Evidence and anecdotes: an analysis of human gene patenting controversies

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When it comes to gene patenting, policy makers may be responding more to high-profile media controversies than to systematic data about the issues.

Gene patenting has attracted intense scrutiny for decades, raising a host of ethical, legal and economic concerns. Much of the policy debate has focused on seemingly quantifiable and practical concerns about the effect of patents on access to useful technologies in the contexts of both research and the clinic. Here, we summarize the dominant policy concerns and the events that have motivated these debates. We then reflect on what the evidence now says about the major concerns articulated in policy reports. We conclude by discussing what might explain some of the disparity between the empirical evidence and the policy focus.

Although policymakers and advisory groups have long recognized the moral and ethical concerns associated with human gene patents[1–3], such concerns have only rarely led to concrete proposals for reform[4]. A systematic review of the content and timing of major policy documents highlights the fact that policy activity has been largely stimulated by a convergence of a general social unease, the emergence of preliminary data and literature on the possible adverse practical ramifications of gene patents, and several high-profile patent protection controversies.

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The timing of the policy activity reflects this tendency. The recommendations for diagnostic-use licensing, for example, followed the international controversy associated with Myriad Genetics' decision to enforce the patents over the *BRCA1* and *BRCA2* mutations[5] (**Fig. 1**). There have been other gene patenting controversies, such as the furor over patents related to Canavan disease, or the attempt by US National Institutes of Health in the early 1990s to patent over 7,000 expressed sequence tags (ESTs)[6]. The mid-1990s was also a period of rapid (roughly 50% per annum) growth in DNA-related patents in the United States[7]. Internationally, however, the Myriad controversy coincides with the most policy activity. Indeed, as **Figure 2** (and **Supplementary Data** online) shows, the Myriad Genetics–*BRCA1/2* story is, by far, the most referenced patent controversy in the policy documents we reviewed.

These controversial gene-patenting stories raised several concerns in the academic and policy literature. A prominent concern was that of a "tragedy of the anticommons," or the possibility that the large number of patents on genes and their diverse set of owners would make it difficult to acquire the rights to all necessary research inputs, which could, in turn, result in the underuse of valuable technologies[8]. Second is the longstanding concern that the owners of patents on fundamental technologies will exercise their rights to exclude in ways that will prevent others from developing or accessing the technology[9–11]. The Myriad case was held out as an example and as a harbinger of the coming problems associated with human gene patents[5]. Such restrictions on access to patented genes were viewed as especially pernicious given a belief that such patents could not be invented around, because of the unique role that genes play in biological processes.

A closely related concern was that the strong commercial incentive built into recent policy changes, and the associated pro-commercial milieu in universities, were undermining the norms of open science[12,13], leading researchers to be more secretive about their ongoing research, to delay publication of result, and to be less likely to share research materials or data. These behaviors, it was held, would retard the progress of science and technology.

Starting around 2001, this literature, together with the Myriad Genetics controversy and similar ones, began to stimulate significant policy activity (**Fig. 1**). In Canada, an Ontario government report recommended a variety of reforms, including strengthening the research exemption and revising the compulsory licensing provisions in the Patent Act to create an exemption for genetic diagnostic and screening tests[14]. The UK's Nuffield Council on Bioethics made similar recommendations[2]. In the United States, the National Academy of Sciences issued two reports[7,15], both of which recommended a research exemption as a means of dealing with the anticommons and restricted access problems. These reports were clearly influenced by emerging empirical evidence about the effects of gene patents on genetic testing services[16,17] and the Myriad controversy (the production of the Ontario report immediately followed the eruption of controversy over Myriad's patent in Canada and the Nuffield Council and the National Academy's 2005 report both used Myriad as a case study)[18].

Reflecting on the evidence

With the passage of time and the accumulation of more data, we can now reflect on what the available data do and do not say about the anecdotes, theories and initial evidence that spurred so much policy activity. Indeed, the policy

debates around these concerns have both led to and been informed by a number of empirical studies designed to find out where and to what extent each of these concerns is manifest in the practice of biomedical research.

The results of these empirical efforts have been fairly consistent. First, the effects predicted by the anticommons problem are not borne out in the available data. The effects are much less prevalent than would be expected if its hypothesized mechanisms were in fact operating. The data do show a large number of patents associated with genes. A recent study found that nearly 20% of human genes were associated with at least one US patent, and many had multiple patents[19]. Another study estimated that in the United States over 3,000 new DNA-related patents have issued every year since 1998, and more than 40,000 such patents have been granted[7]. But despite the large number of patents and the numerous, heterogeneous actors—including large pharmaceutical firms, biotech startups, universities and governments—studies that have examined the incidence of anticommons problems find them relatively uncommon[20–24]. These studies span both academics and industry, and include data from the United States, Germany, Australia and Japan.

Studies on access to upstream research tools find that although some researchers or firms are denied access to a particular technology, others do have access to the same technology, suggesting that the resulting limitations have more to do with a willingness to accept the market price and access terms[25,26]. Similarly, among academic biomedical researchers in the United States, only 1% report having had to delay a project and none having abandoned a project as a result of others' patents, suggesting that neither anticommons nor restrictions on access were seriously limiting academic research[21]—despite the fact that these researchers operate in a patent-dense environment, without the benefit of a clear research exemption.

One important exception is in the area of gene patents that cover a diagnostic test. Here, there are more instances of researchers and firms claiming that the patent owner is asserting exclusivity or license terms that are widely viewed as inappropriate, thus lending some empirical evidence to support the concerns highlighted by the Myriad Genetics story. For example, 30% of clinical labs report not developing or abandoning testing for the HFE gene after the patent issued[17]. In addition, 25% of labs had abandoned one or more genetic test as a result of patents, with Myriad's patents among the most frequently mentioned[27]. Such unlicensed lab testing, from the perspective of the patent owner, competes with its commercial activity, and hence it is not surprising to find owners asserting their rights.

There is also substantial empirical evidence that university researchers are becoming more secretive and less willing to share research results or materials[28–32]. The causes of this

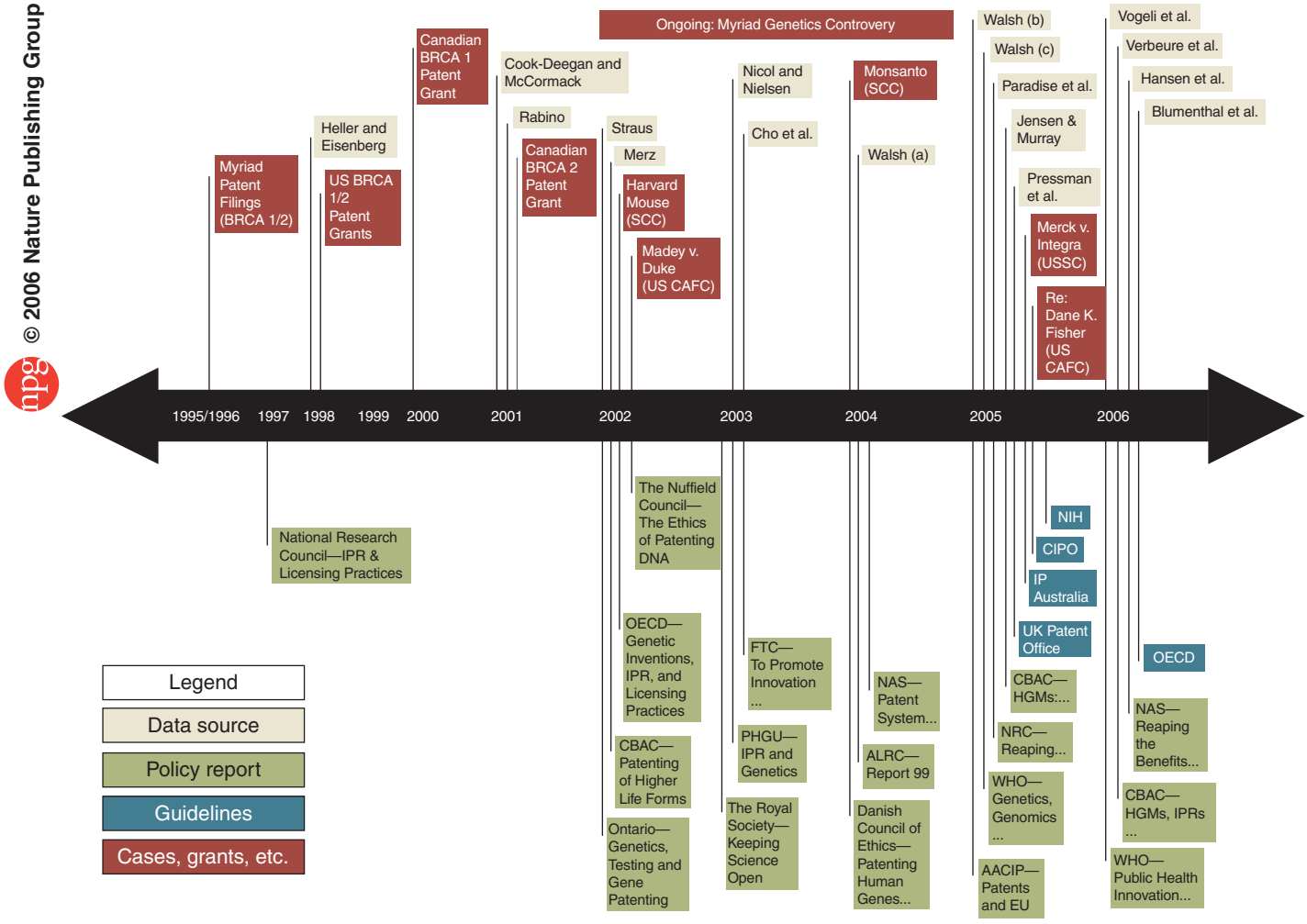

Figure 1 Timeline of gene patenting cases, decisions and studies, and corresponding significant policy activity (refs. 45–56).

secrecy, however, are still in dispute. In particular, we cannot determine the impact of patents themselves on secrecy, in part because many studies of academic secrecy[28,32] use composite measures and, as a result, it is difficult to tease out specific causes thereof. Some studies find that patents *per se* have little effect on discussion of ongoing research or on sharing of research materials[21,29]. In contrast, several studies have found that commercial activity, as well as scientific competition and the cost and effort involved in sharing, all have negative effects on open science[21,28,32].

Industry funding is also often associated with delayed publication[29,33,34]. This failure to share research materials seems to have a negative impact on research. For example, Walsh *et al.* find that 19% of recent requests were not fulfilled (and that failures to supply materials are increasing), and that at least 8% of respondents had a project delayed owing to an inability to get timely access to research materials (compared to 1% who were delayed by an inability to get a patent license)[21]. Finally, some studies show reduced citations of publications once a corresponding patent is granted[35,36]. However, the causes and implications of such a relationship are unclear. In particular, is this a result of a change in research practices or simply of citation practices (that is, an unwillingness to announce infringement in print)? Even if it is the former, does this simply reflect changing incentives causing a shift by researchers (especially industry researchers) toward less encumbered research areas? The overall social welfare implications of this redirection are also uncertain, as there is both the potential loss of fewer people working on a problem, and a potential gain of a more diverse research portfolio[36,37].

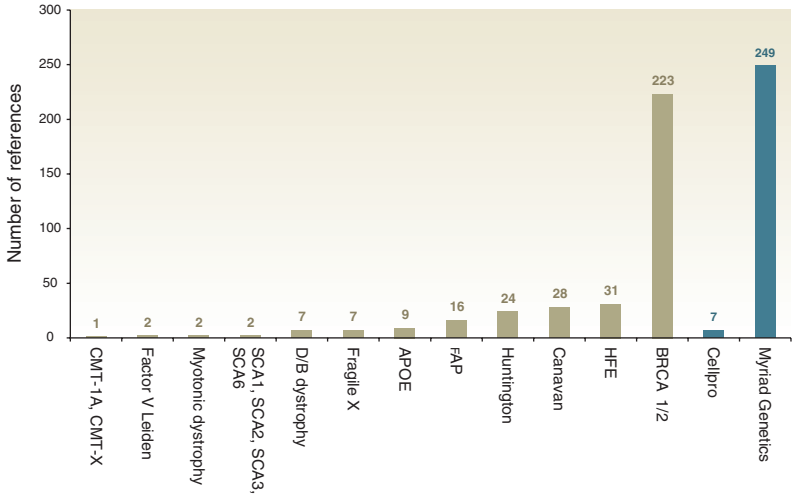

Figure 2 Explicit references to controversial biotechnology patents and firms in major policy documents after 2002.

Analyzing the concerns, evidence and anecdotes

The survey of policy reports reveals that the Myriad Genetics controversy was used as a primary tool for justifying patent reform—thus highlighting the potential of a single high-profile controversy to mobilize both governmental and non-governmental policy makers. In Belgium, for instance, the controversy directly incited the adoption of a research exemption[38]. There were certainly other gene patenting controversies that might have been used in a similar fashion, but it was the Myriad case that emerged as emblematic of the fear that patents on human genetic material would have an adverse impact on access to useful technologies, both for research and for clinical use. This is most likely because the controversy, more than any other, resonated so well with the theoretical concerns that existed in the literature. In addition, the clinical consequences were easy to understand and highly visible breast cancer constituencies were engaged.

Although the available evidence suggests that the concerns associated with the Myriad case have merit in the context of diagnostic tests, the data are hardly definitive, and empirical research suggests that data about diagnostics cannot be generalized to other uses. Furthermore, five years later, there have been few similar gene patent controversies. One possibility is that the Myriad story has become a cautionary tale for the holders of similar gene patents, guiding them toward more constructive patent enforcement strategies.

The evidence regarding the anticommons and restricted access concerns is clearer. The empirical research suggests that the fears of widespread anticommons effects that block the use of upstream discoveries have largely not materialized. The reasons for this are numerous and are often straightforward matters of basic economics[39]. In addition to licensing being widely available[40], researchers make use of a variety strategies to develop working solutions to the problem of access, including inventing around, going offshore, challenging questionable patents and using technology without a license. Though it has been suggested that this latter strategy is an inappropriate and unstable policy[15,41], it is important to remember that the stability of this unlicensed use is supported by a combination of the difficulty of enforcing patents owing to the secrecy of research programs, costs of lost goodwill among researchers, costs of litigation, the relatively small damages to be collected from blocking research use, and the interest of the patent owner in allowing research advances in most cases. An anticommons or restricted access–type failure requires not that any one strategy be unavailable, but that the entire suite be simultaneously ineffective, which may explain why, empirically, such failures are much less common than was first posited.

Finally, the data concerning the increasing secrecy of university researchers seem to indicate that there may be a conflation of patenting and commercial and/or scientific competition as the cause of this trend. It appears that academic researchers are becoming more secretive, but that is not shown to be attributable to the patenting process, suggesting that the solution might not reside in modifying patent policy. Some have suggested tempering the commercial orientation of faculty and facilitating the flow of research materials[42,43]. Another approach might be recognizing the inherently competitive nature of the academic process[44] and developing additional and improved mechanisms for exchange among its members.

Conclusions

Looking back on years of policy debates and the associated empirical work on gene patents, what lessons can be drawn? First, although there may have been good reasons for concern, the feared problems have not widely manifested. And the problems that the data do reveal may have less to do with patents than with commercial concerns, scientific competition and frictions in sharing physical materials. Second, despite the growing acknowledgment of this empirical work, there is still a tendency to recommend policy interventions, usually

including a 'research exemption.' Yet, given the research noted above, a strengthened research exemption seems unlikely to address the anticommons or restricted access problems, especially in diagnostic testing. And such reforms need to be sensitive to the incentives that patents can provide for developing and distributing research technologies.

The combination of a lack of empirical evidence of problems and a mismatch between the problems and proposed solutions may explain why there has been little actual policy change. In addition, our review of the lively policy debate and the limited empirical support for the claims that are driving that debate suggest that policymakers may be responding more to a high-profile anecdote or arguments with high face validity than they are to systematic data on the issues. However, we must acknowledge that one effect of these various high-profile policy debates may have been to sensitize both administrative and funding agencies (for example, the US Patent and Trademark Office and National Institutes of Health) and patent holders to the possible adverse consequences of the overly liberal granting of patents and overly restrictive licensing practices. Whether this swing of the pendulum will help, hurt or have no effect on innovation and the progress of science remains an open question. Thus, further research on the exact mechanisms underlying these effects, as well as their net impacts, should be encouraged.

Note: Supplementary information is available on the Nature Biotechnology website.

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