IN THE

Supreme Court of the United States

LABORATORY CORPORATION OF AMERICA HOLDINGS (DOING BUSINESS AS LABCORP),
Petitioner,

v.

METABOLITE LABORATORIES, INC. AND COMPETITIVE TECHNOLOGIES, INC.,
Respondents.

On Writ of Certiorari To The United States Court of Appeals For The Federal Circuit

BRIEF FOR *AMICI CURIAE* AFFYMETRIX, INC. AND PROFESSOR JOHN H. BARTON

IN SUPPORT OF PETITIONER

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INTEREST OF AMICI CURIAE[1]

Amicus Affymetrix, Inc. is the worldwide leader in providing commercial DNA microarrays to the scientific research community. DNA microarrays are small substrates (such as specially manufactured glass chips) on which millions of different strands of DNA are arranged in an ordered manner, allowing researchers to investigate the genetic properties of humans, plants and animals. Affymetrix DNA microarrays are called GeneChip® arrays.

Since 1994, when Affymetrix introduced the first commercial DNA microarray, microarrays have revolutionized genomic research and related applications. Customers use Affymetrix's GeneChip technologies for two central applications: gene expression monitoring and DNA variation detection. Affymetrix and its customers and collaborators develop clinical applications of GeneChip technologies for diagnosing and treating disease. The value of GeneChip technology for studying complex biosystems is demonstrated by the more than 3900 peer-reviewed publications citing GeneChip technology.

As a member of the life sciences industry, Affymetrix has an interest in ensuring that patents not issue on basic laws of nature so as to impede scientific progress in analyzing DNA and gene expression. While the patent at issue in this case involves a laboratory test, a decision whether it improperly seeks exclusive rights to a natural phenomenon also has implications for patents involving genetic sequences—patents that affect the ability Affymetrix's customers to undertake

[1] Counsel for both parties have consented to the filing of this brief, and their consents have been filed with the Clerk of this Court. No counsel for either party had any role in authoring this brief, and no person other than the named *Amici* and their counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37 & 37.6.

scientific research that will advance the capacity to understand genetic phenomena and advance new medical care.

Amicus John H. Barton is Professor of Law Emeritus at Stanford University, and is an expert in the role of patents in medicine and biotechnology. He has published extensively in both the legal and the scientific literature. He was a member of the London-based Nuffield Commission on Bioethics Roundtable which produced the July 2002 report, *The Ethics of Patenting DNA*, and of the U.S. National Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy, which produced the 2004 report, *A Patent System for the 21st Century*. He has been a Visiting Scholar in the Department of Clinical Bioethics at the National Institutes of Health, supported in part by the National Human Genome Research Institute. His interest in this case is that patent law evolve in a way that serves the public interest by supporting both scientific research and medical innovation.

SUMMARY OF ARGUMENT

The question presented in this case concerns the scope of patentable subject matter under the Patent Act of 1952. The Act provides: "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 therefore, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Although the scope of patentable subject matter is thus broad, it is settled precedent that it does not extend to natural phenomena. "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

The patent claim in dispute in this litigation is claim 13 of United States Patent No. 4,940,658:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

The correlation described in this patent is a scientific fact, a law of nature, relating two phenomena in the human body. Claim 13 thus violates the settled principle that one may not patent a natural phenomenon.

In crossing over the line between patents on human invention and patents on nature itself, Claim 13 upsets the "careful balance" inherent in the patent laws that is "the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). A United States patent confers upon its owner the powerful right to exclude others from practicing whatever invention is claimed in the patent for a defined period of time. *See* 35 U.S.C. § 271 (defining infringement) and § 154 (20-year term). Such a right to exclude can also extend to the substantial equivalent of the patented invention. *See, e.g.*, *Warner-Jenkinson, Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). Such powerful rights should not be conferred upon claims on laws of nature so as to preempt the future progress of scientific research and advances in medical technology.

Allowing Claim 13 to stand would damage such future research and scientific progress. Claim 13 and others like it allow no room to design around, imitate, or improve upon the so-called "invention" of a law of nature. DNA technology

has opened up a vast array of tests based on naturally occurring biochemical mechanisms. But if claims like claim 13 are sustained, such tests will be blocked by patents on the law of nature on which they are based. This is especially harmful given the nature of modern genomic research, which focuses not on one gene or gene function at a time, but rather on complex interconnections among genes and gene functions. Such interconnections cannot be studied if portions of the larger genomic map are blocked out.

By contrast, invalidating claim 13 and reaffirming the principle set forth in *Diehr* will not disrupt or impede scientific research. Contemporary patent practice is to file many claims in a single patent, some narrow, some broad, in order to maximize exclusive rights; for example, Respondent Metabolite holds and receives royalties on many of the other 33 claims of the '658 patent apart from claim 13. Invalidating claim 13, the broadest of these claims and an attempt to push the outer limits of patentable subject matter, will not invalidate Metabolite's patent, nor discourage Metabolite's scientific research. It will simply restore the balance between natural phenomena and human-made inventions that Congress originally sought to strike in the patent laws—a balance that reflects the Constitution and has served the patent system and the progress of science very well. The decision below should be reversed or vacated.

ARGUMENT

I. CLAIM 13 IMPROPERLY REMOVES A NATURAL PHENOMENON FROM THE PUBLIC DOMAIN

A. Patentable Subject Matter Does Not Include Laws Of Nature, Natural Phenomena, Or Abstract Ideas

Congress intended the scope of patentable subject matter to be broad and inclusive, even for technologies that had yet to be imagined. The Committee Reports accompanying the

1952 Patent Act provide that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952), quoted and cited in *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

But Congress likewise established just and appropriate limits to the reach of the patent statutes. The patent laws protect only *inventive* products and processes. Thus not every discovery is necessarily patentable. A bedrock principle of United States patent law is that: "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). Accordingly:

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

Chakrabarty, 447 U.S. at 309 (*quoting Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). *See Parker v. Flook*, 437 U.S. 584, 593 n.15 (1978) ("[R]ecognition of a theretofore existing phenomenon or relationship carries with it no rights to exclude others from its enjoyment."); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").[2]

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[2] The laws of other nations and patent systems likewise preclude patenting natural phenomena and laws of nature. *See, e.g.*, European Patent Convention Article 52(2) (excluding from patentability "discoveries, scientific theories and mathematical methods'); Indian Patent Act 1970 § 3(c) (excluding from patentability "mere discovery of a scientific principle or the formulation of an abstract theory"); Japan, Examination

Whether a claimed invention is a valid subject matter for a patent under these principles has been the subject of several decisions of this Court since the 1952 Patent Act became law.[3] In several of these decisions, the Court upheld the patentability of the subject matter: In *Chakrabarty*, for example, the Court held that a human-made bacteria that exhibits characteristics different from any bacteria occurring in nature is patentable subject matter, 447 U.S. at 310. In *Diehr*, the Court held that a computerized industrial process for control of a rubber curing mold is patentable, even though the process "admittedly employs a well known mathematical equation." 450 U.S. at 187. And in *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc*., 534 U.S. 124 (2001), the Court held that newly developed plant breeds are patentable subject matter.

In several other decisions, however, the Court held the subject matter of a patent to constitute a law of nature beyond the scope of the Act. In *Parker v. Flook*, for example, the Court held that a process for monitoring chemical reactions by using a mathematical formula is not patentable. *See* 437 U.S. at 594. And in *Gottschalk v. Benson*, the Court held that a process related to converting decimal to binary numerals using a formula is not patentable. *See* 409 U.S. at 71-72.

Guidelines for Patent and Utility Model in Japan, Part II, Chapter 1 ("A law of nature as such" is "not considered to be a statutory invention.") (English translation available at Japanese Patent Office website at http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/1312-002_e.htm).

[3] The principle that one cannot patent natural phenomena is longstanding and predates the 1952 Patent Act. *See, e.g.*, *Funk Bros. Seed Co. v. Kalo Inoculant Co*., 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.").

The distinction between the two lines of cases turns on whether the patentholder seeks to preempt the underlying law of nature, precluding others from testing or observing it. As the Court noted in *Diehr*, "an *application* of a law of nature . . . to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187. The Court found such an application in *Diehr* because, in that case, the patent holders "do not seek to pre-empt the use of that equation" but "seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* In contrast, the Court in *Gottschalk* found no patentable subject matter where "the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." 409 U.S. at 72.

The distinction between the two lines of cases also turns, in the case of method claims like the one at issue in this case, on whether the patented process is transformative. In analyzing the patentability of a claimed process, both *Diehr* (which upheld a claimed process) and *Gottschalk* (which struck down a claimed process) focused on the *end result* of the process: "Transformation 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." *Diehr*, 450 U.S. at 184; *see Gottschalk*, 409 U.S. at 70.

For the reasons that follow, claim 13 should be found on the non-patentable side of this well-established line because it involves no such transformation and seeks to preempt all use by others of a basic natural phenomenon.

B. Patent Claim 13 Improperly Asserts Exclusive Rights To Test And Observe A Natural Phenomenon—Namely, That Elevated Levels Of An Amino Acid In The Blood Correlate To A Vitamin Deficiency

The claim at issue in Respondents' patent in this case, claim 13 of U.S. Patent No. 4,940,658 (the '658 patent), is directed to a natural phenomenon. Claim 13 is a method claim, seeking to patent a method of determining a vitamin deficiency by testing a sample for elevated levels of an amino acid, then noticing that the level is elevated, and then correlating that fact with a vitamin deficiency. Through creative patent drafting in the form of a process claim, claim 13 preempts the natural phenomenon by precluding all others from testing and observing this phenomenon.

To grasp how claim 13 seeks to carve out a natural phenomenon, it is useful to examine briefly its technical background: Vitamins are small, but vital compounds that assist metabolism in the human body. Many vitamins are not produced by the body but must be consumed as part of a person's diet. Metabolism is the series of chemical steps performed within the body in order to create or break down substances. For instance, proteins are formed by the amino acids combining into large chains. Each amino acid must be synthesized from building block components or consumed as part of the diet.

In the tissue of a human body, there exists a relationship between the level of a certain amino acid, homocysteine, and the level of two vitamins, B_{12} and folic acid. The amino acid homocysteine is a building block in the creation of other amino acids that are used to form proteins. The relationship between the levels of homocysteine and the vitamins exists because these two vitamins assist in the breakdown of homocysteine as part of the body's natural metabolism. It cannot be disputed that this relationship is "the handiwork of

nature" – it existed long before the inventors named in the patent did their work, and nothing these inventors did changed the relationship.

Like the discoverers of a previously unknown plant in the wild, the inventors named in the '658 patent assert that they were the first to have uncovered this natural relationship:

> "It has been discovered that elevated levels of homocysteine in body tissue correlate with decreased levels of cobalamin [vitamin B_{12}] and/or folic acid in said body tissue."

['658 Patent at col. 5, lines 64-66]. The inventors state that this discovery arose by testing the blood of 78 patients with known vitamin B_{12} deficiency and 19 patients with known folic acid deficiency for total homocysteine. ['658 Patent at col. 36, lines 26-31]. The inventors observed that elevated amounts of the amino acid correlated with the vitamin deficiency. Such basic steps of scientific inquiry—testing, observing, and drawing conclusions—can be applied to all natural phenomena.

Claim 13 seeks to exclude others from performing a two-step process:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> > *assaying* a body fluid for an elevated level of total homocysteine; and
> >
> > *correlating* an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

'658 Patent at col. 41, lines 58-65 (emphasis added). An "assay" is simply a test.[4]

The significance of this claim is that the claimed "invention" is not limited to any particular kind of assay or any assay protocol. Any test infringes. Thus, infringement of this process might occur if a doctor sends a patient's blood sample to a lab to be tested for homocysteine (and perhaps other substances), and then receives the results, notices that there is an elevated level of homocysteine, and concludes that the patient may have a vitamin deficiency. In this scenario, the doctor is a direct infringer even if the doctor had no idea how the testing was done; and the lab that performed the test is liable as an indirect infringer for inducing the doctor's infringement. One may not even test one's own blood to observe the relationship without running afoul of the claim.

Claim 13 thus allows the patent holder to own a naturally occurring phenomenon—the biochemical relationship between an amino acid and a vitamin. As the lower court said, "The correlating step is a simple conclusion that a cobalamin/folate deficiency exists *vel non* based on the assaying step." Pet. App. 18a. The correlation described in this claim is a scientific fact, a law of nature, relating two phenomena in the human body.

In contrast to the patent claim upheld in *Diehr*, there are *no* other steps in the claimed process. Claim 13 covers every substantial practical application of this law of nature. Such a

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[4] *See, e.g.*, *The Merriam Webster Dictionary* 56 (1974) ("n. 1: a test (as of gold) to determine characteristics (as weight or quality);" and "v. 2: to subject (as an ore or drug) to an assay"). Under Federal Circuit claim interpretation precedent, courts are free to consult dictionaries at any time to assist in the understanding of patent claims. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1322 (Fed. Cir. 2005) (*en banc*) ("[J]udges are free to consult dictionaries and technical treatises at any time in order to better understand the underlying technology and may also rely on dictionary definitions when construing claim terms.").

claim relating the magnitude of a measured phenomenon to a correlated phenomenon is little different from one claiming a method of estimating the risk of heart attack on the basis of measurements of blood pressure. Such a patent, like claim 13, would preempt all use of a particular law of nature.

It should be beyond dispute that patent holders may not claim they own the natural biochemical relationship between an amino acid and a vitamin. That relationship exists in every tissue in every human body and other animals and pre-exists any human invention or observation. By drafting their claims in the form of a process, the patent holders have sought to erect a fence around the relationship, depriving the public of access to observation of this natural phenomenon. But creative claim drafting by patent attorneys cannot transform otherwise unpatentable subject matter into a valid invention. *See Flook*, 437 U.S. at 590; *Diehr*, 450 U.S. at 192 ("To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection.").

By way of analogy, consider the commonly known law of nature that Force = Mass x Acceleration. One obviously may not patent this law simply by putting it into patent language: "A two-step method of determining the force on an object by measuring its mass and multiplying the mass by the object's acceleration" is a claim that would certainly be invalid. Similarly, if one were to find a plant growing in the wild in some remote area, one could not patent the plant *per se* no matter how surprising or useful the plant may be. To be sure, one might patent an innovative therapy involving the plant, or methods of extraction of useful substances from the plant, or novel compositions of matter including ingredients from the plant. But the line is drawn at patenting "nature's handiwork" –the phenomenon that already existed in nature before discovery by a person. The natural relationship

between homocysteine and vitamins is just such a phenomenon.

Claim 13 thus seeks exclude from the public domain a natural phenomenon for purposes of scientific research. In the language of *Diehr* and *Gottschalk*, the natural relationship between elevated amino acid levels and vitamin deficiency has been "pre-empted" by the patent claim. Allowing Respondent to appropriate such a phenomenon of nature as its exclusive property would require departure from this Court's long-settled precedents. For the reasons that follow, upholding claim 13 would also cause serious harm to the cause of scientific research, especially in the genomic area.

II. ALLOWING CLAIM 13 WOULD UPSET THE PATENT BALANCE CAREFULLY STRUCK BY CONGRESS AND THIS COURT AND WOULD HARM FUTURE RESEARCH AND INNOVATION IN THE LIFE SCIENCES

The Constitution requires that patents "promote the Progress of Science and useful Arts." Art. I, § 8, cl. 8. Fulfilling this constitutional purpose requires a balance between rewarding existing research and ensuring that other research may go forward freely in the future. Allowing a patentee to remove a natural phenomenon from the public sphere would thwart this constitutional purpose by impeding rather than promoting the progress of biochemical research and medical treatments. Without access to testing and observing natural phenomena, medical researchers cannot build upon the discoveries of others.

Allowing claims such as the one at issue here would block medical information based on natural, biochemical relationships from appropriate further scientific use. This impediment would be especially acute with respect to the information and phenomena that are rapidly being discovered in the field of genome analysis. Disallowing claims such as claim 13, by contrast, will cause little harm to scientific

progress because a wide range of other appropriate claims would remain available to researchers like Respondent. Thus the balance struck in *Diehr* and related cases on the scope of patentable subject matter should be preserved.

A. Existing Limitations On The Scope Of Patentable Subject Matter Reflect A Careful Balance Between Rewarding Existing Research and Ensuring Opportunity for Future Innovation

Patents are fundamentally a balance between allowing free competition and government-granted exclusive rights. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Eldred v. Ashcroft*, 537 U.S. 186, 215 (2003) (citing *Bonito Boats*, 489 U.S. at 146). *See Mazer v. Stein*, 347 U.S. 201, 219 (1954) (noting that the patent system is based upon the "conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of authors and inventors").

Patent law pervasively seeks to strike a balance between these competing interests. Some features of patent law ensure adequate returns to the large fixed costs of research and development. For example, Congress has decided upon a 20-year term for patents. *See* 35 U.S.C. § 154. And by denying an independent creation defense to patent infringement, this Court has permitted liability to attach even if a person has no knowledge of the patent. *See Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 477 (1974). Other features of patent law seek to preserve opportunities for future innovation. For example, there is a statutory safe harbor for activities that would otherwise constitute patent infringement if they are undertaken for purposes reasonably related to the development and submission of information under a federal

law that regulates drugs. 35 U.S.C. § 271(e); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (exemption applies to medical devices); *Merck KGAA v. Integra Lifesciences, Ltd*., 125 S. Ct. 2372 (2005) (exemption applies to preclinical research).

The definition of what constitutes patentable subject matter likewise reflects a balance that has been struck by Congress in section 101 of the Patent Act and by this Court in interpreting that section. This balance – which distinguishes between natural phenomena and human-made inventions – has served the United States patent system and the progress of science in the nation very well.

The key to this balance is the recognition that there are interests in promoting innovation on *both* sides of any patent. As this Court stated in a different context in *Bonito Boats*, "[f]rom their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." 489 U.S. at 146. As Justice Breyer has noted in the related context of copyright law, in ensuring a balance between preserving incentives to intellectual property holders and protecting the rights of others to develop new technologies, it is important to be sure that "the gains on the copyright swings would exceed the losses on the technology roundabouts." *Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd.*, 125 S. Ct. 2764, 2793 (2005) (Breyer, J., concurring).

Here, allowing claims like claim 13 would cause serious "losses on the technology roundabouts," upsetting the balance that Congress and this Court have long struck with respect to patenting laws of nature. By precluding scientific inquiry (*i.e.*, the ability to test, observe and conclude) into naturally occurring phenomena, claim 13 and others like it have and will remove the common tools accessible to all scientists that

allow scientific progress to be made. Invalidating claim 13, by contrast, would still allow wide berth for patenting truly transformative human inventions that add to rather than subtract from the public domain.

B. Allowing Claim 13 To Stand Would Impede Future Biomedical and Genetic Research That Depends Upon Common Access to Natural Phenomena

Science has always proceeded in an incremental way in which one discovery builds upon another. Experts in the scientific method have accordingly noted that scientific progress requires that research results be open for all to "use, attempt to replicate, and evaluate."[5] This aspect of scientific progress would be impeded if patents could extend to natural phenomena. The Council of the [United Kingdom] Royal Society recently drew a parallel implication:

> [P]ure knowledge about the physical world should not be patentable under any circumstances. That it should be freely available to all is one of the fundamental principles of the culture of science. Only by having knowledge unencumbered by property rights can the scientific community disseminate information and take science forward.[6]

Whatever the effect of the scope of patentability on scientific research in the past, however, these principles are even more important to the next generation of biomedical and genetic research. The nature of the information contained

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[5] National Research Council, A PATENT SYSTEM FOR THE 21ST CENTURY 26 (Washington: National Academies Press, 2004), citing R. Merton, THE SOCIOLOGY OF SCIENCE: THEORETICAL AND EMPIRICAL INVESTIGATIONS (University of Chicago Press, 1973).

[6] Royal Society Working Group on Intellectual Property, "Keeping Science Open: the Effects of Intellectual Property Policy on the Conduct of Science" 8 (April 2003).

within the genetic code presents new and unique incentives to try to own natural phenomena. Any holding that one may effectively own a natural biochemical relationship by excluding others from any and all testing of that relationship thus would have especially fundamental implications for future research in the field of DNA and human genetic conditions.[7]

The human genetic code is contained in 23 pairs of chromosomes, which are present in almost every cell of the human body. These chromosomes are passed on from generation to generation. The chromosomes comprise tightly wound bundles of the long, thin molecule DNA. Along its length, DNA contains a sequence of four compounds called bases. This sequence is a code that is the template for protein production in all cells. Every individual (except identical twins) has a slightly different sequence.

The biochemical relationships among an individual's DNA, the individual functional units (called "genes"), the expression of proteins, and the resulting physical manifestation of these processes in the human body are the subject of intense scientific research. Once the genetic code was discovered, researchers quickly developed tools to investigate the relationships between specific portions of DNA and their impact on the physical condition. These tools include databases of the precise sequence of human DNA, databases of differences among different persons' DNA, and testing kits that allow comparison of one person's DNA to another's.

If claim 13 were allowed to stand, all such naturally occurring biochemical relationships would be subject to

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[7] The scope of preemption is significant, for it has been estimated that approximately one-fifth of all human genes are already patented. Kyle Jensen and Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 Science 239 (2005).

ownership rights on the part of the person who discovers them. For instance, it has been discovered over the last generation of genomic medicine that mutations in a single gene may be associated with hereditary diseases or abnormalities in particular body structures. Thus, one common form of a natural relationship might be: a mutation in the DNA at point "X" is related to the physical condition "Y." Under an approach like claim 13's, the first person to discover this relationship could claim the following in a patent: a method of determining condition "Y," by testing for mutation "X" and correlating the presence of mutation "X" with condition "Y."

A claim like claim 13 might thus preclude a person from testing her own genetic code. Yet testing for a relationship between a single gene mutation and a physical condition has demonstrated medical value and may even be life saving. For example, Affymetrix's GeneChip® technologies were recently involved in path-breaking discoveries about two very serious childhood diseases observed disproportionately in the Amish population. One involved a particular type of sudden infant death syndrome; the other a set of crippling neurological diseases. Affymetrix provided a chip that enabled ready detection of the presence or absence of a large number of "SNPs" or "single nucleotide polymorphisms" in a human tissue sample. SNPs are single-base variations, places in which different persons' genes differ in just one nucleic acid. They have been mapped across the whole human genome and can be used as markers to locate the portion of the genetic code contributing to a particular disease or condition. Using Affymetrix chips, researchers' work with 21 persons over 60 days made it possible to identify the gene mutations that were correlated with a form of sudden infant death syndrome.[8] The patenting of SNPs despite their

[8] See E.G. Puffenberger et al., *Mapping of Sudden Infant Death with Dysgenesis of the Testes Syndrome (SIDDT) by a SNP Genome Scan and*

existence as natural phenomena would greatly complicate such research efforts.[9]

The impediments to genetic research if natural genetic phenomena were allowed to be patented is compounded by the fact that modern genomic research has moved past such one mutation/one function examples to explore much more complex interrelationships among genes and genetic functions.[10] Current research focuses on regulatory controls for the genetic code emphasizing that:

> Genes and gene products do not function independently, but participate in complex interconnected pathways, networks and molecular systems that, taken together, give rise to the workings of cells, tissues, organs, and organisms.[11]

Identification of TSPYL Loss of Function, 101 Proceedings of the National Academy of Sciences 11689 (2004). The similar project on the neurological disease is described in Kevin A. Strauss *et al*., *Genome-Wide SNP Arrays as a Diagnostic Tool: Clinical Description, Genetic Mapping, and Molecular Characterization of Salla Disease in an Old Order Mennonite Population*, 138A American Journal of Medical Genetics 262 (2005); *see also* Lisa Belkin, *A Doctor for the Future*, The New York Times Magazine, Nov. 6, 2005, p. 68.

[9] For just this reason, ten pharmaceutical firms, together with the Wellcome Trust, made created a consortium to obtain rights to a large number of such SNPs and to keep the use of these SNPs in the public domain. E. Masood, *Consortium Plans Free SNP Map of Human Genome*, 398 Nature 545 (1999); http://snp.cshl.org/. The pharmaceutical industry would not have had to undertake this expensive program had it been clear that SNPs, as natural phenomena, would not have been patentable.

[10] An example is the U.S. National Human Genome Research Institute's Research Roadmap. *See* Francis S. Collins *et al.*, *A Vision For The Future Of Genomics Research: A Blueprint For The Genomic Era*," 422 Nature 1 (2003).

[11] *Id*. at 4.

As a recent study by the National Research Council of the National Academy of Sciences noted, "Today systems biologists study the complex interplay of a host of genes as these genes give rise to a disease symptom, such as hypertension, or analyze hundreds of proteins in a blood sample to identify patterns that may be indicative of a particular cancer."[12] Thus "[t]he pattern of a single investigator working on a single gene or gene sequence is giving way to more multi-investigator projects entailing work on many genes or proteins simultaneously, more and more of them patented."[13]

Patents that claim the underlying natural phenomena and biochemical relationships will greatly impede this new and more complex genomic research. Unfortunately, this is not a hypothetical example. It has already occurred in at least one case -- that of the heavily criticized BRCA patents, U.S. Patents 5,693,473, 5,709,999, and 5,747,282. These patents describe mutations that contribute to susceptibility to breast cancer, and include claims that reach any method of detecting these mutations. Like claim 13 of patent '658, the operative claims in these patents are on a fact of nature. The U.S. holder of these patents has exercised its exclusivity by prohibiting others from providing the tests,[14] making it impossible for a patient to obtain a second opinion on the result,[15] and preventing other laboratories from effectively building a data base of other mutations affecting breast cancer. As the National Research Council states:

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[12] National Research Council Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH, 35 (2006, Prepublication Copy) (available at www.nap.edu/books/0309100674/html/).

[13] *Id*. at 106.

[14] *Id.* at 19.

[15] *Id*. at 111.

> the exclusive practice of any medical procedure or clinical diagnostic test is an important issue for the medical profession and raises important questions of public health and science policy. For example, the performance of a gene-based clinical test in an academic setting often generates rich databases of newly detected genetic variations that can be correlated with an array of clinical phenotypes. Such admixed medical practice and research provides important new information about the mutational repertory of specific disease-linked genes, as well as the phenotypic correlations that provide new insights into disease mechanisms and identify potential new targets for therapeutic intervention.[16]

For these reasons, there are special dangers in allowing only one laboratory exclusive rights to conduct research on a particular genetic phenomenon, such as the relation between homocysteine and cobalamin or folate, as upholding claim 13 would entail. Science will advance more rapidly, with benefits to patients, if laboratories may both compete with and collaborate with one another through common access to laws of nature.

C. Invalidating Claim 13 Would Neither Eliminate Incentives To Invest In Research Nor Disrupt The Patent System

The state of the law with respect to ownership of genetic relationships is relatively unsettled. This has resulted in a well-documented "land-grab" mentality, in which patent

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[16] *Id.* at 125. In this case, patents may already have harmed research. There are reports that the exclusive supplier of the tests has missed relevant mutations. *See* Jordan Paradise, *European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: a Case Study of the Myriad Genetics' BRCA Patent Controversy*, 59 Food & Drug L. J. 133, 147 (2004).

attorneys seek gene patents at the outer boundaries of the line between human invention and phenomena of nature.[17] This is not surprising, for without guidance about the scope of valid versus invalid subject matter, patent attorneys are obliged seek the broadest possible claims for their clients. *See Solomon v. Kimberly-Clark Corp*., 216 F.3d 1372, 1382 (Fed. Cir. 2000) (a patent attorney has a "professional responsibility . . . to assist his or her client in defining her invention to obtain, if possible, a valid patent with maximum coverage").

Just because these pressures have led patent attorneys to seek and sometimes obtain patents that stretch the boundaries of patentability into the natural realm, however, does not mean that such increased scope is necessary to advances in science. This case presents a vital opportunity for this Court to curb this pressure on the outer boundaries of patentability, and to return the balance to the baseline set by this Court in *Diehr* and related decisions.[18] In so doing, there is little danger that genetic or other biomedical research will be harmed by reduced incentives for making discoveries.

This is so for two reasons. *First*, nothing in the argument advanced by *Amici* here would impede patents in the genetic area if those patents involved more than the mere observation and recitation of a law of nature. Consistent with this Court's test in *Diehr*, *Amici* do not oppose patent claims directed to

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[17] *See* Jensen and Murray, *supra* note 7.

[18] Some guidance in this area might well be provided by developments in areas of patent law other than the scope of patentable subject matter. For example, a recent Federal Circuit decision struck down the validity of patent claims directed to short fragments of DNA sequences (called "Expressed Sequence Tags" or "ESTs") without a known function as lacking specific and substantial utility as required by the patent laws. *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005). But such approaches cannot be as systematic and useful as curtailing the "land grab" in patentable subject matter.

applications of laws of nature. Thus the scope of patentable subject matter still may legitimately extend to innovative tests, or inventive pharmaceutical compositions, or new and useful therapies, or any number of inventions in technology that researchers have yet to imagine, that add human invention to a natural phenomenon. The issue here is whether ownership rights should be able to result from the mere *discovery* of natural phenomenon.

For example, the BRCA example described above involved patent claims on a gene that provides susceptibility to breast cancer. The gene at issue is a stretch of DNA with a particular sequence that codes for a particular polypeptide called BRCA1. The 5,747,282 patent asserts ownership over DNA that codes for this polypeptide; claim 1 of that patent reads: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2."

Like claim 13 of the '658 patent involved in this case, the BCRA patent seeks to claim exclusive rights to an underlying natural relationship. Anyone with this gene has this sequence in her DNA. Like amino acids and vitamins, both DNA and the polypeptide exist naturally in the body, as does the relationship between them. In both cases, the researchers made a discovery, not an invention. Owning such a stretch of DNA thus prevents others from working with that DNA even though it occurs naturally. Simply finding the DNA, however, can readily be distinguished from inventive methods used to find the DNA, or inventive therapies and tests using the DNA. The latter would be legitimately patentable under the principles set forth in *Diehr*, and ownership of rights to such tests and therapies is adequate to ensure research into isolating the gene sequence in the first place.

Second, ruling *claims* like claim 13 invalid will not necessarily invalidate any *patents per se*. Claims define the

metes and bounds of what the patent holders consider their exclusive rights. Each claim defines the scope of a different invention. 35 U.S.C. § 112. Patents contain multiple claims because patent applicants are allowed to claim several inventions based upon a single technical disclosure. Indeed, standard patent practice is to file a number of claims of varying scope precisely to protect against future uncertainty. Broad claims have the greatest coverage, but the highest likelihood of being invalidated (*e.g.*, by prior art). Narrow claims have the best chance of avoiding prior art, but offer the least coverage. Thus, one does not infringe a patent; one infringes a patent claim. Likewise, a court does not determine that a patent is invalid; it determines whether some or all of the claims are invalid.

The inventors of the patent at issue in this suit filed 34 claims based upon their work, only one of which (claim 13) is challenged. Invalidating claim 13 does not invalidate the entire patent. It simply removes the single, unpatentable claim. It is significant that there is no challenge here to the patentable subject matter of many of the '658 patent's 34 claims, and that Petitioner pays royalties for its use of those inventions. Many of the '658 patent's claims are directed to specific testing methods and detailed test protocols, not to the underlying natural phenomenon itself, as is claim 13. These claims will continue to be valid and enforceable even if the outlier claim 13 is struck down.

Thus a decision for Petitioner in this case might call into question certain claims in certain patents, including in the area of gene patents, but need not invalidate all those patents themselves. The claims that are invalidated will be those that are on the outer edge of patentability and reflect not justifiable reliance on the state of the law, but zealous patent attorneys seeking the broadest possible scope for their clients.

If the Court had any lingering concern that invalidation of claim 13 would upset the settled expectation of those who

might have already obtained patents issued under an incorrect interpretation of *Diehr*, then the Court might issue a prospective ruling affecting only patents issued in the future. This approach is not necessary, however, for it is appropriate and expected that judicial rulings upon the scope of patentable subject matter might affect the future application of claims in patents that have already issued. For instance, this Court recently provided guidance on the scope of the doctrine of equivalents. *See Festo Corp. v Shoketsu Kinzoku Kogyo Kabushiki Co.,* 535 U.S. 722 (2002). This doctrine allows for infringement liability even if there is no literal infringement of the claim. Although this decision certainly altered previous expectations about the scope of patent enforceability, it has been applied by the lower courts to all issued patents. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1370 n.4 (Fed. Cir. 2003) (*en banc*) (on remand) (citing *Harper v. Va. Dep't of Taxation*, 509 U.S. 86, 97 (1993) ("When this Court applies a rule of federal law to the parties before it, that rule is the controlling interpretation of federal law and must be given full retroactive effect in all cases still open on direct review and as to all events, regardless of whether such events predate or postdate our announcement of the rule.")).

D. If There Is Any Ambiguity About the Patentability of Natural Phenomena, It Should Be Resolved in Favor of Petitioner In Order to Avoid Serious Constitutional Questions

Just as this Court interpreted copyright law so as to ensure consistency with the Constitution, *Feist Publ'ns, Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340 (1991), so too should it interpret patent law. There are two constitutional problems with the patent claim at issue in this case, and with all patents claiming exclusive rights to the results of a measurement of nature.

The first problem is that patents on measurements of nature, like the copyright struck down in *Feist*, deal with facts themselves. The corresponding lack of originality raises serious questions under Art. I, § 8, which gives Congress authority to issue patents that "promote the *Progress* of Science and useful Arts." Art. I, § 8, cl. 8 (emphasis added). Patents on measurements of nature take information *out* of the public domain rather than putting ideas *into* the public domain as is the intention of the Constitution and of the patent disclosure provisions, 35 U.S.C. § 112. In the present case, for example, a scientist or doctor was free before the patent issued to use a total homocysteine test and make whatever guess he or she might wish about cobalamin or folate deficiency. It was infringement to do so, however, after the patent issued. The subject matter provision of the Patent Act, 35 U.S.C. § 101, therefore should be interpreted to prohibit patents that preempt the use of principles or measurements of nature and that, in effect, bar future researchers from making such measurements or from using information that is available from nature. Otherwise, the patent does not "promote the Progress of Science."[19]

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[19] Nor is this constitutional difficulty resolved by the fact that the Patent Clause gives Congress authority to grant patents to "inventors" for their "discoveries." Contrary to the modern usage of "discovery," the term had a different meaning in the eighteenth century, when the Constitution was ratified. "A discovery in that era, as used in the intellectual property law, denoted something originating from the human intellect and not merely learned by that intellect." Linda J. Demaine and Aaron Xavier Fellmeth, *Reinventing the Double-Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 Stan. L. Rev. 303, 370 (2002); *see also* H.R. Rep. No. 71-1129, at 16-17 (1930); Albert H. Walker, TEXT-BOOK OF THE PATENT LAWS OF THE UNITED STATES OF AMERICA § 2, at 2-3 (2d ed. 1889) ("The word 'discovery' does not have, either in the Constitution or the statute, its broadest signification. It means invention, in those documents, and in them it means nothing else."). Case law from the early days of patent jurisprudence reflects this understanding. *In re Kemper*, 14 F. Cas. 286, 287 (C.C.D.C. 1841)

A second constitutional difficulty with patent claims on measurements of nature is that the patent may have a significant chilling effect on publication in violation of principles of freedom of speech protected by the First Amendment. Under normal patent law principles, if claim 13 is valid, a scientist, doctor, or medical firm publishing an article encouraging the use of a total homocysteine measurement as a way of inferring cobalamin or folate deficiency might be found to have induced infringement under 35 U.S.C. § 271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer."). For a scientist publishing without knowledge of the patent, such liability depends on the relevant standard for the intent requirements needed to trigger liability as a inducing infringer. It is uncertain whether these standards require specific intent, *see Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544 (Fed. Cir. 1990), or only intent to cause the acts which constitute infringement, *see Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464 (Fed. Cir. 1990). *See generally* Mark A. Lemley, *Inducing Patent Infringement*, 39 U.C. Davis L. Rev. 225 (2005).

No scientist should need to undertake an analysis of the intent requirements for inducing infringement before publishing a research article on a direct correlation between a measurement and a natural phenomenon. No one can make such a measurement with the relevant purpose and not infringe a patent claim such as claim 13. Nor can anyone publish an article about the correlation or include discussion of the correlation in a scientific or medical treatise without risking contributory infringement. A spread of such patents

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(Discovery as used in the Constitution is "synonymous with invention. . . . The applicant must invent, contrive, or produce something that did not exist before."). Thus one cannot "discover" a law of nature any more than one can "invent" a law of nature, as those terms were used in within the original meaning of Art. I, § 8, cl. 8.

would have an enormous chilling effect on scientific and commercial publication.

These constitutional considerations should provide an additional reason to reaffirm the *Diehr* principle by ruling for Petitioners in this case.

CONCLUSION

For the reasons stated above, the decision below should be reversed or vacated.

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