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March 15, 2000

# A Call for Sharing of Research Causes Gene Stocks to Plunge

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By ALEX BERENSON and NICHOLAS WADE

President Clinton and Prime Minister Tony Blair of Britain said yesterday that the sequence of the human genome should be made freely available to all researchers. The statement led to a sharp sell-off in the stocks of biotechnology companies, which hope to profit by creating drugs based on genetic data.

The White House quickly said it did not intend to hurt the fledgling biotechnology industry, but investors who have made biotechnology stocks the darlings of the market were unconvinced. In frantic selling, they wiped away tens of billions of dollars in market value from the industry. Genomics companies, which are racing to produce a database of human DNA, were hit hardest, with some off more than 20 percent.

The drop was not confined to the biotechnology sector. After briefly passing 5,000 in morning trading, the Nasdaq composite index, which is heavily weighted in technology stocks, fell steadily. The index closed at 4,706.63, down 200.61 points, its second-largest point loss ever.

For investors, the drop is noteworthy, because biotechnology and Internet companies have led the stock market so far this year, while most other stocks have languished. Despite falling almost 13 percent yesterday, the Nasdaq biotech index remains up almost 30 percent this year, thanks to investors' belief that a new wave of drug discovery and gene therapy is imminent.

Because of the rapid run-up, the stocks are expensive by all traditional valuations. The joint statement from Mr. Clinton and Mr.

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Blair, which said the genome data "should be made freely available to scientists everywhere," served as a spark for excitable investors.

Dr. Roy Whitfield, chief executive of Incyte Pharmaceuticals, which shed 28 percent of its market value during the day, said investors failed to distinguish between genome sequences and gene sequences. The genome, referring to the total human DNA, has no commercial value and cannot be patented. The genes, which occupy only 3 percent of the genome, can be. Researchers can work on the sequences of patented genes in academic work and have to pay license fees only if they wish to sell an invention based on the sequence.

The two leaders' statement, which was eight months in the making, is an outgrowth of the longstanding rivalry between a public consortium of American and British academic centers and the Celera Corporation of Rockville, Md., to complete the sequence of the human genome.

The consortium, largely financed by the National Institutes of Health and the Wellcome Trust of London, is posting its findings daily on a Web site open to all. Celera, a unit of the PE Corporation, promises to make its version of the human genome freely available when it is finished, probably this summer. Celera plans to patent some genes, but its principal business plan is to operate a database of the human and other genomes, charging fees for use of the programs that search and analyze the genetic data.

The statement was intended to codify the government position in the rivalry, that the human genome sequence should be made publicly available to all researchers, but it appears to have been interpreted as a challenge both to Celera's intellectual property rights and to those of other genome and biotech companies. A White House official said neither challenge was intended, noting the statement explicitly endorsed intellectual property protection for patents based on genes.

The statement cuts across a complicated two-way rivalry between the public consortium and Celera, and between Celera and its two chief rivals, Incyte Pharmaceuticals and Human Genome Sciences. Both the consortium and Celera aim to sequence the human genome, which means determining the order of the three billion chemical units in the DNA, the genetic information possessed by each human cell.

The strategy of Incyte and Human Genome Sciences is to focus on the genes themselves, patenting as many as possible. The genes, the programming instructions that operate the cell, are hidden in the DNA, with no obvious signposts, and are hard to find even when the genome sequence is known.

Incyte's stock fell $53.50, to $143.50, while Human Genome's stock fell $29.04875, to $123.51625. Meanwhile, Celera fell $39.75, to $149.25.

The government statement adds to the tension between the public consortium and Celera, which last week announced that it had effectively broken off merger negotiations.

Celera and its president, Dr. J. Craig Venter, have long been at odds with the leading scientists of the public consortium, chiefly Dr. John Sulston of the Sanger Center in Britain and Dr. Robert Waterston of Washington University in St. Louis.

Before merger talks broke off, the public consortium proposed that both sides abandon what it called "the current antagonism and excessive competition."

The initiative for the statement issued today is believed to have come from the Wellcome Trust, a medical-research charity, in London. Dr. Michael Dexter, Wellcome's director, said the trust's concern was over the general ownership of the genome, which in his view "is mankind's, and should not be owned by any one company, individual or country."

Denying that the statement was aimed at any person or company, he said the raw sequence -- the string of chemical units making up the genome -- was not patentable and that the trust "would fight any patents based on sequence if they obstruct academic work and progress."

Dr. Venter, however, indicated that he thought Celera was a target of the statement, but unfairly so.

"We are puzzled by the statement and we think it represents the lack of insight and the confusion that has been generated out there," he said. "Our business is not in patenting the genome or tying it up."

Dr. Venter reiterated his previous position that Celera would make available the sequence of the human genome when it was finished, and said the onus was on the rivals Incyte and Human Genome Sciences to make their data public. "I agree with the President and Tony Blair that Incyte and H.G.S. should publish their data," he said.

Both Dr. Dexter and Rachel E. Levinson, a senior official at the White House Office of Science and Technology Policy, said the joint statement acknowledged intellectual property rights.

Ms. Levinson said nothing in the statement challenged existing patent law. She said she was "very concerned and upset" about the reactions on Wall Street. She said that Dr. Neal Lane, the White House science adviser, believed the statement would not affect Celera because of Celera's known intent to publish the human genome sequence.

Dr. William Haseltine, the chief executive of Human Genome Sciences, said he agreed with today's statement because raw genomic data "has no practical use," an observation that he termed "the biggest untold secret of the human genome project." When researchers with the public consortium published the first DNA sequence of a human chromosome in December last year, he said, "No new medical discoveries were made and no new genes were found."

The reason, he added, was that the computer programs for finding genes were still far less efficient than the method pursued by his company, one based on short DNA sequences called "expressed sequence tags" or E.S.T.'s.

The E.S.T. approach exploits the fact that humans may not be able to spot the genes in the genome but human cells surely can. They regularly make transcripts of the genes whose information is needed to synthesize the cell's various proteins. Researchers can capture and analyze these transcripts, known as messenger RNA, and from just a small portion of their sequence can identify the corresponding part of the gene from which they come. These little snippets of genes -- the E.S.T.'s -- are the basis of gene-searching approaches used by Human Genome Sciences and Incyte.

The Patent and Trademark Office has issued some patents based on E.S.T.'s alone, but any such patents seem likely to be weaker than patents based on full-length genes.

According to figures released by Human Genome Sciences, Incyte leads in the human gene patent race with 353 United States patents issued, followed by Human Genome Sciences (114 patents), SmithKline Beecham (60), the United States government (49), the University of California (46) and Massachusetts General Hospital in Boston (45).

The biotechnology companies have yet to prove their ability to translate their research into revenues, much less profits. Yet these stocks helped drive the Nasdaq composite to an 86 percent gain last year, the best performance by a major index ever in the United States.

By traditional valuation standards, the Nasdaq is extraordinarily expensive, leaving some analysts worried that it is overdue for a sharp drop. The average Nasdaq stock trades at well over 100 times expected 2000 earnings, and some large Internet and computer stocks trade at unheard-of price-earnings multiples of 500 or more.

A drop in the biotech and computer highfliers could shake the broader stock market, analysts said, which has already been rattled by the Federal Reserve's recent increases in short-term interest rates, analysts said. For the year, the Dow Jones industrial average is down more than 14 percent, and the Standard & Poor's 500 index is off 7.5 percent, while the Nasdaq is up 16 percent.

Douglas Cliggott, United States equities analyst at J. P. Morgan, called the market "very fragile" because the stocks that are driving it higher are already so expensive. "We see the kinds of price-earnings multiples that the Nasdaq's trading at as being absolutely, positively unsustainable," said Mr. Cliggott, who turned cautious in January.

Yesterday, broader indexes followed the Nasdaq down. After spending most of the day up, the S.& P. slipped 24.47 points to 1,359.15, a 1.8 percent drop. The Dow industrials fell 135.89 points, or 1.4 percent, to 9,811.24.

Analysts who have dared to be bearish have been wrong for the last

five years. Byron Wien, chief United States investment strategist for Morgan Stanley Dean Witter, said the Nasdaq was very volatile and that investors might shrug off this decline as simply a buying opportunity.

"We've had bad days in the Nasdaq before, and they've snapped right back," Mr. Wien said. "What we have to see is whether the 'buy the dips' mentality is broken."

**Treasuries Up Sharply**

**By BLOOMBERG NEWS**

United States government bonds registered their biggest gains in almost five weeks after the Treasury Department said it would buy back $1 billion of bonds maturing from 2018 to 2021 on Thursday.

Treasuries also got a boost when stocks erased gains and fell in afternoon trading, led down by a 4 percent plunge in the Nasdaq.

The price of the 30-year Treasury bond rose 1 2/32, to 102 7/32. The bond's yield, which moves in the opposite direction from the price, fell to 6.09 percent from 6.16 percent.

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# Nasdaq Swoons After Plea

## Point Drop Is 2nd-Biggest

*By Sandra Sugawara and Ariana Eunjung Cha*
Washington Post Staff Writers
Wednesday, March 15, 2000; Page E01

The Nasdaq composite index experienced its second-worst point drop ever yesterday, triggered by a sell-off in biotechnology stocks that spread to other tech companies.

Investors already jittery about highflying biotech share prices reacted quickly to a joint statement by President Clinton and British Prime Minister Tony Blair urging gene-mapping companies to share their data with the public.

The Nasdaq lost 200.61 points, or 4.1 percent, to close at 4706.63. The drop, extending Monday's 2.8 percent decline, was the Nasdaq's largest percentage loss in 10 weeks. The Nasdaq biotech index was down 12.5 percent.

"I think this is a brilliant illustration of what happens when government policy changes suddenly," said Donald Luskin, president of Metamarkets.com, an Internet-based investment adviser. "A critical component for technology innovation and business innovation is policy stability, not just in patent rights, but also in taxes, property rights, monetary policy and international trade."

Luskin said yesterday's pronouncement caused investors to focus on "all the things that the government can alter with the stroke of a pen that can completely make and unmake whole business models."

The biggest losers yesterday were companies in the business of sequencing and patenting genes, including Human Genome Sciences, which fell 29-3/64, to 123-33/64; Incyte Pharmaceuticals, which dropped 53 1/2, to 143 1/2; and Millennium Pharmaceuticals, which dipped 59 1/2, to 176. Shares of Celera tumbled 40 to close at 149.

The Standard & Poor's 500-stock index fell 1.8 percent, to 1359.15. The Dow Jones industrial average fell 135.89, or 1.4 percent, to 9811.24.

Barry Berman, head of equity trading at Robert W. Baird & Co., a brokerage based in Milwaukee, said there was no panic selling. "The volume was not outrageous," he said. "What happened is the buyers stepped away." Berman said many investors are awaiting inflation figures coming out later this week, as well as a Federal Reserve meeting on interest rates next week, before deciding whether to get back into the market.

Berman said that because many biotech and technology companies don't have any earnings, it is difficult to decide how to value them. Statements like those today from President Clinton refocused the spotlight on the vulnerabilities of those kinds of stocks.

Brian Belski, chief investment strategist at George K. Baum & Co., a Kansas City, Mo.-based brokerage, called Nasdaq's drop a "normal and much-needed bull-market correction." Belski pointed out that the Nasdaq is still up 15.66 percent for the year, and that many of the stocks that dropped dramatically, such as Ciena, Network Appliance and QLogic, are still up over 100 percent for the year.

Belski said that biotech stocks and other technology stocks are associated with the "new economy" and that investors are still uncertain how to invest in them. "The year 2000 is going to be very volatile. . . . It's going to take a while to digest this transition," Belski said. But he said he expects investors to continue to shift their holdings into new-economy companies.

Luskin predicted that in the next few days, investors may start discriminating between those firms that might be truly hurt by any biotech policy change and those pounded just because they had "bio" or related terms in their names.

Joe Dougherty, an analyst with Warburg Dillon Read, said that the broad sell-off was unwarranted. "I think investors who were new to the space didn't appreciate how competitive some of these areas were, so they just got rid of their biotech stocks instead of looking into it more," he said.

Indeed, Incyte Pharmaceuticals chief executive Roy Whitfield called the Clinton-Blair announcement "extremely positive" for the company's future. Incyte sells databases that provide some analysis of how genes and proteins function in the body.

Much of his company's work depends on publicly available human genome information. Having access to the data generated by Celera's huge gene-sequencing facility would be a great boon, Whitfield said.

"Only Celera should be concerned about this, in my opinion," he said. "They are producing the same type of information as the public project. I don't know anybody else that is doing large-scale genomics sequencing as opposed to analysis."

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THE WALL STREET JOURNAL INTERACTIVE EDITION
FROM THE ARCHIVES



UNITED'S GOT A LEG UP ON THE COMPETITION.



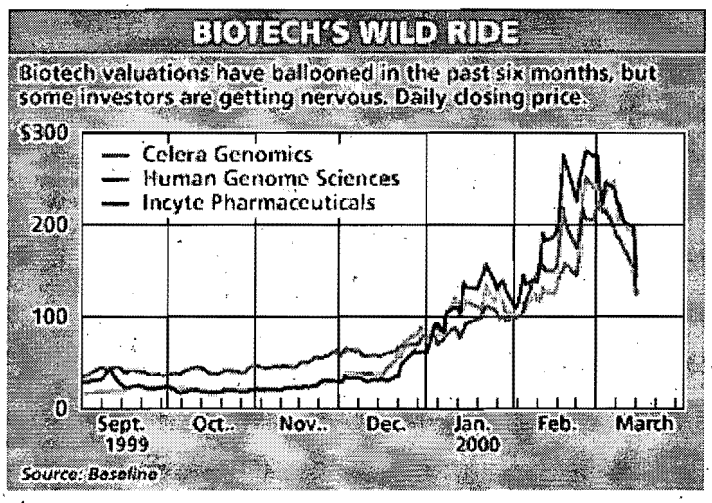
March 15, 2000

# Biotech, Genomics Stocks Plunge On Fear U.S. May Curb Data Sales

By ROBERT LANGRETH and RALPH T. KING JR.
Staff Reporters of THE WALL STREET JOURNAL

Biotechnology and genomics stocks plunged on worries that the government might limit the ability of private companies to sell gene data, following a statement by President Clinton that raw gene information should be made public.

The big sell-off occurred after President Clinton and Britain's prime minister, Tony Blair, issued a joint statement saying that raw gene-sequence information "should be made freely available to scientists everywhere." But rather than representing a shift in the government's position, the statement simply codified a longstanding policy under which federally funded scientists must release gene data immediately after it is discovered.



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Nevertheless, investors reacted strongly, punishing the stocks of companies that mine gene data, apparently fearing that the Clinton-Blair statement would prevent biotech entrepreneurs from developing proprietary gene-based products.

Celera Genomics Group, a unit of PE Corp., fell $39.75, or 21%, to $149.25; Millennium Pharmaceuticals Inc.fell $59.50, or 25%, to $176; and Incyte Pharmaceuticals Inc. dropped $53.50, or 27%, to $143.50.

The rout was seen by biotech entrepreneurs and big investors as an overreaction by skittish investors who in the past few months have driven up biotech shares to unprecedented levels because of enthusiasm over recent advances in genetic science. Some in the industry, in fact, view the runup in biotech stocks as itself an exaggerated response to discoveries that may pay off only decades from now.

**'Any Light Breeze'**

"People have piled into these stocks and have no idea what they're getting into. Any light breeze would have knocked them over," said Jeffrey Casdin, an investment manager at Casdin Life Sciences Partners.

Added William Haseltine, chief executive of Human Genome Sciences Inc., whose stock dropped $29.0469, or 19%, to $123.5156 Tuesday: "Most people have a dim understanding of genes and a dim understanding of patents. When you combine the two, there is hopeless confusion at best."

Dr. Haseltine said the president's statement, far from being harmful to the industry, actually represented an endorsement of the ability of biotech companies to patent medically important uses of genes. In their remarks, the two government leaders seemed to support the notion of patenting certain genes, provided that researchers make them widely available for others to study.

Few major biotech companies were untouched, including Amgen Inc., which dropped $5.75, or 9.9%, to $52.25 Tuesday. The market also was continuing to react to Monday's news that Chiron Corp.'s experimental treatment for regrowing new blood vessels had shown only minimal effects in a large human test. Some, moreover, saw the governments' joint statement as an attempt to pressure Celera and other gene companies to throw open their gene databases in conjunction with the federally funded Human Genome Project. But Francis Collins, director of the U.S. government portion of the international genome project, said that wasn't the case.

"It's ugly out there," said Stuart Weisbrod, chief investment officer for health-care hedge fund Merlin BioMed Group. Biotech stocks "have given back all of February's [gains] across the board."

But "nothing has changed on patent law or policy," said Q. Todd Dickinson, U.S. Commissioner of Patents and Trademarks. "There is no reason these stocks should have gone down."

**Uncertainty About Profits**

Still, the market's reaction to the president's statement reflects uncertainty about the long-term ability of gene hunters to make money from the reams of data they're gathering. Steven Holtzman, chief business officer of Millennium Pharmaceuticals, a gene-hunting company in Cambridge, Mass., said the heart of the matter is whether biotech and drug-industry innovation will be stifled if a handful of companies patent DNA sequences -- and keep them private -- preventing others from using them.

"Millennium believes genes should only be patented if their potential medical use is known," Mr. Holtzman said, "which is pretty much the president's position, as I see it."

Some speculated about a link between the timing of the Clinton-Blair statement on genetic data and the White House's plan to include drug benefits in coverage of **Medicare** patients. The drug industry, long opposed to the **Medicare** plan because of price-control fears, may have sought White House support on gene-data access, since gene data are critical to drug discovery, and restrictions could drive up the cost of research and future products, these people said.

"These genomics companies have a lot of power, and the drug companies might be reacting to it," Mr. Casdin, the investment manager, said. "They want to pay reasonable royalties and not get locked out of this game. So I suspect they are fanning some of the flames." Dr. Collins, however, described this view as "fanciful."

The stock of Incyte, Palo Alto, Calif., was one of the hardest hit, but CEO Roy Whitfield said the company has sustained steep one-day losses several times before, and would recover. "For investors, this is perhaps a little too complicated a story, but ultimately they will get there."

**'Very Positive'**

Mr. Whitfield called the White House statement "very positive." Incyte, Celera and others keep attracting subscribers from the biotech and drug industries; each pay as much as $5 million to $10 million a year for access to vast gene libraries. Academics are starting to sign up, too.

Incyte, Human Genome Sciences and Celera -- the last two based in Rockville, Md. -- say their gene databases will be indispensable to industry and academic researchers long after the genome is fully decoded and freely available to the public, because they intend to go several steps further and identify specific disease-causing genes that will allow drug makers to develop new medicines.

As for whether the government statement was linked to the Human Genome Project's negotiations with Celera and others to help speed the gene-sequencing effort, Dr. Collins, project director, said the timing was just coincidental to his recent talks with these concerns.

Celera's president, Craig Venter, said of the government leaders' statement that he's "puzzled by their timing" and complained that

"they didn't have the courtesy to let us know they were doing this." However, he added, he takes the declaration "at face value" and said it "doesn't change anything in our business planning."

-- *Michael Waldholz contributed to this article.*

**Write to** Robert Langreth at robert.langreth@wsj.com and Ralph T. King Jr. at ralph.king@wsj.com

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# Clinton, Blair Urge Open Access to Gene Data

## President, Briton Step Into Controversy on Code

*By Justin Gillis*
Washington Post Staff Writer
Wednesday, March 15, 2000; Page E01

Declaring open access to the human genetic code a key to medical progress, President Clinton and British Prime Minister Tony Blair yesterday called on private gene-research companies to make their raw data public.

Stepping into the middle of a rising controversy over corporate efforts to create and profit from databases of human genes, Clinton and Blair asked all researchers to provide "unencumbered access" to raw genetic information.

"Already the Human Genome Project, funded by the United States and the United Kingdom, requires its grant recipients to make the secrets that they discover publicly available within 24 hours," Clinton said in a speech. "I urge all other nations, scientists and corporations to adopt this policy and honor its spirit."

Clinton and Blair were careful to emphasize the "important" role of private companies in developing medical treatments. But in an already jumpy stock market where investors were looking for any reason to sell highflying technology stocks, their statement was seen as a threat to the potential profitability of gene companies.

Shares of Celera Genomics Corp., a Rockville company that has become a lightning rod for criticism over secrecy in gene research, fell 22 percent in trading on the New York Stock Exchange. Other companies with big gene-research portfolios dropped by large margins. And the frenzied sell-off of these shares dragged down the whole biotechnology sector, whose share prices had been soaring since late last year.

Whether the Clinton-Blair statement represents any real threat to the business plans of gene companies is another question, however. The leaders emphasized that they support patents for "gene-based inventions," the key to profitability for biotechnology companies. Clinton and Blair asked for no new patent laws or other changes that would significantly alter the rules for biotech companies.

Scientists in Britain and the United States are leading a worldwide effort to unravel the genetic code. Since almost all human diseases involve genes in some way, the effort promises to jump-start the search for treatments for cancer and many other ailments.

"In my lifetime, we'll go from knowing almost nothing about how our genes work to enlisting genes in the struggle to prevent and cure illness," Clinton said. "This will be the scientific breakthrough of the century, perhaps of all time."

It has also become a field rife with jealousy and contentiousness. Celera Genomics, led by maverick gene researcher J. Craig Venter, has put together the world's largest gene-sequencing laboratory and appears on track to beat the government-run Human Genome Project in publishing the first highly accurate version of the human genetic code, probably by this fall.

The competition between public and private researchers has set off jockeying over scientific credit and over policies regarding data access. Celera is keeping its data secret for the moment, sharing it only with big drug companies that have paid millions for early access.

But it is also the only major gene-research company that has promised any degree of public access, saying it will make the full genetic code available for free later this year. Paradoxically, that has made the company a target of criticism by academic scientists who say it is not releasing information fast enough.

Other companies, notably Human Genome Sciences Inc. of Rockville and Incyte Pharmaceuticals Inc. of Palo Alto, Calif., have built large databases of human genes, and, except for information filed in patent applications, they have made almost nothing public and have no plans to do so.

Government scientists and Celera executives have talked privately in recent months about combining their research programs, but those talks fell apart last week amid mutual recriminations.

Francis Collins, director of the National Human Genome Research Institute, and Neal Lane, the president's science adviser, emphasized in a White House briefing yesterday that the timing of the new statement had nothing to do with last week's brouhaha. They said it had been in the works for months and was not an effort to pressure Celera into a deal.

"I want to make it absolutely clear that this statement has nothing to do with any ongoing discussions between the public and the private sector," Lane said.

Executives at Celera and other companies said yesterday that they have no argument with the Blair-Clinton statement. Venter noted that he plans to do what the leaders want--make data public for free--in a matter of months. He plans no changes in the interim.

Without question, competition from Celera has caused the Human Genome Project to speed up its efforts. If the first accurate gene maps do become public this year, that will be five years ahead of the original timetable set by government scientists.

"Their biggest complaint is we're not releasing our data to them fast enough," Venter said. "I have trouble taking that argument seriously.

You can get the data daily over five years, or you can get it all at once four years early."

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DEC 21 1999

The Honorable Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
2121 Crystal Drive
Crystal Park 2, Suite 906
Arlington, Virginia 22202

Dear Commissioner Dickinson:

It was a pleasure meeting with you and your staff. We very much appreciated the opportunity to review the *Revised Written Description and Revised Utility Guidelines* and to further discuss with you the impact of PTO policies on the patenting of genes and gene fragments.

First, we were gratified to learn that the PTO has decided to make, in the words of Mr. Doll, a "180 degree turn" with respect to what constitutes an acceptable utility for patent purposes. One of our primary concerns about the published proposed guidelines has been the extent to which they will open the door to patenting genes and gene fragments of undisclosed (or only partially disclosed) biological function. We therefore applaud the PTO for acknowledging that general utilities for polynucleotides of undefined biological function are not sufficient.

In addition, we strongly support the three-pronged test for utility proposed by PTO, which requires a claimed invention to possess a specific, substantial, and credible utility. We believe that consistent application of this test will provide a sound framework for discriminating between those genes and gene fragments that confer specific benefit in a currently available form and those that are useful merely as an object of further research.

While we are pleased with the PTO's new stance on the utility of polynucleotides for which only generic utilities are asserted, we are very concerned with the PTO's apparent willingness to grant claims to polynucleotides for which a theoretical function of the encoded protein serves as the sole basis for the asserted utility. For example, as we noted in our recent meeting, a bald assertion that a claimed polynucleotide sequence is useful as a kinase, based solely on its homology to known kinases, is no less of a generic assertion of utility than the claim that the polynucleotide is useful for forensic studies or as a chromosome marker. The same argument would apply to many other gene families such as membrane-associated proteins, helicases, zinc fingers, traffic ATPases, etc. We therefore urge PTO to make clear in the Revised Utility Guidelines that a claim to a polynucleotide sequence supported solely by a theoretical characterization of the encoded protein is unlikely to possess specific utility.

Finally, we remain concerned that the PTO's apparent intention to allow "comprising claims" for partial gene sequences lacking any known biological function fails to satisfy the written description requirement and will result in the granting of patents of overly broad scope.

These concerns are addressed in further detail by Dr. Jack Spiegel in an enclosed letter. In closing, we found our recent discussions with the PTO useful toward understanding our respective missions and we look forward to further joint efforts to clarify the perceived ambiguities in the proposed *Revised Written Description and Revised Utility Guidelines.*

Sincerely,

Harold Varmus, M.D.
Director
National Institutes of Health

Francis Collins, M.D.
Director
National Human Genome Research Institute

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard
Rockville, MD 20852

December 21, 1999

Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
2121 Crystal Drive
Crystal Park 2, Suite 906
Arlington, Virginia 22202

Dear Commissioner Dickinson:

I wish to extend my appreciation for your visit to the National Institutes of Health (NIH) to review the proposed Revised Written Description and Revised Utility Guidelines. The comments that follow provide a brief technical analysis regarding specific aspects of the proposed Revised Utility and Written Description Guidelines for the purpose of expanding upon certain concerns and comments discussed generally in the accompanying communication. As you know, our primary concern is that patents of broad scope for genes and gene fragments of undisclosed biological function may hinder, rather than promote, beneficial advancements in the important area of medical genetics and health policy.

As indicated in the accompanying letter, we strongly support the three-pronged test for utility proposed in the Revised Utility Guidelines. The NIH urges that this guideline requiring that a claimed invention possess a specific, substantial, and credible utility be applied in all cases, including situations where the invention is deemed to possess a "well-established" utility.

The proposed Revised Utility Guidelines acknowledge a category of utility that is not affirmatively asserted in the patent application but, nonetheless, is defined as a "well established" utility. Logic dictates that "well established" utilities must also satisfy the requirements to be specific, substantial, and credible. Toward this end, a Patent and Trademark Office (PTO) rejection alleging failure to assert a specific and substantial utility may be rebutted by evidence that the claimed invention possesses a specific and substantial utility that was "well established" at the time of filing. Consequently, the record would be clear as to the identity and nature of this alleged "well established" utility.

However, the PTO may rely upon a "well established" utility under two additional sets of circumstances. One circumstance arises when the PTO itself deems a claimed invention possesses a "well established" utility absent any assertion by applicant of a specific and substantial utility. The other circumstance arises when applicant asserts

utilities deemed neither specific nor substantial, but the PTO envisages the existence of an undisclosed "well established" utility. Unlike the situation where the PTO challenges applicant to identify and justify a "well established" utility, the proposed Revised Guidelines do not require the PTO address on the official record the identity or considerations underlying the specificity and substantiality of any "well established" utilities it accepts *de novo*.

An incomplete and ambiguous official record arising from silent acceptance of a "well established" utility is an unnecessary burden on patents in a complex art already over-burdened with controversial issues. Where a "well established" utility is relied upon to satisfy the utility requirement, the record should be complete and clear regardless who makes the assertion. Therefore, we strongly encourage the PTO to resolve this simple, but potentially serious, oversight in the Revised Guidelines by requiring complete disclosure supporting allegations or conclusions of "well established" utility by either the applicant or the Patent Examiner.

The NIH has also followed with interest the development of the new Revised Guidelines on Written Description. Similar to our concerns regarding utility, the NIH believes there may be potentially serious adverse consequences to the public health and biotechnology research communities in granting patent claims of broad scope on certain gene and partial gene sequences. From the patentabililty perspective, these concerns involve issues of written description and enablement. As communicated by the NIH and many other respondents, the original proposed Written Description Guidelines raised significant patentability issues in this area when disclosed nucleic acid sequences are claimed using open-ended transitional claim language, such as "comprising."

While the newly proposed Revised Written Description Guidelines address some aspects of this issue, the relationship of claim transition language to the scope and written description of nucleic acid sequences still requires clarification in order to adequately address the concerns of the NIH. For example, an anonymous nucleic acid sequence claimed with open language may be interpreted to also encompass any full-length gene containing the claimed subsequence. The concerns of the NIH regarding the potential chilling consequences such an interpretation may have on research and development of genomic products for the public health has been documented in our previous communications.

The Court of Appeals for the Federal Circuit (CAFC) has consistently instructed that nucleic acid sequences be treated under the patent statutes similarly to other chemical compounds. Consequently, the disclosed structural formula (sequence) of a nucleic acid should not be altered in indiscriminate and incalculable ways through choice of transition claim language. By contrast, it is well accepted that open transition phrases, such as "comprising" may broaden the scope of a composition claim by permitting unrecited subject matter to be <u>in combination</u> with the expressly recited subject matter (i.e., chemical or nucleic acid formula).

The newly proposed Revised Written Description Guidelines appear to address this issue by providing endnote definitions for transition terms consistent with general chemical patent practice. Universal application of these definitions to nucleic acid and protein sequence claims would be consistent with the recurrent instructions from the CAFC noted above. This would be consistent also with the Revised Guideline's stated goal that "[t]ransition phrases should be given the same treatment in all cases." Indeed, adoption of such traditional chemical practice usage and meaning for transition phrases in nucleic acid claims would go a long way toward ameliorating the concerns of the NIH in this area.

However, the Revised Written Description Guidelines respond to various comments regarding EST issues in a manner that appears to undermine a clear and consistent resolution of this important consideration. It appears from the responses to comments that the revised guidelines again adopt an interpretation of open "comprising" transition language that would permit holders of patents to anonymous sequence fragments to assert domination over later discovered full-length genes. Such domination may encumber and hinder the development of later discovered genetic information of significant medical consequence. Additionally, recently issued patents claiming partial DNA sequences merely add to this ambiguity, and belie the tone of our discussions to overcome the NIH concerns with these issues

The NIH found our recent discussions with the PTO useful toward understanding our respective missions. It appears the PTO wishes to establish guidelines to address and satisfy NIH and industry concerns related to patenting of genes and gene fragments. This common goal may be advanced significantly by eliminating or amending responses to comments that confuse the clear meaning of the endnote definitions for transition terms. Residual ambiguity regarding this issue should be removed by clear statements from the PTO in the final guidelines confirming the consistent application of chemical practice definitions of transition terms, consistent with the endnotes, to claims reciting nucleic acid and protein sequences. As enumerated in the accompanying letter, the NIH remains open and ready to engage in further constructive discussions toward clarifying the perceived ambiguities in the proposed Revised Utility and Revised Written Description Guidelines.

Jack Spiegel

Jack Spiegel, Ph.D.
Director, Division of
Technology Development & Transfer
Office of Technology Transfer
National Institutes of Health
(301) 496-7056 X289

Gene Research File

# JOINT STATEMENT TO ENSURE THAT DISCOVERIES FROM THE HUMAN GENOME ARE USED TO ADVANCE HUMAN HEALTH

In the last decade of the twentieth century, scientists from around the world initiated one of the most significant scientific projects of all time: to determine the DNA sequence of the entire human genome, the human genetic blueprint. Progressing ahead of schedule, human genome research is rapidly advancing our understanding of the causes of human disease and will serve as the foundation for development of a new generation of effective treatments, preventions, and cures.

To realize the full promise of this research, raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere. Unencumbered access to this information will promote discoveries that will reduce the burden of disease, improve health around the world, and enhance the quality of life for all humankind. Intellectual property protection for gene-based inventions also will play an important role in stimulating the development of important new health care products.

We applaud the decision by scientists working on the Human Genome Project to release raw fundamental information about the human DNA sequence and its variants rapidly into the public domain, and we commend other scientists around the world to adopt this policy.

Chris -

Here are NIH comments on PTO guidelines. I have also enclosed the guidelines + several position papers from scientific / medical organizations

Kathy Hudson

Gene Patent File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DEC 21 1999

The Honorable Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
2121 Crystal Drive
Crystal Park 2, Suite 906
Arlington, Virginia 22202

Chris -
Here are NIH comments on PTO guidelines. I have also enclosed the guidelines + several position papers from scientific/medical organizations
Kathy Hudson

Dear Commissioner Dickinson:

It was a pleasure meeting with you and your st
review the *Revised Written Description and Re*
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generic utilities are asserted, we are very concerned with the PTO's apparent willingness to grant claims to polynucleotides for which a theoretical function of the encoded protein serves as the sole basis for the asserted utility. For example, as we noted in our recent meeting, a bald assertion that a claimed polynucleotide sequence is useful as a kinase, based solely on its homology to known kinases, is no less of a generic assertion of utility than the claim that the polynucleotide is useful for forensic studies or as a chromosome marker. The same argument would apply to many other gene families such as membrane-associated proteins, helicases, zinc fingers, traffic ATPases, etc. We therefore urge PTO to make clear in the Revised Utility Guidelines that a claim to a polynucleotide sequence supported solely by a theoretical characterization of the encoded protein is unlikely to possess specific utility.

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Gene Patent FIG

DEPARTMENT OF HEALTH & HUMAN SERVICES

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DEC 21 1999

The Honorable Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
2121 Crystal Drive
Crystal Park 2, Suite 906
Arlington, Virginia 22202

Dear Commissioner Dickinson:

It was a pleasure meeting with you and your staff. We very much appreciated the opportunity to review the *Revised Written Description and Revised Utility Guidelines* and to further discuss with you the impact of PTO policies on the patenting of genes and gene fragments.

First, we were gratified to learn that the PTO has decided to make, in the words of Mr. Doll, a "180 degree turn" with respect to what constitutes an acceptable utility for patent purposes. One of our primary concerns about the published proposed guidelines has been the extent to which they will open the door to patenting genes and gene fragments of undisclosed (or only partially disclosed) biological function. We therefore applaud the PTO for acknowledging that general utilities for polynucleotides of undefined biological function are not sufficient.

In addition, we strongly support the three-pronged test for utility proposed by PTO, which requires a claimed invention to possess a specific, substantial, and credible utility. We believe that consistent application of this test will provide a sound framework for discriminating between those genes and gene fragments that confer specific benefit in a currently available form and those that are useful merely as an object of further research.

While we are pleased with the PTO's new stance on the utility of polynucleotides for which only generic utilities are asserted, we are very concerned with the PTO's apparent willingness to grant claims to polynucleotides for which a theoretical function of the encoded protein serves as the sole basis for the asserted utility. For example, as we noted in our recent meeting, a bald assertion that a claimed polynucleotide sequence is useful as a kinase, based solely on its homology to known kinases, is no less of a generic assertion of utility than the claim that the polynucleotide is useful for forensic studies or as a chromosome marker. The same argument would apply to many other gene families such as membrane-associated proteins, helicases, zinc fingers, traffic ATPases, etc. We therefore urge PTO to make clear in the Revised Utility Guidelines that a claim to a polynucleotide sequence supported solely by a theoretical characterization of the encoded protein is unlikely to possess specific utility.

Finally, we remain concerned that the PTO's apparent intention to allow "comprising claims" for partial gene sequences lacking any known biological function fails to satisfy the written description requirement and will result in the granting of patents of overly broad scope.

These concerns are addressed in further detail by Dr. Jack Spiegel in an enclosed letter. In closing, we found our recent discussions with the PTO useful toward understanding our respective missions and we look forward to further joint efforts to clarify the perceived ambiguities in the proposed *Revised Written Description and Revised Utility Guidelines*.

Sincerely,

Harold Varmus, M.D.
Director
National Institutes of Health

Francis Collins, M.D.
Director
National Human Genome Research Institute

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard
Rockville, MD 20852

December 21, 1999

Q. Todd Dickinson
Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks
U.S. Patent and Trademark Office
2121 Crystal Drive
Crystal Park 2, Suite 906
Arlington, Virginia 22202

Dear Commissioner Dickinson:

I wish to extend my appreciation for your visit to the National Institutes of Health (NIH) to review the proposed Revised Written Description and Revised Utility Guidelines. The comments that follow provide a brief technical analysis regarding specific aspects of the proposed Revised Utility and Written Description Guidelines for the purpose of expanding upon certain concerns and comments discussed generally in the accompanying communication. As you know, our primary concern is that patents of broad scope for genes and gene fragments of undisclosed biological function may hinder, rather than promote, beneficial advancements in the important area of medical genetics and health policy.

As indicated in the accompanying letter, we strongly support the three-pronged test for utility proposed in the Revised Utility Guidelines. The NIH urges that this guideline requiring that a claimed invention possess a specific, substantial, and credible utility be applied in all cases, including situations where the invention is deemed to possess a "well-established" utility.

The proposed Revised Utility Guidelines acknowledge a category of utility that is not affirmatively asserted in the patent application but, nonetheless, is defined as a "well established" utility. Logic dictates that "well established" utilities must also satisfy the requirements to be specific, substantial, and credible. Toward this end, a Patent and Trademark Office (PTO) rejection alleging failure to assert a specific and substantial utility may be rebutted by evidence that the claimed invention possesses a specific and substantial utility that was "well established" at the time of filing. Consequently, the record would be clear as to the identity and nature of this alleged "well established" utility.

However, the PTO may rely upon a "well established" utility under two additional sets of circumstances. One circumstance arises when the PTO itself deems a claimed invention possesses a "well established" utility absent any assertion by applicant of a specific and substantial utility. The other circumstance arises when applicant asserts

utilities deemed neither specific nor substantial, but the PTO envisages the existence of an undisclosed "well established" utility. Unlike the situation where the PTO challenges applicant to identify and justify a "well established" utility, the proposed Revised Guidelines do not require the PTO address on the official record the identity or considerations underlying the specificity and substantiality of any "well established" utilities it accepts *de novo*.

An incomplete and ambiguous official record arising from silent acceptance of a "well established" utility is an unnecessary burden on patents in a complex art already over-burdened with controversial issues. Where a "well established" utility is relied upon to satisfy the utility requirement, the record should be complete and clear regardless who makes the assertion. Therefore, we strongly encourage the PTO to resolve this simple, but potentially serious, oversight in the Revised Guidelines by requiring complete disclosure supporting allegations or conclusions of "well established" utility by either the applicant or the Patent Examiner.

The NIH has also followed with interest the development of the new Revised Guidelines on Written Description. Similar to our concerns regarding utility, the NIH believes there may be potentially serious adverse consequences to the public health and biotechnology research communities in granting patent claims of broad scope on certain gene and partial gene sequences. From the patentabililty perspective, these concerns involve issues of written description and enablement. As communicated by the NIH and many other respondents, the original proposed Written Description Guidelines raised significant patentability issues in this area when disclosed nucleic acid sequences are claimed using open-ended transitional claim language, such as "comprising."

While the newly proposed Revised Written Description Guidelines address some aspects of this issue, the relationship of claim transition language to the scope and written description of nucleic acid sequences still requires clarification in order to adequately address the concerns of the NIH. For example, an anonymous nucleic acid sequence claimed with open language may be interpreted to also encompass any full-length gene containing the claimed subsequence. The concerns of the NIH regarding the potential chilling consequences such an interpretation may have on research and development of genomic products for the public health has been documented in our previous communications.

The Court of Appeals for the Federal Circuit (CAFC) has consistently instructed that nucleic acid sequences be treated under the patent statutes similarly to other chemical compounds. Consequently, the disclosed structural formula (sequence) of a nucleic acid should not be altered in indiscriminate and incalculable ways through choice of transition claim language. By contrast, it is well accepted that open transition phrases, such as "comprising" may broaden the scope of a composition claim by permitting unrecited subject matter to be <u>in combination</u> with the expressly recited subject matter (i.e., chemical or nucleic acid formula).

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However, the Revised Written Description Guidelines respond to various comments regarding EST issues in a manner that appears to undermine a clear and consistent resolution of this important consideration. It appears from the responses to comments that the revised guidelines again adopt an interpretation of open "comprising" transition language that would permit holders of patents to anonymous sequence fragments to assert domination over later discovered full-length genes. Such domination may encumber and hinder the development of later discovered genetic information of significant medical consequence. Additionally, recently issued patents claiming partial DNA sequences merely add to this ambiguity, and belie the tone of our discussions to overcome the NIH concerns with these issues

The NIH found our recent discussions with the PTO useful toward understanding our respective missions. It appears the PTO wishes to establish guidelines to address and satisfy NIH and industry concerns related to patenting of genes and gene fragments. This common goal may be advanced significantly by eliminating or amending responses to comments that confuse the clear meaning of the endnote definitions for transition terms. Residual ambiguity regarding this issue should be removed by clear statements from the PTO in the final guidelines confirming the consistent application of chemical practice definitions of transition terms, consistent with the endnotes, to claims reciting nucleic acid and protein sequences. As enumerated in the accompanying letter, the NIH remains open and ready to engage in further constructive discussions toward clarifying the perceived ambiguities in the proposed Revised Utility and Revised Written Description Guidelines.

Jack Spiegel

Jack Spiegel, Ph.D.
Director, Division of
Technology Development & Transfer
Office of Technology Transfer
National Institutes of Health
(301) 496-7056 X289

USPQ2d 1016, 1021 (Fed. Cir. 1991)("A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.")(citations omitted). In such instances the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co.* v. *Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994). Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention. *Id.*

49. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

50. *See, e.g., Eli Lilly.*

51. For example, in the genetics arts, it is unnecessary for an applicant to provide enough different species that the disclosure will permit one of skill to determine the nucleic acid or amino acid sequence of another species from the application alone. The stochastic nature of gene evolution would make such a predictability nearly impossible. Thus, the Federal Circuit could not have intended that representative number requires predictability of sequences.

52. *See Wertheim*, 541 F.2d at 263, 191 USPQ at 97 ("[T]he PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims."). *See also* MPEP § 2163.05.

53. *See* MPEP §§ 714.02 and 2163.06 ("Applicant should * * * specifically point out the support for any amendments made to the disclosure.").

54. *See, e.g., In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989)(Original specification for method of forming images using photosensitive microcapsules which describes removal of microcapsules from surface and warns that capsules not be disturbed prior to formation of image, unequivocally teaches absence of permanently fixed microcapsules and supports amended language of claims requiring that microcapsules be "not permanently fixed" to underlying surface, and therefore meets description requirement of 35 U.S.C. 112.).

55. *See, e.g., In re Robins*, 429 F.2d 452, 456–57, 166 USPQ 552, 555 (CCPA 1970) ("[W]here no explicit description of a generic invention is to be found in the specification * * * mention of representative compounds may provide an implicit description upon which to base generic claim language."); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972)(a subgenus is not necessarily implicitly described by a genus encompassing it and a species upon which it reads).

56. *See, e.g., In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950–51 (Fed. Cir. 1999)("To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' ") (citations omitted).

57. When an explicit limitation in a claim "is not present in the written description whose benefit is sought it must be shown that a person of ordinary skill would have understood, at the time the patent application was filed, that the description requires that limitation." *Hyatt* v. *Boone*, 146 F.3d 1348, 1353, 47 USPQ2d 1128, 1131 (Fed. Cir. 1998).

58. *See, e.g., Johnson Worldwide Associates Inc.* v. *Zebco Corp.*, 175 F.3d at 993, 50 USPQ2d at 1613; *Gentry Gallery, Inc.* v. *Berkline Corp.*, 134 F.3d at 1479, 45 USPQ2d at 1503; *Tronzo* v. *Biomet, Inc.*, 156 F.3d at 1159, 47 USPQ2d at 1833; and *Reiffin* v. *Microsoft Corp.*, 48 USPQ2d at 1277.

59. *See, e.g., In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971).

60. *Wertheim*, 541 F.2d at 262, 191 USPQ at 96.

61. *See In re Rasmussen*, 650 F.2d at 1214, 211 USPQ at 326.

62. *See In re Alton*, 76 F.3d 1168, 1176, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Dated: December 16, 1999.

**Q. Todd Dickinson,**

*Assistant Secretary of Commerce and Commissioner of Patents and Trademarks.*

[FR Doc. 99–33053 Filed 12–20–99; 8:45 am]

BILLING CODE 3510–16–P

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## DEPARTMENT OF COMMERCE

### Patent and Trademark Office

**[Docket No. 991027289–9289–01]**

**RIN 0651–AB09**

### Revised Utility Examination Guidelines; Request for Comments

**AGENCY:** Patent and Trademark Office, Commerce.

**ACTION:** Notice and request for public comments.

**SUMMARY:** The Patent and Trademark Office (PTO) requests comments from any interested member of the public on the following Revised Utility Examination Guidelines. The PTO is publishing a revised version of guidelines to be used by Office personnel in their review of patent applications for compliance with the utility requirement based on comments received in response to the Request for Comments on Interim Guidelines for Examination of Patent Applications. Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement; Extension of Comment Period and Notice of Hearing. 63 FR 50887 (September 23, 1998). These Revised Utility Guidelines will be used by PTO personnel in their review of patent applications for compliance with the "utility" requirement of 35 U.S.C. 101. This revision supersedes the Utility Examination Guidelines that were published at 60 FR 36263 (1995) and at 1177 O.G. 146 (1995).

**DATES:** Written comments on the Revised Utility Examination Guidelines will be accepted by the PTO until March 22, 2000.

**ADDRESSES:** Written comments should be addressed to Box 8, Commissioner of Patents and Trademarks, Washington, DC 20231, marked to the attention of Mark Nagumo, or to Box Comments, Assistant Commissioner for Patents, Washington, DC 20231, marked to the attention of Linda S. Therkorn. Alternatively, comments may be submitted to Mark Nagumo via facsimile at (703) 305–9373 or by electronic mail addressed to "mark.nagumo@uspto.gov"; or to Linda Therkorn via facsimile at (703) 305–8825 or by electronic mail addressed to "linda.therkorn@uspto.gov."

**FOR FURTHER INFORMATION CONTACT:** Mark Nagumo by telephone at (703) 305–8666, by facsimile at (703) 305–9373, by electronic mail "mark.nagumo@uspto.gov," or by mail marked to his attention addressed to the Commissioner of Patents and Trademarks, Box 8, Washington, DC 20231; or Linda Therkorn by telephone at (703) 305–9323, by facsimile at (703) 305–8825, by electronic mail at "linda.therkorn@uspto.gov," or by mail marked to her attention addressed to Box Comments, Assistant Commissioner of Patents and Trademarks, Washington, DC 20231.

**SUPPLEMENTARY INFORMATION:** The PTO requests comments from any interested member of the public on the following Revised Utility Examination Guidelines. As of the publication date of this notice, this revision will be used by PTO personnel in their review of patent

applications for compliance with the "utility" requirement of 35 U.S.C. 101. Because this revision governs internal practices, it is exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A).

Written comments should include the following information: (1) Name and affiliation of the individual responding, and (2) an indication of whether the comments offered represent views of the respondent's organization or are respondent's personal views.

Parties presenting written comments are requested, where possible, to provide their comments in machine-readable format in addition to a paper copy. Such submissions may be provided by electronic mail messages sent over the Internet, or on a 3.5" floppy disk formatted for use in a Macintosh, Windows, Windows for Workgroups, Windows 95, Windows 98, Windows NT, or MS–DOS based computer.

Written comments will be available for public inspection on or about April 19, 2000, in Suite 918, Crystal Park 2, 2121 Crystal Drive, Arlington, Virginia. In addition, comments provided in machine readable format will be available through the PTO's Website at http://www.uspto.gov.

## I. Discussion of Public Comments

Comments received by the Office in response to the request for public comment on the Interim Written Description Guidelines regarding the patentability of expressed sequence tags (ESTs) suggested the need for revision or clarification of the final Utility Examination Guidelines as published at 60 FR 36263 (1995) and 1177 O.G. 146 (1995). All comments have been carefully considered. Many comments stated that sufficient patentable utility has not been shown when the sole disclosed use of an EST is to identify other nucleic acids whose utility was not known, and the function of the corresponding gene is not known. Moreover, several comments opined that ESTs are genomic research tools that should be available for unencumbered research to advance the public good. One comment stated that asserted utilities for ESTs, such as mapping the genome or tissue typing, would probably not satisfy the requirements of 35 U.S.C. 101 if the length of the attached DNA sequence were greatly extended. Other comments stated that the disclosure of a DNA sequence alone is insufficient to enable scientists to use ESTs for mapping or tissue typing. Some comments suggested that PTO examination procedures would result in granting patents based on nonspecific and nonsubstantial utilities, contrary to established case law. See Brenner v. Manson, 383 U.S. 519, 534–35, 148 USPQ 689, 695 (1966) (requiring disclosure of "specific utility," and of "substantial utility," "where specific benefit exists in currently available form"); accord, In re Ziegler, 992 F.2d 1197, 1201, 26 USPQ2d 1600, 1603 (Fed. Cir. 1996) (requiring that a specific and substantial or practical utility for the invention be disclosed as a condition of meeting the practical utility requirement of § 101). Consequently, a number of changes have been made to the Utility Examination Guidelines to clarify the position of the Patent and Trademark Office. Updated training material will be developed in the examination corps to address technology-specific issues.

## II. Guidelines for Examination of Applications for Compliance With the Utility Requirement

### *A. Introduction*

The following guidelines establish the policies and procedures to be followed by Office personnel in the evaluation of any patent application for compliance with the utility requirements of 35 U.S.C. 101 and 112. These guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility requirement. The guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112, nor are they designed to obviate the examiner's review of applications for compliance with all other statutory requirements for patentability.

### *B. Examination Guidelines for the Utility Requirement*

Office personnel are to adhere to the following procedures when reviewing patent applications for compliance with the "useful invention" ("utility") requirement of 35 U.S.C. 101 and 112, first paragraph.

1. Read the claims and the supporting written description.

(a) Determine what the applicant has claimed, noting any specific embodiments of the invention.

(b) Ensure that the claims define statutory subject matter (i.e., a process, machine, manufacture, composition of matter, or improvement thereof).

2. Review the claims and the supporting written description to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible.

(a) If the invention has a well-established utility, regardless of any assertion made by the applicant, do not impose a rejection based on lack of utility. An invention has a well-established utility if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process).

(b) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(1) A claimed invention must have a specific and substantial utility. This requirement excludes "throw-away," "insubstantial," or "nonspecific" utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101.

(2) Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

(c) If no assertion of specific and substantial utility for the claimed invention made by the applicant is credible, and the claimed invention does not have a well-established utility, reject the claim(s) under section 101 on the grounds that the invention as claimed lacks utility. Also reject the claims under § 112, first paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed. The section 112, first paragraph, rejection imposed in conjunction with a section 101 rejection should incorporate by reference the grounds of the corresponding section 101 rejection.

(d) If the applicant has not asserted any specific and substantial utility for the claimed invention and it does not have a well-established utility, impose a rejection under section 101, emphasizing that the applicant has not disclosed a specific and substantial utility for the invention. Also impose a separate rejection under section 112, first paragraph, on the basis that the applicant has not disclosed how to use the invention due to the lack of a specific and substantial utility. The sections 101 and 112 rejections shift the

burden of coming forward with evidence to the applicant to:

(1) Explicitly identify a specific and substantial utility for the claimed invention; and

(2) Provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well established at the time of filing. The examiner should review any subsequently submitted evidence of utility using the criteria outlined above. The examiner should also ensure that there is an adequate nexus between the showing and the application as filed.

3. Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

(a) Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention.

The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record.

(b) Where no specific and substantial utility is disclosed or known, a *prima facie* showing of no specific and substantial utility must establish that it is more likely than not that a person skilled in the art would not be aware of any well-established credible utility that is both specific and substantial.

The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that there is no known well established utility for the claimed invention that is both specific and substantial;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record.

4. A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Once a *prima facie* showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by providing evidence in the form of a declaration under 37 CFR 1.132 or a printed publication that rebuts the basis or logic of the *prima facie* showing. If the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the *prima facie* showing, any claim amendments, and nay new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained.

If the applicant satisfactorily rebuts a *prima facie* rejection based on lack of utility under section 101, withdraw the § 101 rejection and the corresponding rejection imposed under section 112, first paragraph.

Dated: December 16, 1999.

**Q. Todd Dickinson,**

*Assistant Secretary of Commerce and Commissioner of Patents and Trademarks.*

[FR Doc. 99–33054 Filed 12–20–99; 8:45 am]

BILLING CODE 3510–16–M

## DEPARTMENT OF EDUCATION

### Submission for OMB Review; Comment Request

**AGENCY:** Department of Education.

**SUMMARY:** The Leader, Information Management Group, Office of the Chief Information Officer invites comments on the submission for OMB review as required by the Paperwork Reduction Act of 1995.

**DATES:** Interested persons are invited to submit comments on or before January 20, 2000.

**ADDRESSES:** Written comments should be addressed to the Office of Information and Regulatory Affairs, Attention: Danny Werfel, Desk Officer, Department of Education, Office of Management and Budget, 725 17th Street, NW, Room 10235, New Executive Office Building, Washington, DC 20503 or should be electronically mailed to the internet address DWERFEL@OMB.EOP.GOV.

**SUPPLEMENTARY INFORMATION:** Section 3506 of the Paperwork Reduction Act of 1995 (44 U.S.C. Chapter 35) requires that the Office of Management and Budget (OMB) provide interested Federal agencies and the public an early opportunity to comment on information collection requests. OMB may amend or waive the requirement for public consultation to the extent that public participation in the approval process would defeat the purpose of the information collection, violate State or Federal law, or substantially interfere with any agency's ability to perform its statutory obligations. The Leader, Information Management Group, Office of the Chief Information Officer, publishes that notice containing proposed information collection requests prior to submission of these requests to OMB. Each proposed information collection, grouped by office, contains the following: (1) Type of review requested, *e.g.*, new, revision, extension, existing or reinstatement; (2) title; (3) summary of the collection; (4) description of the need for, and proposed use of, the information; (5) respondents and frequency of collection; and (6) reporting and/or recordkeeping burden. OMB invites public comment.

Dated: December 15, 1999.

**William E. Burrow,**

*Leader, Information Management Group, Office of the Chief Information Officer.*

### Office of Special Education and Rehabilitative Services

*Type of Review:* Extension.

## American College of Medical Genetics

# Position Statement on Gene Patents and Accessibility of Gene Testing

The fruits of the human genome project are rapidly redefining the medical community's views of patient care and moving us from a focus on the treatment of disease to a broader perspective in which prevention and diagnosis play equally critical roles. The American College of Medical Genetics (ACMG) believes that gene testing – which is vital to all three approaches -- must remain widely accessible and affordable, and that the development and improvement of safe and effective genetic tests should not be hindered. The decision of the Patent and Trademark Office (PTO) to permit the patenting of naturally occurring genes and disease-causing mutations has produced numerous difficulties. While the ACMG disagrees with the PTO over this fundamental issue, we have further concerns over current patterns of enforcement of patents on genes that are important in the diagnosis, management and risk assessment of human disease.

This statement is directed at current practices related to such enforcement. Enforcement has been effected in one or more of these ways: monopolistic licensing that limits a given genetic test to a single laboratory, royalty-based licensing agreements with exorbitant up-front fees and per-test fees, and licensing agreements that seek proportions of reimbursement from testing services. These limit the accessibility of competitively priced genetic testing services and hinder test-specific development of national programs for quality assurance. They also limit the number of knowledgeable individuals who can assist physicians, laboratory geneticists and counselors in the diagnosis, management and care of at-risk patients.

Further, restricting the availability of gene testing has long-term implications beyond patient care. It affects the training of the next generation of medical and laboratory geneticists, physicians, and scientists in the area enveloped by the patent or license. It also retards the usually very rapid improvement of a test that occurs through the addition of new mutations or the use of new techniques by numerous laboratories that have accumulated samples from affected individuals over many years.

Therefore, it is the ACMG's position that:

- Genes and their mutations are naturally occurring substances that should not be patented.
- Patents on genes with clinical implications must be very broadly licensed.
- Licensing agreements should not limit access through excessive royalties and other unreasonable terms.

*August 2, 1999*

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AMA

PolicyFinder

*PolicyFinder*

# H-140.944 Patenting the Human Genome

AMA policy on gene patents is: (1) Patents on processes - for example, processes used to isolate and purify gene sequences, genes and proteins, or vehicles of gene therapy - do not raise the same ethical problems as patents on the substances themselves and are thus preferable. (2) Substance patents on purified proteins present fewer ethical problems than patents on genes or DNA sequences and are thus preferable. (3) Patent descriptions should be carefully constructed to ensure that the patent holder does not limit the use of a naturally occurring form of the substance in question. This includes patents on proteins, genes, and genetic sequences. (4) One of the goals of genetic research is to achieve better medical treatments and technologies. Granting patent protection should not hinder this goal. Individuals or entities holding patents on genetic material should not allow patents to languish and should negotiate and structure licensing agreements in such a way as to encourage the development of better medical technology. (CEJA Rep. 2, I-97)

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## 82. Patenting the Human Genome

### Introduction

The Human Genome Project (HGP) is a joint endeavor overseen by the National Institutes of Health (NIH) and the Department of Energy (DOE). International research efforts are coordinated through HUGO (Human Genome Organization). The 15-year HGP began in 1990 and proposes to find the location of 100,000 (or more) human genes, as well as to read the entire genetic script (approximately 3 billion base pairs) by the year 2005. Initial investments focused primarily on developing computerized tools for mapping, sequencing, storing, and handling genes. Despite this, the development of physical and genetic maps has moved forward faster than originally expected. Recently, with the development of new technologies that enable research to proceed more rapidly and efficiently, larger-scale sequencing efforts have begun.

With genetic research moving ahead at light-speed, patenting has become an important issue. Much of the concern in this area has focused on DNA sequences.[1] These sequences may be fragments of a gene (*i.e.*, they code for certain amino acids), or a full gene (*i.e.*, they code for a full protein). Patenting of the former is more controversial, both legally and ethically, than the latter. In this report the Council provides a brief explanation of patent law and its potential application to genomic sequences. After examining some of the ethical concerns regarding patenting human genomic material, it concludes that caution is warranted in this area.

### United States Patent Law

Patent law is controlled by federal legislation, federal court decisions, and decisions of the Patent and Trademark Office (PTO). The Constitution notes that Congress has the power to "promote the progress of Science and useful Arts, by securing for limited times to Authors and Inventors the exclusive right to their Writings and Discoveries." [2]

Patent holders do not own an invention—they own merely the patent. A patent then grants the holder the right, for a limited amount of time, to prevent others from commercializing their inventions. In this sense a patent does not confer ownership rights, it confers property rights. This is an important distinction. For example, an easement (another type of property right) granting X access over Y's property to the ocean front does not mean that X owns the property, merely that X has certain rights with respect to the property.

The obverse of patent law is trade secret law. It may be more lucrative to maintain an invention as a trade secret than to disclose it under patenting requirements. For example, Coca Cola originally sought patent protection for Coke, but dropped the application in light of the disclosure requirements. The formula for Coke turned out to be much more valuable as a trade secret than if patented (since the company would have had to disclose how to make it).

Patent law is designed to allow inventors to profit from their inventions, safeguarding intellectual property. At the same time, the patent system is designed to foster information sharing since full disclosure of the invention—enabling another trained in the art to replicate it—is necessary to

obtain a patent.[3] One author described a patent as "a contract between its owner and the U.S. government, whereby the owner is given security in exchange for sharing knowledge with the public."[4] The "contract," as such, lasts 20 years from the date of filing.

There are two aspects to consider when a patent application is filed: the first is determining whether the thing is an invention, which is potentially patentable, or a discovery, which is not. In some sense, all inventions can be reduced to naturally occurring substances that are merely discoverable. Another way to think about the difference between a discovery and an invention is to consider the distinction between basic and applied research.[5] This distinction, however, is not always clear-cut in the realm of biotechnology. As a result, whether or not to classify a finding as a discovery or an invention often reduces to the requirement of "utility" discussed below. Second, once a finding is classified as an invention and deemed potentially patentable, it must meet the three requirements of novelty, non-obviousness and utility.

Novelty

To meet the novelty requirement, the invention cannot have been known or used by others in this country, or patented or described in a publication in this or a foreign country.[6] In other words, the invention must not have been in the public domain. This issue becomes crucial when an inventor seeks to disseminate his or her invention before issuance of the patent. The United States grants a one year grace period from the time that the invention is disseminated to the time the patent application is filed. In theory this may keep some inventors from disclosing their inventions, or information about them, until they have met the other requirements and thus are ready to file.

Non-obviousness

To be patentable, the invention in question must not have been obvious to one working in the field at the time of the invention.[7] If all of the elements of an invention were described in a single previous publication, even if the invention itself had not been developed, it is considered to be non-obvious. In this sense, what can be patented changes over time. As the state of the art develops, what was once considered non-obvious or novel, may become routine and thus unpatentable.

Utility

Utility requires that the invention must have a practical use beyond merely being a tool for scientific inquiry.[8] The focus here is not on the degree of utility—if an inventor can articulate at least one use for the invention he or she will have met this requirement. This does not mean that if an inventor can articulate the natural function the test has been met—a commercial use (e.g., a therapeutic use) must be identified.

In practice, people can use a patented invention in the absence of a licensing agreement. First, there is an exception that allows the use of a patented invention for research purposes, although if a commercial product arises from the research an agreement must be negotiated between the original patent owner and the researcher. This "research exception" has never been clearly defined and it is uncertain how it would be interpreted if litigated. Second, not all patents are enforced, either because the patent holder does not mind the use or because of the financial cost of enforcement. The patent holder actively must seek either an injunction to prevent use of the patent or the payment of penalties. Third, all patents can be challenged in court, as they often are by companies who have developed the same or similar technology.

**Patenting DNA**

While naturally occurring DNA sequences can only be discovered, and thus are not patentable, sequences that been manipulated or altered are considered inventions and thus potentially patentable. In 1980, the Supreme Court decided the case of Diamond v. Chakrabarty holding that have genetically engineered microorganisms are patentable.[9] Moreover, other cases have held that a newly isolated or purified material is patentable (for example, purified: prostaglandins, acetylsalicylic acid, adrenaline composition, and bacterial strains have been granted patent protection).[10] Thus a newly cloned human gene that existed naturally in an impure form in human cells (*i.e.*, it existed only in combination with other DNA), may be patentable. For example, the European Patent Office (EPO) recently allowed a patent for a synthetic gene for H2-relaxin.[11]

DNA sequences may be classified as an invention rather than a discovery, but they must still meet the three requirements of novelty, nonobviousness and utility. Although sequences are potentially novel and non-obvious, they may not remain so.[12] Thus DNA sequences may meet this requirement in the early stages of HUGO, but later developed ones may not since the mechanisms and technology needed to establish new sequences might be obvious from the older sequences. The state of the art might have already progressed beyond the point where DNA sequences are non-obvious. In addition, the utility requirement may cause difficulty. This difficulty is what underlies the controversy between patenting partial and full sequences.[13] While the partial sequence might have some use as a tool for scientific inquiry, in order to satisfy the utility criterion, the inventor might need to articulate the specific function of the full gene or resulting protein. In practice, however, the utility requirement has never posed a significant barrier to obtaining a patent; any proposed use generally is considered sufficient for purposes of the application.

In addition to patents on genetic substances, patents of sequencing processes are also possible. Process patents are often thought to be less economically valuable than substance patents from the standpoint of the patent holder since they do not prevent others from developing the same substance through a different process. In addition to patents on genes and gene sequences, patents may also be sought on genetic therapies or technologies. This report does not address the ethical acceptability of patents on genetic therapies.

**Purpose of Patenting**

Before entering into a discussion of the ethical concerns regarding patenting the human genome, it is useful to identify why patent protection is sought. Large outlays of money are necessary to conduct most biotechnology research. A substantial amount of this money comes from private sources.[14] Given the present state of federal funding for science research, it is unlikely that public money will be able to make up for the loss of private funding. Patenting is thought to encourage private investment into research.[15] Leaving aside for the moment the appropriateness or efficacy of a particular incentive (*e.g.*, patenting) it is important to acknowledge the need for incentives to encourage continued private support of research.

In addition, the patent system is designed to foster information sharing since a patent holder must disclose all of the information regarding his or her invention as part of the patent application. However, it is unclear whether this information sharing actually occurs. Clearly the effect of patent law on private research is different from the effect on academic research, where information sharing is generally the norm. With respect to private research, investigators may be unwilling to

share information (or prevented by their company from doing so) until they are prepared to file a patent application. On the other hand, refusing to extend patent protection to DNA sequences will not necessarily result in more information sharing. Industries may choose to keep the sequence information secret until they develop a patentable product.[16] As a result dissemination of information will not only be slowed, as occurs during the period between patent application and patent approval, but possibly cut off completely.

Biotechnology inventions are more like drug or device patents—there may be no direct benefit to the inventor unless he can market it commercially. This is in contrast to medical procedures, where one can argue that the inventor will still benefit from an invention without patent protection because of increases in the number of patients who come to the inventor for the procedure.[17] Moreover, although physicians may be barred from using a patented medical procedure in the course of their practice because of the potential for financial gain, researchers are not barred from using a patented biotechnology invention in the course of their research (as long as the research is not for financial gain). This is the research exception in patent law. As noted previously, the extent of this protection is unclear. There is some concern that the exception will not hold with the recent proliferation of joint endeavors between biotechnology industries and academic institutions. While a patented material may be used for research purposes, if those research purposes lead to commercial inventions, a license agreement must be negotiated between the original patent holder and the subsequent investigator. As a result, research efforts may be hindered because of high licensing fees.

**Ethical Concerns**

Notwithstanding the uncertainties about the benefits of patent protection, there are ethical concerns with patenting in this context. Most of these concerns focus on the idea that patenting human genomic material results in a harm to human dignity. There are a number of different arguments imbedded in this concept of harm and they will each be addressed in turn.

First, patenting may cause harm because it is equivalent to ownership of human beings.[18] The United States Constitution forbids ownership of people (slavery).[19] However, as stated previously, patents grant property rights rather than ownership rights, although this too may be disturbing. However, the property rights involved here are not rights in a full or complete human being (or even an identifiable human being), but only in parts of human material, separate from any one individual. DNA sequences are not the equivalent of a person, or even a partial person. Moreover, most DNA and even individual genes are not unique to humans—it is the combination that is crucial. Thus patenting a DNA sequence does not seem to grant property rights in another human being. Moreover, it is not clear how DNA is different from proteins or other naturally occurring substances found in human beings that are already patentable—it is just one earlier step on the chain.[20] The Danish Council on Ethics suggests that one concern is the lack of knowledge about DNA. Because it remains unclear where and whether certain attributes that are considered uniquely human are found in the genetic material, it is possible that granting patent rights will result in a violation of human worth.[21] In other words, property rights will be granted in something considered fundamentally "human." A solution to this may be to ensure that patent descriptions are carefully constructed so as to exclude the naturally occurring form, something that is not always done at this time.

Even if patenting does not confer ownership rights in a human being, there are other ethical concerns. For example, the commodification of human parts is often seen as improper.[22] Even if

there is continuity between DNA and patentable proteins, commodification of the former may be more problematic than the latter. For example, the manipulation of core parts, such as germ line therapy, is more ethically controversial than manipulation of somatic cells. Likewise, patenting of proteins may be more acceptable than patenting of earlier, or more fundamental elements that control (to a certain degree) who we are. Furthermore, there may be problems with using market rhetoric.[23] Discussions of patenting presuppose an ability to determine the economic value of the patentable entity. Using market terminology in relation to DNA may be ethically troubling because it implies that human beings may be broken down into "salable" parts. Recently, a coalition of more than 100 religious leaders issued a statement asking the government to prohibit the patenting of human genes and genetically engineered animals.[24] The coalition, coordinated by biotech adversary Jeremy Rifkin, director of the Foundation of Economic Trends, argued that patenting reduced the history of humanity to a commodity and violates the sanctity of human life. Some commentators have argued that reducing a life form to a composition of matter that is patentable is equivalent to reducing an organism to an object and creates a troubling precedent for ownership of life, including human life.[25] In essence, this argument rests not on the assumption that patenting results in ownership of human beings, but that patenting results in commodification of human beings and the commodification may lead to harm to human dignity.[26]

A final ethical issue focuses on what may be done with patented material. One element of this is a concern that human genes may be altered thus harming human genetic integrity.[27] Refusing patents on altered human genetic material will only indirectly control manipulation of genes—although patenting is designed to encourage investment is it clearly not the only impetus for research. A solution to this would be, instead, to regulate the research and uses of human genetic material. A second element of this concern is a fairness argument. If human genetic material is shared among all humans it should therefore "belong" to all humans. Although genomic research is being conducted on an international level, the resulting therapeutic technologies are not being distributed on a global level. For example, in one case the United States Department of Commerce filed a patent application for a cell line derived from the blood sample of a woman in Panama's Guyami tribe. No consent had been given for isolation and patenting of the cell line, which was thought to have anti-cancer properties, nor was there any evidence that the woman, or her tribe would gain any benefits from later developed therapies.[28] In a recent California case, a physician-researcher failed to inform a patient that the additional travel to a distant lab and the testing done there were not required for his therapy, but were aimed at isolating a unique cell line that the investigator later sought to patent.[29] Allowing patents on human genetic material gives the patent holder a certain degree of control over the uses of that material. There is no guarantee that the individuals who donate the original genetic material for research will gain any benefit, nor that the resulting therapies will be distributed in a globally just manner.[30] As a result, allowing patent protection for human genomic material may result in greater inequities in the access to beneficial therapies. Patent holders should not be allow to "sit" on a patent or to grant exclusive licenses to institutions which will not seek to develop the patent. Here too, the solution may be to ensure adequate informed consent or to regulate licensing agreements, not restrict patenting. Nonetheless, greater national attention needs to be paid to the implications of genomic patenting as well as to the international coordination of patenting laws.

**Conclusion**

While the Council does not feel that patenting of naturally occurring substances is unethical *per se*, it does urge caution in this area. Genetic research holds great potential for the development of new beneficial therapies. However, it is unclear what role patenting may play in ensuring such

development. While an outright ban on patenting of genomic material is unlikely and may be unwise, the Council makes the following recommendations:

1) Patents on processes—for example, processes used to isolate and purify gene sequences, genes and proteins, or vehicles of gene therapy—do not raise the same ethical problems as patents on the substances themselves and are thus preferable.

2) Substance patents on purified proteins present fewer ethical problems than patents on genes or DNA sequences and are thus preferable.

3) Patent descriptions should be carefully constructed to ensure that the patent holder does not limit the use of a naturally occurring form of the substance in question. This includes patents on proteins, genes, and genetic sequences.

4) One of the goals of genetic research is to achieve better medical treatments and technologies. Granting patent protection should not hinder this goal. Individuals or entities holding patients on genetic material should not allow patents to languish and should negotiate and structure licensing agreements in such a way as to encourage the development of better medical technology.

Report of the Council on Ethical and Judicial Affairs
of the American Medical Association
December 1997

## REFERENCES


1. For example, Dr. Venter while at NIH filed, but subsequently withdrew, a patent application for a number of cDNA sequences. See, e.g., Paul Riley, Comments: Patenting Dr. Venter's Genetic Findings: Is the national institutes of health creating hurdles or clearing the path for biotechnology's voyage into the twenty-first century? *J. Con. H. L. & Policy* 10:309 (1994).

2. U.S. Const. art. I, 8, cl.8.

3. 35 U.S.C.112 (1988) ("The specification shall contain a written description of the invention, and of the manner and process of making and using it, 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, and shall set forth the best mode contemplated by the inventor of carrying out his invention.").

4. Riley, supra note 1.

5. Rebecca Eisenberg, Patents and the Progress of Science: Exclusive rights and Experimental Use, *University of Chicago Law Review* 56:1017-1086 (1989).

6. 35 U.S.C. 102(a)(1988).

7. 35 U.S.C. 103 (1988).

8. 35 U.S.C. 101 (1988). Brenner v. Manson, 383 U.S. 519 (1966).

9. 447 U.S. 303 (1990).

10. Rebecca Eisenberg, "Patenting the Human Genome." *Emory Law Journal* 39:721-745, fn. 27, 1990.

11. The Danish Council of Ethics, "Patenting Human Genes," at 16, 1994.

12. Merck recently established a sequence database in the public domain that may make the question of patenting partial sequences moot due to lack of novelty. In addition, there is a federal DNA sequence database available for public use. C. Thomas Caskey, "Gene Patents—A Time to Balance Access and Incentives," *Bioinformatics* 14:298-301, 1996.

13. Karen Lech, "Human Genes Without Functions: Biotechnology Tests the Patent Utility Standard," Suffolk University Law Review 27:1631-1660, 1993; George Poste, "The Case for Genomic Patenting" *Nature* 378:534-536, 1995.

14. Rebecca Eisenberg, "Patenting the Human Genome" Emory Law Journal 39:721-745, 738, 1990.

15. Reid Adler, "Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization," *Science* 257:908-914, 1992.

16. Rebecca Eisenberg, "Intellectual Property Issues in Genomics." Bioinformatics 14:302-307, 1996.

17. American Medical Association Council on Ethical and Judicial Affairs, Report 67: "Ethical Issues in the Patenting of Medical Procedures."

18. Baruch Brody, "Protecting human Dignity and the Patenting of Human Genes," Draft Paper Baylor College of Medicine, January 22, 1997 (there are four arguments that patenting human genes harms human dignity: (1) it is equivalent to ownership of humans, (2) it commercializes body parts which should not be commodified, (3) it cheapens that which defines human identity, and (4) it leads to inappropriate modifications in our genetic integrity.).

19. U.S. Const. Amendment 13.

20. There are some opponents of patenting who claim that no naturally occurring substances should be patentable. See, e.g., Kathleen Day, "Church Groups to Fight Patenting of Life Forms," *Washington Post*, Saturday, May 13, 1995.

21. The Danish Council of Ethics, *supra* note 14 at 27.

22. See, e.g., Brody, supra note 12.

23. See, e.g. Margaret Radin, Contested Commodities (1996).

24. "Religious Leaders Prepare to Fight Patents on Genes." *New York Times*, Saturday, May 13, 1995

25. Id.

26. See, e.g., Radin supra note 16 and Brody, supra note 12.

27. Brody, supra note 12.

28. "Life for Sale: Europe says no to patienting life forms, but the US moes ahead." *Utne Reader*, June 1995.

29. Moore v. Regents of the University of California, 793 P.2d 479 (Ca. 1990).

30. See, e.g., Bernadine Healy, "Special Report on Gene Patenting," *New England Journal of Medicine*. 327(9):664-668, 1992.

PolicyFinder

## E-2.105 Patenting the Human Genome.

A patent grants the holder the right, for a limited amount of time, to prevent others from commercializing his or her inventions. At the same time, the patent system is designed to foster information sharing. Full disclosure of the invention--enabling another trained in the art to replicate it--is necessary to obtain a patent. Patenting is also thought to encourage private investment into research. Arguments have been made that the patenting of human genomic material sets a troubling precedent for the ownership or commodification of human life. DNA sequences, however, are not tantamount to human life, and it is unclear where and whether qualities uniquely human are found in genetic material.

Genetic research holds great potential for achieving new medical therapies. It remains unclear what role patenting will play in ensuring such development. At this time the Council concludes that granting patent protection should not hinder the goal of developing new beneficial technology and offers the following guidelines:

1) Patents on processes--for example, processes used to isolate and purify gene sequences, genes and proteins, or vehicles of gene therapy-do not raise the same ethical problems as patents on the substances themselves and are thus preferable.

2) Substance patents on purified proteins present fewer ethical problems than patents on genes or DNA sequences and are thus preferable.

3) Patent descriptions should be carefully constructed to ensure that the patent holder does not limit the use of a naturally occurring form of the substance in question. This includes patents on proteins, genes, and genetic sequences.

4) One of the goals of genetic research is to achieve better medical treatments and technologies. Granting patent protection should not hinder this goal. Individuals or entities holding patents on genetic material should not allow patents to languish and should negotiate and structure licensing agreements in such a way as to encourage the development of better medical technology. Issued June 1998 based on the report "Patenting the Human Genome" issued December 1997.

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*November 1991*

# American Society of Human Genetics Position Paper on Patenting of Expressed Sequence Tags

The American Society of Human Genetics (ASHG), a society of over 4500 American and Canadian physicians, scientists and genetic counsellors has followed the development of the Human Genome Project with great interest, and considers it to be of great potential benefit to the field of medicine. In a statement strongly supportive of the Project (Am. J. Hum. Genet. , 687-691, 1991), the Society endorsed an emphasis on the cloning and sequencing of expressed sequences as one route to achieve greater potential relevance for human health. The ASHG is now deeply concerned about the recent submission of patent applications for expressed sequence tags (ESTs) by scientists at the National Institute of Neurological Disorders and Stroke.

The issues relate to two questions, "can they be patented?" and "should they be patented?" (Science, 254 184-186, 1991; Nature 353 485-486, 1991). The Human Genome Committee of the ASHG has taken the view that the issuing of patents for ESTs is likely to do far more harm than good, and that before any patents are issued the impact on the Human Genome Project and on the field of medicine should be carefully examined. This view is supported by the ASHG Board of Directors.

First, it should be pointed out that the ASHG has not opposed patenting of genetic information when that information had utility. This would include, for example, recombinant clones for the production of human proteins (e.g. factor VIII, growth hormone, erythropoeitin) and disease gene probes for diagnostic testing, carrier identification and prenatal diagnosis (e.g. cystic fibrosis, muscular dystrophy, fragile X syndrome).

The attempt to patent ESTs, however, is another matter. The ASHG does not support the concept of patenting a short sequence from a randomly isolated portion of a gene encoding a protein of unknown function. "How can you patent something when you don't know what it is, much less what it will be used for?" (Science, 254, 184-186, 1991).

Furthermore, the ASHG does not consider that the three tenets of patentability (novelty, non-obviousness and utility) have been met. We wish to make two points in this regard. First, there is absolutely nothing novel about the identification of ESTs. An EST is simply a DNA sequence of a short segment of a cDNA clone that is picked more or less at random from a set of cDNA clones obtained by essentially standard published procedures. The idea of picking a large number of cDNA clones and using the sequence of a short piece of each as a genetic marker or tag is also an obvious approach that has been extensively discussed in the human genetics community and it is currently the basis of on-going genome projects both within and outside the USA.

Second, the utility of ESTs can be seriously questioned. Scientific experience suggests that an EST itself is unlikely to have commercial utility. The anticipated utility of an EST is simply as a research tool to identify the remainder of the coding region of the gene. Additional research would allow the determination of its DNA sequence, the deduced amino acid sequence of the encoded protein, reagents to generate antibodies against the protein and clues to the protein's structure and function. Further, if the protein was defective in individuals with a genetic disease or genetic predisposition to disease, then the gene and it's product might have utility in diagnostic or therapeutic applications for that disease. Thus, the utility would not be known until additional research was complete and the utility would almost certainly rest with the full cDNA, the genomic clones containing the gene or the protein product of the gene, and not with the EST itself. The EST is, at best, a starting point for further research, and should not be patentable.

With regard to the second question - should they be patented? - the ASHG is concerned that patenting of ESTs may be quite detrimental to the interests of the Human Genome Project and to society. The issue is complex. Indeed, the genome project itself is a venture whose very nature, magnitude and scope is new to society, and the complex ethical, legal and social issues raised by the project are challenges worthy of careful and considered debate. At this time, the issue of patents for ESTs deserves particular attention.

The primary concern is that the Human Genome Project should be a project of international collaboration. It should not be a competition between laboratories and between countries to see who can "own" the largest portion of the human genome. HUGO, the international Human Genome Organization, has stated this principle since its inception in 1988. The patenting of ESTs clearly and unequivocally contradicts this principle. There is no question that the patenting of ESTs by the NIH group, or by anyone else, will precipitate a race to isolate ESTs in many countries, a race to patent throughout the world and a race to exploit the genome information for all its "worth". It is virtually certain that under such conditions the information would not be shared between the competing groups until after patents are secured, so that duplication of effort will be impossible to avoid.

A second concern is the morass of competing claims that will be created by allowing patents for ESTs. Since an EST is part of a gene it is clear that different ESTs from the same gene may be isolated by different groups. Furthermore, a gene is often part of a gene family so that one EST may recognize more than one gene. We anticipate major problems in dealing with patent claims when several research groups could end up with competing claims for the same gene or genes. In essence, an EST is not specific enough to be the only marker for a gene nor to be a marker for only one gene.

A third concern is the potential inhibitory effect of patenting ESTs on the scientific community, both academic and commercial. Normally, a patent ensures that a gene will be available for all researchers and for any company willing to license it. We fear that in the case of ESTs it may have quite the opposite effect. An EST patent, to be useful to the commercial sector, must make broad claims in regard to future use, including protection for the rest of the gene and its protein product, and their use for diagnostic and therapeutic applications. The academic community is unlikely to put major research effort into an EST-identified gene or its protein product if someone else already has the right to license its use based on the trivial effort required to sequence the original EST. In the commercial sector there may be reluctance to invest heavily in further research on EST-identified genes when a small but unknown fraction of them will turn out to have commercial utility, and when the useful ones may be contested by patents involving other ESTs from the same gene. Genome research could end at the level of ESTs.

Finally, we wish to make one point with regard to urgency in this matter. The ASHG recognizes that the decision regarding patentability of ESTs in the US rests with the US Patent and Trademark Office. Given the high stakes of the decision on medical science, the biotechnology industry, the delivery of health care, and on the international cooperativeness in all these areas, the ASHG urges the patent office to give high priority to the resolution of the EST patent issue.

Furthermore, we urge the patent office to take into account not only the current patent law, but to consider also the implications of the decision for the field of medical science and for the international community in which we live. One argument for patenting ESTs has been that if they were published without patenting this might compromise the patentability of a future diagnostic or therapeutic procedure based on a gene or gene product derived from an EST in the public domain. What is needed without delay is a statement from the US patent office with regard to this potential problem. If it is not a problem, then it takes away the main argument for patenting ESTs. If it is a problem, then perhaps the best course is to rethink current patent law and to amend it to insure that the genome effort is not thwarted by laws developed in simpler times to deal

with simpler issues.

An international collaborative venture as bold as the Human Genome Project should not be jeopardized by the possibility of irrevocable damage inflicted by EST patents, the majority of which may never have any commercial utility. Let us strive to ensure that patents are obtainable at a stage in the process that will still allow commercial exploitation of genetic information, but not so early in the process that it will stifle individual scientific endeavour and lead to international chaos.

*The Human Genome Committee and The Board of Directors*
*The American Society of Human Genetics*

# HUGO Statement on the Patenting of DNA Sequences

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## Summary

HUGO (The Human Genome Organisation) is worried that the patenting of partial and uncharacterized cDNA sequences will reward those who make routine discoveries but penalize those who determine biological function or application. Such an outcome would impede the development of diagnostics and therapeutics, which is clearly not in the public interest. HUGO is also dedicated to the early release of genome information, thus accelerating widespread investigation of functional aspects of genes. This statement explains our concerns.

## Background

HUGO is an international membership organization whose goal is to coordinate and enhance efforts in genome research. HUGO members include the leading scientists engaged in genome research, scientific advisors to biotechnology companies involved in genome research, and representatives from government agencies involved in genome research. The research efforts of these members exceed $250 million per year. HUGO members helped to develop the key technologies and methodologies that led to the Human Genome Project and the development of the genomics industry. In particular, their inventions include DNA sequencing,[1,2] automated devices for DNA sequencing,[3,4] DNA-based genetic mapping,[5-10] genome-wide physical mapping,[11,12] techniques for mutation detection (reviewed in references 13 and 14), computer- based methods for the detection of gene function by sequence analysis,[15] and methods for the construction of high-quality cDNA libraries[16-18] and for the isolation of gene sequences based on partial functional and structural information.[19] In addition, HUGO members have taken leading initiatives in constructing most of the existing maps of the human,[10,12] mouse,[20] rat,[21] fruit fly,[22] nematode,[23] yeast,[24] and bacterial[25] genomes.

HUGO members are carefully following developments in the area of intellectual property protection for the results of genetics and genome research and wish to see these matters resolved in a way that considers the interests of researchers, private firms, and society. In particular, we want intellectual property rights to be allocated fairly, in a manner that appropriately weighs the contributions of different parties to the total research effort, and creates necessary incentives for the ongoing development of products without interfering unduly with scientific research.

Because our expertise is primarily scientific rather than legal, it is not our place to offer an opinion on questions of patentability as such. Nonetheless, we are concerned that public debates about these issues are sometimes based on misinformation concerning the underlying science, and we fear that similar misunderstandings may infect decisions about patentability. In the hope of clarifying these issues, we wish to offer a scientific opinion on some of the underlying technical questions that may affect determinations of patentability.

## Specific issues

An expressed sequence tag (EST) is part of a sequence from a cDNA clone that corresponds to an mRNA.[26] An EST can therefore be used to identify an expressed gene, and can also be used as a sequence-tagged site marker[11] to locate that gene on a physical map of the genome.

Among the issues that have emerged in the discussions to date are the nature and extent of scientific work involved in:
(1) the generation of ESTs;
(2) the use of ESTs to obtain full-length cDNA and gene sequences;
(3) the use of ESTs or full-length sequences to obtain expression of proteins;
(4) the use of ESTs or full-length gene sequences to determine their normal biological functions, association to disease(s) and their RNA and protein products; and
(5) the use of genes or gene fragments for categorizing; mapping; tissue typing; individual or forensic identification; production of antibodies; antisense, triple helix, and ribozyme applications; or locating gene regions associated with genetic disease, etc.

We consider each of these issues in turn.

### (1) The generation of ESTs

The scientific work involved in generating ESTs is straightforward and based on automated sequencing technology that has been well understood since the mid-1980s.[3] Advances in DNA sequencing technology since then have increased the speed of the operation without altering the approach in any fundamental respect.[27] Indeed, the sequencing of any gene involves the sequencing of individual small fragments. Moreover, the sequencing of fragments of genes has long been used as a rapid tool for the characterization of genes encountered in a variety of settings, including library screening.[28]

The current strategy of large-scale EST sequencing[27] represents a useful but straightforward extension of a technique that has been in use on a smaller scale for years. Since the mid-1970s, cDNA libraries have been constructed from many sources, including different organisms, different tissues, and different functional cellular states such as activated immune cells versus naive ones or malignant versus normal.[29] This has allowed cDNA libraries to be enriched for genes of interest. The idea of coupling DNA sequencing to cDNAs was discussed as early as 1986.[30] It has also been understood for some time that considerable information can be gleaned from partial DNA sequences and that putative protein function can be inferred from sequence similarity to previously-characterized genes.[31,32] A laudable but not yet achieved objective of the Human Genome Project is the determination of full-length sequence of all mapped genes. Such information will accelerate (but cannot guarantee) disease gene associations and functional assignments.

**(2) The use of ESTs to obtain full-length cDNA and gene sequences**

The process from EST to full-length cDNA or genomic sequence is not straightforward. The full-length cDNA represents the entire sequence of the mRNA and the genomic sequence includes introns and other flanking regions. Using partial gene sequences to find full-length cDNA and genomic sequences is an important research activity, ongoing in many laboratories on a daily basis. It has been successfully accomplished in many cases, and many specific strategies have been developed over the years for approaching this task. Nonetheless, it remains a task that is fraught with uncertainty. In some cases known techniques such as specific primer extensions may be successful;[33] in others extraordinary skill will be required to overcome obstacles such as secondary structure.[34] Foreseeable obstacles include the difficulty or impossibility of cloning mRNAs that are large[35,36] or that encode poorly clonable sequences;[37] the problems posed by immature, or incorrectly or alternatively spliced messages;[38,39] the difficulties posed by cross- hybridization among members of gene families;[40,41] and the rare but extremely challenging problems posed by post-transcriptional alterations of RNA sequence.[42,43] Having an EST in hand does not guarantee insight into a practical or feasible strategy for overcoming these obstacles. The effort involved may range from a matter of weeks (in case of an extremely short, easily cloned gene) to more than a year. It may be necessary to screen multiple cDNA libraries and tissue sources or to use various cloning-based and polymerase chain reaction-based techniques.[19]

**(3) The use of ESTs or full-length sequences to obtain expression of proteins**

Getting correct expression of a gene sequence presents several obstacles that can complicate the generation of a useful product. For instance, it may be necessary to attempt cloning in multiple hosts, including bacterial, yeast, insect, and mammalian cells, to find a usable host.[44] There is no guarantee as to what expression vector and gene structure will be adequate for the task. Moreover, there is little way to know in advance what cell types will produce the appropriate post-translational modifications. Each expression construction must also allow for appropriate promoters, high affinity translation sequences, and often enhancers and splice junctions.[45]

**(4) The use of ESTs or full-length gene sequences to determine their normal biological functions,**

**association to disease(s) and their RNA and protein products**

The task of identifying biological functions of a gene is by far the most important step in terms of both its difficulty and its social benefit. It therefore merits the most incentive and protection. Because this step is the key to the development of useful products, we are concerned that it will not receive adequate protection under current law. Determining function for a sequence is a matter of tremendous complexity, requiring biological experiments of the highest order of creativity. Nevertheless, with only DNA sequence it is possible to execute a computer-based algorithm comparing the sequence to a database of previously-characterized genes.[31] In about 50% of cases, such a mechanical comparison will indicate a sufficient degree of similarity to suggest a putative enzymatic or structural function that might be possessed by the unknown gene.[46] This process involves straightforward analysis of private or public database information to provide an idea of potential function. In contrast to sequence analysis, the task of establishing actual biological functions requires specific experiments that are individually tailored to the particular gene. These may range from searching for the intracellular location of the gene product,[47,48] testing expressed proteins for a variety of potential enzymatic functions,[49,50] attempting to construct knockout mice,[51,52] attempting to identify human or animal disease states in which the gene is disrupted,[53-55] or attempting to interfere with the function of the gene through antisense,[56] ribozyme[57] or related technologies. In each case it is a major undertaking for which the likelihood of success is frequently unknown.

**(5) The use of genes or gene fragments for categorizing; mapping; tissue typing; individual or forensic identification; production of antibodies; antisense, triple helix, and ribozyme applications; or locating gene regions associated with genetic disease, etc.**

Several uses have been suggested for genes and gene fragments to get past the utility requirement for patent protection. For any random gene, gene fragment, or collection of genes or gene fragments, it is easy to give a list of potential uses without knowledge of their true biological functions. These uses include catagorizing genes according to their expression profile;[58] developing markers for mapping;[11] tissue typing;[59] individual or forensic identification;[60,61] production of antibodies;[62] antisense;[63] triple helix[64] and ribozyme [65] applications; and location of chromosomal regions associated with genetic disease.[66] In all important cases the development of a truly useful tool for these purposes will require the investment of considerable further effort and creativity, far more than that invested in finding the initial fragment. Furthermore, in disease gene mapping, the probes employed, knowledge of their localization, and physical and genetic distances have been determined by a collective scientific community and found in open databases. For example, in order to use DNA fragments for individual identification, one must first find sites of polymorphic variation and identify the distribution of such polymorphisms in appropriate populations.[67] Similarly, to use DNA fragments for tissue typing, one must first establish that a particular fragment or set of fragments provides a sufficiently discriminating signature of a particular tissue type or state.[68-70] Mapping a sequence may sometimes be routine, but in other cases it may involve overcoming problems posed by gene families, pseudogenes, and repetitive elements which lead to mapping ambiguities due to signals from multiple locations.[41] Moreover, with antisense and triple helix applications, it is easy to postulate such uses, but scientists would not pursue them without specific and detailed knowledge of biological function. Each of these asserted uses may not be carried out without considerable further effort and additional biological information not apparent from the information inherent in the sequence alone.

## Conclusion

The discovery process in molecular biology is rich and complicated. Technological advances in recent years have rendered some aspects of the procedure, such as sequencing, increasingly mechanical and

straightforward, which has led to the generation of large quantities of DNA sequence for many organisms.[71,72] Continued developments promise to yield still greater quantities of sequence information, culminating in the complete genetic information of higher organisms.[73,74] Yet other steps in biological discovery, such as the understanding of biological function and the use of genes and gene products in the diagnosis and treatment of human disease, remain exceedingly challenging, uncertain, and needing great creativity.

It would be ironic and unfortunate if the patent system were to reward the routine while discouraging the innovative. Yet that could be the result of offering broad patent rights to those who undertake massive but routine sequencing efforts -- whether for ESTs or for full genes -- while granting more limited rights or no rights to those who make the far more difficult and significant discoveries of underlying biological functions. A second, equally unfortunate outcome would arise if a partial sequence publication or submission to a database precluded patenting of innovative disease gene discoveries leading to improved medical diagnostics and therapeutics. This could lead to inhibition of contributions to databases and lack of investment protection for the innovative. We hope that the system will find some way to adjust to the changing realities in this field to promote and protect this important and ongoing process of discovery in the public interest.

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-from Proceedings of a Public Meeting (5/21/92)
"Federally Funded Genome Research: Science & Tech. Transfer Issues"

## SUMMARY OF COMMENTS FROM PARTICIPANTS

*[EDITOR'S NOTE: In this final session, 14 participants gave five-minute oral presentations addressed to the Genome Patent Working Group. Those comments are summarized below in the order in which they were presented. Only official resolutions of organizations, entered into the record of the meeting, are presented in full. Written statements submitted by most of the speakers are on file for public inspection in the offices of the NSF Directorate for Biological Sciences, Division of Biological Instrumentation and Resources. Copies may be obtained from the Oak Ridge Associated Universities, Science/Engineering Education Division, at 615/576-7393.]*

**Charles M. Chambers** - American Institute of Biological Sciences
Topic: *Testimony of the American Institute of Biological Sciences on Intellectual Property Protection and Genome Research*

Dr. Chambers, Executive Director of the American Institute of Biological Sciences (AIBS), referred to the topic of the meeting as "an issue of fundamental importance to the historically successful relationship between the scientific research community and the Federal Government." He commended the Working Group for seeking broad input about this complex and challenging topic, which lies on the boundary between science--i.e., research to discover knowledge about the natural world--and invention--i.e., creating something useful based on existing knowledge.

Chambers said that the patent system, as an adversarial arbiter of property rights, is ill-equipped to manage or resolve the broad policy questions raised by this topic with regard to ethics, public health, academic freedom, peer review, collegiality, dissemination of knowledge, etc. He urged the Working Group to consider more fundamental principles, such as openness in scientific inquiry and universal access to knowledge about human health, in its deliberations.

He recognizes that, in light of the strong affirmative policy to exploit patents on behalf of government agencies, and given the volatility of the genome research arena and the ambiguities of patenting, it seems very prudent and reasonable for an agency administrator to decide to seek patents for expressed sequence tags (ESTs). The risks that AIBS sees are in the future, in the event that "the patent application take on a life of its own, separate from the invention. There does come a point of diminishing returns in technology transfer when it is wiser for the government just to step back, dedicate the invention, and let the marketplace do the best it can. I would suggest 18 months is a reasonable such horizon."

A second question is whether the patent should be granted. He is concerned about the issue of usefulness, which is "the fundamental quid pro quo for the monopoly." Here the facts of each case are complex and vulnerable to subjective interpretation or manipulation. AIBS is concerned that "a great peril exists, that when the matter being licensed is close to the forefront of scientific research, decisions by non-scientists can alter the way science is done. And we would encourage close involvement on a case by case basis by peer review panels and study groups familiar with it."

Chambers closed with the following statement: "In my view and in the view of the majority of the Congress, the United States should declare that the human genome is non-patentable material and seek international concurrence in this regard, in much the same way that nuclear materials and processes for atomic weapons have been treated."

Walter Nance - American Society of Human Genetics
Topic: *Testimony Regarding Patenting of Expressed Sequence Tags and Other Random or non-specific DNA Fragments*

Dr. Nance spoke as President of the American Society of Human Genetics, which has endorsed the cloning and sequencing of expressed sequences as an effective strategy for rapidly identifying those regions of the genome that are of greatest health relevance. However, he said, in recent months the Society has become increasingly concerned about the submission of patent applications for ESTs by scientists at the National Institutes of Health. Their primary concerns relate to the lack of novelty and specific utility of ESTs.

First, since ESTs are isolated more or less at random as fragments of genes in coding proteins of unknown function, Nance said, they lack the known specific utility that can only be obtained after additional research is conducted to determine the full cDNA sequence and deduce the amino acid sequence of the encoded protein. Further research may then be required to establish the protein structure, its function, and its health relevance. Not until then would it be possible to assess the specific utility of a given EST.

The Society also contends that the idea of isolating a large number of cDNA clones and using the sequence of a short piece of each as a genetic marker or tag is an obvious approach that has been extensively discussed in the human genetic community and is currently the basis of ongoing genome projects, both within and outside of the U.S. Some of these projects were underway at the time of the NIH patent filing, he noted.

If EST patents are allowed, the Society is concerned about the effect that the resulting race to establish ownership of the human genome will have on the spirit of international collaboration that has characterized the Human Genome Project. They are concerned that conflicting patents may be issued on multiple ESTs derived from the same gene. They are also concerned about the chilling effect that EST patents might have on research to develop commercial applications of those cDNAs that are found to be of demonstrable utility. Finally, if patents are allowed on ESTs, they see no rational criterion

for barring the patenting of larger pieces of DNA clones, such as yeast artificial chromosomes (YACs) or even chromosome-specific libraries.

Nance concluded by stating the recommendations of the Society that:

- If DNA sequence information is to be patented at all, the minimum criteria for patenting such information should be demonstrated specific and substantial utility based on specific knowledge of the function or value of the DNA sequence, clone, or fragment, rather than on the general knowledge that some of the ESTs will doubtless be found to have value if they are studied long enough.

- ESTs and other random or nonspecific DNA fragments should be specifically excluded from patent protection, since they would fail to have the specific and substantial utility required by Part I of the patent application.

- A ruling should be obtained to ensure that publication of a sequence of an EST or any other random or nonspecific fragment of DNA not be considered as "prior art" that would interfere with the subsequent patenting of genetic discoveries that do have demonstrated utility.

- International patent law should be made uniform with respect to the intellectual property issues raised by the Human Genome Project.

Nance expressed the belief that an international collaborative effort as bold as the Human Genome Project should not be jeopardized by the possibility of irrevocable damage inflicted by EST patents, the majority of which may never have any demonstrable utility. The objective should be to ensure that patents are obtainable at a stage that will still offer commercial exploitation of genetic information, but not so early in the process that it will stifle individual scientific endeavor and lead to international chaos.

**Richard Lower** - University of Wisconsin, Madison
Topic: *Intellectual Property Considerations for Public Plant Germplasm Development*

Dr. Lower is Associate Dean of the College of Agricultural and Life Sciences at the University of Wisconsin, Madison, and Acting Executive Director of the Wisconsin Agricultural Experiment Station. His comments addressed intellectual property rights as they impact plant germplasm developments at state agricultural experiment stations. About 350 of the approximately 6,000 research scientists employed at these stations, he said, are plant breeders involved in the development of improved germplasm for food, fiber, and ornamental crops.

Much of the vaunted success of the agricultural experiment station system can be attributed, Lower said, to the free exchange of information as well as germplasm in the development of a cooperative infrastructure that allows new germplasm to be acquired,

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THE PRESIDENT HAS SEEN
12-30-99

THE WHITE HOUSE

WASHINGTON

December 17, 1999

MEMORANDUM FOR THE PRESIDENT

FROM: Bruce Reed
Eric Liu

SUBJECT: DPC Weekly Report

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Podesta

**1. Crime – Update on Gun Negotiations.** We have begun to engage various parties in the settlement talks and want to keep you updated. This week we met with representatives of most of the cities and counties that have filed suit against the gun manufacturers. Our message to this sprawling group was the importance of solidarity, and they were roundly supportive of our involvement. We also discussed strategy with the Attorneys General of New York and Connecticut, Eliot Spitzer and Richard Blumenthal, who have led the slow-moving talks to this point and who will be working with us as we push things forward. (We are meeting with Stan Chesley on Monday). Our plan is as follows: we are working now to hone a common "wish list" of remedies that we, the cities, the states and others on our side can bring into the settlement talks; on January 6, Robert Delfay, the lead industry negotiator, will come to the White House for a preliminary visit; on January 21, we will meet the manufacturers at the annual Shot Show in Las Vegas for a round of substantive talks; and sometime in the middle of January we may also meet informally with manufacturers to lay the groundwork for the Las Vegas round. None of this information is yet public. On a separate track, we met with this week with John Podesta and Administration staff to lay out our legislative and regulatory agenda on gun control and enforcement. We have a series of announcements in queue, beginning this weekend with a new budget initiative for ATF on ballistics, that will serve both to fortify our negotiating position and to frame public debate on our terms as talks with the industry get underway.

**2. Education – Civil Rights Investigation of Chicago Social Promotion Policy.** You asked recently about a federal civil rights investigation of the Chicago Public Schools social promotion policy. In October, the Education Department's Office of Civil Rights (OCR) received a complaint from an advocacy group alleging that Chicago's policy discriminates on the basis of race and sex and violates Title VI and Title IX. The complaint alleges that Chicago uses the Iowa Test of Basic Skills (ITBS) as the sole criterion for promoting students to the 4th, 7th and 9th grades; that this has a disparate impact on African American, Latino, and male students; and that CPS is using the test in a manner that the test's makers deem inappropriate. OCR is now gathering information on the allegations, but has determined already that the Title IX claim has no factual basis. Chicago maintains that it takes into account factors other than ITBS scores, such as grades and attendance. The plaintiffs contend that those other factors never mitigate poor scores. While we cannot influence the course of this investigation we are monitoring it closely. The social promotion policy in your Education Accountability Act requires multiple measures, not scores from a single test, for promotion decisions.

What they are doing in Chicago is good -- they need to keep high numbers of low learners going to summer school!

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12-30-99

3. **Health Care – Partial Birth Abortion and Organ Trafficking.** Kate Britton recently wrote to you about partial birth abortion, and you asked two questions about her letter. First, you asked about fetal tissue trafficking. Britton cites an article in the *Wanderer* claiming that women are coerced into having abortions so that fetal tissues and organs can be sold to NIH-funded laboratories. This is simply not accurate. ~~Selling body parts or human tissue is illegal~~, and NIH would not sanction or fund the types of activities described in the article. Second, you asked about Britton's claim that "the vast majority of partial-birth abortions are performed in the 5th and 6th months of normal pregnancies and are completely elective, that is, not associated with maternal or fetal risk." According to a survey by the Alan Guttmacher Institute, the majority of these procedures are indeed performed in the 5th and 6th months of pregnancy, but we do not have good data on the associated risk level. Your position on this procedure is clear: you would sign a ban of late-term abortions if there were an appropriate exception to protect the health and life of the woman. You have consistently opposed the cases Britton objects to – procedures that are "completely elective." We will help draft an appropriate response.

good

4. **Health Care – Update on Gene Patenting.** Following your Millennium Meeting on genetics, the NIH met with the Patent and Trademark Office to discuss growing public concerns about PTO's liberal approval of patents for gene sequences. From the NIH's point of view, such patents severely limit research and development on the genetic underpinnings and treatments of disease. (As you know, there is also considerable debate whether intellectual property monopolies over genetic material should ever, as an ethical matter, be granted). As it happens, PTO is now developing new guidelines for the genetic patent approval process. Under the current draft guidelines, PTO would not grant patents for short genetic sequences that have no known function, but would approve patents for sequences when: 1) a specific function for the sequence has been determined, such as its role in disease development or its use as a diagnostic; or 2) general information about the sequence's location or potential function has been identified. The NIH, while pleased that PTO would refuse patents for sequences with no known function, is troubled that sequences for which merely general information is known could be patented. Indeed, many in the consumer and scientific advocacy communities would prefer to permit patents only for those sequences that are linked to a new diagnostic use or treatment intervention. The final guidelines are subject to an OMB review, and we will work closely with OMB and others to build in more protections against premature application of patents.

↳ Podesta
important issue
NIH is right about this

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Important issue
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about this