101: the machine-or-transformation test. *Prometheus*, 581 F.3d at 1342. Under the machine-or-transformation test, a claimed process is patent eligible if it (1) is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing. *Id.* (quoting *Bilski*, 545 F.3d at 954). We held that both the "administering" and "determining" steps were transformative and not merely data-gathering steps under the second prong of the test, and as such the claims did not wholly preempt

the use of the recited correlations between metabolite levels and drug efficacy or toxicity. *Id.* at 1345-49.

Following our decision in *Prometheus*, the Supreme Court issued a decision rejecting the machine-or-transformation test as the sole, definitive test for determining the patent eligibility of a process under § 101. *Bilski*, 130 S. Ct. at 3226-27. Instead, the Court declined to adopt any categorical rules outside the well-established exceptions for laws of nature, physical phenomena, and abstract ideas, and resolved the case based on its decisions in *Gottschalk v. Benson*, 409 U.S. 63 (1972), *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175 (1981), holding that Bilski's claims to methods of hedging risk are not patentable processes because they attempt to patent abstract ideas. *Id.* at 3226, 3229-30. The Court did not, however, reject the machine-or-transformation test, but rather characterized the test as "a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101." *Id.* at 3227.

The Court then granted Mayo's petition for certiorari, vacated our decision holding Prometheus's method of treatment claims to cover patent-eligible subject matter under the machine-or-transformation test, and remanded the case for consideration in light of the Court's *Bilski* decision. On September 1, 2010, we requested that the parties simultaneously submit briefs, without further oral argument, to address the effect of the Supreme Court's decision in *Bilski* on the disposition of this case. In view of this additional briefing and the Supreme Court's guidance in *Bilski*, we again hold that Prometheus's method claims recite patentable subject matter under § 101.

DISCUSSION

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. 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.

I.

The issue again before us is whether Prometheus's method claims meet the requirements of § 101. The text of the statute 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. The Supreme Court has consistently construed § 101 broadly. Most recently, in *Bilski*, the Court stated that by choosing expansive terms to specify four independent patent-eligible categories of inventions or discoveries—processes, machines, manufactures, and compositions of matter—and by modifying those terms with the comprehensive "any," Congress plainly contemplated that § 101 would be given wide scope. 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). "Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Id.* (quoting 5 *Writings of Thomas Jefferson* 75-76 (H. Washington ed. 1871)).

Yet, it is equally well-established that § 101, while broad, is not unlimited. "The Court's precedents provide

three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Id.* (quoting *Chakrabarty*, 447 U.S. at 309). Although not compelled by the statutory text, the Court has held that "these exceptions have defined the reach of the statute as a matter of statutory *stare decisis* going back 150 years," *id.* (citing *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 174-75 (1853)), and "[t]he concepts covered by these exceptions are 'part of the storehouse of knowledge of all men . . . 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)); *see also Benson*, 409 U.S. at 67 ("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.").

The Supreme Court has also established that while a law of nature, natural phenomenon, or abstract idea cannot be patented, "an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188). In making this determination, the Court has made clear that a claim must be considered as a whole; 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." *Id.* (quoting *Diehr*, 450 U.S. at 188). Nonetheless, a scientific principle cannot be made patentable by limiting its use to a particular technological environment or by adding insignificant post-solution activity. *Diehr*, 450 U.S. at 191-92.

In light of the Supreme Court's decision in *Bilski*, patent eligibility in this case turns on whether Prometheus's asserted claims are drawn to a natural phenomenon, the patenting of which would entirely preempt its use as in

Benson or *Flook*, or whether the claims are drawn only to a particular application of that phenomenon as in *Diehr*. *Bilski*, 130 S. Ct. at 3230. We conclude they are drawn to the latter.

II.

We turn to the parties' arguments on remand. Prometheus argues that neither the Supreme Court's *Bilski* decision nor the Court's *GVR Order* compels a different outcome on remand, and therefore we should again reverse the district court's judgment of invalidity under § 101. Regarding *Bilski*, Prometheus contends that the Court held only that patents that do *not* satisfy the machine-or-transformation test are not necessarily *un*patentable and did not overrule the long-established view that claims that satisfy the machine-or-transformation test, like Prometheus's, necessarily satisfy § 101. But regardless, Prometheus argues, its asserted claims not only satisfy the machine-or-transformation test, but also are not drawn to mere abstractions. Specifically, Prometheus argues that its asserted claims involve a particular transformation of a patient's body and bodily sample and use particular machines to determine metabolite concentrations in a bodily sample (*e.g.*, via high pressure liquid chromatography), thus satisfying either prong of the machine-or-transformation test. Prometheus further argues that its claims also involve an application of a law of nature, not the law itself, because they recite specific means of treating specific diseases using specific drugs, and therefore do not preempt the abstract idea of calibrating drug dosages to treat disease.

Mayo argues that the Supreme Court in *Bilski* reaffirmed that preemption is the controlling standard for § 101 under the Court's *Benson*, *Flook*, and *Diehr* precedents and made clear that while a machine-or-

transformation test may inform the analysis, that test is not outcome determinative. And, according to Mayo, under the governing preemption standard, Prometheus's claims are invalid because they preempt all practical use of naturally occurring correlations between metabolite levels and drug efficacy and any machine or transformation present in the claims is merely insignificant post-solution activity. Mayo also asserts that the carefully considered opinion of three Justices—allegedly cited approvingly by five Justices in *Bilski*—rejected Prometheus's machine-or-transformation argument for nearly identical claims in *Laboratory Corp. of America Holdings, Inc. v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 138-39 (2006), concluding that the claims do not cover a process for transforming a bodily sample, but rather merely instruct the user to obtain test results and think about them. Finally, Mayo claims that the Supreme Court's decision to GVR our earlier decision in this case indicates that a different analysis is required of us on remand.

We disagree with Mayo. We do not think that either the Supreme Court's *GVR Order* or the Court's *Bilski* decision dictates a wholly different analysis or a different result on remand. In our pre-*Bilski* decision in this case, we held not only that Prometheus's asserted claims recite transformative "administering" and "determining" steps, but also that Prometheus's claims are drawn not to a law of nature, but to a particular application of naturally occurring correlations, and accordingly do not preempt all uses of the recited correlations between metabolite levels and drug efficacy or toxicity. The Supreme Court's decision in *Bilski* did not undermine our preemption analysis of Prometheus's claims and it rejected the machine-or-transformation test only as a definitive test. The Court merely stated that "[t]he Court of Appeals incorrectly concluded that this Court has endorsed the machine-or-

transformation test *as the exclusive test*." 130 S. Ct. at 3226 (emphasis added). The Court stated that it had previously noted in *Benson*, 409 U.S. at 70, that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* at 3227. Thus, the Court did not disavow the machine-or-transformation test. And, as applied to the present claims, the "useful and important clue, an investigative tool," leads to a clear and compelling conclusion, *viz.*, that the present claims pass muster under § 101. They do not encompass laws of nature or preempt natural correlations.

III.

As before, we again hold that Prometheus's asserted method claims recite a patent-eligible application of naturally occurring correlations between metabolite levels and efficacy or toxicity, and thus do not wholly preempt all uses of the recited correlations. As discussed below, the claims recite specific treatment steps, not just the correlations themselves. And the steps involve a particular application of the natural correlations: the treatment of a specific disease by administering specific drugs and measuring specific metabolites. As such, and contrary to Mayo's assertions, the claims do not preempt all uses of the natural correlations; 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."). 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 steps comprising

particular methods of treatment. Other drugs might be administered to optimize the therapeutic efficacy of the claimed treatment.

We similarly reaffirm that the treatment methods claimed in Prometheus's patents in suit satisfy the transformation prong of the machine-or-transformation test, as 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 and of its components following the administration of a specific class of drugs and the various chemical and physical changes of the drugs' metabolites that enable their concentrations to be determined. We thus have no need to separately determine whether the claims also satisfy the machine prong of the test.

Contrary to the district court and Mayo's arguments on remand, we do not view the disputed claims as merely claiming natural correlations and data-gathering steps.[2]

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[2] Mayo, as did the district court, points to the opinion of three Justices dissenting from the dismissal of the grant of certiorari in *Lab. Corp.*, 548 U.S. 124 (Breyer, J., dissenting from dismissal of certiorari as improvidently granted). *See Invalidity Opinion*, 2008 WL 878910, at *8 (discussing the dissent in *Lab. Corp.* at length and finding Justice Breyer's reasoning persuasive). Again, with respect, we decline to discuss a dissent; it is not controlling law, and it involved different claims from the ones at issue here. Mayo further claims that five Justices in two concurrences cited *Lab. Corp.* with approval in *Bilski*, but such citations fail to transform a dissent into controlling law. Moreover, one concurrence cites *Lab. Corp.* for the proposition that "*too much* patent protection can impede rather than 'promote the Progress of . . . useful Arts,'" in arguing for a categorical rule that business method patents do not qualify as patent-eligible processes under

The asserted claims are in effect claims to methods of treatment, which are always transformative when one of 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 . . .").

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 adminis-

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§ 101. *Bilski*, 130 S. Ct. at 3255 (Stevens, J., concurring). But this case does not involve business method patents.

tered 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." *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." *Benson*, 409 U.S. at 70.

Not all of the asserted claims, however, 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 we also hold that the determining step, which is present in each of the asserted claims, is transformative and central to the claimed methods. Determining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or some 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. 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. 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 the machine-or-transformation test.

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." *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.

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 are 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. No claim in the Prometheus patents claims only mental steps. Therefore, contrary to Mayo's assertions, a physician who only evaluates the result of the claimed methods, without carrying out the administering and/or determining steps that are present in all the claims, cannot infringe any claim that requires such steps.

This analysis is consistent with *In re Abele*, 684 F.2d 902 (CCPA 1982). 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 mental steps similarly does not detract from the patentability of the administering and determining steps.

As we explained in *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. 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, "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.

In light of the foregoing analysis, we hold that Prometheus's asserted method claims satisfy the preemption test as well as the transformation prong of the machine-or-transformation test.

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