A Primer on Gene Patents

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1 Introduction

Current medical students and recent graduates are well aware that advances in genetics and molecular biology are rapidly changing the face of both clinical medicine and basic research. In the year 2000 alone, we saw the completion of draft sequence of the human genome as well as the genomes of the model organisms *Drosophila melanogaster* and *Arabidopsis thaliana*. Genetic testing offers the potential for earlier and more accurate diagnosis of disease, while new drugs based on recent discoveries are constantly being released. Within the next decade, it seems likely that some genetic diseases will become curable through gene therapy.

Sadly, as is so often the case in medicine, these new medical miracles are most often introduced by entities which seek to maximize their own profits without regard for the public good. Already, private corporations have filed over 20,000 preliminary patent applications covering human genes. Many believe that such patents are unethical because they constitute a declaration of ownership over human beings. Furthermore, permitting the patenting of genes is likely to lead to higher medical costs and a decrease in scientific innovation. This primer is meant to introduce the concerned citizen to the current regulations governing the patenting of genes and to provide some talking points for activists interested in the issue.

2 Why Are Patents Necessary?

Legally, a patent gives its holder "the right to exclude others from making, using, offering for sale, or selling... or importing" the covered invention in the United States[1]. This right lasts for 20 years from the date the application was filed. The general theory behind patents assumes that a person who invents something new and useful will not be likely to tell others how the new invention works. If he/she disclosed the details, a competitor could come along, copy the design, and profit from the invention without having had to put in the work of developing it. Since disclosure of these details is essential to scientific and technological advancement, patents provide an inventor a way to explain the science of an invention while still keeping others from using that invention without permission.

From the perspective of the inventor or business, a patent is an economic claim. By filing a patent, one obtains a temporary monopoly on something which is (in theory) valuable. This allows one to charge the highest price the market will bear and reap the fruit of the hard work put into inventing. When the patent expires, anyone may make and sell the invention, but by then, the inventor has had twenty years to invent something new and get another patent.

There are also companies which do not directly manufacture or sell any products, but merely attempt to obtain as many patents covering as broad a territory as possible. It then becomes likely that some product somewhere will be covered under those patents, and the patenting company may demand royalties for this infringement. Alternatively, the company may obtain a patent on a desirable technology and then seek out manufacturers willing to license the patent and share the profit from the sale of that product; this is part of the business model behind Celera Genomics[2].

As can be seen from Table 1, patenting genes (both human and otherwise) is lucrative enough to lure in large pharmaceutical companies, small genomics startups, and even the Federal government. Table 1 also includes available statistics on provisional patents, placeholders filed while one is assembling a full patent application. In practice, provisional patents are useful for establishing an early filing date on a patent in a situation where multiple groups are racing to patent the same things.

3 What Can Be Patented?

Almost anything which is discovered or created by a human can be patented, as long as it is "useful" [12]. Courts have interpreted the patent laws such that the laws of nature, basic physical phenomena, and completely abstract ideas may not be patented. A "composition of matter" is one of the things which is explicitly declared patentable. Since the canonical form of a gene is a string of nucleotides, which is a specific and unique composition of matter, genes have been declared patentable. New plant strains have also been judged

Gene Patents in the United States of America		
Entity	Provisional Patents Filed	Patents Granted
United States of America	NA	650
Chiron	NA	532
SmithKline Beecham	NA	236
ZymoGenetics	NA	194
Human Genome Sciences	16,000	162
Celera Genomics	6,500	100-300 expected
Roche Pharmaceuticals	NA	62
Merck	NA	56
Pfizer	NA	6

Table 1: Data from companies' own published statements [2,3] and Delphion Intellectual Property Network [4–10]. Total number of US-issued human gene patents is roughly 1,800 [11].

patentable, except for plants found "in an uncultivated state" [13].

Since a patented discovery must be somehow useful, only DNA sequences which have some practical medical or laboratory use are patentable. To date, this has included patents on genes [14], tests for the presence of genes [15], proteins [16], and tests for the presence of proteins [17]. A single patent may cover the entire pathway from gene to protein to therapy, or these items may be split among multiple patents. In one particularly egregious display, Chiron Corporation has obtained patents covering essentially the entire hepatitis C virus genome, tests for the presence of viral DNA, the protein products of the viral genome, and vaccines based on those proteins [18–23]. (The cited patents are only a small sampling of the wide array of claims made on the virus by this single company.)

4 Why Are Gene Patents Harmful to Patients?

4.1 Ownership of Human Beings

A patent on a gene (or on anything else) gives the holder the exclusive right to say what may and may not be done with that gene, at least in the commercial arena. Whether selling copies of the DNA strand to academic researchers or putting it into a gene therapy vector, whoever holds the patent makes the rules for the 20 years until the patent expires. In a very real sense, the patent holder owns the gene. That same gene is found in every person on this planet (except for those who have a deleterious mutation, and who would very much like that patented normal copy). At least in the United States, it is specifically illegal to demand licensing fees from ordinary people just for having a patented gene in their bodies [24]. However, the ownership over all "unnatural" uses of that gene remains. This raises an important ethical question: is it right to allow any entity to claim even partial ownership of any part of an intelligent being?

It is true that in the end, DNA is just another chemical, and it is also true that humans are much more than the sum of our genes. It is nonetheless equally true that our genes encode a large part, possibly even the majority of who we are. When a gene is patented, it is illegal to distribute it in any kind of purified form without permission, even if you extract it from your own cells. No patents are granted on transplanted organs, even though transplantation also involves removing a vital part from a human and placing it somewhere else. In fact, the United States and many other countries have outlawed profiting in any way from the sale of human organs. Our genes are as essential to the body as our organs (if not more so); why should the same rules not apply to them? It is also instructive to consider the case of Watson and Crick, who elucidated the structure and function of DNA. This was certainly a novel composition of matter at the time, and their pure DNA could be considered different from the protein-bound material in a nucleus. However, these two scientists understood what many modern-day researchers do not: human genetic material is too important to allow anyone to stake an exclusive claim on it.

Research and Marketing Expenditures of Pharmaceutical Firms		
Company	Sales and Marketing	Research and Development
Genentech, Inc.	33%	26%
Glaxo Wellcome PLC	57%	15%
Merck & Co., Inc.	16%	6%
Pfizer, Inc.	39%	17%
Roche Group	60%	14%
SmithKline Beecham	38%	13%

Table 2: All numbers represent spending as a percentage of gross revenue for the 1999 fiscal year. Data taken from the 1999 annual reports of the companies listed[26–31].

4.2 Gene Patents Lead To Higher Prices and Discourage Innovation

One interesting property of genetic therapies is that once perfected, they can often be mass-produced quite easily. The genetically-derived therapies currently on the market are primarily antibodies and other manufactured proteins. All of these therapeutic products can be produced by engineering a line of cells to overexpress the desired protein, which may then be purified and sold. This approach, which harnesses the exceptionally efficient synthetic chemistry of living cells, offers a potential for significant savings over the standard synthetic techniques used for "ordinary" drugs.

Logically, one might therefore expect these therapies to be relatively inexpensive. This is not the case. Consider the case of breast cancer. A month's supply of brand-name tamoxifen costs a patient roughly $100. Conversely, a month's supply of Herceptin (an antibody against a known oncogene) will cost approximately $2,800. Knowing that roughly a quarter of all breast cancers express the gene targeted by Herceptin[25], this represents a significant income. While the precise production costs for Herceptin are not public knowledge, it seems very unlikely that it costs hundreds of dollars to produce a single dose. Conversely, it hardly requires a leap of faith to believe that a company with a monopoly on a product that treats a deadly disease would charge whatever the market could bear. This pricing strategy is directly harmful to low-income patients, by placing essential therapies beyond their reach. Programs do exist to help mitigate the cost, but these are insufficient to cover all patients.

The classic rebuttal to this argument is to claim that the price of the drug is so high because the cost of developing drugs is high. Discovering new therapies and winning FDA approval can be difficult and costly. However, it is instructive to examine the financial statements of the companies which claim these high research costs. In the 1999 financial year, all the pharmaceutical firms examined spent approximately twice as much on marketing expenses as they did on research expenses[26–30], in addition to improving their asset bases and rewarding stockholders. (These findings are summarized in Table 2.) This suggests that these firms are hardly struggling to recoup their research costs, and that the rebuttal is a deliberate attempt to mislead.

It is only fair to note that Genentech, manufacturer of Herceptin, had marketing expenses which were only 133% of research expenses. However, it reported a decline in research spending in 1999 while marketing spending grew by 33%[31]. Furthermore, Genentech has strategic partnerships with several large companies that have agreed to market its products, thus hiding the true level of marketing[32].

Of course, ordinary drugs are patented just as genes are. Moreover, patents on drugs (possibly even those derived from genetic discoveries) are generally beneficial to society, since they help protect the incentive to develop new therapies. However, in this particular case, Genentech does not merely hold a patent on the Herceptin antibody; it holds multiple patents related to the her-2 oncogene and its ligand[33–35]. This means that anyone seeking to develop breast cancer therapies based on this oncogene (especially immunomodulating therapies) runs a significant risk of being unable to produce or sell the result without being sued for patent infringement. The same scenario can be found with many other human gene products. This is not an environment which will foster medical innovation and advance the health of humanity; this is an environment where the first firm to patent gains control over the entire market for diseases caused by that gene. Thus, genetic products are likely to have exceptionally high prices, because they face far less competition than

traditional drugs. Moreover, no new (and potentially superior) alternate therapies are likely to be developed. Clearly, both of these results are ultimately detrimental to patients.

4.3 Gene Patents Exploit Research Subjects

In order to locate a disease-related gene, one often requires tissue from patients suffering from that disease. Like all medical research subjects, these patients are willing to endure extra pain and possibly cost in order to help advance medical science and benefit others. Currently, the standard behavior of researchers is to collect the necessary tissue samples, strip away all identifying information, and perform their analyses. If the process of discovery leads to a patent or any other form of profit, those who underwent physical suffering to contribute to the research almost never receive a share of those profits.

A particularly famous example of this problem is the case of Canavan disease, a rare childhood encephalopathy primarily affecting Ashkenazi Jews. The Canavan Foundation, an association of families affected by this disorder, assisted Miami Children's Hospital in Miami, Florida by recruiting families to provide blood samples to researchers. When the gene for the disorder was finally identified, it was patented by the hospital, which now charges a royalty on all tests for Canavan disease. According to the Foundation and the patients who donated material, such a patent was never mentioned in any informed consent documents. Accordingly, the Canavan Foundation is currently suing the Miami Children's Hospital alleging breach of breach of informed consent, breach of fiduciary duty, unjust enrichment, fraudulent concealment, conversion and misappropriation of trade secrets[36].

Even disregarding the ethical questions of the patent, it is especially inappropriate for a non-profit institution to engage in such profiteering behavior. The Miami Children's Hospital has a mission statement claiming that it "will always do what is best for each child." [37]. Profiting from the suffering of others without compensating them for their pain and their contributions is hardly "what is best" for children with Canavan disease. However, in an era where hospitals are desperate for revenue sources, this behavior is likely to continue in medical centers across the nation as long as genes remain patentable. The most effective solution is to remove the temptation entirely, rather than rely on the ethical judgement of those whose eyes may be clouded by financial interest.

5 How Do Gene Patents Violate Traditional Patent Standards?

Another major objection to the patenting of human genes lies in the fundamental hypocrisy of this practice. Under existing patent standards, most genetic patents should not have been granted. However, the biotechnology and pharmaceutical fields are sufficiently lucrative for the United States Patent and Trademark Office (USPTO) to overlook this fact.

5.1 Many Patented Genes Are Obvious

We recently celebrated the completion of a "draft" sequence of the human genome well ahead of the original deadline. This milestone was made possible by the development of automatic systems to extract, sequence, and analyze genetic material. By scanning the sequence for known markers of expressed genes, it is possible to separate out the key information from the "junk" DNA which lies between functional genes. These newly-discovered genes may be compared to the sequences of known proteins and enzymes searching for similarities of sequence (homology) which imply similarities of structure and function. Based solely on this computer-derived guess at the function of a gene, it is possible to file a patent on that gene[24].

The existing USPTO guidelines for all types of patents state that a patented invention must be "nonobvious to a person having ordinary skill in the area" [38]. A computer cannot be said to have more skill in the art of genetics than a human, since it is not capable of anything resembling thought. Therefore, if a gene is discovered primarily through computational analysis (as in the business plans of many biotech/pharmaceutical startups), it meets the USPTO criteria for obviousness and is not patentable.

5.2 Genes Are "Laws of Nature"

As previously noted, it is also impermissible for a "law of nature" to be patented [12]. Since the information in our genes defines the entire physical basis of human life, genetic information may be considered as a fundamental process of nature. As such, human genes (and in fact, the genes of all organisms) should be unpatentable.

5.3 Genes Are Found in an "Uncultivated State"

Since genes exist within the human body, they may reasonably be considered to be "in an uncultivated state". Therefore, under the same logic which prohibits the patenting of uncultivated plants, genes should not be patentable. The USPTO takes the position that since an isolated gene is in a different form from a gene within a cell (lacking a surrounding chromosome and the intron sequence), it is no longer "uncultivated", but is instead a novel "composition of matter" [24].

Ultimately, however, a set of nucleotides within a chromosome, a transcribed messenger RNA, an isolated strand within a test tube, and a sequence of bits within a computer are all different expressions of the same information — the same gene. The USPTO's position appears to be an attempt to bend regulations solely for the benefit of private industry, regardless of the potential societal harm.

6 What Does the U.S. Patent and Trademark Office Say?

On January 5th, 2001, the USPTO released a new set of guidelines regarding gene patents [24]. These guidelines offer some hope for opponents of gene patents, but they also indicate that there is a long way yet to go. More specifically, the guidelines set the minimum requirements for a patented gene. Merely knowing the sequence of a stretch of DNA is not sufficient. It is necessary for the patent applicant to demonstrate some knowledge of what the gene actually does, or to demonstrate some other use for the DNA sequence if it is not an actual gene. However, it *is* sufficient to compare the DNA to a database of known genes, detect similarities, and claim that the similarities in sequence have determined the function of this gene. There are two reasons why this test is still insufficiently strong. First, as noted above, a process which allows a computer to do all the work cannot reasonably be said to be true invention. Secondly, homology studies do not unambiguously establish a gene's function. They provide data on the probability of specific functions, but that is all. Knowing that an invention was "probably" good for a specific purpose would never be sufficient to obtain a patent in any other field.

The new USPTO rules do attempt to reply to the objection that gene patents represent a declaration of ownership over human life. However, as noted previously, they do this by declaring that the isolated form of a gene is not the same as the gene when it is in a human being. While this provides ordinary human beings the comfort of knowing that we are not committing patent infringement simply by existing, it does not truly answer the objection. Regardless of its form, a gene has the same informational content, and that information is still an essential part of humanity. Therefore, ownership of that information in any form is ethically unsound. It is also worth noting the precedent set by plant patents regarding the uncultivated state. A plant would not become patentable simply because it was uprooted from a forest and replanted in a garden; the discoverer would need to modify or improve on nature's design in some way to produce a patentable invention. Similarly, those who wish to patent genetic material should first make some significant change or improvement to the plan which exists in nature.

In response to the objection that computer-derived genetic information is not valid patent material, the USPTO holds that the sequence is not in fact obvious because it cannot be predicted in advance, merely determined. However, the fact remains that making this determination requires no skill or talent. Therefore, the act of invention is absent, as is any originality of the work.

7 What Do Supporters of Gene Patents Say?

7.1 Patents Encourage Invention

The primary argument in support of gene patents is economic. In theory, the researchers who discover a new gene or genetic component are protected from having their discovery exploited by others. If anyone profits from the discovery, it is the group that did the work. This is expected to stimulate innovation by guaranteeing inventors and discoverers the rightful fruits of their labor.

It is obvious that granting patents on genes is indeed encouraging genetic research; biotechnology companies are racing to discover and patent as many genes as possible. However, this economic benefit does not outweigh the ethical cost. There are many ways in which it is profitable to own human beings, but that cannot justify such a practice. Furthermore, society is not truly reaping the benefits of this increased research. As noted above, the therapies which arise from these discoveries are exceptionally expensive, and thus remain out of the reach of many. Finally, patents exist to reward those who have worked hard for a discovery. These companies may have their computers working overtime, but that is hardly the labor patents were intended to reward.

7.2 Patents Encourage Disclosure

Patents are also intended to encourage inventors to disclose the details of their inventions. Without the protection of a patent, discoveries with commercial potential might naturally be concealed from competitors. Therefore, it is argued that allowing the patenting of genes encourages disclosure of genetic discoveries, thus advancing the public body of knowledge.

Aside from the persistent unethicality of patenting human life, this argument fails due to the nature of genetic material. All known genetic tools and tests are based on the complementarity of DNA. As such, the kit includes DNA which complements the target gene. It would be trivial for any purchaser of such a kit to purify that DNA and read its sequence, thus linking the gene to the disease. Therefore, there would be no incentive for non-disclosure if patents did not exist; it would be impossible to have a product that did not disclose the details of its function. It may be argued that this would prevent the development of any genetic technology, but that is absurd. Scientists are not motivated purely by economic considerations; many (perhaps even most) are driven by a thirst for knowledge and a desire to help humanity. The best evidence of this is the public Human Genome Project, which has promised to make its data freely available to anyone who desires it.

7.3 Patents Force Exploration

A final argument in favor of genetic patenting relates to the way patents "fence off" an area of scientific inquiry. Once a particular gene or mode of therapy is patented, uninvolved researchers have little incentive to explore that area. This forces those researchers to search out new, poorly-explored areas, which is expected to accelerate the advancement of knowledge and broaden the base of inquiry.

Again, this argument is valid as far as it goes, but ignores the specific ethical issues surrounding genes. Moreover, it neglects the fact that scientists are naturally driven towards unexplored areas. Just as many scientists seek to help humanity, many seek to become famous by discovering something of great importance. If a researcher works on an area which is targeted by many others, his/her chances of making that great discovery are reduced. Therefore, he/she will tend to seek out areas where few others are working. Since this increased exploration is likely to occur whether or not genes are patentable, the benefits of patenting genes can in no way be said to outweigh the harms. In fact, it may be that genetic patenting is discouraging exploration and innovation; witness the fact that most biotechnology companies are attacking the genome in the same way, merely hoping to discover patentable genes sooner than the competition. Without this "gold rush" mentality, more companies might be focusing on understanding the genes and using them to fight disease.

8 What Can Be Done?

In conjunction with the new ruling, the USPTO has commented that it feels obligated to permit as many things as possible to be patented. The position of that office (as dictated to it by the Supreme Court) is that its original Congressional mandate requires it to issue patents on "anything under the sun made by man". Therefore, any change in the patent process would require legislation placing human genes specifically outside the realm of patentability.

Obtaining this legislative action will be difficult, but is not impossible. The first step is to inform others. Most people remain unaware of the scale or implications of gene patenting, and are likely to become upset once they learn the truth. Change cannot happen unless the public demands it, and thus concerned parties must give them the information they need to begin demanding change. You should also contact your United States Senators and Representative with a brief letter or telephone call. State that you are concerned about genetic patenting because it represents ownership of human life, and ask that the legislator sponsor and/or vote for bills that would place human genes and their products outside the domain of patentability. You may even wish to organize a lobby day for fellow students (and others); AMSA's Legislative Affairs Director can assist you in your planning. There are some references at the end of this document to help you in your efforts.

If you are a student or physician at an academic medical center, it is also important to follow the model of the Human Genome Project. Discoveries of disease genes are generally made in laboratories associated with medical centers. If you contribute significantly to that discovery, then you have a right to be named as an inventor on any resulting patent. As an inventor, you would have the right to license your patented gene in whatever manner you chose, including making it freely available, without regard to the desires of your co-inventors. (It is important to read your institution's policies on patents beforehand; some institutions demand that all patent rights be transferred to them.) By obtaining a gene patent and then licensing it at no charge to all comers, you can keep some small part of humanity free and demonstrate that innovation is possible without exploitation.

9 Further Reading

The following may be of use if you wish to read more about genetic patenting or to educate others on this topic:

- The College of American Pathologists has a position statement against gene patenting at http://www.cap.org/html/advocacy/issues/genetalk.html.
- The American College of Medical Genetics has a similar statement at http://www.faseb.org/genetics/acmg/pol-34.htm.
- The Council for Responsible Genetics (http://www.gene-watch.org) is a nonprofit group dedicated to reform in all aspects of genetic technology. They maintain an online petition calling for an end to gene patents.
- GeneWatch UK (http://www.genewatch.org), often confused with the CRG, is a British organization which also seeks to ensure that biotechnology is used only for the public good.
- The Human Genome Project maintains a fact sheet on genetic patenting at http://www.ornl.gov/hgmis/elsi/patents.html.

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