

“ARE WE FOR SALE”
PATENTING THE HUMAN GENOME

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1. **The Business Side of Genes and the Human Genome**

The promise of genomics is huge – that is the ability to control or even eradicate the worst scourges known to mankind. The economic stakes are equally huge if genomics does one day fulfill its promise. The use of patents to encourage research and state a claim to valuable discoveries is a vital aspect of the genomics industry.

A. **Recent Big Developments**

- * On June 26 of this year, **Celera Genomics, Inc.** and the Human Genome Project (“**HGP**”) publicly announced that they had decoded and mapped the human genome.
- * On September 12 of this year, **Human Genome Sciences** said that its drug for wound healing had accelerated the repair of chronic venous ulcers in an early Phase 2 clinical trial. The drug, repifermin, is a natural human protein and is believed to be the first drug that was discovered using genomics and that showed effectiveness in a randomized clinical trial.

*“Genes” and “Genomics” are front-page news and big business.
How big a business we are only beginning to realize.*

B. **Big Dollar Implications**

Anyone active in the biogenetics area knows the distinction between the human genome – which is the entire sequence of over three billion chemical units in human chromosomes – and the individual genes (the exact number of which is unknown) contained within the genome. It was a confusion between the two that caused the share price of many biotechnology companies to plummet in March of this year after President Clinton and Prime Minister Tony Blair issued a statement

saying the human genome should be publicly available. Their statement sent the share prices of genomics companies sharply downwards and caused double-digit declines in biotechnology indices, with the Nasdaq Biotech Index down 12.5% and the Amex Biotech Index off by 13.2%. White House officials later emphasized that genes themselves, as opposed to the entire human genome sequence, should be eligible for patents. **The officials stated no position as to how easy or difficult it should be to patent a gene.**

If confusion over how to define a word can cause the loss of billions of dollars of market capitalization in a single industry, in a single day, it is clear that the word is at the heart of the affected industry.

In the genomics industry, arguably the most important words are “GENE¹” and “PATENT.”

1. **A Brief History of Gene Patents in the U.S. and Europe**

A. **The U.S. Model - Taking the Liberal Approach**

U.S. patent law allows a discovery from nature (for example, penicillin), to be patented provided that the discovery is isolated and purified as the result of human effort. As for genes, the U.S. Patent and Trademark Office (“PTO”) position is that: “From a patent law standpoint, genes are treated just like any other chemical found in nature.” (Todd Dickinson, director of the PTO.)

Since the early 1980’s, U.S. patent protection in the biotechnology field has been relatively broad. In particular, the U.S. Supreme Court decision in Diamond v. Chakrabarty (1980) opened the way for inventions relating to genetic engineering and living organisms.

Early gene patents (e.g. erythropoietin for anemia) resulted from the cloning of genes that coded for a particular protein. The effort involved years of working backward from the function of a protein to the isolation of the desired gene.

Contrast the years of work that went into isolating the gene that led to erythropoietin with today’s high speed gene sequencing technology; a technology that allows genes and gene fragments to be discovered in mass without knowing the functions of the proteins produced by the genes.

This technological development has had profound implications for the patenting of genes and for the explosive growth in U.S. patent applications related to genes. As examples of this growth:

¹ A Gene can be described as a sequence of bases that encodes a single protein.

- The PTO has now issued patents on over 6,000 genes and about 1,000 of these patents relate to human genes.
- Until recently, many companies filed for U.S. patents on a gene without knowing the functions of the genes for which a patent is sought. Many of these companies contended in their patent applications that the required “utility” of the invention was that, at a minimum, genes make a protein and proteins can be used as animal feed. The PTO has granted some of these patents.
- Currently there are more than 20,000 patent applications related to genes pending before the PTO.
- Applications are pending before the PTO for more than **half a million** gene fragments, which are known as expressed sequence tags (“**EST’s**”) (Information provided by John Doll, director of biotechnology at the PTO). (**EST’s** are expressed by an organism, as opposed to large parts of the genome that are in effect unused.)

B. The European Model -A More Cautious Approach²

The patentability of human genome technologies is addressed by the European Union Directive on the Legal Protection of Biotechnological Inventions, enacted in July 1998. The law requires all member states to amend their patent laws to conform to the provisions of the directive no later than July 30 of this year.

Although there is no prohibition or exclusion in national or European patent law precluding the patentability of biological matter per se, the Directive provides that:

“the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including sequence and partial sequence of a gene, cannot constitute patentable inventions.”

However, the Directive goes on to state that an element of the human body that has been isolated or produced by means of a technical process, including any sequence or partial sequence of a gene, “may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.”

² An excellent article concerning the European approach appears in the International Bar Association’s INT. BUS. LAW. Vol. 28 No. 3 at 97-144 (Mar. 1, 2000), by Trevor M. Cook, *Patenting and Ownership of Genes and Lifeforms: European Perspective*.

These seemingly inconsistent positions illustrate the “product of nature” problem which has always existed in European, and U.S. patent laws. The Directive seeks to clarify that the established principle of European patent law, that isolated substances may be patented, will be extended to genetic sequences.

The Directive also includes a non-exclusive list of unpatentable processes. This list includes cloning, germ line modification, certain embryo processes, and transgenic processes. This list is indicative of a general uncertainty in much of Europe over allowing the commercial exploitation of human genome technology and, for that matter, other biotechnological innovations relating to higher organisms.

In addition, the Directive goes on to acknowledge the national right to prevent the patenting of technology deemed contrary to “ordre public,” and morality. It lets stand the national authorities’ ability to examine the controversial nature of an invention on a case-by-case basis.

C. **Recent Developments in the U.S.**

In response to criticism from numerous sources that gene patents were too easily obtained (but also in reaction to the 1997 federal court decision in University of California v. Eli Lilly and Co.), the PTO sought to raise the bar last December by publishing proposed “utility guidelines” for genetic subject matter. These proposed guidelines require that: (i) more of the gene’s function be known before a patent is issued and (ii) that a representative number of species have to be implicitly or explicitly disclosed in the patent application (this to avoid a situation such as a patent application on “mammalian gene x” even though the researchers had only determined the sequence of gene x for one species (e.g. a mouse.) (The proposed guidelines are expected to be finalized this fall.)

As a result of the Guidelines:

Gene function will now be viewed as an attribute of what the gene does and not merely an attribute of the claimed gene. “One simply cannot patent a gene itself without also clearly disclosing a use to which that gene can be put,” (Todd Dickinson, director of the PTO before the House Judiciary Subcommittee on Courts and Intellectual Property on July 13, 2000.) “As a result, we believe that hundreds of genomic patent applications may be rejected by the U.S. PTO, particularly those that only disclose theoretical utilities.” (Todd Dickinson, as above.)

- Under the proposed Guidelines, it is quite possible that **EST’s** will not qualify for patents. (See the introductory comments of the U.S. Patent Office to the proposed guidelines.)

- Fully characterized genes whose functions are known – like a gene that predisposes women to breast cancer and can be used in a diagnostic test – will continue to be patentable.
- There is still a large middle ground, consisting of full-length genes whose function is not known for certain but whose function can be guessed at by computer analysis. The U.S. National Institutes of Health and the U.S. National Academy of Sciences oppose patents on these genes, but the PTO has said that some such patents could be granted.

The PTO has issued training and guidance materials (see www.uspto.gov) for use by its patent examiners; these materials provide actual examples of how to apply the proposed Guidelines.

Notwithstanding the proposed Guidelines, many believe that even if the Guidelines are adopted as now written there remains the potential for chaos in the use of patents to stake claims to elements of the human genome.

D. Conclusion

U.S. and European regulatory approaches to gene patents have come closer together, without yet becoming synonymous. **At the same time, it has become clear that the ethical and moral debate is over – genes (including human genes) are being patented and will be continued to be patented.** The debate now is not being held over the moral and legal issues of gene patenting, but rather the business/legal issue of just how high a level of scientific utility must be shown before a gene-related patent is granted. **How are the battle lines being drawn in the U.S.?**

3. The Controversy Over Gene Patents

Earlier this year, **Human Genome Sciences**, based in Rockville, Md., was granted a patent on a gene for a protein that turned out to serve as the entryway for the AIDS virus to infect cells. While the company identified the gene as an immune system receptor, its role in AIDS was not discovered until later by other researchers. Still, **Human Genome** says it is entitled to royalties on any drug that takes aim at this entry portal, or (if it so elects) to block development of such a drug.

Is the position of Human Genome Sciences defensible as being in the best interests of society? Certainly, it is the position taken by many companies in the genomics industry.

Some of the commonly heard arguments for and against gene patents are summarized below. In fact, however, the public policy debate and the legal decisions (at least in the

U.S.) seem clear that the question is no longer “can or should a gene be patentable” but rather “how high a standard of scientific discovery (e.g. “utility”) must be shown so as to obtain a patent.”

B. **An Argument - Gene Patents Make for Bad Science and Bad Public Policy**

- Innovation Compromised

John Soderstrom, Director of **Yale University's Office of Cooperative Research** (which facilitates the commercialization of University developed technology) believes that "innovation is hindered by the patenting of individual genes and therefore the proposed Guidelines are an important step in supporting basic research and innovation."

- Licensing Expense Leads to Loss of Potential Public Health Benefit

Many researchers, physicians, politicians and lay people fear that genetic testing of patients could become prohibitively expensive if each gene is patented. Already, royalties paid to holders of patents on genes, research mice and other tools can total 12 to 14 percent of the cost of a drug, making some products uneconomical to produce.

Harold Varmis, President of **Memorial Sloan-Kettering Cancer Center** in New York and former director of the National Institute of Health recently said: "Overly enthusiastic protection of intellectual property, too early in the process of product development, can impede the delivery of public health benefits."

Many commentators note concerns over the possibility that "royalty stacking" from "reach-through royalties" (i.e. royalties on sales of a product developed using a tool, as opposed to royalties on the tool itself) could make licensing prohibitive.

There is also the potential problem, particularly with **EST** patents, that the **EST** patent holder could demand cross-licensing rights from holders of later, more valuable technology (i.e. a later discovered complete gene sequence) that owes little to the work done by the **EST** patentee.

- Bad Policy/Bad Law; Confusion and Delay

Dr. Robert I. Levy, senior vice president for science and technology at **American Home Products**, calls the gene patenting situation a "minefield." Finding out who owns rights to what takes an increasing amount of time, Dr. Levy said at a health care conference in San Francisco earlier this year. (N.Y. Times, June 28, 2000)

"Knowing the sequence of a gene is only useful when the gene product is known and can be used as a target for therapeutic intervention. Patenting gene sequences is analogous to copyrighting the alphabet." (Lisa M.

Dunkle, M.D., Sr. VP, Drug Development **Achillion Pharmaceuticals, Inc.**)

- Moral Wrong

Some see the patenting of genes (most particularly human genes) as a moral wrong.

- Rights of Nations

Some object to patenting the genes of plants and animals indigenous to a less wealthy country unless there is a way to share the economic benefits with the citizens of that country.

An Argument-Gene Patents Make for Good Science and Good Public Policy

- Gene Patents Are a Key Incentive to Innovation

Human Genome Sciences, the leading patent holder of human genes, has noted that the electronics industry continues to innovate rapidly and reduce prices despite numerous patents. The company asks, why is the genomics industry any different? After all, because patents promise a company a period of exclusivity, companies are more prepared to make big financial investments.

- Research and Innovation by Non-Patent Holders Are Encouraged

Many in the biotech industry argue that patents actually promote the free exchange of science. The PTO requires applicants to explain the invention or discovery in enough detail that it can be replicated. Additionally, applicants are required to disclose the “best mode” of the invention so future users can avoid undue experimentation when practicing the invention. Furthermore, researchers are free to use the information, as long as they do not make, use or sell the claimed invention.

- Patents Encourage Licensing

Stephen P.A. Fodor, chairman and chief executive of **Affymetrix, Inc.**, which makes gene chips, is quoted as saying that only one patent holder had refused to allow its gene to be placed on a chip. He states that most patent holders want people to do research on their genes in hopes of finding a drug, which would bring really big royalties.

- Delays in Obtaining Patents

It is common, at least in the U.S., for a biotech patent to be pending for two years or more. Many research tools such as **ESTs** will have a useful life that ends before a patent issues. Also, researchers often simply want the genetic material, not the underlying intellectual property. Thus, many patents will have little practical effect.

4. Some Practical Reactions to the Gene Patent Rush

A. The SNP Consortium

In 1999, a group of leading drug companies and technology companies joined with the Wellcome Trust to form a consortium to study differences in the genome between one person and another. These differences, known as “single nucleotide polymorphisms” (a single base pair mutation), or **SNPs**, could be important in testing susceptibility to disease. The consortium intends to put **SNPs** in the public domain, and will seek to patent **SNPs** but not enforce any **SNP** patents obtained. The idea is to prevent other companies from patenting the **SNPs** before their function is known. “It’s to ensure we have the basic alphabet,” said Arthur Holden, chief executive of the consortium.

B. HUGO

The Human Genome Organization (“**HUGO**”) tries to coordinate international collaborations, to standardize nomenclature and to provide a forum for discussion of genetic research. **HUGO** has expressed concerns that the sheer volume of **EST**’s for which patents are sought could stifle research.

5. Genome Privacy Issues – A Quick Perspective

A. The Current Status of Protections in the U.S.

1. Federal

Federal protection against genetics-based bias exists. In 1995, the Equal Employment Opportunity Commission issued guidelines barring genetic-based bias among employers. In 1996, the Health Insurance Portability and Accountability Act outlawed such bias among insurers.

2. State

More than thirty states have laws purporting to provide some genetic privacy protection. It is an uncertain mix as to the protection provided.

Some laws guard against misuse of the knowledge, some seek to manage dissemination of the knowledge before it gets misused, and a few grant the right to object before a technician spins out a genetic profile in the first place.

Currently, three states, Florida, Georgia and Colorado – attempt to give individuals the exclusive property interests in their DNA samples.

A wide variety of representatives of the biotechnology industry and from research institutions assert that research will be chilled and medical advances (including treatment approaches) will stagnate because researchers and physicians will become hesitant to use genomic databases. “I think reality has shown that you cannot protect the privacy of information,” said Craig Venter, the president of **Celera**, the genomics company, recently on *Meet the Press*. Probably due to concerns that genomics data may become restricted, many biotechnology companies and research institutions have opted to not seek to privatize (or patent) genetics databases but rather are promoting the sharing of genetics information.

B. An Evolving Set of Protections

There are numerous legislative initiatives both at the national and state levels, to better balance the rights of an individual, the potential benefits to society and the economic interests of genomic companies.

This area is alive with debate and should be carefully watched since it is certain to continue to evolve.

5. **Genetics Research-the Moral Issues – A Quick Perspective**

A. The Moral Issue Applied to Entire Populations

Within the past year, there was much discussion and debate, pro and con, over Iceland’s decision to capitalize monetarily on Iceland’s genome by licensing genetic information (and related medical records) as to Iceland’s people.

The debate over the moral appropriateness of marketing a society’s genome continues, most recently with China as the involved country.

“China is proving a gold mine for genetic researchers around the globe. China’s very backwardness is an asset for researchers. Many rural families have lived in isolation for generations, making it easier for genetics sleuths to trace illnesses through relatives.” Wall Street Journal, September 13, 2000. However, there are two serious problems researchers have to overcome in China. First, there is lack

of accurate family records in the rural areas. Second, and possibly more difficult to overcome, is fraud. Many researchers provide incentives for people to participate in genetic research and some take advantage of this by falsifying family records.

The Wall Street Journal article cites the following concerns with genetic studies undertaken in China:

- Safety – DNA is gathered through needles; low quality and reused syringes is an issue.
- Patient Rights – regulations adopted by Chinese authorities in 1998 require informed consent from donors of genetic material; those regulations appear to be often ignored.
- Privacy – many believe the privacy of genetic information cannot effectively be protected in China.

B. The Distinction Between Somatic and Germline Gene Therapy

Somatic gene therapy is the treatment of genes in non-reproductive tissues to alleviate or eradicate a disease. Somatic gene therapy does not modify any germ cells (sperm or eggs) so there is no risk that any genetic modification could be transferred to future generations. In contrast, germline gene therapy does replace defective genes in reproductive cells. Accordingly, it has the potential to transfer modified genetic traits to future generations.

There are clearly ethical concerns for both methods of genetic treatment but germline therapy raises more issues and has more critics. One of the major issues raised by critics of germline therapy is the danger associated with genetic enhancement rather than correction. Initially this distinction may seem more apparent than real, however, critics of germline therapy see enhancement as a possibly irresistible vehicle for genetic tailoring. Aside from the concerns of genetic discrimination, there are serious medical concerns. The selective enhancement of human characteristics has the potential to disrupt the overall metabolic balance of an individual.³

Two arguments in favor of germline therapy are its potential to be more efficient and more comprehensive than somatic therapy. Germline therapy can be more efficient because it can modify future generation's genes and possibly avoid the need for somatic therapy for each successive offspring. Germline therapy may also be more comprehensive because certain hereditary diseases of the central nervous system are not as easily treatable at later stages of human development.

³ For an interesting discussion of the dangers of germ line modification see W.F. Anderson, *Human Gene Therapy: Why Draw a Line?*, J. MED. & PHIL, 14:681 (1989).

5. **Summary**

The fundamental moral/philosophical/legal debate as to whether genes are patentable is over from a legal perspective. Genes have been and will continue to be patentable, however, patent protection will not be accorded to the human genome, or the genome of any species. The fundamental debate in the near term issues now appears to center around: (i) how to assure that patents are not used to stifle innovation and research and thereby adversely affect the public health, (ii) protecting the privacy and economic rights of individuals to their genetic information, and (iii) providing genetic discoveries at reasonable cost.

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