Decoding the Book of Life: Are Genomes Proprietary?

Marla A. Block

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"There are substantive issues about data access at the heart of the situation: Will the sequence of the human genome be freely accessible without restrictions of any sort to researchers in the private and public sectors, or will it not? Regrettably, relatively little of the press attention has focused on those bedrock issues."

-Francis Collins, Director of NHGRI

Introduction

In 1998, Craig Venter of Celera Genomics Corporation claimed that his private firm would be able to map the human genome three times faster than the publicly funded labs and at a fraction of the cost. This spurred a frantic rush for all firms, public and private, to step up their efforts. Two years later, with 95% of the mapping complete, Celera rescinded its initial statements to make their database free to the public. Additionally, they began applying for thousands of patents to control the use of the decoded DNA. Celera is at the forefront of the biotech industry, decoding and patenting genes faster than its competition. Many people fear that their controlling power of this priceless knowledge will create monopoly power. Clearly, the acquisition and use of such knowledge will have significant implications for both society and individuals and will require strictly enforced legislation and public policy initiatives that we currently lack.

The motives of this paper are to define for the reader the brief history of the Human Genome Project, explain the benefits to be reaped by such investigation, and detail the current state of the genomic research realm. The questions addressed concern the right to patent and the right to own nature's creation, and the prospect of a single firm controlling the most valuable knowledge base through monopoly power and a lack of proper ethical incentives.

Biological Terms Used

Genome. A genome is a complete set of coded instructions for making and maintaining an organism. It is master blueprint for all cellular creatures and activities for the lifetime of the cell or organism. The human genome contains approximately 3 billion DNA base pair units, the linear sequence of which represents information dictating how the human organism develops and functions. Only about 5 percent of the DNA in human chromosomes, accounting for 70,000 to 100,000 gene sequences, encodes strings of amino acids, called proteins, which play key physiological roles [1] .

DNA. DNA (deoxyribonucleic acid) is the chemical that stores coded information on how, when and where an organism should make the many thousands of different proteins required for life. DNA contains four different chemical building blocks called bases, abbreviated A, T, C, and G. In humans and other higher organisms, a DNA molecule consists of two strands of DNA whose bases connect with each other to form base pairs. With the exception of identical twins, each person's sequence of DNA bases (the order of As, Ts, Cs, and Gs along a single DNA strand) is different. This difference makes each person unique [2].

Genes. A gene contains instructions for building a particular protein and is part of DNA. Proteins are essential for all aspects of life. All organisms are made up largely of proteins that provide the structural components of all cells and tissues as well as specialized enzymes for all essential chemical reactions. Through these proteins, genes dictate not only how species look, but also how well they process foods, detoxify poisons, and respond to infections.

Genes constitute only a tiny fraction, a mere 3 percent, of our DNA. The gene (coding) regions in our DNA are interspersed among millions of non-coding DNA bases whose functions remain largely unknown. Scientists estimate that we have between 50,000 to 100,000 genes whose sizes range from fewer than one thousand to several million bases [2] .

The Human Genome Project

The Human Genome Project (HGP) began in 1990 as an international research program designed to completely map and sequence human and other organism's DNA. It is a federally funded program conducted through the National Institutes of Health (NIH). The goal of the project is to locate the 50,000 – 100,000 genes within the human genome, and determine the complete nucleotide sequence of DNA, thus creating detailed information about the structure, organization and function of the human blueprint. Utilizing this information, scientists and physicians will be able to pursue biological studies that will improve human health.

In addition to human decoding, HGP conducts parallel studies on other organisms including bacteria. To date, rats, mice, yeast, roundworm, fruit flies and the bacteria E. coli have been or are now being sequenced. Both human and selected model organisms are studied in over 18 countries worldwide.

The human genome is composed of 50,000 – 100,000 genes located on the 23 pairs of chromosomes in a human cell. A single human chromosome may contain more than 250 million DNA base pairs, of which the human genome consists of about 3 million base pairs [3] .

Benefits of Human Genome Project Research

The ultimate goal of genomic mapping and sequencing is to associate specific human traits and diseases with particular genes at precise locations on the chromosomes. Unraveling the human blueprint will revolutionize both therapeutic and preventative medicine by providing insights into the biochemical processes that bring about many human diseases. New gene therapies will prevent, cure or more effectively treat many diseases that previously were untreatable. Genetic tests are currently being used to screen for a number of diseases, including: Huntington's disease, Alzheimer's disease, Down Syndrome, cancer, cystic fibrosis, muscular dystrophy, Tay-Sachs disease and a host of others. Recently, researchers discovered a new genetic test that can easily distinguish between hereditary and sporadic forms of breast cancer. This knowledge will allow physicians to diagnose the cause of the person's cancer and ultimately direct the decisions about treatment. The new technology allows scientists to get a snapshot of exactly which genes are active in a tumor cell. Furthermore, researchers can now view thousands of genes at a time as they interact to form a tumor [4].

Existing and potential applications of this type of exploration are far reaching. The benefits will extend to areas such as molecular medicine, microbial genomics, risk assessments, forensics and livestock breeding. The rapid progress in genome science and its potential applications has positioned biology to be the foremost science of the 21st century.

Moral implications of genomics

Despite the numerous advantages and potential benefits of genetic research, many fears still loom. Questions arise as to whether employers, insurance companies and the government may access a person's genetic information resulting from DNA testing. Further, a concern over genetically altering individuals or prenatal children remains a heated topic.

The ability of insurers to access genetic information has received a great deal of attention. On one hand, insurance companies, particularly life insurers, believe that they should be entitled to genetic information for risk classification purposes. Insurers feel that this step would decrease fraud and lower premiums for policyholders. Consumers, on the other hand, believe that allowing insurers access to their genetic information would prevent many patients from getting the medical help they need and would lead to widespread discrimination against applicants [5]. At present, legislation exists on the state level, and varies highly by state. The Health Insurance Portability and Accountability Act of 1996 (HIPPA) was the first step taken on a federal level to provide protection from insurance discrimination; however it does not (1) prohibit the use of genetic information for charging more for health insurance, (2) prohibit insurers from requiring individuals to take a genetic test, (3) limit the disclosure of genetic information by insurers, and (4) apply to individual health insurers [6].

Employment discrimination exhibits similar deficiencies. Currently, there is no legislation in effect to prohibit employers from using genetic tests to discriminate against workers. In February 2000, an executive order to prohibit discrimination in *federal* employment based on genetic information was signed into action. No such action has been taken to protect non-federal workers. The economic incentive to discriminate based on genetic information will likely increase as genetic research advances and the costs of genetic testing decreases. Clearly, additional legislation is needed in this area.

Perhaps the greatest moral implication concerns directly altering the genetic structure of an organism to provide it with more desirable traits. Gene transfer technologies will make it possible to enhance or replace genes that influence traits such as height, weight, strength, stamina and intelligence [2]. The availability of genetic testing will allow for several types of genetic enhancements, even before birth. In addition to selective abortion, the possibility for *pre-conception enhancement*, in which the decision to conceive, and with whom, to avoid conception with a "carrier" for a recessive trait, can be made on the basis of genetic testing [7]. Furthermore, many people fear that this will open the door for genetic bigotry, or a creation of a "master race" mentality [8].

These new technologies will create a host of ethical and legal controversies, many of which will find their way to the courts for resolution. However, no one can dispute that there are significant positive benefits to be attained in medical treatments, criminal law and forensics, education and the understanding of the human evolution.

Celera: Initiating a biological revolution

When the Human Genome Project initially got underway, scientists at the National Human Genome Research Institute (NHGRI) predicted that they would map the entire human genome by the year 2005. However, they failed to consider the profit motive. Pharmaceutical companies can turn genome research into billion dollar treatments for multiple diseases, and those companies that manage to get the information first stand to make tremendous profits. Given the potential payoffs, it is not surprising that private firms have entered the genome research arena. In fact, one such company, Celera, lead by Craig Venter, has stepped forward to claim that it will have mapped the entire human genome by mid 2001.

Venter gained notoriety while working for the NIH on the HGP. In 1991, he published a paper based on his discovery of decoded DNA, which he uncovered by feeding the DNA "messenger" (called RNA) into an automated gene sequencer. Portions of the decoded regions became what he referred to as ESTs (expressed sequence tags) to help distinguish one gene from another. Venter rushed to patent the uncovered genes he had discovered; however, James Watson, the co-discoverer of DNA and head of the HGP at the time, was outraged. He insisted that "virtually any monkey" could perform the work and that patenting such abbreviated genetic material was "sheer lunacy" [9] . The NIH followed by pulling the patent applications and expelling Venter.

Venter then joined a venture capital group to head up his own research center, The Institute for Genomic Research (TIGR). Partnered with Perkin-Elmer, a DNA sequencing instrument company, Venter formed Celera in 1998. The company now uses a technique known as "shotgunning". This technique pulses high frequency sound waves into the DNA molecule, shreds it into tiny fragments, clones it and then runs it through a gene-sequencing machine. Computers then look for overlaps and sequence each fragment of the gene. However, this method leaves gaps in the information collected where the sequencing of segments cannot be fitted perfectly. To date, no other lab has produced more DNA sequences than Celera.

The Gene Factory

Celera, funded by the capital rich Perkin-Elmer, recently finished construction on their new facility. The new lab has enough computer capacity to decode nearly as much DNA in one day as the HGP labs produced in 1999. At full capacity, Celera expects to read 100 million letters of DNA sequence per day [10].

Based on their results, Celera can market their findings to pharmaceutical companies for large profits. "The truth is that no one can predict exactly what breakthroughs might result from the deciphering on the human genome," said Venter [11] . But he is willing to place large bets that they will find uses. Celera has already submitted patent applications for well over 7000 genes as of April 2000, giving them exclusive rights to those genes. Researchers at Glaxo Wellcome, a pharmaceutical firm, have already begun using genome segments to identify genes involved in Alzheimer's disease, diabetes, psoriasis and migraine, and are working on drugs to cure them [12] . The research conducted on the genome will help pharmaceutical companies create drugs tailored to a patient's genetic profile, making diagnosis and treatment swift and complete.

Laying claim to your genes

DNA sequences are patentable in principal. To gain a patent, a discovery must be novel, useful and non-obvious. Though newly discovered genes are certainly novel and useful, how "non-obvious" they truly are remains debatable. Furthermore, many of the patent applications are submitted for fragments of genes, not the entire gene. This strategy would give the patent holder rights over the whole gene once identified. The fear lurks that only a few companies will hold exclusive rights to a priceless resource.

It may be difficult for the patent office to deny such inventions on morality grounds, particularly in view of the potential medical benefits to patients suffering from inheritable genetic diseases. On the other hand, without the incentive to invest in the costly and time-consuming research to create new medical treatments provided by secure patent protection, development of projects useful in human gene therapy may be discouraged.

Some researchers fear that patenting of biological materials will result in the patent holder attempting or threatening to enjoin research through an action for patent infringement [13]. In other instances, a patent holder may refuse to distribute research

materials unless a license agreement is undertaken, the terms of which may be considered excessive by the requester of the material (these are both tactics currently employed by Celera).

The holder of unique biological materials may want to receive a benefit or compensation for the costs invested in the creation of the material. A researcher or biotechnology company having invested substantial resources would be understandably displeased to distribute such research material to another, whose subsequent use resulted in a highly valuable and commercial product, without some form of compensation or right to use the new product. Mays claims that the nature of information sharing has changed over the years, as stated:

> "The tradition of freely sharing research materials in the early days of biotechnology may have shifted from a communal to a market model. Even in the early days of biotechnology, however, a few researchers may have restricted access to complicated materials they created from distribution to their research competitors. It appears that that there has been confusion between patent rights and access to biological materials, per se. Whether a patent could or would be enforced against a researcher, particularly one conducting basic and noncommercial research, is questionable." [13]

Applications for gene patents are increasing rapidly, but one must question if they are justified. Are they truly intellectual property, consisting of human knowledge and ideas, or are they simply trying to lay claims on nature's creation? Clearly, Sir Isaac Newton did not patent gravity, Einstein did not patent quantum physics, and Mendeleev did not patent the periodic table. So why should scientists patent information found in nature? The case could easily be made that they could patent the technique to uncover the information, but the question remains as to the justification of ownership and control of nature's design.

A court case has yet to emerge in relation to patenting ESTs. However, DNA patent related cases are beginning to surface. The first such court case was *Amgen v. Chugai* [14]. The biopharmaceutical firm Amgen had sued co-defendants Chugai Pharmaceuticals and Genetics Institute for infringement of a claim to a DNA sequence. A Genetics Institute employee, Edward Fritsch, maintained that he had conceived the invention first, based on an earlier idea for a method of isolating that portion of the gene. The Federal court held that conception of

> "a compound of unknown structure--the human…gene--required more than simply knowing how the compound might be isolated. According to the court, "It is not sufficient to define [a gene] solely by its principal biological property,....[W]hen 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."[14]

The court maintained that an adequate description of DNA requires more than just a statement that it is part of the invention and has a potential method for isolating it; what is required is a description of the DNA itself. That is, the Amgen case held because one cannot describe what one has not conceived. Though one can certainly make the claim

that no one actually conceived of DNA, except nature. The Federal court is likely to have the last word on the patentability and scope of DNA and EST claims.

Monopoly Power

Though still in their infancy, patented genes are a hot commodity. SmithKline Beecham, a large pharmaceutical company, has agreed to pay Human Genome Sciences $125 million, plus future royalties, for the exclusive rights to exploit genes isolated by HGS. More recently, a genomics company, Sequana Therapeutics, announced its intention to merge with Arris Pharmaceuticals, a firm with combinatorial chemistry capabilities, to form Axys Pharmaceuticals, touted as "the first gene-to-drug" biotech company [13]. But, by far, the largest player in this field is Celera, the foremost rival for the publicly funded HGP.

When Celera was established, it announced that it planned to patent only a few hundred genes and that its primary source of income would be from analyzing and annotating its database for a fee from drug companies. Further, scientists would be allowed full unrestricted access to the database for free – in essence, making all the data publicly available. Perhaps the largest sense of unease and distrust from the academic and publicly funded HGP comes from the Celera's revised business plan. In 1999 alone, Celera applied for 6500 patents on genes. Furthermore, they rescinded their statement of intention to give full public access and have declared substantial fees to view their files.

Keeping human genetics in the public domain is a view shared not only by HGP, the government and charities, but also by the SNP Consortium (Single Nucleotide Polymorphism- the differences found in DNA that makes us each unique), whose members include many of the large drug companies. Clearly, it would be in the best interest of the pharmaceutical firms to have control over the SNPs themselves. However, rather than let Celera alone control the market on them, these firms are willing to work together with their competitors to see the SNPs put in the public's hands. Competition has become fierce. When Celera came forth to say that they would be have near finished draft of the human DNA sequence by mid 2001, the HGP stepped up their operations to try to finish by Celera's target date. In fact, Celera currently has completed 99% of the sequencing, though many gaps in their data remain.

In a statement made by Venter, Celera would distribute the results of the genome project when completed via publication under a non-redistribution agreement and stringent limitations on use. Philip Green, a leading biocomputing expert, argues that the non-redistribution clause "represents a significant departure from previous promises made by Celera that the sequence would be in the public domain" and furthermore states that "the data will not be submitted to GenBank" [15] , the free public database. The Celera database is certain to be very attractive to scientists and the academic community. The company also has a competitive advantage—it has full access to publicly funded projects, whereas public labs will not have access to Celera's.

Eric Lander, Director of the Whitehead Institute at MIT, and a leading researcher for the HGP, argues that "there is no proprietary genome" and states that he is concerned about the terms of Celera's licensing agreement [15]. Currently, Celera charges $20,000 per lab for basic access to its database, and they contract out for higher levels of access, targeting academic labs.

One must question why drug companies are willing to pay outrageous fees to support firms like Celera, whose business plan is restrictive to academia. Drug companies, like Celera, stand to profit. By using the research from Celera and incorporating bioinformatics (a combination of computer science and biology), firms can find better drug targets earlier in the development process, reduce the number of potential therapeutics in the pipeline and decrease overall costs. Moreover, utilizing Celera's research could also create extra drug company profits by decreasing the time it takes to research and develop a drug, thus lengthening the time a drug is on the market before its drug patent expires.

At a meeting in March of 2000 between members of the HGP and Venter, the discussion of the possibility of combining the efforts of the NHGRI and Celera ended in disappointment and frustration. At the conclusion, the NHGRI issued a letter to Celera itemizing the fundamental differences that emerged between the academics and Celera. The letter described the meeting as "discouraging" and suggested that combining forces between public and private efforts was "no longer workable" [16]. Furthermore, the letter claimed that Celera is looking to retain control over the human genome for as long as 5 years as ensured in their licensing terms. Additionally, the licensing terms would give Celera control over future uses of disclosed data as contracted out to its subscribers. The letter went on to say that this was "not in the best interests of science or the general public" [16].

Celera and its investors are expecting a significant return from their project, while publicly funded research is scrambling to preserve their funding. President Clinton stated in April 2000 that privately financed gene discoveries should be patentable, but publicly funded research should not be. This was a major blow to federally funded public labs seeking to remain competitive with private firms. This statement however, may be ethically flawed. Given the unique nature of the project, Celera should not operate solely on a profit motive; it must also concern itself with the greater good of the public's interests. Furthermore, the former president's statement may have caused irreparable harm to the integrity of both public and private firms, and may have raised substantial ethical implications as well. The underlying principal on which this statement may have been based is questionable. Celera no longer has any form of incentive structure to cooperate with other labs or even academia and no reason to distribute its data to GenBank. The fear of legal action challenging its patents was removed, and because of the removal of this potential downside, Celera's investors pushed the stock price up by 10 dollars (a near 20% gain) on the announcement. Prior to the announcement, the company had accepted the risk factor of legal action to challenge its patent applications in its business operations. After the announcement, it no longer needed to focus on legal issues and could redirect all efforts and finances to research. Now, to reverse the profit-only

motive and realign private firms' incentive compatibility with public interest, extensive legal action challenging the validity of DNA patents will be required.

Celera's investors now have little to worry about. Though the stock price has decreased as the overall market has fallen, the company has consistently beaten its expected First Call earnings estimates for the last 4 quarters. The company announced late February 2001 that its scientists have published an assembly of the human genome. An initial interpretation of the DNA sequences revealed that these sequences represent over 95% of human genetic information. Further, Celera's study shows that fewer than 40,000 human genes exist –far fewer than the 100,000 initially thought. Responding to this announcement, Wall Street analysts rewarded the company with a Strong Buy recommendation on its stock. Moreover, Celera continues to add new subscribers to its network, the latest of which are the University of California and Genset S.A. Given the latest list of subscribers in the academic realm, analysts have raised their price targets for the stock to $151 per share, as its current price is approximately $34 per share (March 2001).

With the dramatic increase in uncovered sequences and patent applications, one must then question the potential for monopoly ownership of genetic makeup. With no ethical motivators in place, there is no inducement to not operate solely on profits. If a single company controls the key to our genetic design, then it has the power to dictate genetic uses and applications. There is no incentive compatibility structure in place to limit the control of DNA patent holders and what they approve for its use. Benefiting science and the greater good of humanity is no longer an issue when profit alone drives a company.

Conclusion

Craig Venter has already rescinded his initial claims that he would allow free public access to the database. He has balked at the prospect of working with HGP and publicly funded labs in unison, rather than in competition. He has withdrawn his claim that academics will have the information for free and taken control of a vast majority of the patents on our DNA. Celera continues to pull in more subscriptions to its database, reaping increasing revenues. What is to stop Celera from controlling how the information is used, or more importantly, not used?

Decoding the human genome will almost certainly be seen as one of the crowning achievements of this century. The "book of life" as it is called, will inevitably reveal secrets of both health and disease, promising treatments and cures for virtually every malady that afflicts living creatures. New drugs that target Parkinson's disease, Alzheimer's disease and cancer will make the advent of penicillin look prehistoric. Decoding genomes will help scientists understand how species evolved and even pinpoint precise bits of genetic information that are uniquely human. Having this "book of life" will, without question, change the world. The question remains though, without the right incentive structures in place, whether the book of life will only be privy to a select few.

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