

Economic Implications of Intellectual Property Rights and the Human Genome Research Program

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I. Introduction

The human genome program is first and foremost a program of research, but it is also a force that can lead to phenomenal improvements in quality of life through advanced medical practices. As such, it also holds the potential for vast economic gain for those who can successfully bring these practices to market. Over the recent past, fundamental changes in gene sequencing technologies have opened up new market opportunities and have sent ripple effects throughout the entire research activity. What was once a knowledge-driven program of fundamental enquiry whose participants consisted largely of publicly funded universities and laboratories is rapidly becoming, a market-driven activity wherein new relationships between private profit-oriented firms, traditional science-oriented research institutions, and governmental agencies are being forged. Within this triumvirate, government plays two distinct roles: it chooses target areas for its research dollars, and it establishes intellectual assets, through the patent process. For it to make wise choices in each of these roles, it must take into account the increasing influence of the market place.

This paper reviews our ongoing research into intellectual property rights issues concerning the human genome. For the first phase of our work, we have addressed issues that were extant in May of 1998, a time we argue below is symbolically a watershed for the growing forces that increasingly influence the human genome program and the larger field of biotechnology. Our new work will extend our enquiry into the directions the program has been impelled by these forces over the past two years.

Thus far, we have studied how two influences affect the efficiency of what we have modeled as a very simplified biotechnology market.¹ One influence is the potential that large numbers of patents will be issued for reference gene fragments and reference genes. Similar issues have arisen in the past in markets for intellectual property rights, such as in the music industry, where sampling methods have been developed to determine how frequently individual songs are played on radio so that royalties can be assessed. The question is whether new institutions will arise to facilitate the exchange of genetic assets. The second influence is the potential for bottlenecks to develop as patent holders discover that rights to individual fragments of genes can command premium prices if they can block the use of the gene in treatments or pharmaceuticals with large potential profits. An analogy to this is the landowner that blocks a larger development by holding out for financial gain or personal reasons. Analogies, however, can describe, but not resolve, issues in markets for genomic products. To help resolve whether or not existing institutions will lead to efficient deployment of genomic innovations, we have developed a first-stage model of the industry and have used the method of experimental economics to capture the behavioral properties of these two issues individually and in combination.

¹ Funding for this activity was awarded in January 1999, with low level activities starting in April 1999. Work with the University of Tennessee began in earnest in September 1999.

Our next phase of work will expand our initial model into a more sophisticated version that we describe below. This model will take into account the completion of the base genome and the importance of genomic research turning to questions of (1) gene function, (2) individual variability from the reference genome and (3) medical treatments. Using this model, we will examine the industry structure that emerges so that we can define market efficiency more meaningfully, understand the implications of alternative private business strategies, and describe attributes of the new partnership that is being formed. With this information we will describe the implications for market efficiency of the choices open to government in establishing intellectual assets and redirecting research.

II. Background

Two events in May 1998 have played pivotal roles in influencing the current state of the human genome research program. The first, a series of articles in *Science* articulated the issues facing the patent office in determining the conditions under which patents would be granted for gene sequences and related information.² One article, by Michael A. Heller and Rebecca S. Eisenberg posited a “tragedy of the anticommons” in biological research. In the traditional tragedy of the commons, an insufficient assignment of property rights creates an incentive structure that leads users to overutilize the common resource. Hence, overgrazing of common meadows occurs. In the anticommons, overassignment of property rights leads to an underutilization of some privately held resource. This analogy is employed to explain why a proliferation of patent rights for anonymous gene fragments may constrain the deployment of this publicly supported research by driving up the costs of transacting trade in intellectual assets. At the time this article was published, the patent office had already issued one patent for a human gene to Incyte which was coterminous with an EST (expressed sequence tag), a process that opened the way to patent additional ESTs for which Incyte had thousands of patent applications. Moreover Incyte announced a business policy of licensing proprietary data bases protected by patents to downstream users. Other firms were seeking to employ similar strategies.

Heller and Eisenberg posited several reasons why underutilization may occur. One was the potential ability for bottlenecks to occur over patents for gene fragments. Another was the transactions costs of assembling patent rights, another was the heterogeneous nature of the institutional players who have diverse incentives, and yet another was the cognitive biases by individual players who may overvalue the worth of their individual intellectual assets. Other papers in this issue by John Doll of the patent office and by other patent attorneys of diverse views led to the conclusion that the government’s choices in establishing intellectual property assets might well significantly affect the efficiency of the process. But there was little evidence on which to predict the causal relationships between choices and outcomes.

² *Science*, vol. 280, May 1, 1998. We have summarized these articles and applicable patent law in detail in our previous proposal entitled, *An Economic Analysis of Intellectual Property Rights Concerning the Human Genome Program*, 9-16-98.

The second event of significance during May of 1998 was the formation of Celera Genomics as a tracking stock of PE Corporation. PE had developed a technology for gene sequencing that promised to increase by orders of magnitude the speed with which the genome could be identified. Whereas there was a clear market for this technology, PE reasoned that by offering first delivery to a partner, it could increase its advantage. It thus formed Celera and, in essence, challenged the government-sponsored research program to a race to establish a reference genome. Prior to this time the government-sponsored program moved at a relatively slow pace producing high quality data, literally one base pair at a time. A rough target date of the year 2005 was set for completion. Celera ultimately declared it could complete a sequence by Spring 2000 and is roughly on track to do so, having completed the sequencing of *Drosophila* (in partnership with Berkeley) along the way. The central question is “When will spring arrive this year?” Moreover, Celera announced a surprising business plan – to make the base sequencing data it developed freely available to other users.

The impact of the forces underlying these two events has been substantial. The U.S. Patent and Trademark office has now issued patents for a wide variety of intellectual assets related to biotechnology and is developing and distributing extensive guidance as to how additional patents will be issued. Incyte apparently has obtained patents for 350 genes and has more than 60,000 patents of various sorts in application. Its website advertises a database of some 3.9 million ESTs and 25,000 “full length” gene sequences.

It is not meaningful to declare winners or losers in this race at this point in time, and, indeed, it would require a large team to merely keep track of the claims by individual companies as to specific accomplishments. However, these activities have clear relevance for patent policy and research policy. For example, at least partly in response to Celera, the government-sponsored sequencing program has rethought its research strategy and has adopted more rapid (and less “accurate”) sequencing strategies to establish the working draft. At this writing, the website of the human genome program states that 64.1 percent of the 5 billion base pair sequence is complete, that a working draft will be 90 percent completed by Summer 2000, and that a complete, high quality draft will be complete by 2003. By that time, the government-sponsored program will have shifted to downstream topics, but immense amounts of work will remain.

III. A working model

The purpose of a behavioral model is to isolate key relationships while relieving the analysis of extraneous information that complicates the study without adding additional insights. This also allows us to examine specific types of behavior while recognizing, but not involving, additional relevant relationships in the analysis at hand.

The model we posit divides the “market” for genomic intellectual assets into four stages, plus the final demand sectors. The first stage is the development of the base genome. The second is the identification of the functional attributes of specific portions of the genome. For simplicity we refer to this as gene function. The third stage of the market is the

identification of individual variability from the base genome, which coupled with gene function, identifies potential genomic dysfunction. The fourth stage is the development of treatments to correct genomic dysfunction.

This market, like all markets, is driven by final demands. Final demands are the demands for the products that ultimately improve people's lives, or more generally, which people are said to have preferences over that represent their willingness to pay for the products. By analogy, individuals value transportation services, but purchase gasoline to obtain these services. The demand for gasoline is said to be derived for the demand for transportation services, or simply to be a derived demand. Technical options and choices can significantly influence derived demands without affecting the benefits enjoyed by individuals. Thus, while it may be of great technical importance whether a car uses gasoline or electricity, the consumer is largely indifferent if the vehicles deliver the same transportation services. This same principle applies to the human genome project. The demand for intellectual assets permitting access to specific base gene information is derived from "downstream" demands for gene function. These are in turn driven by need to understand individual variability and to develop genomic treatments. Consumers of these treatments are indifferent to upstream activities for their own sake, but are concerned over how they influence the quantity and price at which services are supplied.

There are two decision-makers in our model: (1) the private sector agents who make choices in response to final demands, or more precisely, in response to the net revenues (profits) that accrue from meeting final demands, and (2) the government which makes choices in response to social well-being. In general, social well-being can contain many elements, including issues of privacy, distribution, discrimination, and the like. For the present purpose, we focus on the narrower concept of economic efficiency. Economic efficiency is defined as the minimization of resource costs in meeting final demands, where final demands are defined as the total willingness to pay by consumers to obtain genomic goods and services. The difference between final demand and costs of production are referred to alternatively as net revenues, profits, or economics rents. Stated differently, the pursuit of economic efficiency is the pursuit of the largest possible level of economic rents. Rents can accrue at each of the four market stages, or to consumers. For example, if a holder of a valuable gene patent can gain market power he or she can obtain a larger portion of the economic rent that will ultimately accrue from meeting final demands.

Genomic products ultimately arise because government and agents invest in R&D in one or more of the four stages. However, because there are multiple players in this market, discoveries and therefore the rights to intellectual assets will typically not accrue to the specific agents that will ultimately market products to final demand. Thus, there must be a mechanism for exchanging intellectual assets. We refer to this mechanism as a market institution, and there could, in principle, be a number of candidate institutions for this purpose. Institutions of this sort provide information and incentives to participants. The information is generally some reflection of the value that various participants place on different assets and is reflected in prices. The incentive is the ability to collect rents (profits). Hence, individuals have incentives to misrepresent their true, privately held

values. A number of variables, including the institutions that determine market structure determine the degree to which it is profitable to adopt different business strategies. We define public information as that shared by all market participants, like the licensing fee for a publicly offered asset and private information which is known to a smaller number of participants, perhaps only an individual agent. Treatment of information is key to our model, as it is in the real world.

The various players adopt strategies in pursuit of their goals. As was noted, government invests in R&D, establishes rules to define intellectual property rights, and determines the disposition of the property rights to which it holds title. The private agents make decisions to invest in R&D or to buy or sell intellectual assets. By creating assemblages of property rights they are able to market products to final demanders. For simplicity, we focus only on the accumulation of these rights and neglect other production activities. The decision to invest in R&D can be complicated by the addition of new technologies, as was done by the development of “shotgunning” methodologies. Business strategies guide decisions as to which phases of the market to focus R&D, the method of R&D and the pricing strategy of assets that are owned. As noted, Incyte has a strategy of licensing assets, whereas Celera has priced its assets in phase 1 at zero, presumably because it intends to capture rents in downstream phases. Note that Celera’s strategy need not be construed as altruistic, because it in no way diminishes the total available rents, provided other firms cannot capitalize on Celera’s discoveries. Accordingly, Celera has taken steps to prevent them from doing so.

In general, final demand is characterized by demand functions that exhibit a number of consistent policies. For our initial work, we take final demands as fixed.

We can now summarize these relationships symbolically. Let G be government, and A be the private agents. I is investment in R&D such that investment can take place in any or all of the four phases and can be one or more technologies which are unique to each phase. Thus both government and the agents can choose one or more combinations of I_{ij} where i indexes one of the four phases and j indexes technologies specific to each phase. The result of successful I generates a specific intellectual asset which we designate R_{ik} where i again indexes the phase and k indexes the asset. We define “asset” as a primitive concept determined by the patenting process. The relationship between I and R is functional and can be generally thought of as a random draw. In other words an R&D investment may or may not be successful. At any point in time G and A can be thought of as endowed with assets and other resources which we summarize as money (M). Let F_l be final demands, where l indexes the set of genomic goods and services.

Exchange of assets takes place through a market institution where individual assets are exchanged at some price, PR_{ik} . Exchange takes place in terms of specific assets that are unique. This contrasts with a typical market, such as the market for agricultural products where variable quantities of identical products are bought and sold. This specific type of market is called a matching market, the properties of which have been explored

elsewhere.³ Development of this market takes place over time as assets accumulate and exchange occurs. We divide this market into rounds at which decision points occur.

Thus, at any point in time, the governments and the agents find themselves with a set of endowments consisting of some combination of assets and money. They also possess a well-specified business strategy, and face an institutional setting composed of a set of patent rules that define the assets and a set of institutional rules that define the market. The business strategy of some agents will be to meet final demands, and in doing so to claim the value of that market demand which we treat as a fixed sum. Other firms will seek to discover new information, patent that information, and sell or license rights to it to agents focusing on downstream activities.

The available information in the market is designated as public or private. Depending on market structure virtually any information can be private or public. For example, firms can announce the intellectual assets they hold, or keep the information private. They can announce the prices at which sales occur or keep it private. Government typically announces its activities thereby making its activities public.

We can study this market in a number of ways. For example, we can examine the strategies of individual agents using game theory, or we can analyze the properties of market equilibrium at different rounds. Ultimately however, we wish to employ the methodology of experimental economics for this purpose. We thus turn to a brief report of our initial experiments with this model, before outlining our plan that will govern the next phases of research.

IV. Data gathering progress

Data gathering for this analysis takes three forms: (1) examining the literature, and the human genome “industry,” (2) exploring the logical properties of the model, and (3) carrying out economic “experiments” based on the model. We report here on current experimental activities.

Experimental economics studies the attributes of mechanisms of exchange to determine how the information and the incentives provided by the mechanisms affect human behavior. Mechanisms can be full-blown markets, auction mechanisms, or “games” played by a single individual against “nature.” Criteria used to judge outcomes include economic efficiency, individual profits, or the division of profits among players. In the past, this approach has been used to test the predictions of economic theory, to examine institutional properties of exchange not dealt with by the theory (like number of players required to reach equilibrium), and to help design improved institutional mechanisms (like the pollution permit trading mechanism used by EPA). The key element of an experiment is the ability to isolate specific influences on behavior so that the properties of a control element that is varied can be studied. For this reason, “context” such as the nature of the goods being bought and sold is removed and experimental subjects trade generic “units.”

³ Cite literature

For example, a double-oral auction is a mechanism of exchange in which buyers and sellers make bids (to buy) and offers (to sell) following instructions that induce incentives. A buyer may be instructed that a unit is worth \$5.00 and a seller that a unit cost \$3.00 to manufacture. For this unit and for these two agents, potential rent is \$2.00, and can be divided between the two agent in a number of ways. A number of buyers and sellers similarly induced following a set of rules of exchange constitutes a market. The efficiency can be calculated as percent of total potential profits claimed. One form of this classic experiment might vary the number of players to measure the impact on efficiency. For example, a single seller playing against a number of buyers can potentially monopolize the market and claim the bulk of the rent. Two players, a duopoly, who collude will attempt to behave as a monopolist. Without collusion, they may attempt other behavior to achieve the same results, such as establishing a price leader. By convention, players in economic experiments receive actual cash payoffs based on their performance. Federal human subjects protocols are followed.

Our initial experiments were intended to illustrate the types of institutions and market structure embodied in the human genome industry, as described by our model, but not to engage in rigorous hypothesis testing. Details are provided in Appendix A. For our first set of experiments we designed a market that combined the combinatorial properties of the genome patent process with fixed payoffs and allowed the agents to trade assets over a period of rounds. Twenty assets were defined, and a payoff vector for accumulating sixteen specific combinations of the twenty was developed. Each combination could be claimed once and received a specific, unique payoff. The assets corresponded analytically to patents and the combinations to collections of patents required to bring a product to market. Three experiments, each consisting of six rounds, were conducted.

Experiments followed the following format. Subjects entered a classroom setting, received and signed a standard release form, and were given an information packet (material are found in Appendix A). Four subjects took part in each experiment. Units were referred to as “parts” which could be public or private. Public parts were awarded at the start of each round, corresponding to the open access public research program. All players could use these in forming combinations. Private parts accrued to each player each round. At the end of each round, players could claim payoffs for combinations, or could make offers to buy or sell individual parts. At the end of each round payoffs were made, and each player updated his or her inventory of owned or licensed parts. Efficiency was calculated as the number combinations claimed.

For the first experiment, all private inventories were held as private information, which meant that the players did not know which parts were available in any given round. After six rounds seven of the sixteen combinations were claimed. In the second set of experiments privately held information was identified as being available or unavailable. In this experiment, five of the sixteen combinations were claimed. In the third experiment the same rules were applied, but part nineteen, a key part in claiming combinations was made publicly available in the second round. Nine of the sixteen combinations were claimed. Following each of the experiments, players were allowed a final round that was not

previously announced. In this round players were permitted to bargain bilaterally over parts and were allowed to form partnerships with profit sharing rules. Two of the three bargaining sessions led to all sixteen combinations being claimed.

V. Tentative Conclusions

Whereas we did not intend these experiments as theory-testing exercises, we have formed a number of tentative hypotheses. First, we believe that the extent of the set of payoffs will ultimately prove important in fostering competition because individuals who attempt to claim excessive portions of rent by charging excessive prices will find buyers turning to other markets. What this means is that the combinatorial properties of genomic sequences may prove to be less valuable than was originally thought. Second, we believe that the specific mechanism (s) that emerge for exchanging intellectual property rights will be important, especially as numbers of patents increase. The simple mechanism we used in these experiments proved inadequate to achieve efficient results. One candidate for simplifying the market structure without losing rents is to patent base genome information and make it public without licensing fees -- the Celera strategy. This simplifies the market structure by reducing transactions cost without sacrificing rents, and can potentially overcome patenting policies that create large numbers of intellectual assets for the base genome. This policy is not markedly different from Incyte who is collecting licensing fees that appear more closely related to data base management fees than true royalties.

In sum, our early studies show little support for the anticommons thesis. We will address this and other issues further in the months to come.