No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, ET AL., PETITIONERS

v.

PROMETHEUS LABORATORIES, INC.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING NEITHER PARTY

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QUESTION PRESENTED

Whether an improved method of treating a patient with a man-made drug is ineligible for protection under 35 U.S.C. 101 because the therapeutic efficacy of the drug depends on the natural metabolic processes of the human body.

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INTEREST OF THE UNITED STATES

This case presents the question whether an improved method of treating a patient with a man-made drug is ineligible for protection under the Patent Act because the therapeutic efficacy of the drug depends on the natural metabolic processes of the human body. The Court's resolution of that question will significantly affect the work of the United States Patent and Trademark Office (PTO), which is responsible for issuing patents and advising the President on issues of patent policy. See 35 U.S.C. 2(a)(1) and (b)(8). The United States therefore has a substantial interest in the Court's disposition of this case.

STATEMENT

1. Certain gastrointestinal disorders, such as Crohn's disease, result from the abnormal functioning of the body's immune system. For decades, doctors have used a class of drugs known as thiopurines to treat these and other immune-mediated disorders by interfering with certain chemical reactions in the body on which the immune system depends.

Thiopurines are complex, synthetic chemicals that do not occur in nature. Invented and patented more than 50 years ago, the leading thiopurine drugs, 6-mercaptopurine (6-MP) and azathioprine (AZA), were immediately recognized for their utility in inducing the temporary remission of leukemia. See United States Patent Nos. 2,697,709 (1954) (claiming 6-MP and methods of its chemical synthesis, and noting its medical utility), 3,056,785 (1962) (same, AZA).[1] Doctors soon began to use the drugs as immunosuppressants in organ transplantation, and in 1962 a scientific paper described the use of 6-MP to treat ulcerative colitis, a type of immune-mediated gastrointestinal disorder. See Srikumar Sahasranaman et al., *Clinical Pharmacology and Pharmacogenetics of Thiopurines*, 64 Eur. J. Clinical Pharmacology 753, 754 (2008) (Sahasranaman). AZA and 6-MP are also associated with a variety of serious risks and side effects. See Sahasranaman 761-762; *Medical Toxicology* 1042-1043 (Richard C. Dart ed., 3d ed. 2004) (*Medical Toxicology*).

The immunosuppressive effects of AZA and 6-MP arise from the manner in which the drugs are metabolized by the human body. Upon ingestion, 6-MP is

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[1] The AZA patent describes the drug by its alternative chemical name, 6-(1-methyl-4-nitro-5-imidazolyl)-mercaptopurine.

converted by the natural chemistry of the body into various metabolites, including 6-thioguanine (6-TG) and 6-methyl mercaptopurine (6-MMP). Pet. App. 3a; see Sahasranaman 754-755. AZA converts in the body to 6-MP and is metabolized in the same fashion. Although the exact biological mechanism is not fully understood, it is believed that 6-TG interferes with the body's synthesis of certain DNA bases (purines) necessary to the production of lymphocytes, a type of white blood cell critical to the immune system. See *Medical Toxicology* 1042; Sahasranaman 754-755.

2. Respondent is the exclusive licensee of United States Patent Nos. 6,355,623 (2002) (the '623 patent) and 6,680,302 (2004) (the '302 patent), which claim methods of optimizing the dosage of thiopurine drugs in patients with auto-immune disorders based on the observed concentration of 6-TG and 6-MMP metabolites in the patient's blood. Pet. App. 2a-3a. The patents stem from the same priority application filed in 1998.

The patents acknowledge that the immunosuppressive qualities of AZA and 6-MP, as well as the efficacy of those compounds in treating auto-immune disorders, were well known in the art at the time of the original application. See, *e.g.*, '623 patent, col. 1, ll. 41-46. The patents also make clear that the metabolic breakdown of AZA and 6-MP in the human body, see *id.* col. 4, ll. 55-65; *id.* col. 5, ll. 17-39, the importance of the resulting 6-TG metabolites in producing the immunosuppressive effect of the drugs, *id.* col. 1, ll. 49-51, and the techniques necessary for measuring metabolite levels in a patient's blood, *id.* col. 9, ll. 12-65, were all understood in the prior art.

According to the inventors, however, the potential toxicity of thiopurine drugs and the difficulty of deter-

mining the correct dose for each patient made many doctors reluctant to prescribe them. See '623 patent, col. 1, l. 66 to col. 2, l. 7. The methods claimed in the '623 and '302 patents reflect the discovery that, in patients with certain immune disorders, a therapeutically effective but non-toxic dose of a thiopurine drug is a dose that yields a level of 6-TG metabolites in the patient's blood between 230 and 400 picomoles (pmol) per $8x10^8$ red blood cells, and a level of 6-MMP metabolites below 7000 pmol per $8x10^8$ red blood cells. *Id.* col. 3, ll. 31-41.

The Federal Circuit characterized claims 1 and 46 of the '623 patent as representative of the claims at issue in this case. Pet. App. 4a-5a. Claim 1 states:

> 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, col. 20, ll. 10-25. Claim 46 is similar, except that it dispenses with the "administering" step and claims only the step of "determining" 6-TG or 6-MMP levels "in a subject administered a [thiopurine] drug * * *, said subject having said immune-mediated gastrointestinal disorder." *Id.* col. 23, l. 42 to col. 24, l. 18.

3. Respondent markets a thiopurine metabolites test to clinics and hospitals for use in treating patients with immune-mediated gastrointestinal disorders. Consistent with the patented method, respondent's test reports the level of 6-TG and 6-MMP metabolites in the patient's blood relative to the claimed therapeutic range of 230 to 400 pmol/8x10^8 red blood cells. Petitioners initially purchased respondent's test but, in 2004, announced that they intended to begin marketing their own thiopurine metabolites test with somewhat different upper limits for therapeutic efficacy (450 pmol 6-TG and 5700 pmol 6-MMP). Pet. App. 5a-6a, 85a. Respondent, in its capacity as exclusive licensee, brought this suit for patent infringement.[2] *Id.* at 3a, 6a.

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[2] Respondent's status as the exclusive licensee (rather than the owner) of the patents-in-suit raises an issue of prudential standing that does not appear to have been addressed in the courts below. The '623 and '302 patents are assigned to Hospital Saint-Justine in Montreal, Quebec, Canada, which has not been named as a party to the lawsuit. This Court has held that "[t]he presence of the owner of the patent as a party is indispensable * * * to give jurisdiction under the patent laws" when an exclusive licensee brings an infringement suit. *Independent Wireless Tel. Co.* v. *Radio Corp. of Am.*, 269 U.S. 459, 468 (1926). Although *Independent Wireless* arose under a previous version of the Patent Act, the Federal Circuit "continues to adhere" to its holding, requiring that the patent owner be joined as a plaintiff unless the patent owner has assigned "all substantial rights under the patent" to the exclusive licensee and has thereby rendered the licensee "the effective 'patentee' under 35 U.S.C. 281." *Prima Tek II, L.L.C.* v. *A-Roo Co.*, 222

The district court granted partial summary judgment in respondent's favor on the issue of infringement. Pet. App. 115a; see *id.* at 84a-116a. The court construed the phrase "indicates a need" in the patents' "wherein" clauses to require that "when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required." *Id.* at 109a. Finding that the thresholds for toxicity in petitioners' test were sufficiently close to those disclosed in the patents, *id.* at 113a-114a, the district court concluded that petitioners' test "literally infringes all elements of the patents-in-suit," *id.* at 115a.

Petitioners subsequently filed a motion for summary judgment of invalidity under 35 U.S.C. 101. The district court granted the motion. Pet. App. 50a-83a. In so ruling, the court clarified its earlier interpretation of the "wherein" clauses in the disputed claims, construing the phrase "indicates a need" more broadly than respondent itself had urged. Respondent had contended that the patents required an affirmative written or oral warning to a physician about the treatment implications of the metabolite levels. 04-CV-1200 Resp. Opp. to MSJ at 18, 21 (S.D. Cal. Feb. 28, 2007); see Pet. App. 63a. The court rejected that construction, concluding that "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Ibid.*

The district court then declared the claims invalid under Section 101. Pet. App. 83a. The court held that "the patents-in-suit recite a natural phenomenon—the correlations between thiopurine drug metabolite levels

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F.3d 1372, 1377 (2000). Whether the patent owner here has assigned "all substantial rights" to respondent depends on the specific terms of the license agreement between respondent and the Hospital, which is not part of the record below.

and therapeutic efficacy and/or toxicity—and the claims 'wholly pre-empt' use of said correlations." *Ibid.* The court characterized the "administering" and "determining" steps of the claims as "merely necessary data-gathering steps for any use of the correlations," *id.* at 61a, and it observed that the efficacy of particular metabolite concentrations "results from a natural body process," *id.* at 66a. The court held that the patents impermissibly preempt that "natural" relationship because "the only practical use of the correlation is in drug treatment" and "anyone seeking to employ the correlation must conduct the only active steps recited in the claims." *Id.* at 75a.

4. The court of appeals reversed. Pet. App. 25a-49a. The court applied its then-exclusive "machine-or-transformation" test, under which a process is patent-eligible subject matter if it (1) "is tied to a particular machine or apparatus," or (2) "transforms a particular article into a different state or thing." *Id.* at 33a-34a (quoting *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008) (en banc), aff'd on other grounds, 130 S. Ct. 3218 (2010)). The court held that the claims in the '623 and '302 patents "squarely fall within the realm of patentable subject matter" because, *inter alia*, they involve the administration of a drug to transform the patient's body chemistry for a concrete and useful end. *Id.* at 40a; see *id.* at 39a-42a. The court cautioned that "the only issue" before it was "whether the claims meet the requirements of § 101," and that respondent's appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth." *Id.* at 39a.

Petitioners filed a petition for a writ of certiorari (No. 09-490). While that petition was pending, this Court issued its decision in *Bilski* v. *Kappos*, 130

S. Ct. 3218 (2010), which held that the machine-or-transformation test is not the sole test for determining the patent-eligibility of processes, *id.* at 3227. The Court then granted the petition in No. 09-490, vacated the court of appeals' judgment, and remanded for reconsideration in light of *Bilski*. 130 S. Ct. 3543 (2010).

5. The court of appeals again reversed the district court's judgment of invalidity and remanded for further proceedings. Pet. App. 1a-23a. Noting that this Court's decision in *Bilski* did not "dictate[] a wholly different analysis or a different result on remand," *id.* at 14a, the court reiterated its conclusion that respondent's patents are directed to transformative methods of altering a patient's body chemistry with specific drugs, *id.* at 16a-18a, and do not "merely claim[] natural correlations and data-gathering steps," *id.* at 16a. Although the court agreed with petitioners that the final "wherein" clauses "are mental steps and thus not patent-eligible per se," *id.* at 21a, it explained that "[a] subsequent mental step does not, by itself, negate the transformative nature of prior steps," *ibid.*

SUMMARY OF ARGUMENT

The court of appeals correctly held that respondent's patents are directed to patent-eligible subject matter —that is, subject matter that *could* be protected under the Patent Act if the "conditions and requirements" of Title 35 were otherwise satisfied. 35 U.S.C. 101. Petitioners have raised powerful arguments against affording patent protection to respondent's process. Properly conceived, however, petitioners' objections arise not under Section 101, but under the novelty and nonobviousness requirements of 35 U.S.C. 102 and 103. Al-

though the claims are likely invalid under those provisions, the claims describe patent-*eligible* subject matter.

I. A. The disputed claims describe a transformative physical process of (i) administering a man-made drug to a patient and (ii) determining from the concentration of certain metabolic byproducts in the patient's bloodstream whether the patient has received a therapeutically safe and effective dose. That is a classic patent-eligible process: it recites a series of acts, performed in the physical world, that transforms the subject of the process (the body chemistry of the patient) to achieve a useful result. The fact that the relevant physical transformation occurs within the human body does not cast doubt on the patent-eligibility of respondent's process, since the patent laws have long been understood to encompass improved methods of treating patients to alleviate medical disorders. Petitioners' suggestion (Pet. Br. 35-36) that the "administering" and "determining" steps may be ignored because they were well known in the prior art disregards this Court's repeated admonitions that the novelty of a claimed process is irrelevant to the Section 101 inquiry.

B. Contrary to petitioners' contention, respondent's claimed methods do not impermissibly preempt a "natural biological phenomenon" (Pet. Br. 23). First, the correlations at issue here are not "laws of nature," "physical phenomena," or "abstract ideas" in the sense in which those terms have been used in this Court's decisions. Thiopurine drugs are the synthetic products of human ingenuity: neither azathioprine nor 6-mercaptopurine nor any of their active metabolites occurs naturally in the human body, or indeed anywhere else in nature. The reaction of the human body to thiopurine drugs and their metabolites is a "natural"

correlation only in the sense that all drugs depend on the natural processes of the human body for their therapeutic effect. To treat that fact as a basis for denying patent protection would severely disrupt the operation of the patent laws.

Second, the claims do not preempt all practical applications of the relationship between thiopurine drugs and human health. If the allegedly "natural" correlation is described at an appropriately high level of generality (*e.g.*, "when thiopurine drugs are administered, the resulting metabolite levels in the patient's blood correlate with patient health"), there remain substantial opportunities to derive practical value from knowledge of that relationship without infringing respondent's patents. Petitioners' preemption claim is plausible only if the relevant correlation is described at a very fine degree of particularity. But because every useful invention could be described as exploiting a correlation between the attributes of the invention and some desired result, that approach would exacerbate the difficulties caused by treating the link between thiopurine metabolite levels and human health as a "law of nature."

II. Petitioners' fundamental objection to the disputed patent claims is that a doctor's mere mental inference, made at the conclusion of the processes described in the claims, is the only step that distinguishes the claimed processes from the prior art. See, *e.g.*, Pet. Br. 19, 24, 33-34. Although that fact does not render the claims invalid under Section 101, petitioners' argument has considerably more force under 35 U.S.C. 102 and 103, which require that a patentable invention be both novel and non-obvious. To be patentable over the prior art, a claimed process must recite new or different steps that alter what was done before. The "administering" and

"determining" steps of respondent's claimed processes were known in the prior art, however, and the "wherein" clauses merely describe the inferences a doctor could or should draw once those steps are completed. For purposes of patentability under Sections 102 and 103, those inferences cannot distinguish respondent's claimed processes from the prior art.

ARGUMENT

Petitioners contend that the claims at issue are invalid under 35 U.S.C. 101 because the physical processes they recite (*i.e.*, the administration of specified drugs and the determination of the patient's metabolite levels) have been "familiar to physicians for decades." Pet. Br. 36. Petitioners' ultimate conclusion that the claims are invalid appears to be correct. Contrary to petitioners' argument, however, the barrier to patentability is imposed not by Section 101 but by 35 U.S.C. 102 and 103, which require that a patentable invention reflect a novel and non-obvious advance over the prior art. Invalidation of the patents under Section 101, by contrast, could have untoward implications for future cases involving process patents that *do* satisfy Sections 102 and 103. Section 101 is, by design, a "coarse filter." PTO, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of Bilski v. Kappos*, 75 Fed. Reg. 43,922, 43,926 (July 27, 2010). The remaining provisions of the Patent Act permit the nuanced, fact-intensive distinctions necessary to separate patentable from unpatentable inventions.

The judgment of the court of appeals, which addressed only Section 101, therefore should be affirmed. On remand, the courts below can consider the application of Sections 102 and 103 (to the extent petitioners

have properly preserved challenges under those provisions), together with any other challenges petitioners may assert.

I. THE CLAIMED METHODS ARE PATENT-ELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. 101.

"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 therefor, subject to the conditions and requirements of this title." 35 U.S.C. 101. Section 101 marks the "threshold" of the patent system and "defines the subject matter that may be patented." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010). Congress purposefully cast the provision "in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980); see *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130-131 (2001) (*J.E.M. Ag Supply*).

This Court has recognized "three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). These are the "basic tools of scientific and technological work," *Gottschalk* v. *Benson*, 409 U.S. 63, 67-68 (1972), "free to all men and reserved exclusively to none," *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (*Funk Bros.*). Those principles forbid two different but related types of patents.

First, a patent that expressly claims a law of nature, physical phenomenon, or abstract idea is invalid, no matter how important the discovery. Thus, "Einstein could not patent his celebrated law that $E=mc^2$; nor could

Newton have patented the law of gravity." *Chakrabarty*, 447 U.S. at 309. That conclusion follows directly from the text of Section 101, since neither the law that $E=mc^2$ nor the law of gravity is a "process, machine, manufacture, or composition of matter." 35 U.S.C. 101. Second, a patent that ostensibly claims patent-eligible subject matter, such as a machine or process, is nonetheless invalid if, in "practical effect," the patent would "wholly pre-empt" the public's access to unpatentable subject matter and operate as "a patent on the [idea or phenomenon] itself." *Benson*, 409 U.S. at 71-72. But if an inventor claims a "process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing)," the mere fact that the invention exploits a law of nature or physical phenomenon—as all human endeavors must at some level—does not disqualify it under Section 101. *Diamond* v. *Diehr*, 450 U.S. 175, 192 (1981).

A. The Claims At Issue Here Recite A Patent-Eligible "Process"

1. A patent-eligible "process," in this Court's traditional formulation, "is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing." *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877); see *Diehr*, 450 U.S. at 183-184; *Benson*, 409 U.S. at 70. Although the Court recently clarified that this definition "was not intended to be an exhaustive or exclusive test," the Court reaffirmed that the transformative nature of a claimed method "is a useful and important clue, an investigative tool," for determining eligibility under

Section 101. *Bilski*, 130 S. Ct. at 3226-3227; see *id.* at 3232 (Stevens, J., concurring in the judgment) (noting that "the entire Court agrees" that "the machine-or-transformation test is reliable in most cases").

Claim 1 of the '623 patent recites a method comprising two affirmative steps: (1) "*administering* a drug providing 6-thioguanine to a subject," and (2) "*determining* the level of 6-thioguanine in said subject." Pet. App. 4a. Those steps describe a patent-eligible process under Section 101. The claim recites a series of acts in the physical world that achieve a useful end (treatment of auto-immune disorders) by transforming the body chemistry of the patient. As the process is performed, chemicals not naturally found in the human body (AZA and 6-MP) are combined (metabolized) with chemicals already in the body in order to interfere with other, undesired chemical reactions (formation of lymphocytes). The mixing of chemical substances for a useful result is a quintessential patent-eligible process. See, *e.g.*, *Tilghman* v. *Proctor*, 102 U.S. 707, 728 (1881) ("The mixing of certain substances together, or the heating of a substance to a certain temperature, is a process."). The "determining" step likewise involves the manipulation of a physical substance (the blood or tissue sample on which the metabolite test is performed). See Pet. App. 18a-19a; '623 patent, col. 9, l. 12 to col. 10, l. 14.

The "wherein" clauses—which the district court construed to require that the doctor "be warned that an adjustment in dosage may be required," Pet. App. 62a —do not diminish the transformative nature of the process as a whole. Those clauses describe the medical significance of the metabolic byproducts detected in the patient's blood after the transformations caused by the first step of the process. Although the "wherein"

clauses do not distinguish respondent's process from the prior art for purposes of 35 U.S.C. 102 and 103, see pp. 26-30, *infra*, they do not negate, and indeed are premised upon, the transformation of the patient's body chemistry that the administering step entails.

2. The fact that the relevant transformation takes place within the human body does not cast doubt on the patent-eligibility of respondent's claimed process. Methods of practicing the medical arts have long been viewed as "eligible to receive the protection of our patent laws." *Diehr*, 450 U.S. at 184. Shortly after the enactment of the 1952 Patent Act, for example, the Patent Office Board of Appeals (Board) upheld the patent-eligibility of a method of injecting medicine into the human body using a liquid pressure jet. See *Ex parte Scherer*, 103 U.S.P.Q. (BNA) 107 (Pat. Office Bd. App. 1954). Observing that "[t]he method claimed is of a character which would normally be regarded as within the field of patentable subject matter," *id.* at 109, the Board explained that "[c]laims involving treatment of the human body have been allowed on appeal" and that "[t]here is nothing in the patent statute which categorically excludes such methods," *id.* at 109-110. Indeed, as early as 1891 this Court considered a patent on a surgical method for preparing the root of a decayed tooth to receive an artificial crown. *International Tooth Crown Co.* v. *Gaylord*, 140 U.S. 55, 64 (1891). Although the Court rejected the patent for lack of novelty over the prior art, it did not suggest that methods of dental surgery were ineligible for patent protection. See *ibid.*[3]

[3] The Commissioner of Patents declared in *Ex parte Brinkerhoff* that "[t]he methods or modes of treatment of physicians of certain diseases are not patentable." 24 Comm'r Manuscript Dec. 349 (July 5, 1883), *reprinted in* 27 J. Pat. Off. Soc'y 797 (1945). The rationale for

Methods of treating patients are now an integral part of the examination work of the PTO. According to agency databases, the PTO has granted more than 150,000 patents since 1952 that include at least one such claim. Congress has recognized that longstanding practice, establishing statutory limits on the remedies for infringement available against "medical practitioner[s]" with respect to certain medical procedures. 35 U.S.C. 287(c); cf. *Bilski*, 130 S. Ct. at 3228-3229 (construing Section 101 in light of Congress's enactment of a special defense to infringement of business-method patents in 35 U.S.C. 273). Respondent's claimed method for treating auto-immune disorders with thiopurine drugs is thus well within the accepted scope of patent-eligible subject matter.

3. Petitioners contend that, in analyzing the patent-eligibility of the claims under Section 101, the Court should disregard the "administering" and "determining" steps because those steps are "[w]ell-known" and have been "familiar to physicians for decades." Pet. Br. 36. In petitioners' view, the Section 101 inquiry should focus on the only alleged point of novelty in the patents: the specific concentration of thiopurine metabolites that correlates with patient health. See *id.* at 33-34.

Although many doctrines in patent law focus on an inventor's contribution over the prior art, this Court has specifically disapproved that mode of analysis in answering the threshold question of subject-matter eligibility

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that decision, however, was not a legal judgment that such methods were ineligible subject matter, but an empirical judgment that medical processes could not reliably produce consistent results. See 27 J. Pat. Off. Soc'y at 798. As medical science improved, the Patent Office gradually retreated from *Brinkerhoff*, eventually overruling it in 1954. See *Ex parte Scherer*, 103 U.S.P.Q. (BNA) at 110.

under 35 U.S.C. 101. The question "whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter." *Diehr*, 450 U.S. at 190 (internal quotation marks and citation omitted); see *id.* at 193 n.15. Although this Court at one time appeared to endorse petitioners' analytical approach, see *Parker* v. *Flook*, 437 U.S. 584, 591-594 (1978), it subsequently clarified that, for Section 101 purposes, "[i]t is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188-189. The Court recently reaffirmed that principle in *Bilski*, explaining that *Diehr* "established a limitation on the principles articulated in * * * *Flook*" by "emphasiz[ing] the need to consider the invention as a whole" in performing the Section 101 inquiry. *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188). The fact that the only physical steps claimed in respondent's patents were known in the prior art may well render those claims invalid under other provisions of the Patent Act, see pp. 26-30, *infra*, but it has no bearing on the method's patent-eligibility under Section 101.

B. The Claims Do Not Preempt All Practical Uses Of A Law of Nature or Physical Phenomenon

Petitioners contend that the disputed claims are invalid under Section 101 because they impermissibly preempt all practical applications of a law of nature or physical phenomenon—specifically, "the biological correlation between metabolite levels and health" (Pet. Br. 33). That contention fails for two reasons. First, the correlation is not a "law of nature" or "physical phenomenon" in the relevant sense because it exists only as the result of human intervention. Second, the claimed methods do

not preempt all practical uses of the relationship between metabolite levels and human health, at least if the correlation is described at an appropriately high level of generality.

1. a. The essential premise of petitioners' preemption argument is that the relationship between the administration of thiopurine drugs and the health of the patient—and, in particular, the concentration of 6-TG and 6-MMP metabolites that correlates with a therapeutic dose—is an unpatentable natural law. That premise is wrong. Neither azathioprine nor 6-mercaptopurine nor any of their active metabolites occurs naturally in the human body, or indeed anywhere else. Thiopurine drugs are the products of human industry, invented and patented more than 50 years ago.[4] See United States Patent Nos. 2,697,709 (1954) (claiming 6-MP and methods of its chemical synthesis, and noting its medical utility), 3,056,785 (1962) (same, AZA).

To be sure, thiopurine drugs depend for their therapeutic effect on the natural metabolic processes of the human body. The efficacy of *all* pharmaceutical compounds, however, depends on the body's natural reaction to artificial stimuli. More broadly, as the court of appeals observed, "quite literally every transformation of

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[4] One patented method of synthesizing 6-MP, for example, was as follows:

> A mixture of 18.5 g. hypoxanthine and 80 g. of phosphorus pentasulfide in 500 ml. of tetralin was heated at 200° for eight hours. The mixture was cooled and filtered. The solid residue, after being washed with petroleum ether and dried at room temperature, was boiled with 2 liters of water. The hot solution was filtered and the pH adjusted to 5 with ammonium hydroxide. Dark yellow crystals of 6-mercaptopurine hydrate precipitated on standing (12 g.).

United States Patent No. 2,697,709, col. 2, ll. 71-79 (1954).

physical matter can be described as occurring according to natural processes and natural law." Pet. App. 17a; cf. *Funk Bros.*, 333 U.S. at 135 (Frankfurter, J., concurring) ("Everything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature.'"). The utility of every invention turns on its ability to produce a predictable chain of reactions leading to the desired result. If the "natural" character of that link were sufficient to trigger the "law of nature" exception to patent-eligibility under Section 101, the exception would swallow the rule.

b. It is therefore essential to apply the judicially crafted "law of nature" and "physical phenomenon" exceptions to Section 101 in a restrained manner and with an eye toward their animating purposes. This Court has applied those exceptions sparingly, and only to distinguish the pre-existing materials and principles of nature, to which all persons enjoy equal claim as the "basic tools of scientific and technological work," *Benson*, 409 U.S. at 67, from useful applications of those materials and principles, which may be the subject of a patent if the requirements of the patent laws are satisfied. 35 U.S.C. 101; see, *e.g.*, *Chakrabarty*, 447 U.S. at 313 (explaining that "the relevant distinction" under Section 101 is "between products of nature * * * and human-made inventions"); see also *J.E.M. Ag Supply*, 534 U.S. at 130.

The Court has thus affirmed the patent-eligibility of plants and bacteria that have been altered in useful ways through human ingenuity. In *Chakrabarty*, for example, the Court held that an otherwise normal bacterium that had been genetically altered to metabolize multiple components of crude oil was patent-eligible subject matter. The Court explained that the patentee's

discovery was "not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101." 447 U.S. at 310. Similarly, the Court held in *J.E.M. Ag Supply* that new varieties of corn created through the cross-breeding of plants selected by mankind for their desirable characteristics were eligible for protection under Section 101. 534 U.S. at 128, 145.

On the other hand, the Court has held that the "handiwork of nature" is unpatentable when it remains materially unaltered by mankind. *Funk Bros.*, 333 U.S. at 131. The Court likewise has indicated that patent-eligibility does not extend to "manifestations of laws of nature" such as "the heat of the sun, electricity, or the qualities of metals," *id.* at 130 (citing *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1853)), or "a new mineral discovered in the earth or a new plant found in the wild," *Chakrabarty*, 447 U.S. at 309.

The reaction of the human body to thiopurine drugs is not an unaltered "law of nature" or "physical phenomenon" in the relevant sense. Unlike the heat of the sun or the inherent qualities of metals, the correlation between 6-thiopurine metabolite concentrations and patient health exists *because* of human ingenuity, not antecedent to it. A patent directed to a physical phenomenon of that kind is not invalid under Section 101.

2. As framed by petitioners, the question presented in this case assumes that the disputed claims in the '623 and '302 patents "cover[] observed correlations between blood test results and patient health" and "effectively preempt[] all uses of the naturally occurring correlations." Pet. i. Even apart from the fact that the relevant "correlations" are not "naturally occurring," see pp. 18-20, *supra*, petitioners' preemption argument is plausible only if those correlations are described at a very

fine degree of particularity. That approach would exacerbate the problems caused by treating the human body's response to a foreign substance as a "law of nature" for purposes of the Section 101 exception.

a. The correlations implicated by the disputed patent claims could be described at a relatively high level of generality, *e.g.*, "when thiopurine drugs are administered, the resulting metabolite levels in the patient's blood correlate with patient health." Petitioners could not reasonably contend that respondent's patents preempt substantially all practical applications of that general insight. Thiopurine drugs have useful medical applications entirely apart from the treatment of the auto-immune disorders discussed in the '623 and '302 patents.

For example, physicians have used AZA for decades to suppress the immune rejection of kidney, heart, and other organ transplants. See *Medical Toxicology* 1042; Sahasranaman 754. Respondent's patents specifically exclude certain related uses of thiopurine drugs from the scope of the claimed methods. See '623 patent, col. 15, ll. 14-17 (excluding "diseases resulting from a graft versus host response" from the scope of the patent); '302 patent, col. 15, ll. 22-24 (same). Although the patents do not explain that exclusion, it likely reflects the inventors' awareness that the standard recommended dosages of AZA for organ-transplant patients—and thus the metabolite concentrations that correlate with patient health in that context—are much higher than those recommended for the treatment of auto-immune disorders. See *Medical Toxicology* 1042. In addition, 6-TG metabolites have important medical applications wholly unrelated to their immunosuppressive benefits, such as in the treatment of breast cancer. See, *e.g.*, Natalia Issaeva et al., *6-Thioguanine Selectively Kills BRCA2-Defective*

Tumors and Overcomes PARP Inhibitor Resistance, 70 Cancer Res. 6268 (2010) (discussing the utility of 6-TG metabolites in disrupting certain breast cancers). None of these applications of the relationship between 6-TG metabolites and patient health would infringe respondent's claims.

Even as to auto-immune disorders, moreover, there is no reason to believe that the claims encompass every practical application of the general relationship between thiopurine metabolite levels and therapeutic efficacy. For example, one study found that Crohn's disease patients may comfortably tolerate much higher 6-TG metabolite concentrations than those disclosed in the patents when the thiopurine drug that is administered is not AZA or 6-MP but tioguanine, a close chemical cousin that is likewise metabolized into 6-TG in the body. See K.R. Herrlinger et al., *Thioguanine-Nucleotides Do Not Predict Efficacy of Tioguanine in Crohn's Disease*, 19 Alimentary Pharmacology & Therapeutics 1269, 1271-1272, 1274 (2004) (reporting therapeutic 6-TG metabolite levels as high as 1241 pmol/$8x10^8$ red blood cells when using tioguanine, a concentration "much higher than described under therapy with standard thiopurines"). Thus, even if the general relationship between 6-TG metabolite levels and patient health were viewed as a "law of nature," respondent's patents would not preempt substantially all practical uses of that correlation.

b. Alternatively, petitioners could describe the relevant correlations in terms that essentially track the language of the patent, *e.g.*, "when thiopurine drugs are administered, 6-TG metabolite levels less than about 230 pmol per $8x10^8$ red blood cells correlate with insufficient efficacy in treating auto-immune disorders, while levels greater than about 400 pmol per $8x10^8$ red blood cells

correlate with undue risk of toxicity, and levels between those two numbers correlate with an appropriate balance between effectiveness and safety." If the correlations are described at that level of particularity, respondent's patents may preempt substantially all of their practical applications. Although the "administering" and "determining" steps ensure that the claims are not infringed by pure thought unaccompanied by action, those steps are essential prerequisites to most if not all practical applications of the specific numerical relationship described.

To allow "laws of nature" to be defined at that level of particularity would greatly exacerbate the problems caused by treating the body's response to synthetic drugs as a "natural" phenomenon. For any useful invention—*i.e.*, any invention that predictably produces beneficial results—the link between the precise characteristics of the invention and the desired results could be described, under that approach, as a natural correlation. And even the most narrowly drafted patent wholly preempts activity falling within its scope. To be sure, a patent could not be issued on the correlation itself (regardless of the level of specificity at which it was defined) because a correlation is not a "process, machine, manufacture, or composition of matter." 35 U.S.C. 101. But where, as here, a patent claims a transformative method that accords with established understandings of the statutory term "process" (see pp. 13-16, *supra*), invalidation under the "law of nature" exception should be reserved for very unusual circumstances.

In *Diehr*, for example, the Court held that the patent holders' claimed method of curing rubber, which relied on a pre-existing mathematical formula (the Arrhenius equation) to determine more precisely when the curing

press should be opened, was a patent-eligible process. See 450 U.S. at 177-179, 185-191. The Court explained, *inter alia*, that the patentees did "not seek to pre-empt the use of [the] equation," but instead sought "only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* at 187. The invention in *Diehr* might have been said to reflect a correlation between use of the patentees' innovative technique and an increased likelihood of producing properly cured rubber. See *id.* at 178. But the Court's decision in *Diehr* is inconsistent with any suggestion that a patent can be held invalid on the ground that it preempts a correlation stated at that level of specificity.[5]

3. Petitioners rely (Br. 36-37) on Justice Breyer's separate opinion in *Laboratory Corp. of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) (*LabCorp*). *LabCorp* involved a method of diagnosing certain vitamin deficiencies by measuring the level of homocysteine, an amino acid, present in a patient's body fluid; an elevated homocysteine level indicated a deficiency of folate or cobalamin. See *id.* at 125 (Breyer, J., dissenting from dismissal of the writ). Based on the limited record that was before the Court, the government argued that the claim in *LabCorp* appeared to encompass all substantial practical applica-

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[5] This Court's prior discussions of the "law of nature" exception have referred to natural laws that are relatively broad and fundamental. For example, the Court's use of the "law that $E=mc^2$" and the "law of gravity" as examples of unpatentable laws of nature, *Chakrabarty*, 447 U.S. at 309, suggests that the exception encompasses fundamental natural principles whose reservation for the exclusive use of a single patentee would cordon off large spheres of human endeavor. See also *Benson*, 409 U.S. at 68.

tions of a preexisting natural phenomenon. See U.S. Amicus Br. at 24, *LabCorp*, *supra* (No. 04-607).[6]

In both of the respects discussed above, the process claimed in this case is unlike the method at issue in *LabCorp*. First, homocysteine is naturally present in the body, and its relationship to folate and cobalamin deficiencies exists wholly apart from human intervention. By contrast, 6-TG metabolites are present in the bodies only of those persons who have been administered specific synthetic drugs. The correlation between homocysteine levels and folate/cobalamin deficiencies is thus a "natural" relationship in a way that the correlation between thiopurine metabolite levels and patient health is not.[7]

Second, the claim at issue in *LabCorp* appeared to encompass substantially all practical applications of even the very general understanding that an "elevated level of total homocysteine" suggests "a deficiency of cobalamin or folate." See 548 U.S. at 129 (Breyer, J., dissenting from dismissal of the writ) (citation omitted). The claim did not exclude any category of persons whose

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[6] The Court in *LabCorp* ultimately dismissed the writ of certiorari without deciding the validity of the claim under Section 101. See 548 U.S. at 125.

[7] Petitioners contend that this distinction is immaterial because respondent "did not invent" thiopurine drugs. Pet. Br. 37 n.7. But that objection misses the point: regardless of who first invented them, thiopurine metabolites (unlike homocysteine) do not occur in nature. Their relationship to human health is therefore not a "law of nature" in the relevant sense. And while processes involving the administration of "natural promoters" of biological changes may be patent-eligible in some circumstances (for example, injecting a patient with a natural substance not normally found in the human body), see *id.* at 38 n.7, the fact that respondent's patents use synthetic chemicals only underscores the error of petitioners' reliance on Section 101.

homocysteine levels had been tested, nor did it specify what level of homocysteine would be considered "elevated." Respondent's patents, by contrast, specifically exclude patients who have received thiopurine drugs (and thus have 6-TG metabolites in their bodies) to suppress certain immune responses to organ transplants. And because respondent's patents identify specific numeric ranges as reflecting a preferred balance between therapeutic effectiveness and avoidance of toxicity, they appear not to be infringed when doctors (after performing the "administering" and "determining" steps) consider the general relationship between metabolite levels and health but rely on substantially different numbers as defining the optimal ranges. See pp. 21-23, *supra*.

II. THE DISPUTED CLAIMS IN THE '623 AND '302 PATENTS ARE LIKELY INVALID UNDER 35 U.S.C. 102 OR 103

For the foregoing reasons, respondent's claims pass the "threshold test" of the patent system because they define a patent-eligible "process" that does not preempt any "law[] of nature" as the Court's Section 101 decisions have used that term. *Bilski*, 130 S. Ct. at 3225 (citation omitted). It does not follow, however, that the claims are valid. Petitioners' fundamental objection is that respondent's claimed process differs from the prior art only with respect to the mental inference a doctor may draw after the "administering" and "determining" steps have been completed. See, *e.g.*, Pet. Br. 19, 24, 33-34. Although that similarity to the prior art is irrelevant to the Section 101 inquiry, it would likely warrant invalidation of the claims under 35 U.S.C. 102 or 103.

Although petitioners attribute to the Federal Circuit the conclusion that the disputed patents comply with "federal patent law," Pet. Br. 22, the court of appeals

was careful to disavow that broad holding. The court explained that "the only issue" before it was "whether the claims meet the requirements of § 101," and that the appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth." Pet. App. 39a. This Court should not resolve such questions in the first instance. The Court's analysis of the Section 101 question, however, should be informed by an understanding of the way in which other Patent Act provisions address petitioners' central objection to the '623 and '302 patents.

A. Section 102 provides that a person is not entitled to a patent if, *inter alia*, "the invention was known or used by others in this country * * * before the invention thereof by the applicant," or if the applicant "did not himself invent the subject matter sought to be patented." 35 U.S.C. 102(a) and (f). Section 103 withholds patent protection for inventions that, while novel, would have been obvious to a person skilled in the art at the time the invention was made. 35 U.S.C. 103(a). Here, the patents themselves make clear that the "administering" and "determining" steps of the disputed claims were part of the prior art, and that the inventors' only asserted innovation is the specific metabolite ranges cited in the "wherein" clauses of the claims. See, *e.g.*, '623 patent, col. 1, ll. 41-49, 66-67; *id.* col. 2, ll. 1-13; *id.* col. 9, ll. 12-18.

A patent applicant cannot, however, avoid a rejection under Section 102 or 103 merely by appending a purely mental step or inference to a process that is otherwise known in (or obvious in light of) the prior art. A "process" is a series of steps for achieving a useful result in the physical world. See, *e.g.*, *Cochrane*, 94 U.S. at 788. Here, the only affirmative steps described in the patent are (1) administering thiopurine drugs, and (2) deter-

mining metabolite levels. The district court construed the "wherein" clauses to require a kind of passive inference: the doctor must "be warned" of the medical significance of the metabolite levels. Pet. App. 62a. That is not a continuation of the process to be performed, but a description of how a doctor should interpret the result.

Such medical knowledge may be new, and it may be valuable. But identifying a new way in which the results of a prior-art process may be understood, or a new benefit that the pre-existing process may help its users to realize, does not create a new "process" that is entitled to separate patent protection. See *General Elec. Co.* v. *Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect.").[8] Rather, to be patentable over the prior art, a process claim must recite a series of steps in the physical world that differs from any series of steps that was previously known. Although a patent-eligible process may involve a "new use of a known process," 35 U.S.C. 100(b), as when a pre-existing process is incorporated into a new, larger series of steps, it does not satisfy Section 102 or 103 merely to identify new and useful inferences from the prior art. Because the "wherein" clauses of respondent's claims do not recite any physical step to be performed by a doctor (or anyone else), they add no

[8] This does not mean that every process claim that recites a mental step is unpatentable. Claims that recite concrete processes with a "decision tree" structure (*e.g.*, "Perform steps A and B, and then do either C or D, depending on the results of A and B.") are both common and acceptable. In that sort of process, the mental step affects the physical steps to be performed. But the mere recitation of a mental inference at the *end* of a claimed process—in effect, a guide to interpreting the results—does not distinguish the process from the prior art.

patentable weight to the "administering" and "determining" steps.

That conclusion follows *a fortiori* from patent law's "printed matter" doctrine, under which the mere addition of novel printed matter to a product, such as instructions for using a device, does not add patentable weight. See, *e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004).[9] If the district court had accepted respondent's argument that the "wherein" clauses require the laboratory performing the metabolite test to provide an explicit written or oral warning to the doctor, see pp. 6-7, *supra*, the PTO would have treated the content of any printed warning as irrelevant to patentability under the printed-matter doctrine. Likewise, if the claims had instead required the use of a medicine bottle for thiopurine drugs with the recommended metabolite range printed on the label, the PTO would have afforded the content of the label no patentable weight. If such explicit written statements of the optimal metabolite range would not have distinguished the claimed process from

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[9] This doctrine is the reason a newly published book is not patentable, even though a book (a man-made assembly of paper, glue, and ink) is a patent-eligible "manufacture" within the meaning of Section 101. Although differences between the printed matter contained in different books are obviously crucial for other legal (*e.g.*, copyright) and practical (*e.g.*, reading) purposes, they are irrelevant in the eyes of the patent law. Thus, while one who devises a new method of binding books might be entitled to a patent, the creator of new written content is not. Similarly, a process is not novel if it differs from the prior art only by including "wherein" clauses reciting the substantive medical significance of the results of the prior art process. See *King Pharms, Inc.* v. *Eon Labs, Inc.*, 616 F.3d 1267, 1278 (Fed. Cir. 2010) (method that was otherwise known in the prior art did not become patentable by adding the step of "informing" someone of an inherent property of that method because prior art method itself was unchanged).

pre-existing processes, a doctor's mental state of "be[ing] warned" (Pet. App. 62a) cannot have that effect.[10]

B. A practicing physician would use the information acquired through the "determining" step of respondent's claimed method to decide whether to adjust the patient's dosage or to maintain it at the original level. If the physician altered a patient's dosage based on the metabolite levels that the "determining" step revealed, he would presumably initiate a further "determining" step to ascertain whether the adjustment had produced the desired effect. In the world of actual medical practice, the process described in the '623 and '302 patents would thus be a part of a larger course of treatment; and that larger course of treatment might represent a meaningful (and potentially patentable) improvement over methods previously known in the art.

From a physician's standpoint, it may therefore be artificial to treat the "administering"/"determining" method claimed in the '623 and '302 patents as a discrete two-step process that culminates with the measurement of a patient's metabolite levels. The need to analyze the claims in that manner under the patent laws, however, results directly from the drafting choices made by the inventors (respondent's predecessors-in-interest). The

[10] Under the reasoning set forth above, the claim at issue in *LabCorp* appears to have been invalid under Section 102 or 103, since that claim simply appended a mental "correlating" step to an "assaying" step that was already well known in the art. See 548 U.S. at 129, 136 (Breyer, J., dissenting from dismissal of the writ). The amicus brief for the United States in *LabCorp* argued that the claim appeared to be invalid under Section 102, although the brief discussed that question in terms of the claim's potential to remove pre-existing assaying methods from the public domain. See U.S. Amicus Br. at 28-30, *LabCorp*, *supra* (No. 04-607).

inventors could have attempted to distinguish the claimed process from methods known in the prior art by drafting the claims to include concrete treatment steps (the details of which presumably would have varied depending on the results of the "determining" step). Cf. note 8, *supra*. The inventors declined to do so, however, presumably because inclusion of such steps would have made it more difficult to prove infringement.[11] Indeed, in (successfully) arguing in the district court that petitioners' tests infringed the patents, respondent relied in part on the fact that the claims do not require an actual adjustment of drug dosage. See Pet. App. 108a. Such strategic trade-offs between claim scope and the risk of invalidity are common in patent prosecution, and respondent presumably made an informed appraisal of that risk in accepting an exclusive license under the patents.

C. By the same token, it might be viewed as exalting form over substance to deny under Section 101 relief to which petitioners are likely entitled under other provisions of the Patent Act. The only role of Section 101, however, is to identify the types of subject matter that may be *eligible* for patent protection if "the conditions and requirements" of Title 35 are satisfied. 35 U.S.C. 101. It is "a dynamic provision designed to encompass

[11] Other factors influencing the patient's health, such as allergies or drug interactions, may sometimes induce a doctor not to adjust a patient's dosage even though the determined metabolite levels fall outside the optimal range as delineated in the '623 and '302 patents. And because liability for infringing a process patent generally requires proof that every step of the infringing conduct was attributable to the defendant, see 35 U.S.C. 271(a); *BMC Res., Inc.* v. *Paymentech, L.P.*, 498 F.3d 1373, 1378-1379 (Fed. Cir. 2007), adding a treatment step would make it more difficult to sue actors who do not themselves make treatment decisions.

new and unforeseen inventions." *J.E.M. Ag Supply*, 534 U.S. at 135.

The '623 and '302 patents describe a transformative method that falls squarely within the established understanding of the statutory term "process" and involves the administration of therapeutic compounds not found in nature. To hold that the method nevertheless falls outside Section 101 because its efficacy depends on the body's "natural" reaction to foreign substances would cast doubt on a host of patents for transformative medical processes that *are* novel and non-obvious. It would also exacerbate PTO's already formidable task of ensuring that more than 6500 patent examiners apply Section 101 in a predictable and consistent fashion. The remaining provisions of Title 35, which permit more nuanced factual distinctions, are the principal tools that Congress has provided for "drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not." *Graham* v. *John Deere Co.*, 383 U.S. 1, 9 (1966) (quoting Letter from Thomas Jefferson to Issac McPherson, Aug. 13, 1813, *in* 6 *Writings of Thomas Jefferson* 181 (Henry Augustine Washington ed., 1853)).

CONCLUSION

The judgment of the court of appeals reversing the district court's ruling under Section 101 should be affirmed.

Respectfully submitted.

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