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GENOMIC PATENTS AND PRODUCT DEVELOPMENT INCENTIVES

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Patents on human genetic information have been controversial among different groups for different reasons. The purpose of a patent system is to motivate the commercial development of new technologies; it is thus unsurprising that those who have fundamental misgivings about commercial biotechnology would oppose gene patents. More intriguing is the controversy over gene patenting among those who welcome the commercial development of biotechnology products by private firms. While many proponents of commercial biotechnology assert that gene patents are essential to motivate product development, some have expressed more nuanced views, endorsing patents under some circumstances and condemning them as unnecessary or even counterproductive in others.

The most striking example of this ambivalence has been the opposition -- some of it from industry trade groups and entrepreneurs -- to patent filings on cDNA fragments (expressed sequence tags or ESTs). Perhaps it was this outspoken opposition, from sources beyond the usual suspects, that provoked the U.S. Patent and Trademark Office (PTO) to take the extraordinary measure of calling for public comments on the question of "[whether] the patenting of human genome fragments [would] inhibit rather than promote advancement of the biotechnology arts[, and] if so, why?"[1] The PTO promptly repented of its unwonted foray into open-ended questions of public policy and cancelled the request for comments within two weeks,[2] it subsequently issued a revised request for comments that was more narrowly focused on the administrative burden and costs associated with examining applications containing large numbers of sequences or excessively long sequences, with no mention of broader policy questions.[3] Yet the question the PTO originally posed remains important and unanswered.

More recently, as human genomic sequencing gets underway, the National Center for Human Genome Research (NCHGR) has taken the unusual step of discouraging grantees from patenting "large blocks of human primary DNA sequence", advising that it considers "raw human genomic DNA sequence, in the absence of additional demonstrated biological information ... inappropriate material for patent filing" and that patent applications on such sequences "could have a chilling effect on the development of future inventions of useful products." While acknowledging that the Bayh-Dole Act

gives grantees the right to elect to retain title to inventions made with federal funds and to apply for patents, NCHGR has admonished its grantees that it "will monitor grantee activity in this area" and that it may consider making a determination of "exceptional circumstance" (required under the Bayh-Dole Act before an agency may restrict the right of grantees to retain patent rights to discoveries) in the future if necessary "to ensure that sequence generated by these grants is maximally useful to the research and commercial sectors."

Given that pharmaceutical and biotechnology firms are big users of the patent system, it may seem surprising that they do not join together in an equivocal endorsement of gene patents. What can we make of this debate? Are gene patents good for business or bad for business? More specifically, how will the existence or absence of patents on human DNA sequences affect the incentives of private firms to develop commercial products that emerge from knowledge of such sequences?

The answer to this question is likely to vary depending on the type of product at issue and the type of firm whose incentives are under consideration. Most firms involved in the development of biotechnology products are both consumers of technology developed by others and producers of technology embodied in products and processes that they hope to sell to their own customers. Firms are more likely to view patent rights as essential to their incentives when they cover the technology they sell to their own customers than when they cover technology that they need to acquire from others.

This is entirely unsurprising given the function of patents. A patent confers a monopoly in a new invention for a limited term, allowing sellers of products embodying new technologies to charge higher prices by excluding competitors from the market. This is how patents motivate firms to invest in R&D, an investment that might be unprofitable if free riders were permitted to enter the market for new technologies that prove successful without having shared in the initial cost and risk. But what makes patents attractive to firms is the prospect of *charging* monopoly prices - not the prospect of *paying* them. When R&D is conceived not as a single-firm enterprise culminating in the creation of a patented end product for sale to consumers, but rather as a more complex stream of successive innovations, in which firms use the discoveries of others in the course of making their own discoveries, it is easy to see how firms might disagree about the impact of patents at different points in the stream on their own R&D incentives. Thus firms welcome the patents that allow them to charge higher prices, while cursing the patents that require them to pay higher prices. At any given point in the stream, downstream patents motivate R&D, while upstream patents make it more costly.

Patents on DNA sequences are thus likely to have different impacts on firms that occupy different market niches in the biotechnology industry. Firms that specialize in identifying novel DNA sequences are likely to be motivated by patents on such sequences, while firms that use DNA sequences

in their research as targets for drug discovery are more likely to be indifferent or hostile to such patents. Thus a firm like Merck, that makes its money primarily from the sale of small molecule drugs, is willing to dedicate new DNA sequences to the public domain, while DNA-sequencing firms like Human Genome Sciences and Incyte hold them as proprietary resources. One firm's research tool is another firm's end product.

A complicating factor that changes the alignment of incentives somewhat in the case of DNA sequences is government sponsorship of the Human Genome Project. Governments presumably do not require patents to motivate them to sponsor research in the public interest; one might therefore expect that publicly-funded contributions to the stream of innovation could safely be dedicated to the public domain to reduce the costs to firms of downstream R&D. The prevailing wisdom is otherwise: since passage of the Bayh-Dole Act[4] and the Stevenson-Wydler Act[5] in the U.S. in 1980, recipients of government research funds have generally been encouraged to patent their inventions in order to promote their development as commercial products. By discouraging its grantees from patenting raw genomic sequence data, for the avowed purpose of averting "a chilling effect on the development of future inventions of useful products", NCHGR is challenging the validity in this particular setting of the ordinary presumption in favour of patents as a mechanism for promoting product development. For better or worse, a likely consequence of this move is that a considerable amount of DNA sequence data will enter the public domain through the Human Genome Project.

Is this good or bad? In the absence of patents on DNA sequences, are we likely to lose out on the development of new products? Or can firms be expected to welcome free access to DNA sequences generated with government funds as a subsidy for their own research? There is no simple, obvious answer to this question, but we can engage in a bit of cautious speculation. In all likelihood the bottom line will be uneven, favouring incentives to develop some types of products, while diminishing incentives to develop others.

Most likely to suffer from the absence of patents on DNA sequences are therapeutic products that are closely related to the sequences (such as therapeutic proteins that the sequences encode). Such products require costly clinical testing before they may be brought to market, and firms have rarely been willing to make such an investment in an unpatented product. A patent on a DNA sequence encoding a therapeutic protein (which would typically include claims to any recombinant vector or host cell incorporating the sequence) allows the patent holder to exclude competitors from making the encoded protein by recombinant means. In some case, process patents on methods of using proteins for particular therapeutic purposes may be adequate to ensure market exclusivity, but process patents are generally considered less advantageous than product patents (and therefore provide less motivation to invest in clinical testing). One problem with relying on therapeutic process claims to protect a pharmaceutical product is that such a

patent does not prevent competitors from making and selling the unpatented product for other purposes, and thereby bringing down the price of the product. In theory the owner of the process patent could still enjoin the particular use of the product described in the patent claims, but it is impractical to monitor what individual consumers are doing with a product that is available from multiple sources for multiple uses. A patent on the DNA sequence encoding the protein provides a direct remedy against any competing firm that uses the sequence to manufacture the protein and thus is a much more effective means of securing market exclusivity even after new uses are found for the product.

As a general rule, incentives to develop diagnostic applications of DNA sequences are likely to be less sensitive to the absence of patents on the sequences themselves than incentives to develop therapeutic proteins. For one thing, diagnostic products are less extensively regulated, and therefore considerably cheaper to bring to market, than therapeutic products, reducing the need for exclusive rights to recoup development costs. Second, process patent claims may offer more effective commercial protection for diagnostics than for therapeutics. While therapeutic products are widely distributed to individual consumers whose activities are difficult to monitor, DNA diagnostic services are typically supplied by a more limited number of laboratories that a patent holder can more readily keep an eye on. Diagnostic laboratories might be able to infringe a process patent surreptitiously, but so might they infringe a product patent on a DNA sequence used in a diagnostic test. Thus in contrast to the therapeutic setting, in the diagnostic setting product patents do not clearly offer a more efficacious remedy than process patents. Moreover, a DNA diagnostic product may be less likely than a therapeutic protein to have multiple uses that would leave the patent holder vulnerable to competition from other suppliers.

Nonetheless, some DNA diagnostic products may be quite costly to develop, and the absence of patent rights on DNA sequences may undermine incentives to develop such products. For example, developing tests for genetic susceptibility to certain diseases may require identification of numerous mutations, particularly in the case of complex polygenic disorders. Moreover, the use of such tests has been controversial, and it is entirely possible that ethical concerns raised by genetic susceptibility testing may ultimately lead to further regulatory measures that increase the risks and costs associated with commercial development of such products. Patents on DNA sequences may help motivate firms to develop diagnostic products in the face of these risks and costs.

Least likely to suffer from the absence of patents on a DNA sequence are incentives to develop products that are only indirectly related to the DNA sequence (such as a small molecule drug for which the DNA sequence, or the peptide it encodes, is a target). Such products are far enough downstream from the identification of the DNA sequence itself that a patent on the DNA sequence is unlikely to provide innovating firms with a source of exclusive

rights in the products they ultimately bring to market, yet DNA sequence patents could impose royalty obligations on innovating firms that make R&D more costly. More important to the profit expectations of the firms that bring these products to market is the prospect of obtaining patents on their own end products the small molecules that they hope to sell to consumers.

The impact on product development incentives of placing DNA sequences in the public domain thus depends in part on what type of product is at issue, and whether other patent rights are likely to preserve for an innovating firm an exclusive position in the market for that product. In addition, the presence or absence of patents on DNA sequences may be more or less significant to different types of firms.

Both established pharmaceutical firms and younger biotechnology firms are likely to be sensitive to patent incentives, but their interests in the patent system are not exactly the same. Young biotechnology firms typically have a problem that established pharmaceutical firms don't need to worry about: if they are not yet earning significant revenues by selling products to consumers, they need to raise funds from other sources to keep their research operations moving forward. For these firms, a patent portfolio may be critical at an early stage in their R&D efforts in order to attract financing from investors or research partners; otherwise they will lack the resources to continue the effort, and they will never have any products to sell. But the discoveries available for patenting at this early stage may be far upstream from a final product.

Established pharmaceutical firms are also very sensitive to intellectual property rights, but for different reasons, and at a different stage in the R&D process. Pharmaceutical firms typically have no need to go to the capital markets to fund their research; they are already selling products and can fund their next generation of research projects out of profits on existing products. They are therefore less likely than cash-poor biotechnology firms to require patent rights on early stage research discoveries that are far-removed from the marketplace, so long as they anticipate a strong enough patent position further downstream to ensure them of an effective commercial monopoly in the products they sell to consumers at the end of the day.

Thus although both big pharmas and smaller biotech firms want patent rights in the products they sell to their consumers, biotech firms are more likely to require patents on discoveries made further upstream in the R&D process as well in order to attract research funding. For this reason, the absence of patent rights on DNA sequences may undermine the incentives of smaller, younger firms to develop products that would still be attractive to larger, more established firms. The presence or absence of patents on DNA sequences may thus determine not only what type of product is profitable to develop, but also what type of firm is able to summon the resources for product development.

Endnotes and References

1 U.S. Dep't of Comm., Pat. & Trademark Off., Notice of Hearings and Request for Comments on Issues Relating to Patent Protection for Nucleic Acid Sequences (Nov. 8, 1995), 60 Fed. Reg. 57223 (Nov. 14, 1995).

2 60 Fed. Reg. 58601 (Nov. 28, 1995).

3 U.S. Dep't. of Comm., Pat. & Trademark Off., Notice of Hearings and Request for Comments on Issues Relating to Patent Protection for Nucleic Acid Sequences (Mar. 6 1996), 61 Fed. Reg. 9980 (NIar. 12 1996).

4 Pub. L. No. 96-517, 94 Stat. 3014 (1980) (codified as amended at 35 U.S.C. §§ 200-11, 301-07 (1994).

5 Stevenson-Wydler Technology Innovation Act of 1980, Pub. L. No. 96-480, 94 Stat. 2311 (1980) (codified as amended at 15 U.S.C. § 3701 et seq. (1994).