LabCorp v. Metabolite Laboratories: The Supreme Court Listens, but Declines to Speak

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Introduction

Molecular genetic testing has increasingly been incorporated into clinical medicine, and this trend is likely to accelerate in the future.[1] The introduction of genetic testing into medical practice is beginning to collide head on with patents that claim ownership of correlations between human genetic variants and predisposition to disease, response to therapeutic drugs, and susceptibility to pharmacologic side effects. Patent holders or licensees of genes, genetic variants, and their genotype-phenotype correlations are already using the threat of litigation to monopolize genetic tests for important well-known syndromes like Duchenne Muscular Dystrophy and inherited breast and ovarian cancer, in addition to a host of less commonly discussed conditions.[2]

Technical advancements have made the process of setting up many genetic tests straightforward, inexpensive, and routine through the use of existing, justifiably patented instruments and techniques. The Human Genome Project has brought the free availability of reference sequences with which patients' DNA can be compared. Consequently, gene patents *in the genetic testing context* decrease innovation in test development and limit the number of test providers, thereby raising health care costs and reducing or eliminating patient opportunities to confirm results. Recently, the Supreme Court had an opportunity to rule on a case with direct implications for the validity or enforceability of gene-related patents that have restricted the development and implementation of genetic testing. In October 2005, the Court granted certiorari in *Laboratory Corporation of America v. Metabolite Laboratories, Inc.*[3] However, after oral argument, the Court dismissed the case. In so doing, the Supreme Court passed up an opportunity to add reason and clarity to a complex, unsettled area of law that is certain to profoundly impact medical practice in the United States.

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Certiorari

To appeal a lower court ruling to the Supreme Court, a litigant petitions the Court for a "writ of certiorari." The Justices then vote on whether or not to accept the case. When the Court agrees to decide one or more of the issues presented, it grants "certiorari." Occasionally, the Supreme Court finds that it mistakenly accepted an appeal. In these situations, it may dismiss its writ of certiorari as "improvidently granted."[4] The Court took this unusual step in *LabCorp* on June 22, 2006.[5]

Patent Overview

A United States patent confers the right to exclude others from making, using, or selling an invention for 20 years from the filing date. Under the Patent Act, patentable inventions must be novel, nonobvious, and useful.[6] Patent *claims* define an invention's features much as a deed delineates the boundaries of a plot of land. Patent applications are submitted to the Patent Office (PTO) where they are rejected, or allowed and issued. "Processes, machines, manufactures, and compositions of matter" can be patented,[7] but patents may

not be obtained on products of nature or, under the "natural phenomenon doctrine," "laws of nature, natural phenomena, and abstract ideas."[8]

History of the Case

In 1990, Drs. Robert H. Allen, Sally P. Stabler, and John Lindenbaum were awarded patent number 4,940,658 – the central claims of which cover the use of gas chromatography/mass spectrometry (GC/MS) to measure levels of homocysteine, an amino acid, in human body fluids. The medical school faculty members in turn assigned the patent to University Patents Inc. (UPI). The use of GC/MS for the measurement of blood homocysteine levels was an improvement over earlier chromatographic methods. Included in the patent was a claim that, in effect, asserts ownership over the physiologic relationship between elevations in blood homocysteine and deficiencies in cobalamin (vitamin B12) and folate. Claim 13 reads:

> 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.[9] (Emphasis added.)

The "inventors" initially submitted patent applications that claimed the biological relationship between homocysteine and cobalamin and folate levels more directly, but the PTO twice rejected them. Claim 13 was then permitted to issue after it was revised to include distinct assay and correlation steps.[10] However, it is noteworthy that the involvement of folate and cobalamin in the conversion of homocysteine to methionine was well known at the time.[11] As has since been learned, plasma homocysteine levels have limited specificity for diagnosing vitamin B12 and folate deficiencies, entities for which generally accepted definitions remain elusive.[12]

Metabolite licensed the rights to use patent 4,940,658 from UPI's successor corporation, Competitive Technologies, Inc. Metabolite subsequently granted a sublicense to LabCorp's predecessor company in exchange for royalties equal to 27.5 percent of attributable test revenue. A clause in the license permitted LabCorp to terminate the agreement upon availability of a more cost-effective test that did not infringe "a valid and enforceable claim of" the patent.[13]

LabCorp performed homocysteine-only tests by GC/MS and paid royalties on this testing from 1992 to 1998. That year it switched to a faster, less labor intensive immunoassay method and discontinued payments to Metabolite. (LabCorp continued to pay royalties on a homocysteine test it performed by GC/MS as part of a panel.)[14] In response, Competitive Technologies and Metabolite sued LabCorp for patent infringement and breach of the license agreement.[15] In November 2001, a Colorado jury found that LabCorp *indirectly*, but "willfully" infringed claim 13, and breached its sublicense agreement with Metabolite.[16]

During the relevant time period, LabCorp had published continuing medical education articles and a test catalog describing the relationship between homocysteine and vitamin levels for its referring physicians. According to the jury, these activities "induced" the physicians who had ordered and reviewed test results to *directly* infringe the patent.[17] As later explained by the Court of Appeals for the Federal Circuit (CAFC), the exclusive U.S. patent appeals court, "The record must show the presence of direct infringement, however, to support the verdict of indirect infringement….The record shows that physicians order assays and correlate the results of those assays, thereby infringing."[18] This CAFC holding raises serious issues about the patentability of the practice of medicine, and the propriety of "medical process patents" generally.[19]

The jury found that LabCorp's liability extended to each of 351,458 immunoassay-performed homocysteine tests. The total award was in excess of $7.4 million, including interest, $1.1 million in attorneys' fees, and a doubling of damages because of the jury's finding of willfulness. The court also permanently prevented LabCorp from performing any homocysteine-only tests.[20] The CAFC affirmed the trial court's judgment.[21]

LabCorp appealed the CAFC's decision to the U.S. Supreme Court. Recognizing the importance of delineating the boundaries of the natural phenomenon doctrine, the Court invited the Solicitor General to opine as to whether the patent claimed statutory subject matter under 35 U.S.C. § 101, *sua sponte* raising the issue.[22] In response, the Solicitor General filed a brief acknowledging that claim 13 "appears to involve an unpatentable natural phenomenon." Nevertheless, the Solicitor General recommended that the Court not accept the case, arguing LabCorp did not challenge the patent on this basis at trial or on appeal.[23]

By the time the infringement case against LabCorp was filed, a consensus had emerged among patent lawyers and the PTO, encouraged by the CAFC, that modern claim-drafting techniques had rendered subject matter considerations irrelevant to biotechnology patents.[24] This pragmatic view among the patent bar reflected the CAFC's approach to the substantive policy issues associated with statutory subject matter

under § 101 following the Supreme Court's decisions in the key cases *Diamond v. Chakrabarty*[25] and *Diamond v. Diehr*.[26] *Chakrabarty* and *Diehr* represent the High Court's last forays into § 101 jurisprudence.

In *Chakrabarty*, the Supreme Court ruled that a man-made, living organism could be patented. Ananda Mohan Chakrabarty, a research scientist at General Electric, applied for a patent on a *Pseudomonas* bacterium that had been bioengineered to carry multiple plasmids. These plasmids conferred upon the newly created microorganism the ability to digest complex mixtures of hydrocarbons, potentially offering a biotechnological solution to oil spill cleanup. The PTO rejected Chakrabarty's patent application on the grounds that living organisms were unpatentable, but Chakrabarty appealed the PTO's decision to the courts. Eventually, the case made its way to the United States Supreme Court.

The Supreme Court held that Chakrabarty's invention was not rendered nonstatutory under § 101 simply because it was living. Moreover, in its opinion the Court urged a broad interpretation of patent eligibility, reciting the now famous quote from the legislative history of the 1952 Patent Act, that "anything under the sun that is made by man" can be patented.[27] Thus, *Chakrabarty* opened the door to the allowance of innumerable patents on biotechnology inventions ranging from transgenic mice and leukemia-derived cell lines to recombinant drugs and vaccines.

Further, it was a small step for the PTO, with encouragement from the CAFC, to combine *Chakrabarty* with chemical law precedents that upheld the validity of patents on purified, natural compounds like aspirin,[28] epinephrine,[29] vitamin B12,[30] and prostaglandins[31] so as to allow patents on another natural chemical, deoxyribonucleic acid (DNA).[32] The PTO has subsequently issued thousands of patents on DNA sequences, variations from normal or "wild-type" sequences, and associated genotype-phenotype correlations. The PTO's application of the chemical analogy to DNA has allowed gene-related patents to circumvent the prohibition on patenting natural products known as the "product of nature" doctrine.

At issue in the other important Supreme Court case, *Diamond v. Diehr*,[33] was the patentability of James Diehr's use of a computer to automate and iterate a process for molding and curing rubber. Diehr's innovation was to continually measure the temperature within the press, and to automatically transfer the value to a computer that repeatedly calculated the requisite cure time using the well-known Arrhenius equation. When the optimal cure time equaled the elapsed time, the computer signaled a device that automatically opened the press.

The PTO believed that Diehr's patent application was in substance directed toward a mathematical algorithm, rendering it nonstatutory under § 101. The Court of Customs and Patent Appeals, a predecessor court to the CAFC, reversed the PTO's decision. On further appeal, the Supreme Court, in a 5 to 4 decision, upheld the validity of Diehr's patent. The Court found that when viewed in toto, Diehr's claimed activities constituted sufficient application of the algorithm to render it a patentable process.

The Supreme Court made a point to reconcile *Diehr* with two of its previous decisions, *Gottschalk v. Benson*[34] and *Parker v. Flook*.[35] The validity of process patents that incorporated programmed computers was at issue in both *Benson* and *Flook*. However, in contrast to the result in *Diehr*, the Court in each of these cases held that an application of a mathematical formula within a particular process was insufficient to establish an independent invention. The proposed patents in dispute in *Benson* and *Flook* can be distinguished from that in *Diehr* because their claimed processes had numeric rather than physical outputs, and were either less well defined or produced less tangible results than Diehr's process. Nevertheless, the newly formed CAFC interpreted *Diehr*, like *Chakrabarty*, as a liberalization of the Supreme Court's approach to patent eligible subject matter under § 101.

In a series of disputes over the patentability of processes which increasingly began to resemble naked computer programs,[36] the CAFC held in favor of patentees, thereby expanding patentable subject matter to include software. In addition, the CAFC eliminated a longstanding prohibition against the patenting of business practices. Subsequently, the PTO issued thousands of patents on software applications and business methods.

The CAFC may well have overreached in its interpretation of *Diehr*. In *Diehr,* the Supreme Court rebutted the presumed invalidity of patents that incorporated programmed computers writing, "[A] claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula, computer program, or digital computer."[37] Yet, the CAFC's decision in the high profile case *State Street Bank & Trust Co. v. Signature Financial Group*[38] appeared to turn this presumption on its head.

In *State Street*, the CAFC upheld the validity of a patent on a data processing system used to administer a pooled investment fund. In its decision, the Court redirected the patentability inquiry in software cases under § 101 away from statutory subject matter toward utility. In apparent contravention of prior Supreme Court precedent[39] and the dictates of the 1952 Patent Act,[40] the CAFC wrote, "The question of whether

a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to – process, machine, manufacture, or composition of matter – but rather on the essential characteristics of the subject matter, in particular, its practical utility."[41] (Footnote omitted.)

Under the "written description" and "enablement" requirements of § 112, a patent must describe its invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." If the written description and enablement mandates had been viewed more broadly, claim 13's failure to specify a particular method of measuring homocysteine levels and the lack of specificity in its correlation step could have proved fatal to its validity. Instead, the CAFC applied a narrow, literal construction to § 112 and found that the unambiguous description of two sequential generic acts – i.e., measuring a homocysteine level and mentally correlating that level with possible vitamin B12 and folate deficiencies – was adequate to satisfy § 112's dictates. However, complying with the aforementioned provisions of the Patent Act does not address patentability of the claim's subject matter.

In general, the availability of patent protection provides incentives for inventive activities. However, it is difficult to imagine that pressures to generate the traditional academic currencies of original scholarship, research grants, publications, and peer recognition were insufficient to encourage empiric confirmation of the relationship between homocysteine and cobalamin.

Moreover, in *Diehr*, the Supreme Court reaffirmed the principle expressed in *Benson* that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to patentability of a process claim that does not include *particular* machines."[42] (Emphasis added.) The Court found, "That respondents' [Diehr's] claims involve the transformation of an article, in this case raw, uncured synthetic rubber into a different state or thing cannot be disputed."[43]

It is against the preceding historical backdrop that LabCorp's apparently fatal failure to raise a section § 101 argument during its defense, as well as its overreliance on § 112, which sets forth patent law's disclosure requirements, must be viewed. Despite the Solicitor General's recommendation against certiorari, the Supreme Court agreed to accept the case. Oral argument took place on March 21, 2006. In a 5 to 3 vote (Chief Justice John Roberts did not participate) the Court thereafter declined to decide the issues before it. This result was opposed by Justice Stephen Breyer who, joined by Justices John Paul Stevens and David Souter in a written dissent, expressed his unequivocal belief that claim 13 is invalid under the natural phenomenon doctrine.[44]

Issues

Empiric demonstration of the biological relationship between homocysteine and vitamin B12 led to significant improvements in our ability to diagnose vitamin B12 deficiency. In addition, this work introduced the important concept of subclinical cobalamin deficiency, a physiologic state which has yet to be fully clarified. Therefore, it can legitimately be argued that the discovery satisfies the novelty and nonobviousness criteria set forth in the Patent Act as codified in §§ 102 and 103.

Metabolite argued that claim 13 sets forth a two-step method for detecting vitamin B12 and folate deficiencies. Rather than claiming ownership of the homocysteine-cobalamin-folate association, Metabolite averred that claim 13 provides a practical use for it. But does the claim represent a patentable *practical application* of a natural phenomenon? Or is it merely the declaration of a property right in a biological relationship that has been artificially characterized as a stepwise process? Claim 13's enormous breadth, and its failure to describe any patentable, man-made, or transformed products derived from its proposed process, necessitate the latter conclusion.

Claim 13 preempts all homocysteine testing performed for the diagnosis of vitamin B12 and folate deficiencies by any known or future-developed methods. The CAFC reasonably and accurately found that irrespective of their reasons for ordering homocysteine testing, physicians nearly always consider homocysteine's association with cobalamin and folate levels when interpreting a result. Consequently, the Court held that any and all homocysteine testing falls within claim 13's ambit.

Cobalamin and folate are necessary cofactors in the conversion of homocysteine to methionine. Deficiencies in either of these vitamins results in elevations of total homocysteine. The latter, which is also an intermediary in the conversion of methionine to cysteine, exists in the blood in protein bound and several unbound forms. The variants of homocysteine must therefore be partially purified and derivatized prior to measurement by GC/MS.[45] Measuring these fractions by GC/MS entails "transformations of matter," which under other circumstances could suggest the presence of an inventive step. However, not only does claim 13 not specify the use of GC/MS, but instead it describes measuring homocysteine levels *by any method*, whether discovered previously or in the future. It then claims, as its next step, the *mental process of correlating*. As Justice Breyer noted, "[T]he process described in claim 13 is *not* a process for transforming blood or any other matter. Claim 13's process instructs the user to (1) obtain test results and (2) think about them."[46] Consequently, the Justice concluded, "At most, respondents have simply described the natural law at issue in the abstract patent language of a 'process.'"[47]

Interestingly, the Metabolite patent is not the first biochemical relationship patent that has been used to extract royalties from diagnostic laboratories. The "triple screen" is a prenatal test that is commonly performed on maternal blood to identify pregnancies at risk for delivering a child with certain chromosomal abnormalities including Down Syndrome (trisomy 21). In the mid-1990s, Dr. Mark Bogart began to enforce his 1989 patent claiming the association between elevations in one of the test markers, human chorionic gonadotropin (hCG), and Down Syndrome[48] against laboratories performing triple screen testing. However, all laboratories eventually settled out of court, and no decision on the validity of the patent was ever reached.[49]

Metabolite and the Solicitor General argued that deciding the case could call into question the validity of "thousands of patents," improperly and unfairly contravening investor expectations and potentially engendering untoward economic effects.[50] However, the likelihood of such a result would have depended upon the breadth of the Court's opinion in any decision adverse to the validity of Metabolite's patent.

There is no way to be certain of the number of patents that could potentially have been placed at risk. However, the Court's history of intervention in the patent realm suggests that it would have been unlikely to rule in a sweeping manner that produced major economic consequences.[51] Ironically, *LabCorp* presented an ideal § 101 case in this regard because the essence of the patent is clearly an ownership claim over an invariant physical relationship that is fundamental to human physiology. One clue to the claim's weakness was the courts' need to find that ordering physicians directly infringed the patent by performing a routine, professionally obligatory diagnostic correlation.

For these reasons, a narrow decision that called into question only the validity of similarly weak patents could and probably would have been crafted, and the economic impact of such a decision would probably have been minor. First, broad correlation claims are typically included within a series of claims, the majority of which are directed toward statutorily valid subject matter. The legitimate claims would have been unaffected by any decision in the case. Second, one must assume that sophisticated business people investing large sums of money will perform appropriate due diligence on the intellectual property that forms the basis for their ownership or lending decisions. Consequently, the relative strength or weakness of patent claims is likely to be reflected in valuations generated before investment decisions are made. Third, because the patent claim addresses an esoteric medical relationship, it would be difficult to generalize a result in *LabCorp* to unrelated fields like software and business methods. Finally, to the extent that a decision would have rendered invalid analogous biological patents, the result would have been desirable for reasons similar to those that apply in the case under study. That is, innovation in test methods and competition within the diagnostics industry would have been encouraged, ultimately resulting in higher quality, less expensive services.

In general, the availability of patent protection provides incentives for inventive activities. However, it is difficult to imagine that pressures to generate the traditional academic currencies of original scholarship, research grants, publications, and peer recognition were insufficient to encourage empiric confirmation of the relationship between homocysteine and cobalamin. This is particularly true when one considers that at the time the association was validated, enforceable patent protection was not assured, and the financial value of homocysteine measurements as a cardiac risk factor was not recognized. It is even harder to argue that claim 13 promoted the investment of risk capital in the development and commercialization of new ways of testing for plasma homocysteine levels. As is typical of patents of this genre, claim 13 actually discouraged development of new homocysteine tests by limiting entrants to the field. This fact was clearly demonstrated by Metabolite's lawsuit against LabCorp after it had adopted a less expensive, more efficient test method than GC/MS. Claim 13's ultimate effects, therefore, were to decrease the availability of

diagnostic testing, limit innovation, and increase test costs.

Medical tradition has always demanded the unrestricted dissemination and free use of clinically relevant knowledge. This vital purpose is served by the distribution of continuing medical education publications such as those provided by LabCorp. It is noteworthy that the trial and appellate court findings of liability for this activity stand in direct conflict with medical ethics in addition to the established law of patentability. Central to the activity of physicians is the assimilation of disparate information, for example history, physical examination, and laboratory testing, to arrive at a diagnosis in a patient. From a medical standpoint, the processes of observing a patient's gait, listening to her heart, measuring her blood homocysteine, or examining her DNA for changes that predispose her to breast cancer do not qualitatively differ. To what extent will patents on clinical thought processes impede doctors' future work?

The reasoning Justice Breyer expressed in his dissent extends to the patentability of other natural associations that can be uncovered by medical or scientific research. Foremost among these are the analogous relationships between genetic variants and human diseases.[52] The current era is characterized by the rapidly expanding use of genetic markers to define disease states or risks for them. Yet, by the CAFC's reasoning, the correlation between mutations in a specific gene and a physical condition or illness risk can be patented by the first person to discover the relationship. Such patents permit patentees to monopolize testing for given genes, variants, or diseases, and allow them to impose specific test methods on laboratories. These patents present no opportunity to design around or better their purported "inventions." Thus, they discourage academics and diagnostics manufacturers from improving test methodologies. The consequences are more expensive, lower quality DNA-based testing for inherited and somatically acquired diseases.

Although in *LabCorp* ordering physicians were the direct patent infringers, any *person* who orders a plasma homocysteine level and correlates the result with possible deficiencies in vitamin B12 or folate infringes claim 13. Extending this reasoning to gene-related patents, the bizarre holding can be interpreted to preclude individuals from examining their own DNA for the presence of disease-related changes without first negotiating licenses.

The stated concerns are not hypothetical. Anecdotal and empiric evidence suggest that gene-related patents already limit the availability of molecular diagnostic testing.[53] Patents relating to the breast and ovarian cancer predisposing genes *BRCA1* and *BRCA2* represent perhaps the most notorious example of a patent holder's restriction of DNA-based diagnostic testing.

Claim 6 of patent 5,709,999 attempts to assert a monopoly over the use of DNA sequencing to detect cancer-predisposing variants in the *BRCA1* gene. This claim in pertinent part reads, "[A] germline alteration is detected by amplifying all or part of a *BRCA1* gene in said sample using a set of primers specific for a wild-type *BRCA1* gene to produce amplified *BRCA1* nucleic acids and sequencing the amplified *BRCA1* nucleic acids."[54] Such patents, whether they claim gene sequences as isolated chemical compounds or as components of processes, serve to establish ownership of associations between deviations from the "normal" gene sequence and risk of disease. Although under the natural phenomenon doctrine the *BRCA* patents appear unenforceable with respect to diagnostic testing,[55] the owner's threat of litigation has dissuaded others from performing diagnostic and research testing for variants in both the *BRCA1* and *BRCA2* genes. This has resulted in increased costs of genetic testing for inherited breast cancer susceptibility, a lack of availability of confirmatory testing by other laboratories,[56] and a greatly reduced number of investigatory mutation databases.

While gene sequence patents *in the context of genetic testing* confer ownership of the underlying associations of genetic variants with diseases upon the patent holders, recent patents overtly claim genotype-phenotype correlations. For example, patent 7,083,921 entitled, "Method to determine the risk for side effects of an SSRI treatment in a person," claims the relationship between a variant in a serotonin receptor (5-HT2A) and side effects attributable to serotonin reuptake inhibitors. The patent issued on August 1, 2006, and has been assigned to Stanford University.[57]

Patent protection has contributed greatly to the development of therapeutic drugs, biologics, medical devices, and diagnostic equipment by providing individuals, universities, and corporations with incentives to undertake inventive and commercialization activities. The possibility of patent protection undoubtedly stimulates the development of true test *method*s, such as the polymerase chain reaction (PCR), a patented nucleic acid amplification technique whose inventor received a Nobel Prize for the invention;[58] the automated instruments now used to perform PCR; and the automated sequencers that read the genetic code of the technique's amplicon products. Creating inventions of these types ordinarily requires huge sums of risk capital for inventive effort, development, and product commercialization. Such investments are predicated on the prospect of greater than average

financial returns, which necessitates the availability of patents.

When genes have been used as chemicals, for example in the manufacture of recombinant biologics, gene patents have served as integral stimuli for new biotechnology drug and vaccine development. However, in contrast to the physical manipulations of nucleic acids that are used to produce recombinant pharmaceuticals, genetic testing merely involves analysis of sequence variants. Thus, the chemical analogy breaks down in this setting because it fails to acknowledge that DNA's sole utility for genetic testing is as an informational medium.

As with the homocysteine-vitamin B12 correlation, the prospect of gene-related patents adds little to existing incentives to discover genotype-phenotype correlations that are the subject of medical diagnostic tests. Take, for example, the patent portfolio of Athena Diagnostics, a well-known commercial enterprise that focuses on genetic and immunologic testing for neurologic disorders.[59] Athena seeks to monopolize genetic testing for a number of severe, inherited neurologic diseases through the acquisition of patents on the genes responsible for the disorders. The company claims rights to 65 gene-related patents applicable to 51 putative disease-causing genes, among which are genes implicated in the pathogenesis of Duchenne Muscular Dystrophy and a host of less well-known inherited syndromes.[60]

The majority of assignees listed on patents to which Athena claims ownership rights are United States universities, medical schools, or related academic medical centers alone (30), or in combination with foreign universities or research institutes (5), or corporations (2). Two other U.S.-based patent assignees are non-profit research foundations. Athena also claims ownership rights to U.S. patents whose assignees are foreign entities, the majority of which (16/22) are government or university-affiliated research institutes. Most (31/37) of the domestic academically based "inventors" and all of the inventors working in other American non-profit organizations reported receiving U.S. government funding for the research underlying their patents.

These data, along with the well-described race to find the *BRCA* genes associated with hereditary breast and ovarian cancer,[61] strongly support the contention that U.S. patents were unnecessary to stimulate the relevant discoveries. Moreover, the majority of human genes have been identified despite the fact that most disorders caused by mutations in single genes are rare. Thus, these discoveries provided physicians and scientists with little prospect for diagnostic testing-associated economic gain.

Finally, gene-related patents are unnecessary to encourage the development of genetic tests, the underlying methods for which justifiably receive patent protection. Genetic testing simply involves comparing a patient's DNA sequence with a reference sequence. Technical advancements have made the process of setting up many genetic tests scientifically straightforward, inexpensive, and routine using PCR, thermocyclers, automated sequencers, and other legitimately patented instruments and techniques. In fact, the Human Genome Project has made reference sequences freely available. Thus, many hospital-based and commercial molecular diagnostic laboratories are capable of rapidly and inexpensively designing, developing, and validating genetic tests, or utilizing commercially sold test kits as they become available.

Because most genetic diseases that are inherited in a Mendelian pattern are rare, commercially offered test kits for individual syndromes have to date presented in vitro diagnostics manufacturers with limited opportunities for financial gain. Consequently, few FDA approved test kits are available, although their numbers will likely increase in the future. Almost none of the available kits have been premised on ownership of gene-related patents. Instead, research by diagnostic test manufacturers has focused on the development of novel test devices, methods, and reagents. The intellectual property accruing to these inventive activities has attracted substantial investment capital into the field. Gene-related patents act in opposition to the salutary effects of legitimately issued patents on instruments, reagents, and methods, because they reduce the number of providers that can develop and offer a given test. The result is decreased innovation, higher test costs, and an inability to confirm test results.

Molecular genetic testing is in a nascent stage, with only a small number of commercial ventures strategically relying on the acquisition of gene-related patents to monopolize disease testing. Therefore, the economic impact of denying the validity of such patents under the natural phenomenon doctrine would be limited. For example, Athena Diagnostics performs over 200 diagnostic tests, but reported revenues of only $55 million in 2005, and had just 200 employees in 2006.[62]

The commercial testing laboratory that appears to have placed the greatest reliance on gene-related patent protection is Myriad Genetics in Salt Lake City, Utah. Myriad owns patents on the *BRCA1* and *BRCA2* genes, mutations in which predispose to the most prevalent hereditary breast and ovarian cancer syndromes. The company performs genetic testing for mutations in these genes, and in genes responsible for inherited colorectal cancer and familial mela-

noma.[63] The company sequences causative genes for the diseases, and then compares the patient's results to "normal," reference sequences. Although these are predominantly automated, straightforward activities that could be performed in many molecular diagnostics laboratories, intellectual property concerns have allowed Myriad to monopolize genetic testing for *BRCA1* and *BRCA2* mutations.

Its monopoly position in *BRCA1* and *BRCA2* testing allowed Myriad's genetic testing division to accrue 2006 profits of $35 million on revenues of $100.6 million.[64] While these numbers are not insignificant, they seem paltry when compared to, for example, the tens of billions of dollars in revenue Amgen has received from the sale of recombinant erythropoietin.[65] Thus, they provide additional support for arguments that holding gene-related patents invalid in the genetic testing context would have negligible economic effects.

Enforcement of the natural phenomenon doctrine so as to preclude gene-related patents from conferring disease testing monopolies on patent holders would increase the number of institutions that perform testing for affected disorders and reduce dead weight loss from monopoly profits. Therefore, society's overall economic gain would be positive. More importantly, the benefits from lowered cost, improved access, and enhanced quality accruing to patients and their family members who require testing far outweigh the costs of any temporary dislocations that may occur.

Lastly, predisposition to much human illness stems from combined variations in multiple genes. In the future, the encumbrances gene-related patents impose on genetic testing will be magnified, as advancing knowledge demands that we acquire and integrate information about possible variants in multiple genes that act in concert. Clarifying the law so as to preclude patents on genetic correlations will have dramatically positive long-run effects as molecular genetic testing expands from classically inherited Mendelian disorders to common polygenic diseases like hypertension, heart disease, and cancer, and medically relevant genotypes that predict therapeutic drug response, development of pharmacologic side effects, and other phenotypic traits.[66]

Conclusion

The Supreme Court appears to have denied certiorari in *LabCorp v. Metabolite Labs* for procedural reasons. The Court's refusal to decide the case does not speak to the case's merits or the validity of claim 13. Nevertheless, the CAFC upheld the trial court's decision, and LabCorp must pay the judgment entered against it.

During oral argument, Justice Scalia addressed Metabolite's counsel. The Justice stated, "But here what [claim] 13 involves is simply discovery of the natural principle that when…there is the presence of one substance in a human being, there is a deficiency of two other ones. That's just a natural principle." "What," he went on to ask, "is made by man about that?"[67] Although the Supreme Court declined to answer this question in *LabCorp*, it will undoubtedly have additional opportunities to clarify and refine the relationship of patent law to natural, biological phenomena. Justice Scalia's comments together with Justice Breyer's dissent offer hope that the Court will provide sensible, appropriate, and essential guidance in this area as society moves into the era of genomic medicine. Until that time, the United States Patent Office and the Federal Circuit, in determining patent eligibility, should foremost consider the welfare of the many patients who will benefit from standards that encourage innovation while increasing the availability and lowering the costs of diagnostic laboratory testing in the United States.

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21. See *LabCorp*, *supra* note 17, at 1372.
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28. *Kuehmsted v. Farbenfabriken*, 179 F. 701 (7th Cir. 1910), cert. denied, 220 U.S. 622 (1911).
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30. *Merck & Co. v. Olin Mathieson Chemical Corp.*, 253 F.2d 156 (4th Cir. 1958).
31. *In re* Bergstrom, 427 F.2d 1394 (C.C.P.A. 1970) (PGE, PGF).
32. See e.g., *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed Cir 1991) ("A gene is a chemical compound, albeit a complex one…").
33. See *Diehr, supra* note 26.
34. *Gottschalk v. Benson*, 409 U.S. 63 (1972).
35. *Parker v. Flook*, 437 U.S. 584 (1978).
36. *Arrhythmia Research Tech. v. Corazonix Corp.*, 958 F.2d 1053 (Fed. Cir. 1992) (EKG system that utilizes programmed computer to analyze electrocardiographic signals is statutory subject matter); *In re* Alappat, 33 F.3d 1526 (Fed. Cir. 1994) (*en banc*) (digital processing circuitry programmed to generate anti-aliased oscilloscope tracing is statutory subject matter); *State St. Bank & Trust v. Signature Fin. Group*, 149 F.3d 1368 (Fed. Cir. 1998) (data processing system used to administer investment fund is statutory subject matter); *ATT Corp. v Excel Commc'ns Inc.*, 172 F.3d 1352 (Fed. Cir. 1999) (computerized system for recording and billing long distance telephone calls that has ability to recognize called party's long distance carrier is statutory subject matter).
37. See *Diehr, supra* note 8, at 187.
38. *State Street Bank & Trust Co. v. Signature Financial Group,* 149 F.3d 1368.
39. See *Diehr*, *supra* note 8, at 189-191.
40. *Id.*
41. See *State Street, supra* note 38, at 1375. The omitted footnote reads, "Of course, the subject matter must fall into at least one category of statutory subject matter."
42. See *Diehr*, *supra* note 8, at 184.
43. *Id.*
44. *Laboratory Corp. of Am. v. Metabolite Labs., Inc.*, 126 S.Ct. 2921, 2927 (2006), dismissed as improvidently granted (Justice Breyer dissenting) ("But this case is not at the boundary. It does not require us to consider the precise scope of the 'natural phenomenon' doctrine or any other difficult issue. In my view claim 13 is invalid no matter how narrowly one reasonably interprets that doctrine.")
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48. M. Bogart, "Method for assessing placental dysfunction," U.S. Patent No. 4,874,693, filed October 10, 1986, and issued October 17, 1989.
49. G. Barzo, "Lawsuit Heats Up over Patent on Common Prenatal Test," *American Medical News*, January 12, 1998, at 1.
50. Brief for Respondents on Writ of Certiorari at 43-46, *Laboratory Corp. of America v. Metabolite Labs., Inc.*, 126 S.Ct. 2921 (2006), dismissed as improvidently granted; Brief for the United States as Amicus Curiae on Petition for a Writ of Certiorari at 14, *Laboratory Corp. of America v. Metabolite Labs., Inc.*, 126 S.Ct. 2921 (2006), dismissed as improvidently granted.
51. See generally, J. F. Duffy, "The Festo Decision and the Return of the Supreme Court to the Bar of Patents," *Supreme Court Review* (2002): 273-342, particularly at 285 ("Because patent law is a fairly technical system of property rights, the Court has always behaved conservatively in the area, accepted doctrinal changes only incrementally, and looked to specialized actors in the patent system to take the lead in developing the law.")
52. R. D. Klein, "Gene Patents and Genetic Testing in the United States," *Nature Biotechnology* 25, no. 9 (2007): 989-990.
53. See Leonard, *supra*, note 2; Cho et al., *supra*, note 2.
54. D. M. Shattuck-Eidens, J. Simard, F. Durocher, E. Mitsuuru, Y. Nakamura, "Linked breast and ovarian cancer susceptibility gene," U.S. Patent No. 5,709,999, filed June 7, 1995, and issued January 20, 1998.
55. See Klein, *supra* note 52.
56. See Leonard, *supra* note 2.
57. G. M. Murphy and A. F. Schatzberg, "Method to determine the risk for side effects of an SSRI treatment in a person," U.S. Patent No. 7,083,921, filed August 29, 2002, and issued August 1, 2006.
58. Kary B. Mullis won the 1993 Nobel Prize in Chemistry for his invention of the polymerase chain reaction (PCR).
59. Athena Diagnostics Web site, *available at* <http://www.athenadiagnostics.com/content/about/> (last visited September 21, 2007).
60. Athena Diagnostics, "List of Patents," *available at* <http://www.athenadiagnostics.com/content/about/patents> (last visited September 21, 2007); the company also has patent rights to a number of immunologically related gene patents having less direct relationships with diseases.
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65. A. Pollack, "Rivals Laying Siege to Amgen's Near Monopoly in Anemia Drugs," *New York Times*, December 23, 2005, at C1, Late Edition.
66. R. D. Klein, Editorial, "The Pain Protective Haplotype: Introducing the Modern Genetic Test," *Clinical Chemistry* 53, no. 6 (2007): 1007-1009.
67. Transcript of Oral Argument at 40, *Laboratory Corp. of America v. Metabolite Labs.*, Inc., 126 S.Ct. 2921 (2006), dismissed as improvidently granted.