COMMENTARY

Genome Patents: A Case Study in Patenting Research Tools

Over the course of the last decade, the subject of patenting the human genome has engendered considerable controversy. In reviewing this controversy, it is important to differentiate two sets of objections. Some objections are genome-specific. Addressing these objections would presumably require some sort of sui generis regime for genome-related patenting. Other objections are more general. These objections focus on the costs associated with patenting "research tools"—in other words, invention that is, at least in part, the foundation for further invention. Objections to patenting research tools would suggest reform that is not genome-specific. The essays in this issue of *Academic Medicine* make both sets of arguments. This commentary examines aspects of the articles by Goldstein and Golod, Murashige, Barton, and Scherer. I begin the commentary by arguing that patent reform should address only broader concerns associated with patenting research tools. Concerns that appear specific to genomic patents either misunderstand the nature of these patents or are, in reality, part of the broader problem associated with patenting research tools.

All of the contributors to this special issue of *Academic Medicine* address the broader problem of research tool patenting. Determining how the patent system should address research tools is, however, a more complicated question than some acknowledge. Not all research tools serve the same function. While certain research tools represent fundamental research platforms that open up new and uncharted areas of investigation, others are narrower in scope and can even be marketed as end-products to ordinary consumers. The weight of economic analysis suggests that broad patents on fundamental research platforms impose costs that may outweigh the usual benefits of stimulating invention and development. This commentary offers some suggestions on how doctrines relating to patent scope could be used to restrict the private appropriation of fundamental research platforms while nonetheless allowing appropriation of more downstream research tools. In terms of institutional response, we need to look beyond the confines of the patent statute, however. In this regard, the commentary highlights the recent public-domain-enhancing actions taken by the National Institutes of Health (NIH), acting in conjunction with various grantee universities.

Objections Specific to Genome Patents

Lay commentators often object to genome patents (whether patents on full genes, gene fragments, or single-base DNA mutations known as single nucleotide polymorphisms, or SNPs) on the grounds that these patents represent an assertion of property rights on "life." The contributors to this volume do not make this mistake. To the contrary, as Goldstein and Golod emphasize, what researchers seek to patent is not the genome (or parts thereof) operating in its natural state but, rather, a particular gene sequence that has been isolated, divested of "junk" elements, and sequenced through human intervention. Goldstein and Golod also discuss at length the case law under which isolated and purified versions of what exists in impure form in nature have long been considered patentable subject matter.[1]

To the extent some contributors to this volume suggest sui generis treatment of genome patents, it is primarily in the context of diagnostic tests that rely on patented DNA sequences. For example, John Barton suggests that non-commercial medical researchers might be exempt from liability for the use of diagnostic tests that rely on patented DNA sequences.[2] Similarly, a bill recently introduced by Congresswoman Lynn Rivers (D.-Mich.) would exempt purveyors of diagnostic testing services from patent infringement liability. Barton's argument is bolstered by recent empirical studies indicating that a number of research laboratories have stopped performing diagnostic tests because they cannot afford the supra-competitive prices charged by gene patent holders.[3]

From an economic standpoint, the case for a non-commercial research exemption runs as follows: because non-commercial researchers would not be able to pay supra-competitive prices in any event, little in the way of profit (and hence innovation incentives) is lost if we allow free access to these researchers. Alternatively, to put the same point another way, if patent holders can not successfully price discriminate with respect to non-commercial researchers —that is, charge such researchers a price that does not exceed their ability to pay—the law should impose price

discrimination in the form of a research exemption. Whether we can craft a research exemption that achieves price discrimination in this manner is an open question, however.[4] The key problem with any research exemption is that, given the commingling of research and commercial activity even in nonprofit institutions such as universities, delineating the activities to which the exemption should apply is likely to prove very difficult. Indeed, the diagnostic testing situation is a case in point. Although such testing is important for further research, it is also an end product that laboratories market to paying patients.

For present purposes, it suffices to say that if we are going to have a research exemption to reduce deadweight loss, that exemption should apply to all research.[5] Introducing amendments to the patent statute that seek to address only one small aspect of a much more general problem may masquerade as reform, but it leaves the larger problem untouched. Indeed, to the extent that broader reform gets ignored in favor of special exemptions for particular groups that lobby hard on behalf of their constituencies, needlessly specific reform may be worse than no reform at all.

General Objections to Patenting Research Tools

The more general concern about patenting research tools is an underlying theme in all of the essays. Murashige puts it well when she notes the patent system does not "work quite so well when it comes to protection for products that are useful as 'research tools' rather than end consumer products."[6] Like all patenting, the patenting of research tools encourages supra-competitive pricing and deadweight loss.[7] Patenting research tools has deleterious consequences that extend well beyond deadweight loss, however. The most important research tools are fundamental research platforms that open up new and uncharted areas of investigation. These platforms can most fruitfully be developed by a variety of follow-on researchers. As Scherer points out, a single patent holder is unlikely to see the myriad directions in which a broadly enabling research platform could be developed.[8] Proponents of patenting research platforms sometimes argue that the patent holder will be inclined to license follow-on researchers who will then develop the platform in different directions. Even if a follow-on researcher can afford to pay a supra-competitive price for a particular platform, however, coming to agreement on license terms may be very costly. Historical research conducted by Robert Merges and Richard Nelson demonstrates that, in many important industries, including the automobile, aircraft, and radio industries, costs associated with concluding licensing agreements (known in the economics literature as "transaction costs") prevented research platforms from being licensed and developed further.[9] This empirical evidence also indicates that transaction cost difficulties are likely to pose a particular problem where patents on the research platform are broad and/or where there are a number of different patents on the relevant platform.

It is important to emphasize, however, that not all research tools represent research platforms.[10] For example, genetic sequences that are used in diagnostic testing for a particular disease may be relevant to future research but they hardly open up an entirely new field of investigation. By way of contrast, the Cohen–Boyer research on recombinant DNA was a quintessential research platform: the Cohen–Boyer techniques could be (and were) developed in many different directions by many different investigators. The clearest contemporary example of a research platform is probably human embryonic stem cell lines.

Rather than rejecting patents on all research tools, we should attempt more narrowly calibrated steps that focus on broadly enabling research platforms. Careful calibration is particularly important because, as Scherer points out,[11] the biotechnology and pharmaceutical industries appear to be uniquely dependent on patents. These include patents not simply on end products but also on more upstream research. The latter set of patents plays an important role in attracting capital for further development and commercialization.[12] For example, a patent on a gene linked to a particular disease (and perhaps on the use of the sequence for diagnostic purposes) may help to attract the funding necessary for the eventual development of a therapeutic.

Distinguishing broad research platforms from more downstream research is difficult, however. For example, it is not clear whether genes encoding receptors or enzymes that may be useful as drug targets should be considered research platforms. The case of the Human Genome Sciences' patent on the gene that codes for the HIV receptor illustrates the difficulty of the analysis. Once this gene had clearly been identified as the HIV-receptor gene, the gene probably did not represent a broad research platform. When a gene has been fully characterized, it's difficult to say that the research in that area is really inchoate or uncharted. On the other hand, at the time that HGS isolated the gene, much less was known about it. At that point, the gene plausibly could have been thought of as a research platform. The argument for thinking as targets as broad research platforms is bolstered by the fact that some targets may play roles in different disease pathways. Identifying a target's role in one disease pathway should not necessarily give the patent owner plenary rights over all uses of the target.[13]

Clearly there is no bright-line distinction between inventions that represent broad research platforms and those that represent more downstream research tools. By the same token, one

should not assume, as Goldstein and Golod apparently do,[14] that the legal system cannot take on the task of making some rough distinctions. Investigating legal options, even imperfect options, is particularly important because, contrary to Goldstein and Golod, there is every reason to believe that market actors might choose to maximize their profits by filing patents on research platforms even when such patents are not in the overall public interest. Moreover, patent law does provide some mechanisms for making rough distinctions between upstream and downstream research tools.

For example, a relatively strict interpretation of the utility standard (comparable to that articulated by the Supreme Court in the 1966 case *Brenner v. Manson*[15]) might serve as a mechanism for making a rough distinction. Indeed, the Patent and Trademark Office (PTO) has, in recent years, begun to use the patent law's utility requirement to put some limits on the extent to which the most upstream research can be patented. For example, the PTO's most recent guidelines indicate that inventions of unknown or speculative function are not patentable.[16]

On the other hand, the Federal Circuit, which is under no obligation to follow the PTO guidelines, may not ultimately agree with the restrictive scope of the PTO's recent utility guidelines. The Federal Circuit has tended to consider utility a very low-threshold barrier to patentability. In the 1994 case *In re Alappat*,[17] for example, the Federal Circuit found an algorithm that merely produced smooth waveforms to have the requisite usefulness. Perhaps more importantly, relying on the utility standard requires an all-or-nothing approach: either one gets full patent protection or one gets nothing. Given the importance of patents to the biopharmaceutical industry, and the lack of a bright-line division between what constitutes a fundamental research platform and what constitutes more downstream research, a more finely calibrated mechanism may be necessary.

The limitation on patentability that is perhaps most susceptible to calibration is patent scope. Moreover, scope limitations can reduce transaction costs significantly. As Scherer points out, both empirical and theoretical evidence indicates that patents on research platforms tend to be much less of a hindrance to follow-on research if they are narrow.[18] Narrow patents increase the bargaining power of the follow-on researcher vis à vis the original inventor, thereby decreasing the likelihood that the original inventor will be able to engage in strategic behavior.

Moreover, unlike a heightened utility standard, narrow patent scope has clearly been embraced by the Federal Circuit. A variety of recent Federal Circuit cases, perhaps most prominently the 1997 decision in *Regents of California v. Eli Lilly*[19] and the 2002 decision in *Enzo Biochem, Inc. v. Gen-Probe*,[20] indicate that broad biotechnology claims are highly susceptible to rejection for failure to meet the disclosure requirements enumerated in section 112 of the patent statute. Although the court's very strict construction of the disclosure requirements has rightly been attacked by many in the biotechnology community as failing to apprehend the relevant technology[21] (and perhaps also the relevant law),[22] this flawed jurisprudence may have a silver living: it is likely to keep the scope of claims on research platforms narrow.

The example of gene fragment patenting—e.g., expressed sequence tag (EST) patenting—represents a concrete example of a situation where narrow scope has played a significant role in averting a transaction cost problem for follow-on researchers. Prior to the Federal Circuit's recent decisions, patent applications on gene fragments were claiming not only the fragment itself but also the full gene of which the fragment was a part (and sometimes even therapies that emerged from use of the gene). Many analysts were concerned that the transaction cost problems associated with licensing broad and overlapping EST patent rights might delay research. By contrast, now that it is clear that the scope of EST patents will be limited to the EST itself, the prospect of EST patents' creating a thicket of overlapping rights for follow-on research has been reduced very significantly.

We should be wary, however, of narrow claim scope as research moves further downstream. For example, as Goldstein and Golod point out, the degeneracy of the genetic code creates a situation where a protein can be coded for by many different gene sequences. If a patentee is allowed to claim only gene sequences that it has actually isolated, a rival can "invent around" the gene patent by making trivial base-pair changes to the patented sequence. The recent PTO guidelines on the written description requirement of section 112 soften the strictness of the *Eli Lilly* decision by indicating that patent applicants may be able to claim not only those gene sequences it has actually isolated but also homologous sequences. The PTO's efforts notwithstanding, it may be difficult to use the Federal Circuit's current interpretation of the disclosure requirements in a manner that keeps claim scope narrow on upstream research while allowing wider scope as research moves downstream. A more straightforward and intellectually honest approach would involve some explicit recognition by the Federal Circuit that Section 112 disclosure requirements can, and should, encompass an evaluation of how far upstream the research is. The more upstream and uncharted an area of invention, the narrower the allowable scope of patent claims on that invention.

Although narrow scope on upstream research is probably the best legal mechanism for solving transaction cost problems, it bears mention that this approach will not solve all such problems.

For example, as Barton suggests, a designer of a SNP chip may need access to a variety of patented SNPs.[23] The transaction costs associated with assembling the relevant SNP patents might be significant even if each patent is limited to the SNP itself. More generally, transaction costs can be a problem when the number of upstream patents is numerous, even if any individual patent is narrow. Relatedly, even in situations where patents do not exist, follow-on researchers and developers may be stymied by the existence of a thicket of restrictive biological material transfer agreements.[24]

Some commentators have suggested that transaction cost problems posed by numerous, even if relatively narrow, upstream rights are not a problem for the patent statute. Rather, the market, acting through formal or informal patent pools, can circumvent such costs. In these pools, which have arisen, at least informally, in the semiconductor industry, patentees essentially agree to refrain from enforcing their patents against each other. Institutional responses outside the patent statute are clearly important. However, for reasons perhaps related to the diversity of players in the biopharmaceutical industry, we have not (at least thus far) seen patent pools arising to address transaction costs.

Outside the confines of the patent statute, the most noteworthy institutional response has been activity enhancing the public domain on the part of the major agency that sponsors biomedical research, the National Institutes of Health (NIH). In the context of the human genome sequencing project, the NIH, acting in conjunction with major grantee institutions, resolved to make all raw human genome sequence data immediately available. Such public availability undermined the possibility of any assertions of proprietary rights, no matter how narrow, on raw sequence data. More recently, NIH guidelines that address the patenting of research tools[25] urge its grantee institutions to distinguish between those research tools that are broad research platforms and those that are more narrow in scope. The NIH guidelines specifically counsel against the patenting of broad research platforms. They also urge that grantee institutions engage in free exchange of unpatented research materials; indeed, they suggest that grantees also require such free exchange from industry.

Because of the constraints of the Bayh–Dole Act—the legislation that allows private patenting of publicly funded research in the first instance—the NIH's ability to enforce its guidelines against recalcitrant grantees is limited. Thus far, informal research norms under which universities have tended to refrain from patenting fundamental research platforms have secured some compliance with the guidelines. For example, as Goldstein and Golod point out, at least some universities have refrained from seeking patents on genes that code for targets.[26] Given that these norms may be unraveling, however—witness the very broad patent that the University of Wisconsin has on human embryonic cell lines—amending Bayh–Dole so as to give the NIH (and federal agencies more generally) more authority to limit patenting of publicly-funded research platforms is worth considering.[27] In the case of publicly funded research, eliminating patents on research platforms altogether does not pose the same risk as it might for privately funded research. The only role of patents on publicly funded research is to stimulate further development of such research, not to generate it in the first instance. Moreover, the NIH should have the requisite combination of knowledge and motivation to make reasonable decisions regarding what constitutes a research platform. With respect to knowledge, the NIH could draw upon the resources not only of researchers but also of policy analysts and economists. As for motivation, because the NIH not only benefits from patenting (through its own technology licensing programs) but also bears the burden of such patenting (in that its research grants must cover licensing costs faced by grantees), it should have at least some desire to distinguish carefully between research tools that are best developed through patenting and those that are best developed through more open access.

Conclusion

Legal changes over the last five to ten years have made it more likely that research tools will be patentable. We need to be particularly concerned about broad patents on that subset of research tools that I have called broadly enabling research platforms. Decision such as *Eli Lilly* and the recent *Enzo* case, which are rightly maligned by many in the biotech industry as misunderstanding the technology, may have a silver lining to the extent they keep claims to such research platforms narrow. On the other hand, as an economic matter, *Eli Lilly* and its progeny go too far to the extent that they appear to apply to all biotechnology inventions, not just to upstream research platforms. We need to ensure that narrow patent scope is limited to cases where research platforms are at issue. The remedy of narrow patent scope does not, however, solve transaction cost difficulties that may arise when upstream patents are narrow but nonetheless numerous. Here certain other public-domain–enhancing solutions, perhaps most notably those recently undertaken by the NIH, may be in order.

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The Articles that this Commentary discusses immediately precede it in this special issue.

Endnotes

[1]Goldstein J, Golod E. Human gene patents. *Acad Med.* 2002;77:1315–28.

[2]Barton J. Patents, genomics, research, and diagnostics. *Acad Med.* 2002;77:1339–47.

[3]Merz JF. Kriss AG. Leonard DG. Cho MK. Diagnostic testing fails the test. *Nature* (2002) 415(6872):577–9.

[4]Historically, there have been a few cases in which judges have alluded to the possibility of a narrow common law research exemption in the patent law. However, this common law exemption has never been used. Moreover, recent decisions by the Federal Circuit call into question even this narrow exemption. *See* Embrex, Inc. v. Service Engineering Corp., 216 F.3d 1343 (Fed. Cir. 2000).

[5]Goldstein and Golod suggest that a research exemption already exists de facto. They assert that there are "very few cases alleging patent infringing activities by universities." The lack of litigated cases does not mean, however, that university researchers are not deterred from using patented materials. Moreover, there are documented cases of private companies imposing stringent restrictions on the transfer of unpatented biological materials to universities. *See* Heller MA, Eisenberg RS. Can patents deter innovation? The anticommons in biomedical research, *Science* (1998) 289:698.

[6]Murashige K. Patents and research—an uneasy alliance. *Acad Med.* 2002:77:1329–38.

[7]In layman's terms, deadweight loss is the inefficiency that arises when consumers who would be able to pay the competitive price (i.e., marginal cost) are excluded from the market.

[8]Scherer FM. The economics of human genome patents. *Acad Med.* 2002:77:1348–67.

[9]Merges RP, Nelson RR. On the complex economics of patent ccope. *Columbia Law Review*, (May 1990), 90:839–916, as cited in Scherer, *ibid*.

[10]Moreover, some of the genome patents discussed in the articles in this issue of *Academic Medicine* do not even cover research tools. For example, a significant number of patented genes serve not as research tools but as end-product therapeutics.

[11]Scherer, *op cit*.

[12]*Ibid*.

[13]For further discussion of this particular question, see Rai AK. Fostering cumulative innovation in the biopharmaceutical industry: the role of patents and antitrust, (2001) Berkeley Tech. L.J. 16:813.

[14]Goldstein *et al*. *op*. *cit*.

[15]383 U.S. 519 (1966). In *Brenner v. Manson*, the Supreme Court established a rather high threshold for the utility standard by holding that a patent applicant had to demonstrate a specific and practical utility for a claimed invention. Demonstrating that an invention would be useful in further scientific testing (as the applicant had with respect to the steroid discussed in the patent application) was not sufficient.

[16]PTO Utility Examination Guidelines, 60 Fed. Reg. 1092, 1098 (Jan 5, 2001) (noting that assertions of utility must be "credible," "specific," and "substantial.")

[17]33 F.3d 1526 (Fed. Cir. 1994).

[18]Scherer, *op*. *cit*.

[19]119 F.3d 1559 (Fed. Cir. 1997).

[20]296 F.3d 1316 (2002).

[21]*See* Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 Berkeley Tech. L.J. 615 (1998).

[22]Mark Janis, *On Courts Herding Cats: Contending with the "Written Description" Requirement and Other Unruly Patent Disclosure Doctrines*, 2 Wash. U. J. L. & Pol'y 55 (2000).

[23]Barton, *op*. *cit*.

[24]*See* Heller & Eisenberg, *op*. *cit*.

[25]Department of Health and Human Services, National Institutes of Health, Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Bioemedical Research Resources: Final Notice, 64 *Federal Register* 72090 (1999).

[26]Even more directly, these norms secured compliance with NIH's "no proprietary rights" policy on the human genome. *See generally* Arti K. Rai, *Regulating Scientific Research: Intellectual Property Rights and the Norms of Science*, 94 N w. L. Rev. 77 (1999).

[27]For an argument along these lines, *see* Arti K. Rai & Rebecca Eisenberg, *Bayh–Dole Reform and the Progress of Biomedical Research, Law & Contemp*. *Problems*. (2002) (forthcoming).