No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

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

BRIEF OF *AMICUS CURIAE* INVITAE CORPORATION IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*[1]

InVitae Corporation ("InVitae") is a San Francisco, California-based company providing genetic testing and genome management services based on human DNA sequencing. InVitae's goal is to aggregate all the world's genetic tests into a single assay with higher quality, faster turn-around time, and at a lower cost than most single gene tests performed today. InVitae is one of many companies in a rapidly evolving industry utilizing advances in massively parallel DNA sequencing to analyze large numbers of genes, as well as to sequence whole genomes or large regions of the genome for diagnostic purposes. *See, e.g.*, Tracy Tucker et al., *Massively Parallel Sequencing: The Next Big Thing in Genetic Medicine*, 85 Am. J. Hum. Genet. 142, 142 and 148-152 (2009), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2725244/. The future and promise of personalized medicine rests on the ability of medical practitioners to access comprehensive information about patients' genetic information, including whether a patient possesses clinically relevant variations in any of a broad panel of human genes. *Id.*

Since the 1990s when the sequencing of the first full human genome began, the technologies and chemistry available for genomic sequencing have evolved rapidly. While the first genome was sequenced at a cost of $437

1. No person other than the *amicus curiae* or their counsel has made any monetary contribution to the preparation or submission of this brief. Further, no counsel for any party authored this brief in whole or in part. Petitioners have lodged a blanket consent to the filing of amicus briefs, and a letter of consent to the filing of this brief by Respondents has been lodged with the Clerk of the Court.

million over 13 years,[2] today's widely available "Next Generation" methods can, with a single laboratory assay, sequence the genome of an individual patient in a few days at costs of around $5,000 - $10,000, and sequencing subsets of a patient's genes or the complete set of roughly 20,000 genes (called "the exome") cost well below $1,000 today.[3] Current estimates suggest that these prices will continue to decline rapidly thereby greatly expanding the uses and market for large scale DNA sequencing. *See, e.g.*, Matthew Harper, *Biotech Firms Battle Over Same Day Genomes*, Forbes Magazine, January 10, 2012, available at http://www.forbes.com/sites/matthewherper/2012/01/10/biotech-firms-battle-over-same-day-genomes; Christianne Bird, *Next-Gen Sequencing Services: An Expanding Role in Clinical Applications Opens New Markets*, Genet. Eng'g & Biotech. News, May 1, 2012, http://www.genengnews.com/gen-articles/next-gen-sequencing-services/4088/; Ivan Karabaliev, *The $1,000 Genome is Almost Here—Are We Ready?*, Scientific American, Oct. 15, 2012, http://blogs.scientificamerican.com/guest-blog/2012/10/15/the-1000-genome-is-here-are-we-ready. Comprehensive genetic information has become both affordable and

2. *E.g.*, U.S. Dept. of Energy Genome Programs, Human Genome Project Information (2004), http://www.ornl.gov/sci/techresources/Human_Genome/project/budget.shtml.

3. Some observers have likened the exponentially rapid pace of change in the speed and cost reduction for genomic sequencing technology to Moore's Law which states that "[t]he number of transistors on a [semiconductor] chip will double approximately every 24 months." *See, e.g.*, Moore's Law and Intel Innovation, http://www.intel.com/content/www/us/en/silicon-innovations/moores-law-consumer-technology.html; National Human Genome Research Institute, Cost per Genome (2012), http://www.genome.gov/images/content/cost_per_genome.jpg.

easily available to clinicians and researchers to help them improve human health.

Current commercially available genomic sequencing technologies achieve such great improvements in speed and efficiency through massively parallel processes. *See, e.g.*, Tucker, *supra* at 142. A patient's genetic information is determined by collecting a sample of the patient's DNA, breaking those DNA molecules into millions of fragments and simultaneously copying and sequencing all or some of those fragments side by side. *Id.* at 142-144. InVitae is concerned that patents claiming individual human genes or fragments of such individual human genes, if asserted, could impair a patient's ability to have his or her own relevant genetic information sequenced for use in connection with the patient's own medical care. A patent holder might claim that one of those millions of gene fragments being sequenced is putatively covered by a claim to a specific gene fragment. Worse, in the circumstance in which there are multiple distinct patentees each claiming a different gene, any one patentee could threaten to prevent the sequencing of a patient's exome or entire genome because such sequencing necessarily includes sequencing each human gene contained in the human genome. Worse yet, within any individual gene there could be hundreds or even thousands of individual mutations identified and separately patented as they are discovered so that no single patentee could permit the sequencing of such a gene. No patent should foreclose an individual's right to self-knowledge of their own genetic information.

InVitae is a strong believer in the importance of a vital U.S. patent system. Nonetheless, InVitae is concerned that some patentees holding patent claims on specific

genes or on individual mutations within a gene could foreclose its ability to provide patients with access to their genetic information which is naturally present in the human genome as well as preventing the research and commercial life sciences communities from developing further understanding of the medical significance of aspects of that genetic information. A circumstance in which myriads of genes and variations in the human genome are privatized through separate patents could substantially impair the development of the genomic testing industry and erode U.S. competitiveness in a critical area of healthcare innovation.

SUMMARY OF ARGUMENT

The human genome is constituted of human genes and other related sequences which are naturally occurring information. With respect to a human gene, such information includes the normal (or wild type) sequence as well as common and uncommon variants of the sequence and associations between such variations and medical conditions or predispositions. This Court has long held that laws of nature and pre-emption of their use are not patentable subject matter. *E.g.*, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1294-1295 (2012). Human genetic information, including sequences of human genes, gene fragments and correlations between variations in human genes and medically relevant patient information all constitute laws of nature akin to the correlation between drug metabolite concentrations measured in a patient and the determination of the suitable drug dosage for that patient which was found to be a law of nature under the *Mayo* test for patentable subject matter. *Id.* at 1296-1297.

Patent claims which pre-empt the use of laws of nature in the form of human genetic information embrace patent ineligible subject matter. Even if a patent claim is directed to a gene as a composition of matter, that gene is defined in terms of its genetic sequence and it embodies a law of nature in the form of the relevant genetic sequence. Consequently, to the extent that patent claims to nucleic acids defined with respect to human gene sequences (or fragments thereof or variations therein) can pre-empt the use of a law of nature including uses such as determining a patient's genetic sequence, the patent claim is directed to unpatentable subject matter.

The opinions of the Court of Appeal illustrate a tension between (1) the majority's view of a patent claim directed to an isolated nucleic acid as a patentable composition of matter distinct from the gene in its native chromosome and (2) the dissent's view of such a claim as unpatentable in that it may pre-empt the use of a law of nature in the form of the claimed sequence information. Amicus suggests a rule of claim construction for human gene patents that would exclude as patent ineligible from the scope of a patent claim any subject matter to the extent it serves to pre-empt the use of a law of nature. Such a rule of claim construction could preserve claims to human genes, to the extent that they claim additional inventive subject matter beyond the patent ineligible law of nature—any portion of the sequence of the human gene—or otherwise cover compositions of matter in contexts where their use would not preempt a law of nature.

ARGUMENT

I. UNDER THE *MAYO* STANDARD, SEQUENCES OF HUMAN GENES AND GENE FRAGMENTS, AND VARIATIONS IN THEIR SEQUENCES, SHOULD BE CONSIDERED UNPATENTABLE LAWS OF NATURE.

The human genome is fundamentally information and DNA is simply nature's most efficient information storage and retrieval device.[4] Nucleic acids, principally DNA in the form of long sequences comprised of four nucleotide bases (adenine, thymine, guanine, and cytosine, or A, T, G and C), embody this information.[5] It consists of 23 pairs of chromosomes with each chromosome including a sequence of between approximately 50 million to 250 million base pairs long which together include approximately 20,000 human genes.[6] Each embodiment of

4. Recent reports of the encoding of the entire collection of Shakespeare's sonnets in a single DNA molecule (weighing much less than a billionth of a gram) illustrates the extraordinary data storage capacity of nucleic acids. *See, e.g.*, Ian Sample, *Shakespeare and Martin Luther King demonstrate potential of DNA storage*, The Guardian, Jan. 24, 2013, http://www.guardian.co.uk/science/2013/jan/23/shakespeare-sonnets-encoded-dna.

5. The decisions below discuss the nature of the human genome, nucleic acids and the genetic code in some detail, and InVitae will not revisit the science here except in a summary fashion.

6. While less than 2% of the full human genome is made up of genes, all of its 3 billion base pairs are inheritable information. *See, e.g.*, Brendan Maher, *ENCODE: The Human Encyclopedia*, Nature, Sept. 5, 2012, at 46, 46, available at http://www.nature.com/news/encode-the-human-encyclopaedia-1.11312. As its role becomes better understood, the clinical significance of the non-

a human gene in a human cell includes a genetic sequence providing the information necessary for the expression of a corresponding protein. Not every occurrence of a specific human gene, however, has an identical sequence and variations in those sequences can give rise to differences in the proteins expressed from those genes.

Even though much of the sequence information in the human genome is consistent from person to person, there are millions of specific variations which have been identified. In an ever-increasing number of cases, these individual variations or certain collections of variations are being identified as correlating to certain diseases or increased risks of contracting certain diseases.[7] The sequences of human genes, variations and mutations in these genes observed in individual patients are all naturally occurring information. Even fragments of more than a few nucleotides in length can act as distinctive "bookmarks" within the human genome and thus serve as a tool to reference a particular gene, and consequently they too are "laws of nature" which are highly relevant to the act of sequencing their corresponding gene. Similarly, the correlations between this genetic information and medically relevant information such as diagnosis of a disease, susceptibility to certain diseases, responsiveness to certain pharmaceuticals, and likelihood of adverse reactions to certain pharmaceuticals constitute naturally occurring information. Access to this genetic information

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gene sequences to patient care may come to rival that of human genes. *Id.* at 46-48.

7. BRAC1 and BRCA2, the subject matter of the patents at issue in the case below, are merely two examples of human genes for which certain variations have been identified as correlated with risk of certain diseases.

is becoming increasingly important in routine patient medical care as its costs have plummeted.[8]

This Court has held that while the Patent Act defines categories of patentable subject matter, 35 U.S.C. 101, laws of nature and pre-emption of their uses are nonetheless excluded. *Mayo*, 132 S. Ct. at 1294-1295 and 1302. Specifically, the Court in *Mayo* found that an observed correlation between the concentrations of certain metabolites of an administered drug in a patient and the clinical suitability of the administered dosage of that drug for that patient constituted a law of nature for the purposes of determining that patent claims directed to such correlations did not constitute patentable subject matter. *Id.*at 1296-1297. By analogy to the *Mayo* decision, human genomic information including a patient's sequence for a particular gene, the presence or absence of variations in the genetic sequence and associations between that sequence information and medically relevant consequences are all laws of nature. In comparison with the metabolite correlations at issue in *Mayo*, the sequences of human genes and information relating naturally occurring variations in human genes to diagnoses and other patient care are more fundamental and more of a law of nature than a correlation between metabolites and suitable dosage for a drug where the correlation is based upon administration of the particular drug.[9]

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8. While the first human genome was completed in 2003 at a cost of hundreds of millions of dollars, today, just ten years later the cost is approaching a thousand dollars. *See, e.g.*, Tucker, *supra* at 142; Harper, *supra*; Karabaliev, *supra*.

9. Other correlations with genetic information—such as use of certain genetic markers to identify patients who are suitable for a particular pharmaceutical treatment or susceptible to certain

II. PATENT CLAIMS TO HUMAN GENES, GENE FRAGMENTS AND VARIATIONS SHOULD BE CONSTRUED TO EXCLUDE AS UNPATENTABLE SUBJECT MATTER ALL GENETIC INFORMATION CONSTITUTING A LAW OF NATURE

Patent claims directed to human genes are frequently drafted such that the sole distinctive feature of the claim is the sequence of the gene or a fragment of the gene.[10] While such human gene claims are styled as claims to a composition of matter or molecule such as an "isolated gene" having a particular genetic sequence or an "isolated nucleic acid" having a particular genetic sequence, the defining characteristic of such human gene claims is presented with reference to the genetic sequence information embodied by such a molecule. In its holding below, the Federal Circuit majority emphasized the distinction between an isolated nucleic acid molecule having a sequence for a human gene (or a fragment of a human gene) and the same sequence as it appears naturally within a human chromosome. *Ass'n for Molecular Pathology v. U.S. P.T.O.*, 689 F.3d 1303, 1341-1344 (Fed. Cir. 2012). The majority's reliance upon the isolation of a claimed gene or gene fragment fails to account for the fact that such a claim to an isolated

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adverse effects of certain pharmaceuticals—would constitute correlations which are laws of nature analogous to the correlation found to be a law of nature in the *Mayo* decision.

10. Such gene sequences are typically defined in terms of a sequence of nucleotides or a sequence of amino acids for which the gene codes. By way of illustration, Claim 1 of U.S. Patent 5,747,282 reads as follows: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." 2J.A. 821.

gene may nonetheless be exploited to pre-empt a law of nature—the human gene sequence it embodies.

The pre-emptive effect of a patent claim is measured by the properly construed scope of the claim in the context of the statutorily defined categories of activities which constitute patent infringement. *See, e.g.*, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372-374 (1996). The Patent Act provides that the activities of, *inter alia*, making or using a claimed composition of matter constitute patent infringement. 35 U.S.C. 271. Consequently, activities involving the making or using of an isolated nucleic acid having the sequence of a claimed human gene (or human gene fragment) in the course of determining a patient's genetic sequence could be asserted to pre-empt the use of such a law of nature. For example, the determination of a patient's genetic sequence typically entails the steps of extracting genetic material from a biological sample (blood, saliva, biopsy, etc.) from the patient, digesting the genetic material into numerous fragments, selecting some or all of the fragments for analysis, making copies of the selected fragments and then reading the sequences of the fragments. Using a claim covering an isolated human gene fragment to stop the making of copies of such fragments and the using of such fragments in the course of determining a patient's genetic sequence information would pre-empt the use of a law of nature and therefore should be excluded from the patentee's monopoly provided by a patent. By contrast, to the extent that a claim referencing a human gene includes other inventive subject matter and/or does not serve to pre-empt the exploitation of a law of nature such other subject matter should remain patent eligible subject to

the other requirements governing patent eligibility under 35 U.S.C. 101 and this Court's precedents.

CONCLUSION

For the foregoing reasons, the *amicus curiae* InVitae Corporation respectfully suggests that the Court consider (i) adopting a rule of construction of patent claims to exclude from the scope of the claims that subject matter which serves to pre-empt the use or exploitation of a law of nature and (ii) confirming that human genetic information, including sequences, variations and correlations between such variations and medical consequences thereof, all constitute patent ineligible laws of nature.

Respectfully submitted,

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