Report Number: JIEE 2002-05

AN INTRODUCTION TO ISSUES UNDERLYING PATENT POLICY FOR THE EMERGING GENETIC INFORMATION AND MEDICAL TREATMENT INDUSTRY

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August 2002

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PREFACE AND ACKNOWLEDGEMENTS

The Human Genome Program of the Department of Energy's Office of Science, Office of Biological and Environmental Research provided support for this paper. The paper is addressed to legal and economic scholars and government policy officials concerned with society's efficient use of intellectual property rights and particularly with the use of public and private research directed at genomic medical treatments and technologies. It is the first of a series of papers exploring patenting and regulatory issues in this topical area.

A series of circumstances combined to focus attention on patenting issues surrounding use of the base human genome in spring of 1998. A principal event was the advent of technologies that permitted significant reductions in gene sequencing time and costs. This led a rival relationship between the public and private genome research industries. A second event was the realization of the potential issuance of numerous patents on individual segments of the base genome. It was feared that large numbers of complementary patents would delay downstream genomic medical research, and the stacking of licensing fees would drain away resources from that research. Potentially, monopoly-licensing practices could even block access to some information.

This paper traces the events from spring of 1998 until the summer of 2002. During this period, incredible intellectual progress was made leading ultimately to the simultaneous publication of the draft base human genome in spring of 2001 by both public and private research teams. Since publication, progress has continued, patents for some genetic fragments have been issued, and it is presumed that numerous other patents have been filed. To date, the patent issues have not hampered progress, but this issue is far from being resolved. Both public and private research activities are currently recharting their paths to meet the challenges ahead. Our work presents a "progress report" on the current state of genomic property rights issues.

We would like to take this opportunity to thank the many individuals who have contributed to this paper. John Cogburn helped in gathering the base data for the report and Kevin Price provided numerous comments on intellectual property rights law. At JIEE, Milton Russell provided comments and encouragement on several drafts, and Sherry Estep edited the report. Glenda Hamlin prepared it for publication. Dan Drell of the Office of

Science provided support and advice. The authors, of course, retain responsibility for any remaining shortcomings.

1. INTRODUCTION

In May 1998, two events played pivotal roles in influencing the emerging market for genetic information and related medical treatments. The first was a series of articles in *Science* magazine. These articles articulated the issues facing the U.S. Patent and Trademark Office (USPTO) in determining which patents should issue among the then-rapidly growing backlog of applications for gene sequence discoveries and related information, much of which was financially supported through the Federally funded human genome research program. The second event of significance that May was the formation of Celera Corporation. Celera's mission was to sequence the human genome at breakneck pace using new technologies. In doing so, Celera challenged the Federal program to a "race" wherein the finish line would demarcate the complete identification of the base genome—the genetic code of the "representative human." Fueled by the hubris of the late 1990's, the emergence of new gene sequencing technology, and the potential for immense corporate gains, Celera confronted the fundamental basis for public support of basic research—the belief that private dollars would not support basic inquiry because investments could not be recovered in the market place. It was clear that fundamental changes were at work. What was less clear was whether these changes would spell the emergence of greater social benefits from genetic research than would have been true under the previous state of affairs and whether, and how, public policy should respond.

This paper traces the development of patenting and other public policy issues that have surfaced from this apparent sea change. In a sense, it is a mid-course assessment, because the final events that will lead to the emergence of a settled market for genomic medicine are far from settled, if indeed they will ever be settled. Moreover, change in this industry is cloaked by a lack of accessible information concerning the "facts" at any given point in time. Some facts are proprietary to private firms participating in this new marketplace; other facts are protected by policies of government, such as those of the USPTO; others remain obscure because the pace of events has far outstripped the publication of thoughtful reviews and analyses; and others are simply not well understood and are therefore subject to reinterpretation. The specific events and facts contained herein will be quickly dated and, in any event, will be interpreted differently by others. Our goal is to

present one interpretation of the current state of affairs and to delineate topics worthy of further study.

The paper is organized into four major divisions and a conclusion. First, we provide a brief history of the Human Genome Project (HGP). Second, we examine the nature of genomic intellectual property and its protection via patents and other instruments. For this we take as our point of departure the *Science* articles and their relation to the evolving body of genomic information. Third, we examine the structure of the "market" for genomic information, with particular interest in the role played by the need to license multiple patents and the role played by economic forces within this market. We also consider the potential types of public policy responses that might be considered and the types of considerations that might underlie these responses. Fourth, we summarize our findings and discuss a path forward.

2. BACKGROUND

The Human Genome Project began in 1990 as a publicly funded effort to sequence the human base genome and to make the sequence freely available to the public.[1] The goal of the project was to develop a map of the "representative" human genome with 99.99 percent accuracy and to complete the task within fifteen years. The base genome contains the fundamental genetic information required for reproduction and development of fertilized eggs to mature adults and also provides the "regulatory" process that governs human physiology. Whereas sequencing the base genome is, by itself, only a starting point, developers of the project believed that free access to this information would lead to subsequent innovations and improvements in medical care and in the identification, prevention, and treatment of diseases. Apart from structural problems such as broken limbs, or disease organisms such as germs, virtually all health-related problems stem from genetic disposition, and to some degree susceptibility to broken limbs and germs has genetic bases. While much modern medicine treats effects, genetic medicine could potentially correct causes. The developers of the HGP hoped that providing a free starting point for further research would spur "downstream" investment on the part of the private sector. Some felt that this information was of such a fundamental nature that freedom of access was virtually required so that benefits from technical advances would occur more quickly and at lower cost.

This project can be viewed as a foundation for downstream genetic researchers who would conduct the research and development that would ultimately supply improvements in diagnostic, preventative, and treatment medicine. It would largely eliminate the need for individual researchers to study the base genome on a piecemeal basis. Further, it was generally believed that the private sector would avoid most fundamental research because it could not recover its investments. In this view, information from fundamental research is much like a "pure public good." Once created, it is difficult to restrict access, and, indeed, the combination of high fixed costs coupled with low costs of dissemination meant that charging a positive price would lead to under-utilization of the resource. Stated differently, the optimal social price of the information resource would be zero, because the cost of supplying the

[1] U. S. Department of Energy, Oak Ridge National Laboratory, "Human Genome Project Information"web site, online at www.ornl.gov/TechResources/ Human_Genome/, accessed August 7, 2002.

already-developed information to prospective users is essentially zero. Under such a circumstance, the private sector typically would not find it profitable to supply the good. There was also concern that reliance on the private sector could lead to the outcome that the most profitable medical markets would be served first, less profitable ones more slowly, and unprofitable ones not at all. The private side of the medical industry would not target patients with rare illnesses or limited financial resources.

Causal empiricism would tend to support this conclusion. Most prior research in the field of genetics was concentrated on specific targets, typically genes that triggered a single disease or illness. Privately supported researchers tended to restrict inquiry to topics offering the best return on their R&D investments. If researchers could isolate a gene or fragment that caused a debilitating disease, they could seek patent protection and subsequently concentrate efforts on developing methods to detect, cure, or prevent that disease. This protection would provide incentives for this type of inquiry, but would potentially reduce competition among researchers and would slow the course of discovery as the patent process delayed disclosure of information related to new innovations. To avoid these problems in producing the base genome, the HGP adopted information protocols that called for daily publication of accumulated new information.

The breadth of discoveries that can potentially follow from the reference genome is vast. Building from the information provided by the HGP, advances in virtually all areas of medical technology, prevention and treatment of disease, and genetic testing are possible. For example, researchers could identify departures from the base (or "normal") genome, trace these departures to "abnormal" outcomes, and potentially develop treatments to correct the "defect." This would constitute a new medical option. Old options could also be made productive. Many potentially useful pharmaceutical discoveries cannot be used because of side effects that cannot be predicted. By using genetic information to identify patients subject to side effects, physicians could restrict medications to those not subject to side effects, thereby increasing medical options from the current technical base. It is also possible, using genetic information, to design unique drug regimes tailored to an individual's characteristics. These practices are termed pharmacogenomics. Research can also establish technologies that test for susceptibility to specific diseases or identify markers that suggest the potential for a disease to manifest itself in a human. This could lead to the practice of genetic testing to

determine the likelihood that an individual will develop a disease or that their offspring will develop the disease. Pre-testing is controversial because, even though it could improve health through early intervention, it could also lead to discrimination by employers or insurers, or could subject individuals to excess stress as they waited to see if potentially undesirable outcomes came about. Finally, a better understanding of genetic structure permits more systematic inquiry into the role of environment in forming personality and other behavioral attributes.[2] All of these developments were possible based on the old method of genetic research, but were more time consuming and costly, leading to delays in new discovery. The provision of a reference genome "jump starts" these developments by providing a free starting point.

To illustrate why the sequencing of the reference genome is such an important initial step for continued research in genetics, it helps to understand the downstream components of the industry that will benefit from the provision of the reference genome. Much of the genome is characterized by repetitive combinations and contains little obvious information. Research must sort out the valuable from the less valuable, and the dividing line between the two changes with additional information. While identifying and codifying unique genetic information is relatively mechanistic, the assignment of functionality, particularly complex functionality, is much more difficult. The recent publication of the base genome suggests that functionality may be more difficult to sort out than previously thought, owing to the smaller number of genes. This suggests that combinations of genes, perhaps regulated by portions of the genome previously thought less relevant, may be more common than was once believed.

Other researchers are involved in identifying common occurrences among genomes that they may use as reference points or markers to help determine differences among genomes. Expressed Sequence Tags (ESTs) and Single Nucleotide Polymorphisms (SNPs) are examples of this type of research.[3] ESTs can be organized into larger segments of information such as genes. SNPs can be used to identify departures from the reference gene that lead to individual variability. Some variability is associated with susceptibility to disease

[2] It is noteworthy that DOE's initial interest in the topic was motivated by a desire to gain better understanding of low-level radiation effects.

[3] Expressed Sequence Tags (ESTs) are short sequences of DNA that have single occurrences in the genome and whose location and base sequence are known. They can be viewed as unique since they occur in the same sequence and at the same location in every human genome. Single Nucleotide Polymorphisms (SNPs) are

or other dysfunctional processes. Other variability results from mutations, which can lead to more radical dysfunctionality. Dysfunctionality provides targets for researchers involved in developing treatments or identification methods such as drugs and genetic tests and provides the input to firms that will test, license, and market the treatments. The final component of the industry is the consumers, typically patients, who benefit from the research conducted upstream in the form of prevented disease, drug therapy, genetic testing, and the like. Of course, this worldview focuses on medical benefits and omits many other benefits, such as the ability to trace the evolution of life, which may ultimately prove highly valuable.

One way to view the body of knowledge emerging from this overall process is as the assembly of a complex puzzle. In the early days of the HGP, researchers would essentially identify the long string of paired protein molecules making up the base genome puzzle one pair at a time—a process akin to starting at one corner of a puzzle and searching until each sequential piece had been located. This was slow and cumbersome, but accurate, complete, and without gaps. Daily publication of information kept peers abreast of current information.

Technological advances soon permitted identifying longer segments of DNA (e.g., ESTs). These longer segments were identified through techniques that required reassembling the segments into genes and other genetic structures. This is similar to assembling a puzzle by finding individual pieces that fit together and starting to assemble the larger puzzle from smaller groups of pieces. This approach was much faster, though less accurate, and lent itself to choosing targets for scrutiny that had relatively high values in the market place. It also reduced the costs of identifying gene segments that could potentially be patented.

Despite the publicity associated with the base genome, it has long been known that many other puzzle parts are required to reach the stage of validated medical treatments. We have noted the need for understanding complex regulatory processes, the need to identify dysfunctionality markers, treatments, and so on, down through the often long and costly licensing process. In a sense, these stages are hierarchical and build upon one another. If discoveries could not be patented, the process might proceed smoothly, but slowly, limited by the budget of the HGP, those of other non-profit institutions, and private firms whose business plans did not require a direct return on investment from "upstream research." One

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differences in a DNA sequence that can be used for linkage analysis. These differences are found at the single base-pair level.

way to draw additional resources into the arena was to offer the opportunity to patent a broader set of genetic information, thereby offering greater prospects to profit from fundamental research. By establishing a system of private property rights to genetic information, more private resources would become available, but access to information would require payment to patent holders.

This led to a dilemma. On the one hand, daily disclosure led to free information exchange, but also to a limited resource base for research. If all information were free, all resources would necessarily have to be funded by groups, like government, that promoted free disclosure and were non-profit. On the other hand, permitting profit making through issuance of patents drew in the very large resource base of the private sector, but also led to delays in information disclosure, the requirement of license fees for using information, and other potential difficulties we discuss below. However, one thing appeared clear. The hierarchical nature of the genomic medicine industry would require a mixture of public and private resources—the public resource to establish basic upstream concepts and the private resource to carry out developmental studies to bring products to market. This too would soon be rethought.

The HGP was initially planned as a 15-year effort, focused on providing a reference genome of extremely high accuracy.[4] Following a series of technical advances in gene sequencing, the private sector also began to sequence portions of the base genome. In May 1998, Celera Genomics announced its plans to join this sequencing effort.[5] At that time Celera stated it would seek patents on some data and would necessarily withhold this data from publication until after patent applications were filed. Celera was fairly certain, given the evolution of biotech patent policy, that it could be granted patent protection for its sequenced data. This caused unease among the public-sector researchers because withholding sequence

[4] High accuracy means that the entire sequence is known with a very small degree of expected error. Much of the genome is repetitive and the provision of such high accuracy requires numerous iterations and comparisons to ensure that the sequence is correct.

[5] Craig Venter, president of Celera, left his position at the National Institutes of Health (NIH) in 1992 to form The Institute for Genomic Research (TIGR). At TIGR, Venter began to develop the now controversial "shotgunning" method and was engaged in joint research with Human Genome Sciences (HGS). Problems arose between the leaders of HGS and TIGR over the public release of data and patenting. In 1998 Perkins Elmer (PE) developed a faster sequencing machine and formed Celera Genomics. Due to the tension between HGS and TIGR, PE succeeded in hiring Dr. Venter as president of Celera. Celera then combined Dr. Venter's shotgunning method with PE's faster sequencing machine and announced plans to begin its own sequencing effort.

data from the public or attempting to gain monopolistic control over basic genomic data flew in the face of the HGP's underlying philosophy. Concerns were heightened in October 1998 when Incyte Pharmaceuticals was issued a patent for a human genetic sequence. It became obvious that Celera was not the only threat to keeping the genome publicly available.[6]

At this point, there was increasing worry that private-sector researchers, who could potentially tie up parts of the sequence with patents and demand fees for the use of the protected data, could thwart the goal of the public project. Thus, at about the same time Celera entered the race to sequence, HGP leaders announced plans to increase the pace of the public sequencing effort.[7] At one point Celera and HGP leaders discussed the possibility of joining efforts to sequence the genome, but they quickly reached an impasse because they could not agree on the frequency of data release.[8] Because the two groups could not reach an acceptable agreement, they continued to sequence the genome on their own and, in 1999, HGP leaders announced plans to complete a "working draft" of the sequence by spring 2000.[9] This working draft would not provide as high an accuracy level as the final product, but it would allow the public researchers to publish the data and thereby preclude Celera and others from obtaining patent protection on those published sequences.[10]

Apart from the public program, others involved with the biotechnology industry were also concerned about private-sector firms gaining control of parts of the genome through patent protection. As one example of a response, the SNP Consortium was formed in April 1999. The Consortium is a group of ten pharmaceutical companies who announced their intention to pool their resources, and to sequence and place 300,000 SNPs in the public

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[6] Tony Reichhardt, "Patent of Gene Fragment Sends Researchers a Mixed Message," *Nature* 396 (December 10, 1998): 499. This patent covered a genetic sequence that was coextensive to both a complete gene and to a number of expressed sequence tags (ESTs). Some argued that the patent was for a full gene while others argued that the precedent meant that ESTs could be individually patented.

[7] Paul Smaglik, "Human Genome Project Deadline Moves up Two Years, to 2003," *The Scientist* 12, no. 19 (September 28, 1998): 1.

[8] Colin MacIlwain, "Energy Department Revises Terms of Venter Deal After Complaints," *Nature* 397, no. 93 (January 14, 1999).

[9] Eugene Russo, "Genome Project Moves Up Deadline for Working Draft," *The Scientist* 13, no. 7 (March 29, 1999).

[10] During this time, other private-sector research firms and large pharmaceutical companies were also developing an interest in the results of the sequencing effort. Some companies began their own sequencing efforts and some even began to file patent applications for gene sequences. Examples of other research firms that began their own efforts and filed patent applications for their research are Human Genome Sciences, Incyte Genomics, and Genentech.

domain.[11] The project has been quite successful and has made available about 1.5 million SNPs for public use.

While HGP leaders and Celera were unable to reach an agreement on collaborating to finish sequencing the genome, they did finally reach an agreement to publish their sequencing results simultaneously. During the week of February 12, 2001, Celera and the HGP published the first draft of the genomic sequence in separate scientific publications.[12] Work had actually been completed several months earlier, but the two groups agreed to postpone publication until analysis of the information could summarize the significance of the results. Publication in this case is symbolic, because the actual sequences are much too large to be published on paper and have little utility in that format in any event. The overall effort, however, did provide many new insights into genetic structure. It appeared, for example, that there were only about 30,000 human genes, rather than the more than 100,000 previously thought.[13] This implies greater complexity, because fewer discrete genetic elements must be providing greater function.

Following publication of the base genome, the publicly sponsored program is providing its data free of charge. Celera is providing limited amounts of data to non-profit researchers meeting certain requirements at no charge and is charging a subscription fee for profit-seeking groups, sometimes including universities.[14] In exchange for the fee, Celera provides some software support to the users and offers more extensive data processing support at additional cost. It is presumed that Celera has filed for extensive patent protection for information it believes to have market value. As we discuss below, publication of information prior to filing for patent protection places information in the public domain and, in principle, makes it impossible for any group to obtain protection for the same information.

During the period of time that Celera and the HGP were concentrating on the completion of the first round of sequencing, numerous other private companies were engaged in sequencing efforts of their own. Firms such as Human Genome Sciences (HGS), Incyte, and Genentech were investing their research dollars in related sequencing activities in the

[11] Ken Garber, "Homestead 2000: The Genome," *Signals Magazine* (March 3, 2000).
[12] The HGP published its working draft of the sequence in *Nature* on February 15, 2001 (pages 860-921) while Celera published its working draft in *Science* on February 16, 2001. In fact, the entire February 16 edition of *Science* was dedicated to human-genome-related material.
[13] Elizabeth Pennisi, "The Human Genome," *Science* 291, no. 5507 (February 16, 2001): 1177.
[14] Eliot Marshall, "Celera and *Science* Spell Out Data Access Provisions," *Science* 291, no. 5507 (2/16/01).

hopes of gaining patents. These groups had entered into licensing or cooperative agreements with large pharmaceutical companies to share their information. For example, HGS and SmithKline Beecham Pharmaceuticals entered into a $125 million exclusive agreement whereby SmithKline would pay HGS for exclusive access to its EST database.[15]

To provide a perspective on the rapid increase in R&D activities in this industry, Table 1 shows expenditures by the four largest firms, the industry, and the public sector.

Table 1—Genomics R&D Expenditures of Genomics and Pharmaceutical Firms (in dollars), 1993-2000

Year	Big 4*	Public Firms[16]	Government[17]	Total[18]
1993	24,223,000	81,686,540	169,100,000	250,786,540
1994	49,457,000	149,192,487	190,300,000	339,492,487
1995	70,029,000	210,140,978	222,500,000	432,640,978
1996	116,139,000	318,829,566	243,200,000	562,029,566
1997	197,396,000	507,895,229	266,800,000	774,695,229
1998	268,667,000	690,170,340	303,800,000	993,970,340
1999	415,765,000	845,776,220	315,600,000	1,161,376,220
2000	720,583,000	2,170,406,462	360,600,000	2,531,006,462

*Big 4: Celera, HGS, Incyte, Millennium Pharmaceuticals

The most noteworthy aspect of this table is the rapid growth in private sector R&D investment. In less than ten years, government has gone from being the dominant player in genomics research to providing less than fifteen percent of total R&D, despite the fact that government spending doubled over this period. As things now stand, the genetic medicine industry is increasingly poised for takeoff. One determinant of the speed with which this takeoff will occur lies in the ability of the nation's intellectual property rights system to facilitate the flow of information into its most productive uses. We now turn to a discussion of the patenting issues that will influence this flow.

[15] Jon Cohen, "The Genomics Gamble," *Science* 275, no. 5301 (February 7, 1997): 767-772.
[16] Robert M. Cook-Deegan, Amber Lynn Johnson, and Carmie Chan, "World Survey of Funding for Genomics Research," Stanford-in-Washington web site, online at www.stanford.edu/class/siw198q/websites /genomics/entry.htm, accessed August 7, 2002. This column includes the "Big 4."
[17] U. S. Department of Energy, Oak Ridge National Laboratory, "Human Genome Project Budget," available online at www.ornl.gov/hgmis/project/budget.html, accessed August 7, 2002. Spending excludes the National Science Foundation (NSF).
[18] This total is generated as the sum of public firms and government—the previous two columns.

3. ISSUES IN GENOMIC PATENT POLICY

The May 1, 1998 issue of *Science* magazine contained what could best be described as a symposium on emerging issues surrounding the patenting of innovations developed through biomedical research. The principal paper, by Michael A. Heller and Rebecca S. Eisenberg, postulated the existence of specific attributes in this field that could lead to under-utilization of the fruits of biomedical research and development.[19] A second paper, by John J. Doll of the USPTO, described the ability of the patent process to accommodate past departures from traditional patenting due to technical innovations and projected that only modest corrections might be required to avoid the difficulties posited by Heller and Eisenberg.[20] Several other eminent patent-law experts also weighed in with opinion and analyses. In the end, no clear-cut conclusion as to the need for revolution or evolution in patent policy emerged. Before discussing the papers in this symposium, we review the general background within which the issues raised in this symposium must be framed.

3.1 Patent-Policy Background

The patent process is of longstanding stature. Its roots are found in common law, statutory law, USPTO policies, and case law. Patents essentially create monopoly property rights of a special kind. These rights permit the patent holder to exclude others from the use of some protected idea or other creatively produced innovation. The right to exclude differs from the right to access or use in the following way—the holder of a patent can block or exclude some second party from making use of the information protected by the patent. However, the patent holder might not be able to make use of the information because doing so might require obtaining permission from related patent holders. Thus, patents grant a unique right that guarantees ability to exclude, but not to use.

Governments typically seek to avoid conferring monopoly rights, but for patents, the creation is purposeful, and intended to provide an incentive for inventors to create new products and processes. Stated differently, patents create rights in intellectual property. In general, intellectual property is costly to create, but costless to reproduce. Without protection, there would be a strong incentive to free ride, with a resulting under-investment in private

[19] Michael Heller and Rebecca Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research," *Science* 280, no. 5364 (May 1, 1998): 698-701.

R&D. With protection, there is an incentive to patent virtually anything of potential value, particularly for firms in rival situations where patents can play the role of "intellectual currency." Nearly all of the issues discussed in this paper result from the need to license multiple patents from multiple patent holders.

Patented ideas and innovations can take a variety of forms, including new products or processes, or improvements to old products or processes. The criteria inventors must meet to obtain patent protection encompass four elements. First, a new "invention" must be legally patentable. As is discussed below, prior to a specific judicial ruling, the patenting of genetic information was not considered legal. Second, it must be novel, in the sense that it constitutes a departure from the existing body of knowledge. Prior publication of an idea precludes subsequent patenting. Third, it must be non-obvious, such that the innovation must not be readily apparent to an expert in the field. Fourth, it must possess utility, meaning that it must permit the holder of the knowledge to actually do something. Hence, an astronomer discovering a new star cannot patent the discovery, whereas an engineer developing a new telescope can. These criteria provide the USPTO with a good deal of latitude to accommodate technological change through executive branch prerogative, thus avoiding the need for new statutes. [21]

If these criteria are met, the patent application must meet disclosure requirements, which also have four components. The first disclosure requirement is the written description, which must demonstrate that, at time of filing, the inventor was in possession of the information claimed. The second disclosure requirement is enablement, which means that the inventor must be able to teach others how to follow the same steps taken by the inventor. Stated differently, the inventor must be able to describe the innovation in a way that advances the state of the art. The third requirement is to demonstrate that the invention for which protection is sought is the superior application among alternatives. This prevents the inventor from protecting parts of the invention under a patent, which requires public disclosure, and others as a trade secret, which does not require public disclosure. Finally, the written disclosure must be definite, that is, it must contain concrete examples of the boundaries of the claim.

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[20] John J. Doll, "The Patenting of DNA," *Science* 280, no. 5364 (May 1, 1998): 689-690.
[21] The requirements for patentability are described in Title 35 of the U.S. Code, sections 101, 102, 103, and 112.

The boundaries or breadth of the claim set the basis for protection. Breadth is sometimes referred to as the patent's scope. There is often a thin line dividing patents from other forms of intellectual property protection, such as trade secrets or copyrights. Thus, while an inventor is preparing materials for a patent she may rely on trade secret protection, which prevents disclosure by parties in her firm, but not protection from independent discovery by other inventors.

To be able to legally use the ideas protected in the patent, secondary parties must, alternatively, negotiate terms with the inventor, meet specific criteria, such as making use of the information for an acceptable type of university research, or successfully challenge the validity of the patent protection proffered by the USPTO. Illegal use is termed infringement and is a civil offense. Contractual terms can take any of a number of forms ranging from non-exclusive licenses to exclusive sales. Many distinctions are nuanced in ways that are non-obvious to laypersons and stem from the fact that invention is a dynamic process with truly unique innovations being the exception rather than the rule. Most innovations use previously developed ideas as points of departure, and, in turn, serve as points of departure for subsequent research. In general, the broader the scope afforded by a patent, the more difficult subsequent users of the innovation will find obtaining successive patent protection for related ideas, and the narrower the scope the easier they will find it.

To the extent that the USPTO issues large numbers of related patents that have interdependencies, "stacking" will occur, i.e., to obtain access to some innovation, the users will be required to obtain access to a number of prior innovations. The degree of protection afforded by the patent largely dictates the contractual arrangements the patent holder can enforce. A user of an innovation created on top of preceding patents may require a large number of licensing arrangements, whereas a user of a single patent of broad or unique scope may require only one.

Further, licensing arrangements can in themselves create stacking issues. Upstream researchers may issue licenses to downstream researchers that allow the upstream researchers to maintain some rights to the discoveries made by the downstream researchers. Thus, subsequent users may have even more parties with which to deal. Licenses of this sort are called "reach-through" licensing agreements.

The traditional processes employed by the USPTO create a set of unique incentives for the inventor and influence the ability of the innovation to generate subsequent technical or technological change. First, in the U.S., patents have been traditionally granted to the "first to invent," whereas other nations typically apply a "first to file" criterion. "First to invent" requires demonstration that an inventor has "reduced an invention to practice," whereas "first to file" is a largely administrative criterion. Second, patent applications prohibit access of interested parties to the description of the innovation until the patent is granted (unless the inventor permits access). This process is inefficient because competitors to the inventor may find their inventions trumped by evidence that another inventor previously reduced the same idea to practice. It also delays publishing advances in the state of the art. Third, U.S. patent protection extends from the point at which the patent is granted, rather than from the point of filing. Sometimes delays in the patent process can cause shifts in market power, because downstream researchers (i.e., researchers whose work builds upon "upstream" work), unaware that specific research will emerge with patent protection, invest in R&D that makes use of the protected information. These patents are sometimes called submarine patents, because they surface unexpectedly. Submarine patents can give rise to so-called holdup problems in which a downstream researcher, having invested in technology that uses the submarine patent, may be willing to pay more for the license than would have been the case prior to undertaking research.

To a degree, the American Inventors Protection Act (AIPA), implemented in November 1999, makes U.S. patent law more comparable with patent practices in other parts of the world. The legislation calls for the publication of patent applications eighteen months after application date if the application was also filed abroad. The Act also made changes to patent terms, guaranteeing a minimum period of non-disclosure due to USPTO delays, and providing a means for defending infringement claims based on a "first inventor" defense. The publication requirements apply only to inventors who seek patent protection abroad as well as in the U.S. Inventors who seek only domestic protection will be "grandfathered" under the old law, and early publication will not be required.[22] [23]

[22] See the Intellectual Property Owners Association web site at http://www.ipo.org/, accessed August 7, 2002.
[23] A review of recent changes to U.S. patent law and practices may be found in Nancy T. Gallini, "The Economics of Patents: Lessons from Recent U.S. Patent Reform," *Economic Perspectives* 16, no.2 (Spring 2002):131-154.

The process of patenting the outputs of biomedical research, i.e., "living things," is not a new topic. This type of patenting dates from *Diamond v. Chakrabarty,*[24] which decided that "products of nature" were patentable under certain circumstances, even while recognizing that the USPTO was ill equipped for the number and type of patent applications that this rule would ultimately elicit. In *Chakrabarty*, a patent application was filed for a bacterium that was genetically engineered to break down oil. Such an innovation would have numerous applications, especially in remediating oil spills, and would have corresponding commercial value. Chakrabarty filed an application to receive patent protection for what he assumed would be considered an invention. The USPTO, however, denied the application on the basis that the bacterium was a naturally occurring substance and was therefore unpatentable. Chakrabarty then appealed the ruling, and the U.S. Supreme Court eventually accepted the case for review. In affirming the Court of Customs and Patent Appeals, the Supreme Court ruled that the bacterium that was the subject of the patent application was genetically engineered in the laboratory and therefore was not to be considered naturally occurring.[25] This determination meant that the bacterium was to be considered an "invention" for purposes of patent law and was therefore patentable. The effect of the decision was to set a precedent that opened the door for other researchers to file patent applications on other DNA-based "inventions." Since *Chakrabarty*, a rapidly increasing backlog of DNA-related patent applications has been filed.

Prior to the start of the HGP in 1990, private firms had long sought patent protection on a wide variety of inventions related to genetic data using the decision in *Chakrabarty* as a supporting argument. Filings of this sort continued to increase, independently of the HGP, as knowledge on the topic accumulated and the apparently large prospective payoffs drew additional support into this area. Patents had been granted prior to 1990 for drugs based on specific DNA targets, both human and animal. Patents for tests and other diagnostic tools based on specific, but limited, DNA sequences had been granted as well. When the USPTO began to make decisions on patent applications for human DNA sequences it naturally

[24] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[25] Chakrabarty appealed the USPTO's decision to the Patent Office Board of Appeals on Patent Appeals (POBAPA). The POBAPA affirmed the USPTO's decision to deny the patent. Chakrabarty then appealed this decision to the Court of Customs and Patent Appeals who reversed the POBAPA's decision to deny Chakrabarty's patent application. The Supreme Court granted certiorari to determine whether live, human-made organisms are patentable under 35 U.S.C. §101.

applied this experience. Not all observers agreed this experience would provide efficient practices for the granting of genomic patents.

3.2 The *Science* Dialogue

A debate soon arose over the principles that should guide the patenting of human gene fragments. Given the immense size of the body of information contained within the genome, the patenting of uniquely identifiable fragments, such as ESTs and SNPs, gave rise to a number of issues. These issues centered around the fact that because there was no on-point guidance detailing required claim language and providing indications of the breadth of patents, issued patents could reasonably extend to all future uses of the patented sequence, even if the uses were not anticipated at the outset.[26] This was the topic addressed by Heller and Eisenberg in their *Science* article, "Can Patents Deter Innovation? The Anticommons in Biomedical Research."[27]

Heller and Eisenberg were concerned that holders of stacked patents on gene fragments or holders of reach-through licensing agreements could demand license fees from others seeking to patent larger sequences, such as whole genes, of which the patented fragment was a part, thereby potentially hindering downstream research.[28] It is possible, given the number of applications filed to date, that stacking problems could lead to the necessity of multiple licenses, thereby increasing the costs of research and negatively impacting potential profits from an innovation. In fact, the genome presented the ultimate stacking problem. Potentially, a different agent could own each EST and tens, hundreds, or even thousands of licenses might be required. The technology unleashed by Celera and the other private firms, competing with the HGP, which published its data each day, presented a significant challenge. As it happened, Heller and Eisenberg were writing slightly before the Celera challenge and addressed, in large part, the issue of university patent holders, but their argument was sufficiently general to apply to Celera and its rapidly growing group of competitors as well.

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[26] Robert Mullan Cook-Deegan, Letter, *Science* (1998), available online at http://www.sciencemag.org/feature/data/980465/cook_deegan.shl, accessed August 7, 2002.
[27] Heller and Eisenberg.
[28] For a general review of issues surrounding the need to license multiple patents see Carl Shapiro, "Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Stand-Setting," in *Innovation Policy and the Economy*, eds. Adam Jaffe, Joshua Lerner, and Scott Stern (National Bureau of Economics, 2001).

To illustrate this problem, Heller and Eisenberg introduce a powerful analogy, that of the "anticommons." A mirror image of the "tragedy of the commons," which postulates that an *under-assignment* of property rights leads to the over use of a commonly held resource, the anticommons postulates that an *over-assignment* of property rights can lead to the under-utilization of a privately held resource. The tragedy of the commons occurs because individuals, unable to exclude others from using the common resource, face incentives that lead them to use the commonly held resource until, at the margin, their *private* return from doing so just matches their *private* cost. This leads to a greater use than would occur when the *social* rate of return is equal to the *social* cost, with the result that the resource is dissipated.

The anticommons analogy employed by Heller and Eisenberg is somewhat less rigorous, and somewhat less incentive based, but equally compelling. In this case, a combination of transactions costs, heterogeneous interests, and cognitive biases lead to under-utilization. Transactions costs have served as a major underpinning of legal discourse since Ronald Coase wrote his famous piece in the *Journal of Law and Economics*, which criticized conventional economic analysis for omitting the costs of carrying out business activities.[29] Heller and Eisenberg point out a number of instances where costs of doing business interfere with efficient patent practices. First, they argue that many upstream patent owners are public institutions with limited abilities and resources to deal with the "fast-paced business environment," which extensive patent licensing would require. Second, the diversity of rights would drive up the costs of establishing value. Third, non-comparabilities among basic rights holders would require case-by-case negotiations. Fourth, if downstream researchers are required to have licensing agreements prior to undertaking research, research costs will increase and less research will be undertaken. Finally, if the number of required licenses is large, it is inherently more costly to negotiate and obtain the needed agreements. Noting that other industries have overcome these costs through pooling arrangements, the authors caution that antitrust law may be increasingly threatening and that even a "remote prospect of facing treble damages" could give firms pause.

In addition, Heller and Eisenberg consider the rigidity of the production process that embodies upstream genomic information. If genomic medicine requires licenses for

[29] Ronald Coase, "The Problem of Social Cost," *Journal of Law and Economics* (October 1960):1-44.

sequences that comprise some specific gene, the license requirements are set in stone, and by holding out, a patent holder could block downstream applications. In most other applications downstream researchers have the opportunity to "invent around" or "reverse engineer" patents, giving rise to a backstop price. In this case, these opportunities may not be available, and Heller and Eisenberg speculate that recourse to a non-exclusive licensing requirement may be needed.

John Doll, the USPTO director of biotechnology, addresses related concerns over the impact of patenting gene sequences, independently of the Heller and Eisenberg paper, following statutory patent requirements and the procedures used by the USPTO to implement the requirements. Noting apprehension over the impact of the granting of patents on progress in biomedical research, Doll argues that patents are necessary to create incentives for private investment in R&D and, further, that existing patent legislation is sufficient to facilitate efficient and effective patenting.

Unlike the legal theorists Heller and Eisenberg, Doll builds his arguments from the perspective of a practitioner, arguing first that the statutory requirements are clear, and second that modifications of the written requirements can fine-tune the process if the need arises. At the same time he notes that the development of new guidance as to written requirements was currently underway within the USPTO. Doll's point is not that patenting practices for biomedical innovations are finalized, but that no new legislation is required. However, he also points out that once issued, a patent extends downstream to even non-obvious uses, opening the door for unexpected impacts due to stacking. His example of the issuance of separate, yet complementary, patents for a television tube and a television set that must also license the tube patent seems more simple than the prospects described by Heller and Eisenberg.

The editors of *Science* also invited several legal experts to comment on these two papers. Like the two lead papers, these tend to fall out into theory-based and experience-based arguments. Robert Mullan Cook-Deegan is sympathetic to the Heller and Eisenberg position and critical of the Doll position. He suggests, "The absence of calamity is a weak argument for a policy, particularly if harms can be foreseen." Cook-Deegan suggests that the technology exists to put a few firms "in the catbird's seat" regarding control of basic gene

sequences.[30] The issue is less whether or not a mechanism exists to issue patents for downstream research than whether the mechanism works well. He questions the relationship between science and technology, accepting, as do most others, that profit incentives proffered by patents are for the development of technology, while science is typically government funded. But he qualifies this, noting that most scholars no longer use the terms upstream and downstream automatically, because of the obvious feedbacks from technical needs to basic inquiry. In this sense, he essentially anticipates the issue arising around the Celera challenge and the business strategies discussed below.

Sanyin Siang raises other issues. He points out that Doll's arguments are based on circumstances that can change. Doll, for example, argues that ESTs and SNPs meet the utility test, but Siang cites *Brenner v Manson* (1966) in which the U.S. Supreme Court held that an invention useful only for research fails to meet the utility test. He also points out that the Federal Technology Transfer Act of 1986 was designed to foster academic/industry relationships, but that such relationships could generate tensions. He cites an example in which Oxford University asked researchers at the University of California, San Francisco, to sign a letter allowing Oxford the right to review and comment on research resulting from DNA sequences Oxford was providing.[31]

In contrast, Seide and MacLeod suggest the blocking issue may not be as dire as Heller and Eisenberg suggest. They note that while the number of required licenses could be large, the number of license owners will be small, simplifying negotiations. They also suggest that exemptions exist for researchers to use patented information without penalty and that, in any event, there is little experience to suggest that broad-based biomedical patents have stymied downstream research in the past.[32]

Thomas G. Field, Jr., makes perhaps the most sweeping observations. He notes that in *O'Reilly v Morse* (1853) the U.S Supreme Court struck down a claim by the inventor of the telegraph asserting exclusive rights to all downstream innovations to communication via

[30] See Cook-Deegan, Letter to *Science*.
[31] Sanyin Siang, Letter, *Science* (1998), available online at www.sciencemag.org/feature/data/980465/siang.shl. accessed August 7, 2002.
[32] Rochelle Seide and Janet MacLeod, Letter, *Science* (1998), available online at www.sciencemag.org/feature/data/980465/seide.shl, accessed August 7, 2002.

electric current, based on his patent. On this basis, Field argues, unreasonable claims could be denied or struck down after issuance.[33]

3.3 New Patent Guidance

In March 2000, after receiving comments from the public, the USPTO issued new interim training materials that attempted to make clearer the requirements for patenting sequence data. More precisely, the USPTO sought to clarify the question "How much information on function is enough?" when it comes to patenting DNA sequences. The interim guidelines called for a "specific and substantial utility that is credible."[34] This meant that the old standby of claiming a sequence to be a "useful probe" for subsequent sequencing would no longer be enough information as to specific utility. The applicant must understand the sequence well enough to specify a utility that is considered credible based on current state-of-the-art.

The interim guidelines also provided a new description of the required level of sequence data necessary to claim an invention.[35] The new guidance suggests that if the gene sequence is complete, the written description requirement is met. The guidance goes on to suggest that if the sequence data are not complete, more information needs to be known as to specific function. It would appear that the USPTO has instituted a balancing mechanism that weighs sequence information and knowledge of function against one another. The effect of these revisions is to require applicants to possess a substantial degree of knowledge about the sequence, but to reduce the ability to use the patent as a necessary basis for a placeholder until the applicant is able to delve more deeply into the function of the sequence. The resultant guidance is not a law, but is the effective measuring stick against which patent applications for DNA-based innovations are examined. It means, in general, that fewer patents will be issued.

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[33] Thomas G. Field, Jr., Letter, *Science* (1998), available online at www.sciencemag.org/ feature/data/980465/field.shl, accessed August 7, 2002.
[34] Douglas Steinberg, "Biotech Faces Evolving Patent System," *The Scientist* 14, no. 5 (March 2, 2000).
[35] See U. S. Patent and Trademark Office web site, "Synopsis of Application of Written Description Guidelines," available online at www.uspto.gov/web/ offices/pac/writtendesc.pdf, accessed August 7, 2002.

3.4 Recent Patenting Events

The debate over the influence of patent policy on genomic research has continued since the 1998 *Science* dialogue. In a follow-up on that issue, Cook-Deegan and McCormack report that more than 25,000 DNA-based patents had been issued by the close of 2000.[36] These include purified and cloned gene fragments and full-length genes, regulatory sequences, sequencing and diagnostic methods, and any number of research tools. Although the precedent for patenting these and other DNA-related products and processes is well established, there remains sentiment for reducing the range of patentable products, or at least for reducing restrictions on the ability to infringe, especially for researchers.[37]

Litigation over infringement has become increasingly active in the biotech arena. In general, firms seek to achieve the largest possible patent scope in order to threaten infringement. They may also attempt to license closely related inventions, either to avoid infringement or to have something to offer up if accused of infringement, though the courts limit this practice through the "doctrine of equivalents." If a firm is found guilty of infringement, the courts may require a range of compensation, limited by fair royalty payments and ranging up to the entirety of the gains achieved through infringement.[38] The debate over gene patenting will likely continue. As an example, a bill introduced in Congress in March 2002 called for a study on the impact of gene patenting.

[36] Robert M. Cook-Deegan and Stephen J. McCormack, "Intellectual Property: Patents, Secrecy, and DNA," *Science* 293, no. 5528 (July 13, 2001): 217.
[37] Beth E. Arnold and Eva Ohgeilski-Zei, "Patenting Genes and Genetic Research Tools: Good or Bad for Innovation," *Annual Review of Genomics and Human Genetics* 3 (2002):415-32, available online at http://genom.annualreviews.org/cgi/reprint/032102.170635v2.pdf, accessed August 7, 2002.
[38] Mark Shankermeyer and Suzanne Scotchmer, "Damages and Injunctions in Protecting Intellectual Property Rights," *Rand Journal of Economics* 32, no. 1 (Spring 2001): 199-220.

4. ISSUES IN THE ECONOMICS OF GENOMIC PATENTS

Despite the importance of economic behavior for patent policy, the principles that relate economic behavior to patent policy are not fully established. For instance, if patent protection promotes innovation, should there be an economic analysis of proposed patent policies in the same way that executive orders require economic analysis of proposed executive branch regulations? This subject is the topic of debate among legal scholars. Mercuro and Medema, for example, describe five identifiable schools of thought within the evolving discipline termed law and economics.[39] They also describe a number of alternative principled bases for broader judicial issues, including common law, doctrinalism, and legal realism. The following section outlines the relationships between economic behavior and patent policy using microeconomic theory, in the tradition of regulatory economics. Our immediate interest is in pointing out issues, rather than in generating solutions.

We begin this section with the simplifying assumption that information flows can be viewed as being driven by final demand for genomic medicine. If one firm undertook all R&D, production, and sales, we would describe the market as fully integrated, a form of organization that we take as a benchmark for efficiency. In the real world, this industry is horizontally and vertically stratified. We are interested in examining: (1) horizontal stratification, in particular, the issues that arise when patent stacking for a common body of information exists; (2) vertical stratification, the issues that arise when patents on different sorts of information are stacked; (3) the implications of transactions costs related to the number of licenses required; (4) firm business strategies; and (5) policy tools.

4.1 Horizontal Stratification

Horizontal stratification (horizontal patent stacking) gives rise to the anticommons issue associated above with Heller and Eisenberg. Gene fragments can be thought of as factor inputs to further research that are strict complements. This means that if a downstream researcher wants to work on a gene, she must license the entire gene, a process that may require licensing a large number of patented fragments. Failing this, she could be charged with infringement. She cannot substitute some other information, or independently sequence

[39] Nicholas Mercuro and Steven G. Medema, *Economics and the Law* (Princeton, NJ: Princeton University Press, 1997).

the needed fragment. In general, the downstream production process requires a set of complementary inputs whose costs increase with each additional input (patented gene fragment). Thus, a single patent per gene would be more efficient than multiple patents. Heller and Eisenberg provide the argument that costs rise for a number of reasons, including the transactions costs that arise from assembling large numbers of licenses, the costs of doing business with universities and non-profit institutions, and the general uncertainty associated with successfully acquiring the needed licenses. The larger the number of patent holders, the larger will be the costs.

More recently, a second description of the anticommons, by Buchanan and Yoon, has emerged.[40] This description focuses on the pricing strategy adopted by patent holders and the implications of this pricing strategy for access to the intellectual resource. Buchanan and Yoon seek to understand how access to a single intellectual resource changes as the number of owners who can exclude access to the resource increases. To do this they develop a model that uses oligopoly theory to demonstrate that with an increasing number of patent holders, the sum of all license prices increases, i.e., the total fee required for gaining access to the intellectual resource increases. This results in a smaller number of total licenses sold, equating with lesser access to the intellectual resource. Although Buchanan and Yoon and Heller and Eisenberg deal with similar phenomena and achieve similar results, the behavior they describe is quite different. For this reason, we divide the effects into separate elements for further study.

4.2 Vertical Stratification

Vertical stratification (vertical patent stacking) is closely analogous to horizontal stacking. It can result from: (1) requiring downstream users to obtain multiple upstream licenses, and (2) having upstream firms issue reach-through license agreements that automatically transfer property interests in downstream products or processes to the upstream licensor. Both lead to multiple licensing requirements. We separate vertical from horizontal stacking to permit examination of a phenomenon referred to as double marginalization.

[40] James Buchanan and Yong J. Yoon, "Symmetric Tragedies: Commons and Anticommons," *Journal of Law and Economics* 43, no. 1 (April 2000): 1. Shapiro presents a similar result in a technical appendix. See also Cournot's theory of complements.

Double marginalization is the well known effect that, when a monopolist sells to another monopolist, the downstream monopolist will incorporate the monopoly rent paid to the upstream monopolist into the sales price, which reduces overall welfare. Our interest is in understanding the impacts of a larger number of patent holders selling to a downstream monopolistic or oligopolistic structure and how this market organization affects economic welfare.

4.3 Transactions Costs

As noted above, it has been argued that it is more expensive to assemble larger sets of intellectual property rights than smaller sets. This drives up the costs of research and development and can reduce access to the intellectual resources. We separate this effect from the behavioral effect described by Buchanan and Yoon.

4.4 Business Strategies

In describing the history of the human genome research effort, we have noted a number of different approaches to R&D taken by the private sector, presumably in an effort to generate revenues from information and other sales. HGS aligned itself with individual pharmaceutical companies and sold exclusive licenses to its data. Celera published its version of the base genome, sought patent protection on specific information it thought valuable, and offered non-exclusive licenses to access its database. It also tied specialized computer processing services to its data access fees. The SNP consortium is pooling resources and sharing R&D results by placing its findings in the public domain.

Business strategies in the biotechnology sector are interesting for a number of reasons. First, some strategies would appear to fly in the face of the "conventional wisdom," namely that the private sector would not undertake basic research because the foundational nature of basic research makes it difficult to capture revenue streams to compensate for R&D outlays. Celera, in following a strategy to sequence the entire base genome, by-passed this rule of thumb by creating a revenue strategy based on access to its (patented and unpatented) database elements using specialized computer support. In doing so, Celera provided an impetus for the Federally funded human genome program to also change its research strategy.

Several results emerged from this outcome. One is that the base sequence emerged earlier than the one that would have resulted from following the original HGP plan, but it has been characterized as less accurate. The implications of "accuracy" are not well understood. A second is that some argue that Celera would not have been able to complete its sequence without the assistance of daily publication by the public program. This implies that the public program could have succeeded without Celera, but not the opposite. Perhaps of greatest interest, Celera has now made an apparent course correction in its business plan. Former President, J. Craig Venter, has left, and Celera is following an announced strategy to work more closely with the pharmaceutical industry. This, at least in part, may reflect the fact that Celera's initial business plan proved less profitable than was anticipated.

The SNP consortium appears to be an attempt at vertical integration. By generating upstream intellectual information and sharing it, the firms basically agree not to compete in that market for information. By making the information freely available to anyone who would like it, they hedge against antitrust exposure. [41]

4.5 Policy Instruments

The public and private sector are motivated by different goals. Generally, the private sector will not invest in R&D without the prospect of recovering its outlays plus earning profits. The public sector, on the other hand, is motivated by a desire to promote the efficient use of genomic medicine, that is, to achieve the greatest benefit at the lowest cost, to provide incentives that will draw in private research dollars, and to promote the equitable use of science in society. It may also have other goals, including equity.

Equity is the concern that individuals in similar circumstances not be treated in a markedly different manner. Thus, if a person was much like all others, failing some small deviation in genetic makeup beyond her control, should policy take steps to reduce the impacts of the difference? Genetic equity concerns can take a number of forms. Certain treatments may have too small a patient base to offer significant profit potential. Should government fund research in these areas? Knowledge from genetic tests provides the potential for both public and private entities to discriminate against those with tendencies

[41] In general, the Justice Department tends to view patent pools for complements to be procompetitive and patent pools for substitutes to be anticompetitive. See Shapiro, 17.

toward specific disease profiles. Can such discrimination be effectively prohibited, given that insurance companies can currently discriminate against clients with known disease profiles? Even the definition of disease has been changed by genomic research, such that one might seek certain treatments in advance of developing a condition, a process akin to an exercise in real options investment practices. In principle, those with the resources to do so could reduce their susceptibility to any number of conditions or improve their performance in any number of ways.

To the extent that government wishes to pursue its goals, it has a number of tools to employ. One tool is patent policy. As has been noted, policy that affects patent scope has significant impacts on the degree to which stacking occurs. But more generally, there are a large number of options over the nature of the asset that a patent confers open to the USPTO. In addition to scope, there are issues of timing (i.e., for how long does protection extend), limitations on the ability to license or transfer, limitations on reach- through licensing, and concepts of "eminent domain." Some of these are statutory issues, while others could be adopted by the USPTO without new legislation.

A second tool is the posture adopted by the judicial system regarding infringement.[42] In general, the courts have two options when faced with infringement: (1) they can enjoin further infringement; and/or (2) they can impose damages. If damages are imposed there are two further options: (1) reimburse the patent holder for lost royalties; or (2) force the infringer to pay all unjust enrichment. The first form of damages is a *de minimus* penalty, which might consist only of the value of royalties paid to similar patent holders. For a stacked genome patent, it might be the payment made to other holders of patents for (say) gene fragments. An unjust enrichment penalty is a maximum penalty. In principle, it could include all profits earned by the firm. There are many complicated incentives embedded in different contexts for applying infringement penalties. For example, under certain circumstances, purposeful infringement can call forth antitrust penalties.[43] Shankerman and Scotchmer have examined the incentive effects inherent in infringement remedies in some detail.[44]

[42] For a review of infringement issues, see Arnold and Ohgeilski-Zei.
[43] Gallini, 140.
[44] Schankerman and Scotchmer.

A third tool is government R&D policy. For example, when Celera announced its intention to sequence the entire genome using an alternative sequencing technology that yielded what would be arguably a less accurate genetic map, the HGP followed suit, adjusting its own timetables and research strategy. At the same time, the HGP maintained its position of daily publication of data. This meant that the HGP chose to accept Celera's challenge to a "sequencing race," but to handicap itself through daily publication of results. Daily publication meant that the HGP did not have access to the Celera data, but Celera did have access to the public program's data, perhaps giving Celera the opportunity to acquire patents it would otherwise have not. However, the policy also left open the argument that Celera could not have completed the map without HGP input, a position that supports continued HGP activity. Had the government chosen to continue its deliberate pace and Celera chosen to move forward, Celera might have had the option to file for patents on the entire gene map, though to do so might also have risked Congressional or Executive Branch response.

It should also be noted that government R&D is not government-owned R&D. Following the Bayh-Dole Act (1980), universities and other Federally funded facilities have had the ability to obtain patents on the intellectual products produced with Federal dollars. Although many university-based discoveries are for research techniques, the ability of universities to apply for patents prior to publishing results creates a mixed set of incentives for universities and sometimes sets the academic faculty at odds with university business administrators.

One additional set of issues on R&D policy center on equity concerns. If the private sector follows a "value of information" R&D strategy, they may simply ignore low-value targets, for which information voids might impose significant burdens on specific populations. Government R&D could fill these gaps.

However, most generally, the amount of information now available on genomic function is miniscule compared to that which will be required to take full advantage of genomic medicine. As noted above, the private sector is rapidly searching for gaps that, once filled, will yield profit opportunities. HGP R&D policy, unlike the private program, is largely driven by the logic of science, in other words, by the consensus of the research community as to opportunities to press forward the boundaries of fundamental knowledge.

The final tool is regulatory policy, which can interact with patent policy and with other policy instruments. The Department of Justice and the Federal Trade Commission determine the legality of various partnering and cooperative arrangements dealing with patents. Examples include patent pools, patent licensing arrangements, and the existence of and remedies for infringement. The Food and Drug Administration tests new drugs and drug therapies, and determines how drugs should be dispensed, i.e., over the counter, by prescription, or otherwise. For example, pharmaceutical firms that hold patent rights typically adopt business strategies to exploit the monopoly position the patents confer. They may seek to acquire brand-name recognition and restrict others from competing, or they may license generics. They may lobby to maintain "prescription status" while they hold patents and "over the counter" status once patents run out. Opportunities for policy to exploit these interactions have not been studied extensively.

5. SUMMARY, CONCLUSIONS, AND PATH FORWARD

The events of May 1998 are symbolic, but they are also quite real. Since that time, the joint publication of the base genome has closed out one era and sent the principal actors down separate, but related, paths. The HGP has begun to refocus on genetic regulatory topics, even while continuing to add to the accuracy and completeness of the base genome. A notable new activity is the Genomes to Life program, begun in 1999 and targeted at continuing the quest for a fundamental, comprehensive, and systematic understanding of life processes. On July 23, 2002, the U.S. Department of Energy announced awards that will total $103 million over the next five years.[45] Celera has revised its business plan, hired new leadership, and moved on to more distinct markets. As recently as June 11, 2002, Celera restructured, eliminating positions in gene sequencing and making way for a greater focus on pharmaceuticals, a move accentuated by its acquisition of Axys Pharmaceuticals. The former Celera President, J. Craig Venter, has also moved on. Recently he announced the organization of three new not-for-profit organizations "to help educate the public and our elected leaders on these important scientific issues and to help drive the applications of genomics into environmental and social policies."[46] On August 15, Venter announced the formation of a new center that would utilize these three organizations to speed up gene sequencing while driving down costs. The non-profit center would open the door for sequencing individuals' DNA to develop treatments based on individual attributes.[47]

At the same time as Celera garnered major public attention, the entire industry has continued to move forward. Virtually every day, additional information relating genomic science to medicine appears in the popular press.

This review has traced the course of genomic research over this relatively brief period, which despite its brevity has seen a number of major shifts:

[45] U.S. Department of Energy, "Energy Department Awards $103 Million for Post Genomic Research," Press Release dated 7/23/02, Genomes to Life web site, doegenomestolife.org/research/index.html#currentawards, accessed August 7, 2002.
[46] The Center for the Advancement of Genomics, News Release, "J. Craig Venter, Ph.D., Announces Formation of Three Not-for-Profit Organizations," available online at www.tcag.org/news.html, dated 7/23/02, accessed August 7, 2002.
[47] Justin Gillis, "Rockville on Venter's Gene Map," *The Washington Post,* August 15, 2002, available online at www.washingtonpost.com/wp-dyn/articles/A19590-2002Aug14.html, accessed August 20, 2002.

- Initial progress in sequencing the base genome was clearly due to the HGP. However, since then, the government's share of the genomic R&D budget has fallen, even while increasing in absolute scope.

- The USPTO has taken steps to increase the utility test for gene fragments, thereby reducing the number of patents that will be issued. This occurred for a variety of reasons, but was likely influenced by the *Science* debate. Despite this, the newest round of challenges to patent policy has not yet surfaced.

- The base genome has been "completed." Fundamental R&D has moved to the study of regulatory pathways that determine gene function and interactions among multiple genes, while applied R&D continues to be focused on the development of pharmaceutical products, as it has for many years.

- Non-traditional business strategies for genomic commerce seem not to have produced significant new profits. That profits will occur, however, is undeniable.

- The anticommons phenomenon seems not yet to have become a forcing factor in handicapping R&D. This may be due to the USPTO's new guidance, or it may be due to the lack of profitable opportunities. It may also be too soon to tell.

- A number of court cases have provided moderate reshaping of patent policy. These will likely increase as profitable genomic medicines emerge, with costly and potentially protracted litigation.

- Federal policy toward genomic research has evolved slowly following the logic of scientific inquiry.

Perhaps the most notable outcome is a negative one. Despite the promise of immense profits that has drawn forth a growing private investment in biomedical R&D, broad-based profits have not yet been realized. This undoubtedly will change, and when it does there will

likely be continuing challenges to intellectual property rights policy. One particular challenge will likely take the form of increased litigation. Lerner has estimated that the ultimate cost of patent litigation begun in 1991 will equal 27 percent of the total expenditures on basic research by firms in that year.[48] While a firmly entrenched part of the system, such costs reduce resources available for R&D.

To prepare for these challenges, it is desirable to bring data to bear on the various issues of economic policy described above. However, as has been stressed throughout this review, there are relatively few data describing firm behavior available for this purpose. This concern is general and affects much of the field of law and economics.

For this reason, it is desirable to state the issues of concern with some rigor and then seek out alternative means of testing the relationships between their logical implications and actual behavior.

To carry out the first activity, we are preparing a conceptual paper that develops the theory necessary for more rigorous analysis. This paper draws heavily on the work by Buchanan, Heller and Eisenberg, and the general body of literature broadly described as industrial organization and regulation.

After the completion of this coming paper, we will conduct a series of data gathering exercises to consider the predictive validity of these logical propositions. A principal data gathering activity will entail the use of laboratory experimental economics. This approach makes the theory operational by supplying behavioral mechanisms and subjecting these mechanisms to tests. This is typically done by using human subjects in controlled situations who are subjected to choice situations in which they earn dollar rewards based on the quality of their choices. The approach can provide a cost-effective means for gathering data on theoretical validity, though it stops short of providing a real-world test.

Real world tests, however, are certain to follow. The initial test focused on the ability of the science to provide the base genome. Meeting this trial created a new, but unsettled, relationship between the public and private research communities. Closely related was the harbinger of gene fragment patenting, a test that was met by modification to USPTO policies. How gene patenting ultimately promotes social welfare remains to be seen, in part because the organization of the biotechnology industry is far from settled. As this industry develops it

[48] Joshua Lerner, "Patenting in the Shadow of Competitors," *Journal of Law and Economics* 38, no. 2 (1995).

will be driven by R&D technology and patent policy, but most importantly by the demands for biomedical products. The ability of this industry to focus its resources on new technical and production challenges, and away from excessive payments to the intellectual property investments of the past and from excessive payments to litigation will soon be tested. To the extent the industry can achieve this focus, medical treatments will be more rapidly directed, both to market signals and to social needs.

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