1 Gene Patent History-1980

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TIME

Monday, Jun. 30, 1980

Science: Test-Tube Life: Reg. U.S. Pat. Off.

By John S. Demott

The Supreme Court protects the genetic engineers

When Thomas Jefferson, an an amateur scientist himself, wrote the nation's first patent law in 1793, he was deter mined to ensure that "ingenuity should receive a liberal encouragement." Under his law, "any new and useful art, machine, manufacture or composition of matter" was patentable and thus legally shielded from theft. Last week, in a 5-to-4 decision, the Supreme Court applied the Jeffersonian measure to one of the latest examples of human ingenuity. It ruled that new forms of life created in the laboratory could be patented.

The decision, climaxing an eight-year legal battle, should give a boost to an emerging industry, genetic engineering, which seeks to create new life forms. This promising field offers the prospect of advances in everything from medicine and food production to alternate energy forms. The court's ruling also revived fears — vastly exaggerated in the opinion of most responsible scientists — about the dangers of tampering with life.

The center of dispute was a new human-made variation of the common bacterium Pseudomonas. While working at General Electric's Schenectady, N.Y., labs in the early 1970s, Indian-born Microbiologist Ananda M. Chakrabarty made a significant discov ery. Chakrabarty knew that cer tain bacteria are able to break up hydrocarbons. What he found was that the genes responsible for this capacity are not contained in the bacterium's single chromosome, or principal repository of DNA, the genetic times Instead, they reside in small, auxiliary parcels of genes, called plasmids, elsewhere in the cell. Taking plasmids from three oil-eating bacteria, Chakrabarty transplanted them into a fourth, thereby creating a crossbred version with a voracious appetite for oil.

Freeze-dried until needed, then sprinkled on straw and tossed into the ocean, the superbugs could presumably make quick work of oil spills by breaking down the crude into harmless protein and carbon dioxide. Says Chakrabarty, 42, now a researcher at the University of Illinois Medical Center: "You can make tons of these microorganisms in a matter of days." Nor, he says, would the bacteria pose any danger. After the feast, they would die for want of oil.

When GE tried to patent the bacterium in 1972 under Chakrabarty's name,

U.S. patent officials balked. They argued, in effect, that if either Jefferson or Congress had intended life to be patentable, special laws would not have been needed to protect certain new plant hybrids like the Red American Beauty Rose. But when GE pressed its case, the Court of Customs and Patent Appeals rejected the Government's argument, and the Supreme Court last week went along with that position. As Chief Justice Burger explained, the issue is "not between living and inanimate things, but between products of nature—whether living or not —and human-made inventions."

Though GE was pleased by the decision, it seems in no rush to exploit the bug commercially. Ronald Brooks, head of the GE environmental unit where Chakrabarty did his work, says that the company would entertain licensing agreements with those who want to develop the oil eater. But he adds that GE does not see a market big enough for it to become directly involved.

Others are less hesitant. Awaiting the outcome of the GE appeal are patent applications for at least 100 different kinds of organisms or processes to make organisms. All are products of genetic engineering activities in more than a dozen companies and countless university laboratories in the U.S. and abroad. Most of this work does not involve the relatively simple process of plasmid reshuffling used by Chakrabarty, but the more complex and promising technique of recombinant DNA, or gene splicing. With it, scientists actually break apart DNA, using so-called restriction enzymes, and isolate certain desirable genes. These genes are then inserted into plasmids, again using enzymes, and transferred into another bacterium. The recipient bug, in effect, becomes a new life form with all the characteristics and capabilities carried by the spliced-in genes.

Even in its infancy, the technology has led to the making of new bacteria that are in fact microscopic chemical factories. Already the common intestinal bacterium E. coli, the favorite tool of such researchers, has been genetically "re-engineered" to produce human insulin and interferon, the antiviral protein that could be effective against several types of cancer, as well as the hormone that stimulates growth in humans. In the future, scientists should be able to use such reprogrammed bugs to meet other medical needs: manufacturing malaria vaccine, for example, or creating chemicals to heal burns, kill pain or stanch the flow of blood from wounds.

Yet the new technology should ixtend far beyond medicine.

Scientists are talking about creating bugs that will enable plants to "fix" nitrogen directly from the air, thereby reducing the dependence on fertilizers. Others could be created to make amino acids, a building block of proteins and thus a basic food source. Some organisms, like Chakrabarty's oil eater, might be developed to degrade metals and other materials; these could help mining companies leech ores from hard-to-reach veins or assist in the cleanup of such toxic waste sites as Love Canal. Even the energy crisis might be alleviated by the genetic engineers, who are devising new ways of using yeast to make alcohol, and other superbugs for making fuels, antifreeze compounds and plastics. Says Molecular Biologist Herman Lewis, the National Science Foundation's adviser on recombinant DNA: "Theoretically, any process occurring in nature can be harnessed for man's use. We could even learn how to duplicate photosynthesis, the basic energy-converting process in green plants." Basically, says Eli Lilly Vice President for Research Irving Johnson "You're talking about a process that could affect all living species. I can't think of a single event that is as broad as that, except maybe the discovery of atomic particles."

With so much research already going on, the Supreme Court's decision mainly gives formal sanction to what had been happening for some time, a classic example of the law's lagging behind technology. Millions of dollars have been invested without patent protection. Says Bernard Talbot, special assistant to the director of the National Institutes of Health: "Recombinant DNA work is going on in numerous labs. This would have gone on whatever the court decided." Chief Justice Burger himself acknowledged that a patent law "will not deter the scientific mind from probing into the unknown any more than Canute could command the tides."

The most important patent application now pending is for the key gene-splicing processes developed by Microbiologists Stanley Cohen of Stanford and Herbert Boyer of the University of California: both have signed over royalty rights to their respective universities, but Boyer is a major stockholder in Genentech Corp., a Bay Area genetic engineering firm, and obviously stands to make money from the process. No one quarrels with that. But there is a mixed view of just how much good will accrue from the introduction of patents to the infant industry.

Biochemist Ronald Cape, chairman of Berkeley's Cetus Corp., a rival firm, sees patents as increasing the "free flow of ideas." More companies and investors are sure to plunge into the expensive business with less fear of having ideas stolen, or at least with an assurance of legal recourse if they are. But others fear that just the opposite will happen: that scientists will be cautious about sharing information, long an essential part of the scientific process. Warns M.I.T.'s Jonathan A. King, a molecular biologist: "Now you have the prospect of keeping a strain [of bacteria] out of circulation until you have the patents." Wolfgang Joklik,

chairman of Duke University's department of microbiology and immunology, wants to see scientists rewarded for what they do. But he adds with concern, "I just don't want to see organisms patented for commercial exploitation. I would like to be sure that everything is available for basic research."

There will almost certainly be efforts to get around the patents of others through slight variations. Says James Watson, Nobel laureate and co-discoverer in the 1950s of the double-helix structure of DNA: "It will be awfully hard to show uniqueness, to prove that one man's microbe is really different from another's." That, says J. Leslie Glick, president of Genex Corp. in Bethesda, Md., could lead to modifying bacterial strains mainly for "defensive reasons, a waste of research." Lawyers especially stand to gain if patenting life becomes their way of making a handsome living. Quipped Stephen Turner, president of Bethesda Research Laboratories: "I call this the Patent Lawyer's Employment Act of 1980."

For others, the decision stirred renewed anxieties. They argue that altering life, to say nothing of patenting it, is not the wisest of human activities. Better, they say, to leave the doomsday bugs to fiction. Said the Peoples Business Commission, a Washington-based consumer group, in a hyperbolic press release greeting the court's decision: "The Brave New World that Aldous Huxley warned us of is now here." Nobel Laureate George Wald, a guru of various antiestablishment causes, echoed those concerns. If the GE bug ever gets loose in the world, he said, "it could digest petroleum that has not been spilled. You can't put bacteria on a leash once you introduce them into the environment."

Chakrabarty, who stands to make no money from his discovery because GE will own the patent, crisply dismisses such dissent. "I can't respond to imaginary scenarios," he told TIME Correspondent

David Jackson. He insists that his Pseudomonas is safe, although it was developed before the Government imposed strict containment rules for lab experiments with such organisms. Indeed, in the past few years, researchers in dozens of labs have been performing similar experiments, and as Burger put it, there has been no "gruesome parade of horribles" forecast by the naysayers to the new research. Yet with Shakespeare, Burger acknowledged, "It is sometimes better to 'bear those ills we have than fly to others that we know not of.' " If Hamlet's wisdom had prevailed, there probably would be no such thing as genetic engineering with all its potential for good. For that matter, there probably would be no science.

Patents on DNA have not caused the severe disruption of biomedical research

OWNING

By Gary Stix

There is a gene in your body's cells that plays a key role in early spinal cord development. It belongs to Harvard University. Another gene makes the protein that the hepatitis A virus uses to attach to cells; the U.S. Department of Health and Human Services holds the patent on that. Incyte Corporation, based in Wilmington, Del., has patented the gene of a receptor for histamine, the compound released by cells during the hay fever season. About half of all the genes known to be involved in cancer are patented.

Human cells carry nearly 24,000 genes that constitute the blueprint for the 100 trillion cells of our body. As of the middle of last year, the U.S. Patent and Trademark Office had issued patents to corporations, universities, government agencies and nonprofit groups for nearly 20 percent of the human genome. To be more precise, 4,382 of the 23,688 genes stored in the National Center for Biotechnology Information's database are tagged with at least one patent, according to a study published in the October 14, 2005, *Science* by Fiona Murray and Kyle L. Jensen of the Massachusetts Institute of Technology. Incyte alone owns nearly 10 percent of all human genes.

The survey of the gene database confirmed that the patenting of life is today well established. Yet it still strikes a lot of people as bizarre, unnatural and worrisome. "How can you patent my genes?" is often the first question that comes up. How can someone own property rights on a type of mouse or fish when nature, not humans, "invented" its genes? What happens to the openness of scientific research if half of all known cancer genes are patented? Does that mean that researchers must spend more time fighting in the courts than looking for a cure?

Ethicists, judges, scientists and patent examiners continue to immerse themselves in these debates, which will only grow more acute in a new era of personalized medicine and of genomics and proteomics research that examines the activities of many different genes or proteins at the same time. Doctors will rely increasingly on patented tests that let clinicians match genetically profiled patients with the best drugs. Investigators are already assessing the functioning of whole genomes. Potentially, many of the biological molecules deployed in these complex studies could come burdened with licensing stipulations that would prevent research leading to new therapies or that would fuel the nation's already robust health care inflation.

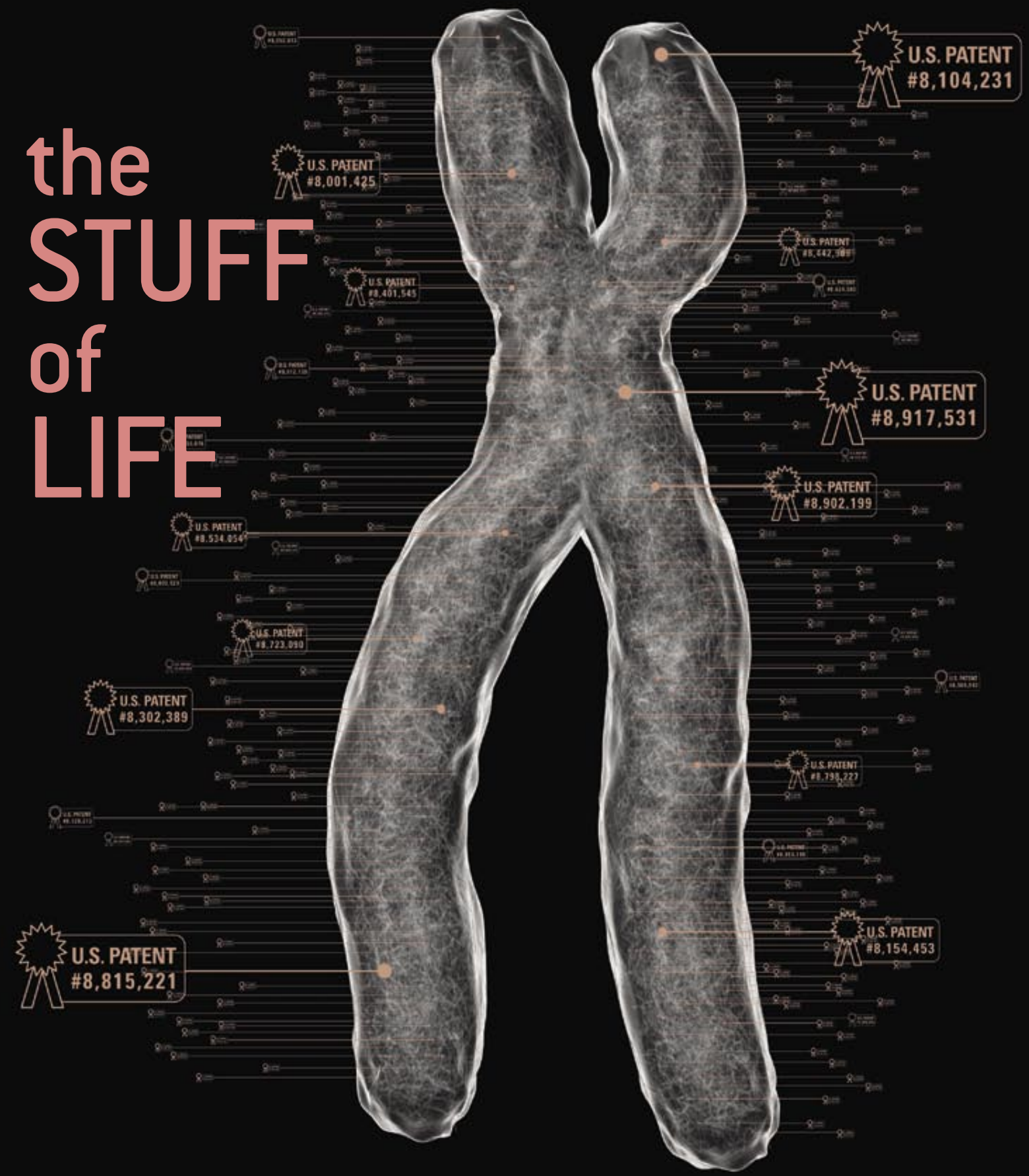
Anything under the Sun

THE QUESTION of "who owns life" has been asked before. But the M.I.T. researchers' taking stock of the intersection of intellectual property and molecular biology came fittingly at the 25th anniversary of a landmark decision by the U.S. Supreme Court that

BRYAN CHRISTIE DESIGN

and societal norms anticipated by critics. But the deluge may be yet to come

the STUFF of LIFE



held that living things are patentable—as long as they incorporate human intervention—in essence, that they are "made" by humans.

Ananda M. Chakrabarty, a General Electric engineer, filed for a patent in 1972 on a single strain of a *Pseudomonas* bacterium that could break down oil slicks more efficiently than if a bioremediation specialist deployed multiple strains for the task. Chakrabarty did not create his strain by what is usually meant by genetic engineering—in fact, recombinant DNA splicing methods were not invented until the year of his filing. Instead he tinkered with the bacterium in a more classical way and coaxed it to accept plasmids (rings of DNA) from other strains with the desired properties. The patent office rejected Chakrabarty's application, saying that "products of nature" that are "live organisms" cannot be patented.

By the time the Supreme Court decided to hear the appeal of the case in 1980, the landscape of molecular biology was changing radically. The splicing of DNA from one organism to another had become commonplace. A new firm called Amgen had formed that year to take advantage of the nascent technology of cutting and pasting DNA. A paper had just appeared detailing how recombinant methods had been used to synthesize interferon. Stanley Cohen and Herbert Boyer received a patent on a key technology for manipulating DNA. Technological boosterism was in the air. Congress passed the Bayh-Dole Act, which allows universities to engage in exclusive licensing agreements for technology they have patented. The Stevenson-Wydler Act let the National Institutes of Health and other federal agencies do the same.

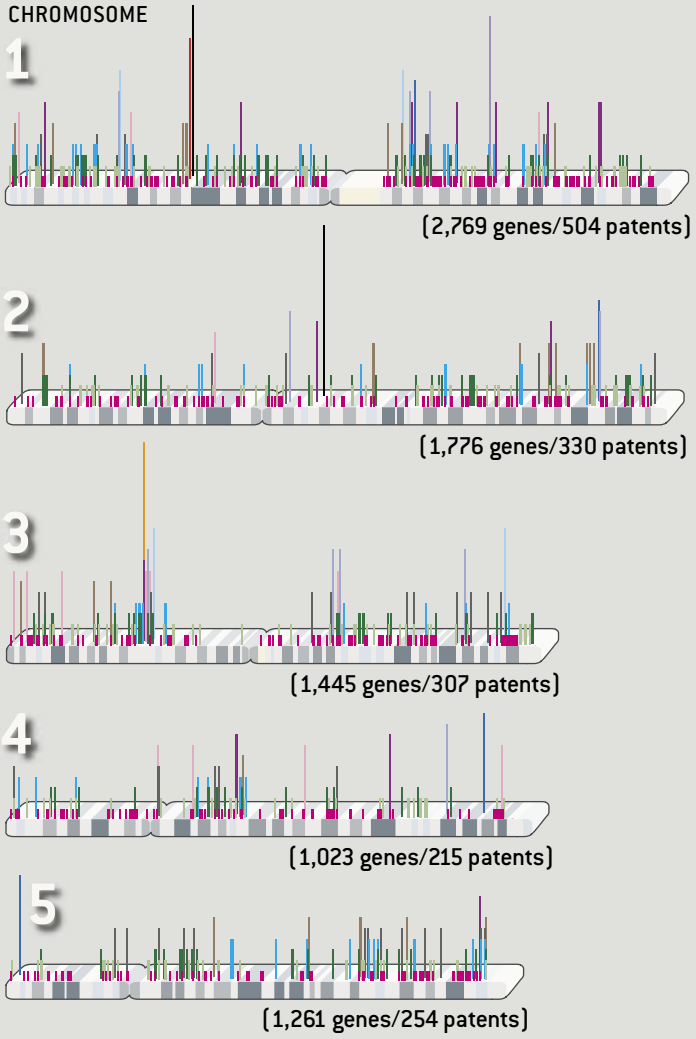
The Supreme Court justices received friend-of-the-court briefs arguing both for and against granting the claims in the Chakrabarty patent. Groups ranging from Genentech to the Regents of the University of California urged that the patent application be granted, citing benefits for pharmaceutical development, environmental remediation and new sources of energy, to name a few. The Peoples Business Commission, co-directed by activist Jeremy Rifkin, decried the commodification of life and described environmental disasters in the offing.

Overview/*Genetic Patenting*

- Last year marked the 25th anniversary of the landmark court decision that opened a floodgate of patenting on both DNA and even whole organisms.
- Nearly one fifth of the nearly 24,000 genes in the human genome have one or more patents on them. Almost 50 percent of known cancer genes have been patented.
- Overall the feared blocking of basic research by ownership of both gene-based tools and critical knowledge has not yet occurred, but it still could materialize as genomic and proteomic discoveries are commercialized.
- In the U.S., ethical issues about patenting life have been largely ignored in enacting legal decisions and policy, but they are still a consideration in Europe and Canada.

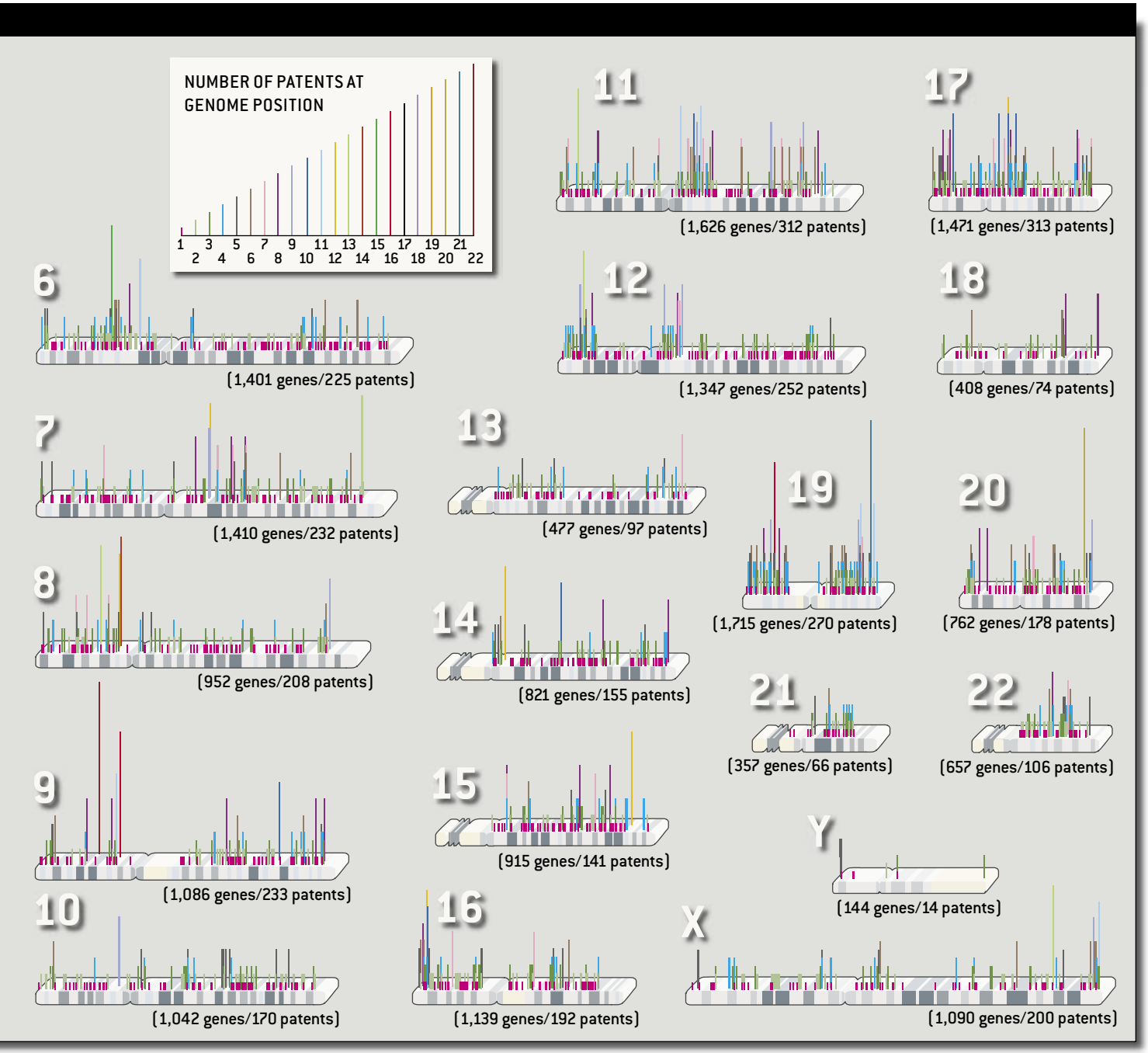
THE HUMAN PATENTOME

This map of the chromosomes offers an indication of how often genes have been patented in the U.S. Each colored bar represents the number of patents in a given segment of a chromosome, which can contain several genes. Patents can claim multiple genes, and one gene may receive multiple patents. As a result, the number of patents indicated for each chromosome does not necessarily match the sum of the values represented by the colored bars.



In the majority opinion, Chief Justice Warren Burger waved away the objections to patenting life as irrelevant, saying that "anything under the sun that is made by man" could be patented. The only question for the court was whether the bacterium was a "product of nature" or a human invention. "Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity," the opinion acknowledged. But as a "product of human ingenuity," Chakrabarty's engineered bacterium was different. Dismissing Rifkin's "gruesome parade of horribles," the court suggested that it was incapable of standing in the way of progress. "The large amount of research that has already occurred when no researcher had sure knowledge that patent protection would be available sug-

LAURIE GRACE; SOURCE: KYLE JENSEN AND FIONA MURRAY *Massachusetts Institute of Technology*



gests that legislative or judicial fiat as to patentability will not deter the scientific mind from probing into the unknown any more than Canute could command the tides," Burger noted.

After the close 5–4 ruling, industry and academia have looked to the broad interpretation of patentability in the Chakrabarty case as justification for patenting not only genes but other stuff of life, whole organisms and cells—including stem cells—to give but an incomplete list. The early patents on genes followed closely in the tradition of patents on chemicals. Incyte does not actually own the rights to the gene for the histamine receptor in your body but only to an "isolated and purified" form of it. (At times, patent examiners or courts have invoked the U.S. Constitution's prohibition of slavery to explain why a patent cannot be issued on an actual human or on his or her body parts.) A patent on an isolated and cloned gene and the protein it produces grants the owner exclusive rights to market the protein—say, insulin or human growth hormone—in the same way that a chemical manufacturer might purify a B vitamin and file for a patent on it.

Little Effort, Less Originality

BY THE 1990S the inexorable pace of technological development had overturned the status quo again. The high-speed sequencing technologies that emerged during that decade—which powered the Human Genome Project—muddied the simple analogy with chemical patenting.

An expressed sequence tag (EST) is a sequenced segment of DNA only a few hundred nucleotides long located at one end of a gene. It can be used as a probe to rapidly fish out the full-length gene from a chromosome. Researchers started filing patents on ESTs—sometimes by the hundreds. They did so without really knowing what the ESTs in question did: the applicants often guessed at the biological function of the gene fragments by poking through protein and DNA databases. "This involves very little effort and almost no originality," once remarked Bruce Alberts, former president of the National Academy of Sciences.

The justification for patenting DNA sequences of unclear function was that these ESTs could serve as research tools. Yet this reason was precisely what concerned much of the scientific community. Owners of patents on EST probes might demand that researchers license these tools, adding expense and red tape to medical research and possibly impeding the development of new diagnostics and therapeutics.

In a 1998 article in *Science,* Rebecca S. Eisenberg of the University of Michigan Law School and Michael A. Heller, now at Columbia Law School, worried about the emergence of an "anticommons," the antithesis of the traditional pool of common knowledge that all scientists share freely. Those concerns were heightened by the audacious scope of some of these applications, which staked out not only the ESTs but any DNA that resides adjacent to them. Such a claim could translate, in theory, into granting property rights for an entire chromosome.

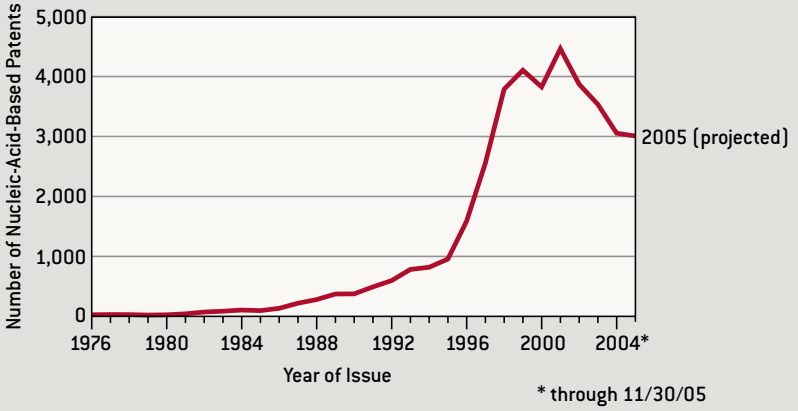
But a further, more intellectual objection to the concept of these patents was that the use of ESTs to pin down the location of genes actually occurs in a database, not in a laboratory. The value of ESTs exists more as information than as one of the tangible "processes, machines, manufactures and compositions of matter" that are eligible for patenting. Abstract ideas have traditionally been considered outside the realm of patentable subject matter, although a number of federal court cases have blurred this distinction during the past 10 years.

Allowing information to be patented would tend to undermine the balancing act that is a cornerstone of the whole system. In exchange for a 20-year monopoly, the patent applicant must disclose how to make an invention so that others can use that knowledge to improve on existing technology. But how does the traditional quid pro quo work if the information disclosed to others is the patented information itself? Does the

WHO OWNS THE PATENTS?

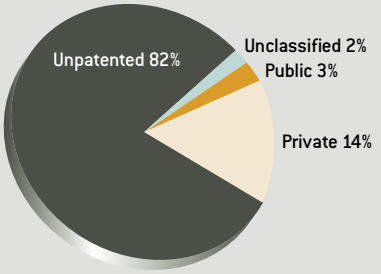
YEARLY U.S. PATENTS RELATED TO DNA OR RNA

The granting of patents involving nucleic acids, including from nonhumans, peaked in 2001 and then declined (*graph*), probably because of tightening requirements. The holders of many of the patents are listed in the table (*right*).



PATENTS ON HUMAN GENES

As the pie chart shows, private interests in the U.S. were the largest holders of patents on the 23,688 human genes in the National Center for Biotechnology Information database in April 2005.



LARGEST PATENT HOLDERS	NUMBER OF PATENTS†
University of California	1,018
U.S. government	926
Sanofi Aventis	587
GlaxoSmithKline	580
Incyte	517
Bayer	426
Chiron	420
Genentech	401
Amgen	396
Human Genome Sciences	388
Wyeth	371
Merck	365
Applera	360
University of Texas	358
Novartis	347
Johns Hopkins University	331
Pfizer	289
Massachusetts General Hospital	287
Novo Nordisk	257
Harvard University	255
Stanford University	231
Lilly	217
Affymetrix	207
Cornell University	202
Salk Institute	192
Columbia University	186
University of Wisconsin	185
Massachusetts Institute of Technology	184

† as of 9-14-05

LAURIE GRACE; SOURCES: KYLE JENSEN AND FIONA MURRAY *Massachusetts Institute of Technology* (*pie chart* and *graph*); LORI PRESSMAN, ROBERT M. COOK-DEEGAN AND LEROY WALTERS ET AL. IN *NATURE BIOTECHNOLOGY* (IN PRESS) AND MELISSA SOUCY *Kennedy Institute of Ethics, Georgetown University* (*table*)

PATENTING LIFE: A CHRONOLOGY

The patent system—both courts and patent examiners—has always wrestled with the question of what is truly an invention (and therefore deserving of a patent) and what constitutes a mere attempt to expropriate in unaltered form a physical law or material from the natural world, a reason for rejecting an application.

1889
The commissioner of patents determines that plants, even artificially bred ones, are "products of nature," and therefore ineligible for patenting. The applicant in this case—*Ex parte Latimer*—had tried to patent fibers separated from the plant and was turned down


Iris

1930
The U.S. Congress passes the Plant Patent Act, which allows the patenting of new plant varieties that reproduce asexually

1948
A Supreme Court ruling held that simply combining bacteria does not count as an invention (*Funk Brothers Seed Company v. Kalo Inoculant Company*)

1971
Cetus, the first biotechnology company, opens its doors

Continued on next page

mere act of using that information in the course of conducting scientific research run the risk of infringement?

In response to some of these pressures, in 2001 the U.S. patent office made final new guidelines that directed examiners to look for "a specific and substantial utility" in granting biotechnology patents. In most other technological pursuits, the requirement that a patent be useful is secondary to criteria such as whether an invention is truly new, because most inventors do not seek protection for worthless inventions. In the arena of life patents, the assessment of an invention's usefulness has become a crucial filter to maintain a check on patent quality. Designating a sequence of DNA simply as a gene probe or chromosome marker is not enough to meet the new rules.

These changes have had an effect. So far only a small number of EST patents have been issued, according to the NAS. An important affirmation of the patent office's approach to weeding out useless and overly broad patents came in a decision on September 7, 2005, by the U.S. Court of Appeals for the Federal Circuit (CAFC), which hears appeals of patent cases. The court upheld the patent office's denial of Monsanto's application for a patent for five plant ESTs that were not tied to a given disease. The patents would have amounted to "a hunting license because the claimed ESTs can be used only to gain further information about the underlying genes," wrote federal circuit chief judge Paul Michel.

Data on the extent of a feared anticommons have just begun to emerge in recent months. A survey performed as part of an NAS report—"Reaping the Benefits of Genomic and Proteomic Research," released in mid-November 2005—received responses from 655 randomly selected investigators from universities, government laboratories and industry about the effect of life patents on genomics, proteomics and drug development research. The study found that only 8 percent of academics indicated that their research in the two years prior had anything to do with patents held by others; 19 percent did not know if their research overlapped; and 73 percent said that they did not need to use others' patents. "Thus, for the time being, it appears that access to patents or information inputs into biomedical research rarely imposes a significant burden for academic biomedical researchers," the report concluded.

The number of patents actively being sought has also declined substantially. Patents referring to nucleic acids or closely related terms peaked at about 4,500 in 2001, according to a recent report in *Nature Biotechnology,* and declined in four subsequent years—a trend that may result, in part, from the patent office's tightening of its utility requirement [*see box on opposite page*].

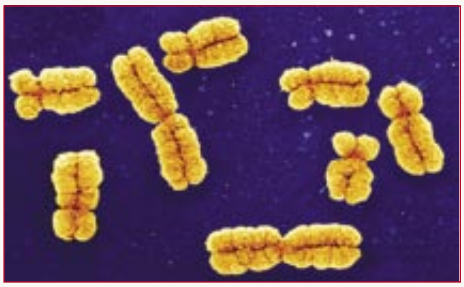
Some of the downturn may relate to the success of a de facto open-source movement in the biomedical sciences, akin to the one for information technologies. In 1996 scientists from around the world in both the public and private sectors devised what are referred to as the Bermuda Rules, which specify that all DNA sequence information involved in the Human Genome Project should be placed immediately into the public domain. Data sharing was later encouraged in other large-scale projects, such as the Single Nucleotide Polymorphism Consortium, which mapped genetic variation in the human genome. In some cases, researchers have taken out patents defensively to ensure that no one else hoards the knowledge. Both companies and public health groups involved with discovering and sequencing the SARS virus are trying to form a "patent pool" to allow nonexclusive licensing of the SARS genome.

This embrace of the public domain torpedoed the idea of building a business on public information. Both Celera Genomics and Incyte—two leaders in the genomics field—restructured in the early years of the new century to become drug discovery companies. J. Craig Venter, who spearheaded the private effort to sequence the human genome, left Celera and turned into an open critic. "History has proven those gene patents aren't worth the paper they were written on, and the only ones who made money off them were the patent attorneys," Venter commented at a 2003 conference.

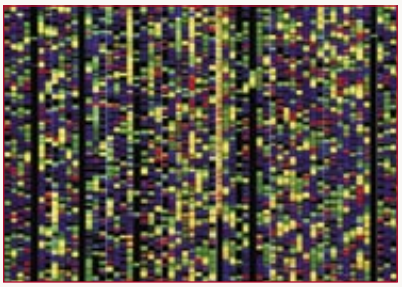
A patent thicket that blocks basic research has also failed to materialize because academics tend not to respect intellec-

1980
The Supreme Court rules that Ananda Chakrabarty's bacterium is not a "product of nature" and so can be patented; other living things "made by man" are declared patentable as well

Ananda Chakrabarty



Human chromosomes



DNA sequencing

1990
The Human Genome Project is launched

1996
Both public- and private-sector scientists from all over the world involved in DNA sequencing pass a resolution—the Bermuda Rules—that states that "all human genomic sequence information, generated by centers funded for large-scale human sequencing, should be freely available and in the public domain"

Congress passes the Bayh-Dole Act (the Patent and Trademark Laws Amendment), which allows universities to enter into exclusive licensing for their intellectual property

1988
Harvard University gets a patent for the OncoMouse, a rodent with a gene inserted that predisposes it to cancer

tual property. Noncommercial research, in their view, receives an exemption. Yet a 2002 case decided by the CAFC—*Madey v. Duke*—disabused universities and other nonprofit institutions of any notion of special status. The court decided that noncommercial research furthers the "legitimate business objectives" of a university, and so both research tools and materials, which would include DNA, do not merit an exemption. (An exemption does exist for research that is specific to preparing an application to file for a new drug.)

Patent holders generally have little interest in beating down lab doors to track down infringers. In the wake of the *Madey* decision, the level of notification from patent owners has picked up a bit, according to the NAS survey, but this increase has not caused major disruption. A growing awareness of the absence of an exemption, however, could lead to a more restrictive research environment, which is why the NAS panel recommended that Congress put in place a statutory research exemption.

Major intellectual-property hurdles may begin to appear as genomics and proteomics—fields in which many genes or proteins are studied together—reach maturation. "The burden on the investigator to obtain rights to the intellectual property covering these genes or proteins could become insupportable, depending on how broad the scope of claims is and how patent holders respond to potential infringers," the NAS panel remarked.

Genomics and proteomics are only starting to bear fruit in the form of medical diagnostics and drugs. "You really get ownership issues coming up when things get closer to market," says Barbara A. Caulfield, general counsel for Affymetrix, the gene-chip company that has opposed DNA patenting because it could impede research with its products.

Already, Caulfield says, examples of patents with a very broad scope burden both industry and academia. Genetic Technologies Ltd., an Australian company, holds patents that it is using to seek licensing arrangements from both companies and universities that conduct research on the noncoding portion of the genome. The breadth of its patents—covering methods of obtaining information from the approximately 95 percent of the genome that is sometimes erroneously called junk DNA—would make most scientists rub their eyes. Genetic Technologies, however, has already entered into licensing arrangements with the likes of U.S. biotechnology giant Genzyme and Applera, the parent of Celera and Applied Biosystems.

Keeping the *Ordre Public*

U.S. POLICYMAKERS and courts have, in general, taken a no-holds-barred approach to the commercialization of new biotechnologies. Though often debated by government advisory panels, ethical, philosophical and social questions have seldom entered into actual decision making about whether to extend patent protection to living things. In *Chakrabarty,* the Supreme Court justified its decision, in part, by quoting the statement of the first patent commissioner, Thomas Jefferson, that "ingenuity should receive a liberal encouragement."

One of the obvious questions raised by the *Chakrabarty* decision was, Where does patenting life stop? Does it extend to creatures above the lowly *Pseudomonas* on the phylogenetic tree? In 1988, eight years after *Chakrabarty,* the patent office issued No. 4,736,866, the patent for the Harvard OncoMouse, which contained a gene that predisposed the animal to contract cancer, a valuable aid in researching the disease. The justification for granting the patent could be traced directly to the reasoning of the justices in *Chakrabarty:* the addition of the oncogene meant that this was a mouse "invented" by a human.

Not every country has handled the issue of patenting higher organisms with the same utilitarian bent demonstrated by U.S. courts and bureaucrats. Much more recently, Canada reached an entirely different decision about the small mammal with the extra gene. On appeal, the Supreme Court of Canada rejected the Harvard OncoMouse patent. In 2002 it decided that the designation "composition of matter"—in essence, an invented product that is eligible for patenting—should not apply to the mouse. "The fact that animal life forms have numer-

TED SPIEGEL *Corbis (Chakrabarty)*; BIOPHOTO ASSOCIATES/PHOTO RESEARCHERS, INC. *(chromosomes)*; DAVID PARKER *Photo Researchers, Inc. (DNA sequencing)*

Cancer mice

2000
A working draft of the human genome is announced

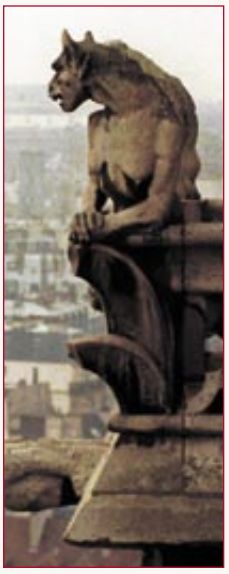
Heads of state Bill Clinton and Tony Blair issue a statement that "raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere." Biotechnology stocks drop sharply

2001
The U.S. patent office issues final guidelines that raise the standard for usefulness and the amount of disclosure of details of an invention needed for granting, in part, patents—an action prompted by the many patent applications on gene fragments

2002
The Supreme Court of Canada hears an appeal that results in the refusal of a patent for the Harvard OncoMouse

2003
Congress puts a provision in the patent office budget prohibiting patents on a "human organism," a codification of the office's existing policy

2005
The patent office issues a final rejection of a patent application filed by Stuart Newman and Jeremy Rifkin for a hypothetical chimera: a part-human, part-animal hybrid. The two opponents of patents on living things want to obtain a patent to block anyone from ever creating such an animal



Chimera

ous unique qualities that transcend the particular matter of which they are composed makes it difficult to conceptualize higher life forms as mere 'compositions of matter,' " Justice Michel Bastarache asserted. "It is a phrase that seems inadequate as a description of a higher life form."

Europe, too, was more circumspect than the U.S. about embracing the cancer mouse. The European Patent Office narrowed the scope of the OncoMouse patent to cover only mice instead of all rodents. It did so by invoking a provision of its patent law that has no comparable clause in U.S. statutes. It brought to bear Article 53 of the European Patent Convention, which bars patents that threaten " '*ordre public*' or morality."

European regulators have also eviscerated the patent portfolio on breast cancer genes held by the Utah-based Myriad Genetics. In the U.S., patents on diagnostic genes, more than other DNA patents, have inhibited both research and clinical medicine. Myriad has used its patents to stop major cancer centers from devising inexpensive "home-brew" tests for the breast cancer genes *BRCA1* and *BRCA2*. In Europe, a coalition of research institutes challenged Myriad's patents, invalidating some and limiting others. Because of the paring back of Myriad's rights, the tests are now free for everyone except Ashkenazi Jewish women, who must pay Myriad's licensing fees. The mutations that are still covered by Myriad's remaining patents are most commonly found in Ashkenazi women. By law, a doctor must ask a woman if she is an Ashkenazi Jew, which has provoked howls from geneticists.

A replay of these scenes is unlikely in the U.S. In *Chakrabarty,* the Supreme Court remarked that the type of ethical questions raised by Rifkin's group should be addressed by Congress, but most legislative attempts have foundered so far. If any fundamental change does come, it will most likely happen through the Supreme Court's examination again of one of the key decision points in *Chakrabarty:* the definition of the ever shifting line between laws of nature and invention.

Legal analysts are eagerly awaiting a Supreme Court decision expected this year that may help clarify how far to push back the borders of what was once considered unpatentable. The high court has agreed to hear a case—*Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*—that will determine whether the simple correlation of an elevated level of the amino acid homocysteine with a deficiency of two B vitamins "can validly claim a monopoly over a basic scientific relationship used in medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result," in the language of Laboratory Corp., the plaintiff. The patent claim covers only the correlation itself, not the electrical and mechanical equipment that is used to carry out the test. The case is of intense interest not only to a biotechnology industry in which raw information has become increasingly valuable but also to the information technology industry, where the patentability of software and business methods has also been a matter of dispute. "This could have an impact not just on DNA patenting but on emerging areas such as nanotechnology and synthetic biology," says Arti K. Rai, a law professor at Duke University.

Friend-of-the-court briefs will argue that the Jeffersonian doctrine of promoting invention should prevail. But the case also resonates with *Chakrabarty* and case law that preceded it. As technology advances, courts will have to come to grips again and again with defining the meaning of the phrase "anything under the sun that is made by man." Should tinkering with a single gene in a mouse—or the mere act of detecting an inverse relation between two molecules—suffice always to confer on an "inventor" a limited monopoly for two decades? SA

MORE TO EXPLORE

Who Owns Life? Edited by David Magnus, Arthur Caplan and Glenn McGee. Prometheus Books, 2002.

Intellectual Property Landscape of the Human Genome. Kyle Jensen and Fiona Murray in *Science,* Vol. 310, pages 239–240; October 14, 2005.

Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health. Committee on Intellectual Property Rights in Genomic and Protein Research and Innovation. National Research Council, National Academies Press, 2005.

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The New York Times

June 13, 2013

Justices, 9-0, Bar Patenting Human Genes

By ADAM LIPTAK

WASHINGTON — Human genes may not be patented, the Supreme Court ruled unanimously on Thursday. The decision is likely to reduce the cost of genetic testing for some health risks, and it may discourage investment in some forms of genetic research.

The case concerned patents held by Myriad Genetics, a Utah company, on genes that correlate with an increased risk of hereditary breast and ovarian cancer. The patents were challenged by scientists and doctors who said their research and ability to help patients had been frustrated.

After the ruling, at least three companies and two university labs said that they would begin offering genetic testing in the field of breast cancer.

“Myriad did not create anything,” Justice Clarence Thomas wrote for the court. “To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.”

The course of scientific research and medical testing in other fields will also be shaped by the court’s ruling, which drew a sharp distinction between DNA that appears in nature and synthetic DNA created in the laboratory. That distinction may alter the sort of research and development conducted by the businesses that invest in the expensive work of understanding genetic material.

The decision tracked the position of the Obama administration, which had urged the justices to rule that isolated DNA could not be patented, but that synthetic DNA created in the laboratory — complementary DNA, or cDNA — should be protected under the patent laws. In accepting that second argument, the ruling on Thursday provided a partial victory to Myriad and other companies that invest in genetic research.

The particular genes at issue received public attention after the actress Angelina Jolie revealed in May that she had had a preventive double mastectomy after learning that she had inherited a faulty copy of a gene that put her at high risk for breast cancer.

The price of the test, often more than $3,000, was partly a product of Myriad’s patent, putting it out of reach for some women.

That price "should come down significantly," said Dr. Harry Ostrer, one of the plaintiffs in the case, as competitors start to offer their own tests. The ruling, he said, "will have an immediate impact on people's health."

Myriad's stock price was up about 10 percent in early trading, a sign that investors believed that parts of the decision were helpful to the company. But the stock later dropped, closing the day down by more than 5 percent.

In a statement, Myriad's president, Peter D. Meldrum, said the company still had "strong intellectual property protection" for its gene testing.

The central question for the justices in the case, Association for Molecular Pathology v. Myriad Genetics, No. 12-398, was whether isolated genes are "products of nature" that may not be patented or "human-made inventions" eligible for patent protection.

Myriad's discovery of the precise location and sequence of the genes at issue, BRCA1 and BRCA2, did not qualify, Justice Thomas wrote. "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated," he said. "It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes."

"Groundbreaking, innovative or even brilliant discovery does not by itself satisfy the criteria" for patent eligibility, he said.

Mutations in the two genes significantly increase the risk of cancer. Knowing the location of the genes enabled Myriad to develop tests to detect the mutations. The company blocked others from conducting tests based on its discovery, filing patent infringement suits against some of them.

"Myriad thus solidified its position as the only entity providing BRCA testing," Justice Thomas wrote.

Even as the court ruled that merely isolating a gene is not enough, it said that manipulating a gene to create something not found in nature is an invention eligible for patent protection.

"The lab technician unquestionably creates something new when cDNA is made," Justice Thomas wrote.

He also left the door open for other ways for companies to profit from their research.

They may patent the methods of isolating genes, he said. "But the processes used by Myriad to

isolate DNA were well understood by geneticists," Justice Thomas wrote. He added that companies may also obtain patents on new applications of knowledge gained from genetic research.

Last year, a divided three-judge panel of a federal appeals court in Washington ruled for the company on both aspects of the case. All of the judges agreed that synthesized DNA could be patented, but they split over whether isolated but unaltered genes were sufficiently different from ones in the body to allow them to be protected. The majority, in a part of its decision reversed by the Supreme Court, said that merely removing DNA from the human body is an invention worthy of protection.

"The isolated DNA molecules before us are not found in nature," Judge Alan D. Lourie wrote. "They are obtained in the laboratory and are man-made, the product of human ingenuity."

Long passages of Justice Thomas's opinion read like a science textbook, prompting Justice Antonin Scalia to issue a brief concurrence. He said the court had reached the right result but had gone astray in "going into fine details of molecular biology."

"I am unable to affirm those details on my own knowledge or even my own belief," Justice Scalia wrote.

The ruling on Thursday followed a unanimous Supreme Court decision last year that said medical tests relying on correlations between drug dosages and treatment were not eligible for patent protection.

Natural laws, Justice Stephen G. Breyer wrote for the court, may not be patented standing alone or in connection with processes that involve "well-understood, routine, conventional activity."

NATURE BIOTECHNOLOGY | FEATURE | PATENTS

A patent perspective on US stem cell research

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Nature Biotechnology **32**, 633–637 (2014) doi:10.1038/nbt.2945
Published online 08 July 2014

What are the implications of recent US Supreme Court decisions on the patent eligibility of stem cells?

Introduction

Research into stem cells has developed greatly since the first proof, more than 50 years ago, of their existence[1]. Stem cells are regarded as promising agents in personalized medicine owing to their self-renewing and pluripotent properties. Human embryonic stem cells (ESCs), adult stem cells and induced pluripotent stem cells (iPSCs) have been extensively studied for their potential uses in personalized medicine, and stem cell technology has been extended successfully from the laboratory to clinic—as in the generation, for example, of an artificial trachea from epithelial cells and chondrocytes derived from a patient's own mesenchyme stem cells[1], and of retinal-pigmented epithelium cells derived from human ESCs for the treatment of age-related macular degeneration[2].

As estimated on ClinicalTrials.gov, a US government website providing information of clinical studies worldwide, there have been more than 4,490 clinical trials employing stem cells. Thirty-four trials were found to include the term 'embryonic', suggesting that ESCs are rarely used for direct treatment of patients. By contrast, adult stem cells have been proven useful in treating patients with a wide range of diseases, including cancers, autoimmune diseases and neurodegenerative diseases, as well as wounds and injuries. Moreover, with reports of the creation of human stem cells from somatic cells[3] and the absence of ethical concern over the use of adult stem cells and iPSCs, these cells are likely to be frequently engaged in future therapeutics.

But despite the optimistic outlook for stem cell research, the risk involved is still extremely high owing to the costs and time for research and development[4]. It is therefore essential for researchers to have an articulated intellectual property strategy for the protection of their inventions as well as to attract financial support for R&D.

The United States has long been an active region for stem cell research and patenting[5]. In this article, we analyze two recent US Supreme Court decisions and discuss the possible impact, from a stem cell perspective, of the cases on patenting biotechnological or pharmaceutical inventions. We then suggest a course for applying for patents in light of the recent case law. The two fundamental questions involved are: how and when is a process applying law(s) of nature patentable, and how and when is a product of nature patentable?

Mayo v. Prometheus

Mayo v. Prometheus[6] concerned patents owned by Prometheus Laboratories concerning the use of thiopurine drugs in the treatment of autoimmune diseases. At the time of invention, it was already known that blood levels of 6-thioguanine and its nucleotides (6-TG) and 6-methylmercaptopurine (6-MMP) correlated with the likelihood that a particular dosage of a thiopurine drug could cause harm or prove ineffective. However, the precise correlations between the metabolite levels and likely harm or ineffectiveness are not known. The patents at issue set forth method claims that embody the findings that identified these correlations with some precision[6].

On 20 March 2012, the Supreme Court ruled that the claims simply recited a natural law that is patent-ineligible subject matter under 35 USC §101, thereby rendering the patent invalid[6]. But although laws of nature are patent ineligible, a process applying laws

of nature may be patentable[7], provided it contains “inventive concept” to ensure that the process amounts to significantly more than a patent upon the natural law itself[8]. The court viewed Prometheus's patents as setting forth a law of nature—namely the correlation between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm. Although it requires human action—the administration of a thiopurine drug—to trigger a manifestation of this correlation in a particular person, the relation itself exists in principle apart from any human action[6]. Hence, the question before the court became: did the patent claims add enough to their statements of the natural correlations for the claimed method to qualify as a patent-eligible process that applies the natural law[6]?

The answer from the court was no. After analyzing the individual steps of the claim (Table 1), the court concluded that “the steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field. ...upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries”[6]. The court reasoned that the steps in the claim do not add anything specific to the laws of nature and do not lead to an inventive application of them; that is, the steps are not sufficient to transform the claimed method to a patent-eligible process.

Table 1: Analysis of the three individual steps of Prometheus's claim

In light of *Mayo*, the US Patent and Trademark Office (USPTO) issued a memorandum on 3 July 2013 to provide guidelines to patent examiners on the determination of subject-matter eligibility of process claims involving laws of nature[8]. The memo instructs that a claim focusing on use of a natural principle must also include additional elements or steps to show that the inventor has practically applied, or added something significant to, the natural principle itself. The additional steps must be sufficient to ensure that the claim amounts to significantly more than the natural principle itself by including one or more elements or steps that limit the scope of the claim and do more than generally describe the natural principle with generalized instructions to 'apply it'. The additional elements or steps must narrow the scope of the claim such that others are not foreclosed from using the natural principle (a basic tool of scientific and technological work) for future innovation. Elements or steps that are well understood, purely conventional and routinely taken by others to apply the natural principle, or that only limit the use to a particular technological environment (field of use), would not be sufficiently specific. Patentable claims are those that confine their reach to particular patent-eligible applications of those natural laws[8].

Association for Molecular Pathology v. USPTO and Myriad Genetics

Association for Molecular Pathology v. USPTO and Myriad Genetics is a case of significant impact because it touches on the USPTO's 30-year practice of granting gene patents. It was estimated that the USPTO had issued patents covering more than 40,000 genes by 2005 (ref. 9).

On 12 May 2009, 20 entities, including the Association for Molecular Pathology, filed a lawsuit against the USPTO and Myriad Genetics challenging the validity of 15 claims in seven Myriad patents related to *BRCA1* and *BRCA2*, two human genes that were found to be associated with increased risk of breast and ovarian cancers[10] (Table 2). The plaintiffs claimed that the human genes were materials found in nature and thus not a patentable subject matter under 35 USC §101. They also contended that the method claims have no transformative steps and therefore only cover abstract and mental steps. The district court invalidated the claims and ruled that isolated DNA containing naturally occurring sequences is not patentable subject matter.

Table 2: Myriad's claims challenged by the Association for Molecular Pathology

The case was appealed and heard twice by the US Court of Appeals for the Federal Circuit[11, 12], which held that the isolated DNA claims are patent eligible, with each of the three judges on the Federal Circuit panel writing separately on the case (Table 3). The three method claims were analyzed in a similar fashion as in *Mayo*, with consideration on whether transformative steps are provided to turn the processes from abstract ideas to patentable subject matter. The court decided that the “analyzing” or “comparing” claims are patent ineligible because they claim only abstract processes. Nonetheless, the Federal Circuit overturned the district court's decision and ruled that the “screening” claim is patent eligible because there is a transformative step involved. Table 3 summarizes the key opinions on the patent eligibility of Myriad's claims from various judges and courts.

Table 3: Summary of opinions on Myriad's claims from various authorities

A petition for certiorari was filed with respect to the Federal Circuit's second decision, and the US Supreme Court revisited the case on patent eligibility of the isolated DNA and cDNA claims. The Supreme Court unanimously ruled on 13 June 2013 that an isolated DNA with identical sequence to natural DNA is not a patentable subject matter[13]. The court held that even though the company had found an important and useful gene, separating that gene from its surrounding genetic material is not an act of invention, and extensive effort alone was not sufficient to satisfy the demands of 35 USC §101. On the other hand, cDNA is patent eligible because it is not naturally occurring. However, a short strand of cDNA that is indistinguishable from natural DNA may not be patentable[13].

The USPTO acknowledged in a memo to its patent examiners that *Myriad* would significantly change the examination policy regarding nucleic acid–related technology[14]. Claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, are not patentable[13]. On 4 March 2014, the USPTO issued an examination guideline[15] on patenting natural matters including laws of nature/natural principles, natural phenomena and natural products. Echoing the previously issued memos in light of *Mayo* and *Myriad*[8, 14], the new guideline instructs that claimed natural matters must be “significantly” or “markedly” different from what exists in nature to be patent eligible. Under the guideline, a claimed natural product must possess a structural difference to be “markedly” different, whereas a functional difference does not necessarily lead to a marked difference. Patent-eligible applications or uses of natural matters must be significantly limited and do more than general instructions to apply or use the natural matters.

On 9 May 2014, the USPTO held a forum to collect public feedback on the guideline and interpretation of the Supreme Court precedents[16]. Various public parties profoundly expressed their dissent over the guideline and contended that the USPTO has misinterpreted or overlooked some of the precedent cases[17]. The USPTO indicated that the office is “open to hearing alternative interpretations and considering examples”[16].

Impact of *Mayo* and *Myriad*

The full impact of *Mayo* and *Myriad* on biotech and pharma patenting is not yet known, as much depends on subsequent measures taken by the USPTO and Congress. Nevertheless, it is beneficial for inventors to recognize the issues of patent eligibility in question and the rationale behind the rulings.

First, whether an isolation of subject matter is a patent-ineligible discovery or patent-eligible invention is essentially determined by whether the isolated product is identical to the naturally occurring product. The Supreme Court held that Myriad did not create or alter any of the genetic information encoded in the *BRCA1* and *BRCA2* genes. The isolated DNA has a sequence identical to that of the naturally occurring DNA and thus not a “new composition of matter” under §101. Human effort in discovering and isolating the DNA is insufficient to turn the isolated DNA into a patent-eligible subject matter under §101. By contrast, cDNA is patent eligible because it is not naturally occurring but created in the lab (except those very short fragments of DNA that have sequences identical to those of the naturally occurring DNA)[13].

Applying this reasoning to determine the patentability of stem cells isolated from a human body, one has to consider whether the isolated stem cells are fundamentally identical to the natural cells in our body. For instance, do the isolated embryonic and adult stem cells have more pluripotency and/or a higher rate of regeneration than the stem cells of the body? Do the isolated stem cells have a distinct structure (e.g., genomic or proteomic profile) from the natural stem cells? Or do the isolated stem cells have any features that are not found in the stem cells of the body? One may argue that the isolation of stem cells has opened up the potential for *in vitro* use of the stem cells. However, in view of *Myriad*, it may not be persuasive, as the possible new uses of the isolated DNA and cDNA were not considered to be as crucial as their intrinsic properties[13]. Conversely, iPSCs induced from somatic cells or ESCs derived by somatic cell nuclear transfer are more inclined to be patentable subject matter because they are not naturally occurring and are products resulting from human intervention.

It should be noted that 35 USC §101 is not the exclusive criterion for determining patentability. An isolated product that qualifies as patentable subject matter under §101 must also fulfill other statutory requirements such as novelty and nonobviousness, and the patent application needs to fulfill the enablement and written description requirements. In other words, the applicant must demonstrate a novel and nonobvious invention with clear and sufficient support in the patent application.

Second, the patent eligibility of a process applying abstract mental processes or laws of nature lies in whether the physical steps in the claims add enough to transform the abstract mental processes or laws of nature into an inventive application of these processes and laws. As instructed in the USPTO's memo[8], the fundamental inquiry for determining the patent eligibility of a process claim involving a natural principle (i.e., a law of nature, a natural phenomenon or a natural correlation) is: is the claim merely a description of and general instruction to apply the natural principle, or is it a practical application of a natural principle that amounts to more than the natural principle itself?

The following must be satisfied for a process claim to be patent eligible: (i) the claim is not merely a generalized statement or instruction to apply the natural principle; (ii) the claim contains at least one additional element or step that imposes a meaningful limit on the scope of the claim such that it does not seek a monopolized use of the natural principle; (iii) additional elements or steps inserted into the claim are not well-understood, routine, conventional activities previously engaged in by the researchers in the field and are not those that must be taken by one practicing the natural principle; and (iv) steps, such as data gathering and storage, that are merely nominally, insignificantly or tangentially related to the application of the natural principle are not sufficient.

In *Mayo*, the method claim includes steps of 'administering' and 'determining', and there are steps of extracting and sequencing DNA for the 'comparing' or 'analyzing' claims in *Myriad*. However, these steps were deemed insufficient to render the claims patentable because these are conventional steps specified at a high level of generality[6, 12]. Conversely, for the 'screening' claim in *Myriad*, the Federal Circuit recognized the step of inserting a foreign gene into cells as transformative, as the step results in artificial cells with enhanced function and utility. The claim is thus not purely covering an abstract mental step of comparing the growth rate of two host cells and is patent-eligible[12].

Applying the above principles to inventions involving the uses of stem cells, the following methods may risk rejection under §101: (i) a method of determining whether a cell is pluripotent or differentiated by detecting the expression of specific, naturally occurring protein marker(s) on the cells, and (ii) a method of evaluating a treatment for neurodegenerative diseases by comparing the number of neurons in a subject receiving the treatment and a subject receiving no treatment. Method (i) is likely to be rejected because it merely recites the natural phenomenon wherein pluripotent or differentiated cells express particular protein(s). To render method (i) patent eligible, one needs to further limit the scope of the claim; for example, by reciting a step of using a particular antibody (especially one that is not known in the field) for detecting the protein marker. Method (ii) is likely to be rejected because it simply recites a natural correlation, wherein an effective treatment of a neurodegenerative disease would increase the number of neurons in a subject, without providing any practical application of the correlation. To survive the §101 test, one needs to further limit the scope of the claim by including additional steps, such as cell-viability assays that are not routinely used in the field. The key is to avoid simply reciting or generally applying the natural principle. A claim merely reciting a general concept or natural principle would effectively monopolize the concept or principle and thus would not be patent eligible. Patent-eligible method claims must include physical or nonconventional steps that impose limits on the natural principle so as not to cover all substantial applications of it.

Beyond the rulings

The court in *Mayo* and *Myriad* expressed its concerns about the impact of the rulings on various aspects of society, such as incentives for research entities, the loss of patent rights of current patent holders and the benefit to patients[18]. Judge Stephen Breyer takes the view that patent protection is a double-edged sword and that a balance is needed between providing “incentives that lead to creations, invention and discovery” and “impeding the flow of information that might permit, indeed spur, invention”[6].

It has been estimated that the USPTO has granted patents covering 41% of genes in the human genome[19]. Worries over a too-broad product or method claim that will deter scientific development or jeopardize public welfare continue to persist. After *Mayo* and *Myriad*, a broad claim that monopolizes the use of a product or method, or restricts others from further developing the product or method, may not be patentable. In the stem cell area, claims encompassing general stem cell lines or routine culture methods that cover virtually all human stem cells may no longer be patentable[20].

In view of these rulings, we suggest the following to inventors to facilitate patent procurement and enforcement: first, discriminate the difference(s) between the isolated and natural forms of a natural product and stress the distinctive features of the isolated product. Demonstrate useful application(s) of the isolated product with sufficient experimental support in the application. Second, avoid simply applying the natural principle in a process claim and avoid high levels of generality and well-understood, routine and

conventional steps or elements in the process claim. Finally, limit the scope of a process claim that applies natural principle so that it does not seem to preempt the use of the principle or block every substantial practical application of the principle. Try to insert 'man-made ingredients' such as a machine or other specific reagents into the claim. Features that merely cover essential steps for applying the natural principle are too general and insufficient to limit the scope of the claim.

Conclusions

Changes in US patent policy in relation to biotech inventions are on the horizon. The USPTO may revisit the guideline on examining natural matters, and is expected to release a study on “effective ways to provide independent, confirming genetic diagnostic test activity”[21] that would touch on whether providing secondary genetic diagnostic tests would infringe gene or diagnostic method patents. Inventors are advised to revisit their patenting strategy and portfolio regularly to seek sufficient protection for their inventions.

References

1. Armstrong, L. *et al*. *Stem Cells* **30**, 2–9 (2012).
2. Schwartz, S.D. *et al*. *Lancet* **379**, 713–720 (2012).
3. Tachibana, M. *et al*. *Cell* **153**, 1228–1238 (2013).
4. Burrone, E. Patents at the core: the biotech business (2006). http://www.wipo.int/sme/en/documents/patents_biotech_fulltext.html
5. Bergman, K. & Graff, G.D. *Nat. Biotechnol.* **25**, 419–424 (2007).
6. *Mayo v. Prometheus*, 566 US 132 (2012).
7. *Parker v. Flook*, 437 US 584 (1978).
8. Hirshfeld, A.H. *2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature* (USPTO memorandum, 3 July 2012). http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf
9. Rogers, E.J. *J. Pat. Trademark Off. Soc.* **19**, 93 (2011).
10. *Ass'n v. USPTO*, 702 F. Supp. 2d 181 (S.D.N.Y., 2010).
11. *Ass'n v. USPTO*, 653 F. 3d 1329 (2011).
12. *Ass'n v. USPTO*, 689 F. 3d 1303 (2012).
13. *Ass'n v. Myriad*, 569 US 12–398 (2013).
14. Hirshfeld, A.H. *Supreme Court Decision in* Association for Molecular Pathology v. Myriad Genetics, Inc. (USPTO memorandum, 13 June 2013). http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf
15. Hirshfeld, A.H. 2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products (USPTO memorandum, 4 March, 2014). http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf
16. Zuhn, D.L. USPTO Holds Forum on Subject Matter Eligibility—Part I (Patent Docs, 12 May 2014). http://www.patentdocs.org/2014/05/uspto-holds-forum-on-subject-matter-eligibility-part-i.html
17. Zuhn, D.L. USPTO Holds Forum on Subject Matter Eligibility—Part III (Patent Docs, 15 May 2014). http://www.patentdocs.org/2014/05/uspto-holds-forum-on-subject-matter-eligibility-part-iii.html
18. Offit, K. *et al*. *J. Clin. Oncol.* **31**, 2743–2748 (2013).
19. Rosenfeld, J.A. & Mason, C.E. *Genome Med.* **5**, 27 (2013).
20. Thomson, J.A. US Patent No. 6,200,806 (2001).
21. Section 27 of Leahy-Smith America Invents Act. Public Law 112-29 (2011).

22. *In re Bilski*, 545 F.3d 943 (2008).

Acknowledgments

We thank N. Yi-Chen Su for insights into and comments on this article.

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Competing financial interests

The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.2945).

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Nature Biotechnology ISSN 1087-0156 EISSN 1546-1696

The New York Times

Myriad Genetics has essentially given up trying to stop other companies from offering tests for increased risk of breast cancer, ending a dispute that was the subject of a landmark Supreme Court ruling that human genes cannot be patented.

The company has settled or is in the process of settling patent-infringement lawsuits it filed against other companies that now offer such testing, a Myriad spokesman said on Tuesday.

Myriad's lucrative monopoly on testing for mutations in two genes linked to an increased risk of breast and ovarian cancer ended in 2013, when the Supreme Court ruled that human genes were not eligible for patents because they were products of nature.

Numerous laboratories began offering tests, some for much less than the roughly $4,000 Myriad charged for a complete analysis of the two genes, known as BRCA1 and BRCA2.

Myriad sued many of those companies, saying they were infringing other patent claims that had not been invalidated by the Supreme Court.

But last March, a federal district judge in Utah ruled against Myriad's request for a preliminary injunction against one competitor, Ambry Genetics. Last month, the Court of Appeals for the Federal Circuit upheld the lower court's decision and ruled that those remaining claims were also ineligible for

patents.

After that ruling, “we decided it was in the best interest of the company to settle these matters,” the Myriad spokesman, Ronald Rogers, said.

Settlements have been reached with LabCorp, Invitae and Pathway Genomics. Mr. Rogers said Myriad was in talks with Ambry, Quest Diagnostics, GeneDx and Counsyl.

In the settlements announced so far, the companies have agreed to dismiss the claims and counterclaims against one another, and Myriad has promised not to sue the companies on any remaining patents in the litigation.

Myriad is shifting from the BRCA gene test to a more comprehensive test of 25 genes linked to cancer risk. It is also developing new types of tests to reduce its reliance on the BRCA test.