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Abstract

Questions about the effects of patents and licensing are becoming critical in the United States, Europe and other developed countries as more genes are discovered and patented, and as genetic testing becomes an integral part of standard medical care. The award of patents for the diagnostic test for haemochromatosis, a progressive iron-overload disease, joins an ever-growing list of such tests that have been, or will very soon be, patented. We have found that US laboratories have refrained from offering clinical testing services for haemochromatosis because of the patents. A lot of clinical study is needed to validate and extend the early discovery of a disease gene such as that for haemochromatosis, so our results give us reason to fear that limiting clinical testing will inhibit further discovery as well as the understanding that emerges naturally from broad medical adoption.

Comments

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(title) Diagnostic testing fails the test

(strapline)The pitfalls of patents are illustrated by the case of hemochromatosis

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Questions about the effects of patents and licensing are becoming critical in the United States, Europe and other developed countries as more genes are discovered and patented, and as genetic testing becomes an integral part of standard medical care. The diagnostic genetic test for the condition of hemochromatosis, a progressive iron-overload disease, is one of many that have been, or will very soon be, patented. We have found that US laboratories have refrained from offering clinical testing services for hemochromatosis because of the patent. Much clinical study is necessary to validate and extend the early discovery of a disease gene like that for hemochromatosis, so our results give us reason to fear that limitation of clinical testing will inhibit further discovery as well as the understanding that emerges naturally from broad medical adoption¹.

As the looming patent battle between Myriad Genetics and the French Curie and Gustave Roussy institutes highlights (see ref. 2), restrictive licensing and monopolization of clinical testing services will not for long be limited to the United States. Indeed, four patents relating to hemochromatosis testing are pending in the European Patent Office, suggesting the situation in the US described here may soon spread to Europe.⁷

New human genes are being patented as rapidly as they are discovered^{3,4}. Gene patents generally cover the clinical diagnosis of mutations, as well as use of the gene sequence in

potential therapies. Setting aside the debate about whether it is wise to allow patenting of human gene sequences at all, many are concerned about the ramifications of gene patents for biomedical research and clinical medicine.

Unfortunately, few empirical data exist about the effects of patents on the translation of genomic discoveries into medical advances, so it is not clear how justified these concerns might be. Here, we present the results of a survey of US clinical laboratories regarding their adoption and performance of the genetic test for hereditary hemochromatosis.

Hereditary hemochromatosis is a common autosomal recessive disease, affecting an estimated 1 in 200 to 300 people of northern European descent, with a carrier frequency of up to 1 in 10⁵; as much as 80-85% of hemochromatosis is caused by the two most common mutant alleles of the HFE gene (C282Y and H63D). Hemochromatosis is a preventable disorder, hence a candidate for population screening -- and offers a potentially large market for clinical genetic-testing services.

We have discovered that many laboratories in the United States began performing genetic testing for hemochromatosis before the patents were awarded, but 30% of those in our survey reported discontinuing or not developing genetic testing in light of the exclusive license granted on the patents covering clinical testing services. This result raises obvious concerns about test quality, patient access to testing services, the costs of clinical testing, innovation of testing methods, and the potential for placing limitations on clinical research.

Effects of Patents on Hemochromatosis Testing

US patents (nos 5,712,098; 5,753,438; and 5,705,343) covering the HFE genetic test for C282Y and H63D were first issued to Mercator Genetics in early 1998. The patents grant to the owner the right to exclude others from performing testing for these two mutations. Mercator went out of business after spending about US \$10 million developing its patented method of positional cloning and discovering the association between HFE mutations and hemochromatosis. Progenitor, Inc. merged with Mercator and was assigned its pending and issued patents. Progenitor then licensed the patents exclusively for clinical-testing purposes to SmithKline Beecham Clinical Laboratories, Inc. (SBCL) for an up-front payment and guaranteed continuing fees worth on the order of US \$3 million. SBCL's exclusivity and payment guarantees continued until a kit became available for use by clinical laboratories. (Exclusive licensing of gene patents is common, particularly for clinical diagnostic uses⁶.)

In summer 1998, SBCL began enforcement of its patent rights. The company wrote to laboratories, stating its willingness to grant sublicenses for an up-front fee of US \$25,000 from academic laboratories and an amount 5 to 10 times higher from commercial laboratories, plus per-test royalties of as much as \$20 per test. In January 1999, SBCL was sold to Quest Diagnostics, but the sale was not completed until autumn 1999. During and after the sale, SBCL and Quest curtailed active enforcement of the patents, creating uncertainty for laboratories that were or were interested in performing HFE testing.

In April 1999, Bio-Rad Laboratories, Inc. ⁷ acquired the portfolio of pending and issued patents covering HFE and its mutations from Progenitor, subject to the exclusive clinical-

testing licence held by SBCL. Following the acquisition of SBCL in late 1999, Quest did not enforce the clinical-testing licence and, in October 2000, transferred it to Bio-Rad for terms that were not made public. In 2001, Bio-Rad began offering a test kit consisting of analyte-specific reagents for the C282Y and H63D alleles. According to several laboratory directors to whom we have recently spoken, Bio-Rad is now offering to licence laboratories to perform testing without its kits -- but at a cost that makes its kit more economically attractive than the laboratories' own tests, with up front payments inversely proportional to the testing volume of the laboratory, plus a per test fee of about US \$20.

To understand how gene patents affected laboratories, we ran a pilot survey of a convenience sample of laboratory directors and staff in November 1998⁷. Drawing on these results, we developed a comprehensive telephone survey, the results of which we report here, to measure the effects of the HFE patents and the SBCL licensing strategy on clinical laboratory practices. We identified 117 laboratories in the GeneTests database (see <http://www.genetests.org/>) and Association for Molecular Pathology test directory that were or appeared capable of offering the HFE test. With approval of the University of Pennsylvania committee on studies involving human beings, we (A.K.) performed interviews in July and August 1999. Snowball sampling (asking respondents for referrals) yielded 11 additional laboratories, for a total sample of 128. We completed 119 interviews (93%) – staff at 9 laboratories declined to participate.

Ninety-two respondents (77%) were laboratory directors, 12 were supervisors (10%), and the rest were other types of laboratory staff. Two-thirds (80) of the laboratories in our

represented sample were affiliated with universities, hospitals or other non-profit institutions. Most (111; 93 %) respondents reported knowing about the HFE patents; 61 had first heard about them from colleagues or at meetings, and 35 from SBCL's letter. Overall, 54 respondents received the letter, and the 58 laboratories performing HFE testing were more likely than those not offering the test to have received the letter (Odds Ratio = 4.4, $P < 0.001$).

Significantly, in September 1999, 31 (26%) laboratories reported they had not developed and were not performing the test, and another 5 (4%) stated they had stopped performing the test. There was no difference between commercial and non-profit laboratories. Of these 36 laboratories, 22 reported that the patents were "the reason" and 10 stated the patents were one of several reasons they had not developed or had discontinued offering the test.

We believe that testing volume is a dominant factor in a laboratory's decision to perform a particular clinical test. For hospital-based laboratories in the United States, the non-reimbursed expenses incurred by sending samples out to other laboratories for testing can be very high, motivating institutions to develop in-house tests. Although we did not ask for specific reasons why laboratories were not performing HFE testing, it is likely that low usage or perceived demand was one of the factors.

In sum, the patents on HFE had a measurable effect on the development and performance of HFE testing services in the United States, as many laboratories that had the capability to perform the test reported not doing so because of the patents.

We asked respondents when they started offering the HFE test, and present a timeline (Figure 1) of the filing of patent applications, publication of the HFE discovery ⁸, and issuance of the patents. Superimposed on this timeline is the accumulation of respondent laboratories as each began HFE testing. The mean time from publication to adoption (of the truncated distribution) was 14 months. Significantly, 35 laboratories (60% of the 58 performing HFE testing at the time of our survey) reported introduction of the clinical test before the first patent issued.

Based on our data, we can not say whether the decrease in the rate of laboratory adoption after the time the patents issued was due to the perception by laboratory staff of inadequate demand to justify their development of the test or due to concerns about patent enforcement. While our respondents overall reported the patents weighed heavily in their decisions not to perform HFE testing, we do not know when those decisions were made, and responses may well have been biased by hindsight or by the nature of our questioning.

Our data show that there was very rapid adoption of HFE testing by laboratories soon after publication of ref. 8, which was about 17 months before the first patent was issued and almost 2 years before SBCL began enforcement. Thus, as is typical with genetic tests, the patents were unnecessary for rapid translation of the HFE discovery into clinical-testing services ¹. On the contrary, our data demonstrate that the patents inhibited adoption, perhaps by creating a financial risk for laboratories and a disincentive

to develop and validate a clinical assay that could be stopped by enforcement of the patents.

Of course, but for the potential value of the patented discovery, the private investment of venture capital in Mercator Genetics might not have been made and the gene discovery delayed. Yet the question remains whether the exclusive licencing strategy embarked on by Progenitor and SBCL was the best method for capturing financial patent rewards in lieu of, for example, broad non-exclusive licencing of all laboratories who wished to perform the testing with payment of a reasonable per-test royalty, or development and sale of a test kit, the latter being the current strategy of Bio-Rad. This last strategy, however, may compromise test quality by restricting laboratories to use of a single kit, thereby limiting innovation and development of alternative methods.

Our data highlight several concerns that have been expressed about patents on biotechnology discoveries. First, at least one study⁹ has shown a delay in publication of new biotechnology discoveries attributable to patenting activities. The paper reporting the discovery of HFE (ref. 8) was submitted more than a year after the first US patent application was filed and several months after the last of the four. Given that laboratories can rapidly develop, validate and offer clinical tests, then delays in publishing scientifically validated findings of clinical importance may adversely affect patients by delaying access to diagnostic testing.

Second, the two most common mutant alleles covered by the US patents account for up to 85% of hemochromatosis in the northern European population; there are many other rare polymorphisms that have clinical relevance¹⁰. Laboratories forced to use Bio-Rad's

kit for financial reasons may decide to develop alternative tests for other mutations¹¹, which can increase the cost of testing, the likelihood of laboratory errors due to increased handling of samples, and, if any of the new mutations are also being patented, further increase the cost and licensing complexity for hemochromatosis.

Third, gene patents affect the cost and availability of clinical diagnostic testing. Royalties charged for this and other non-exclusive licences include SBCL's and Bio-Rad's charge of up to US \$20 per test (in addition to substantial up-front payments), and US \$12.50 per test for Canavan disease, \$5 per test for Gaucher disease, and \$2 per test for volume greater than 750 tests a year for the most common allele ($\Delta F508$) of the CFTR gene that causes cystic fibrosis (CF), all with no up-front fees. Although these amounts seem modest, they can present various problems. For example, so-called stacking of royalties¹² occurs for laboratories offering a panel of tests for the Ashkenazi population including Tay Sachs disease, several CF mutations, Gaucher disease, Niemann-Pick disease and Canavan disease. One respondent indicated his cost for this panel was about US \$100. The royalties for the tests sum to roughly 20% of cost; this percentage will increase as new tests are added to the panel and technology drives down the marginal cost per test. We believe that royalties must be reasonable, and, given the rapid advances being made in testing technology, they should not be fixed amounts but should be a percentage of the marginal reimbursement, cost or price allocable to the patented test.

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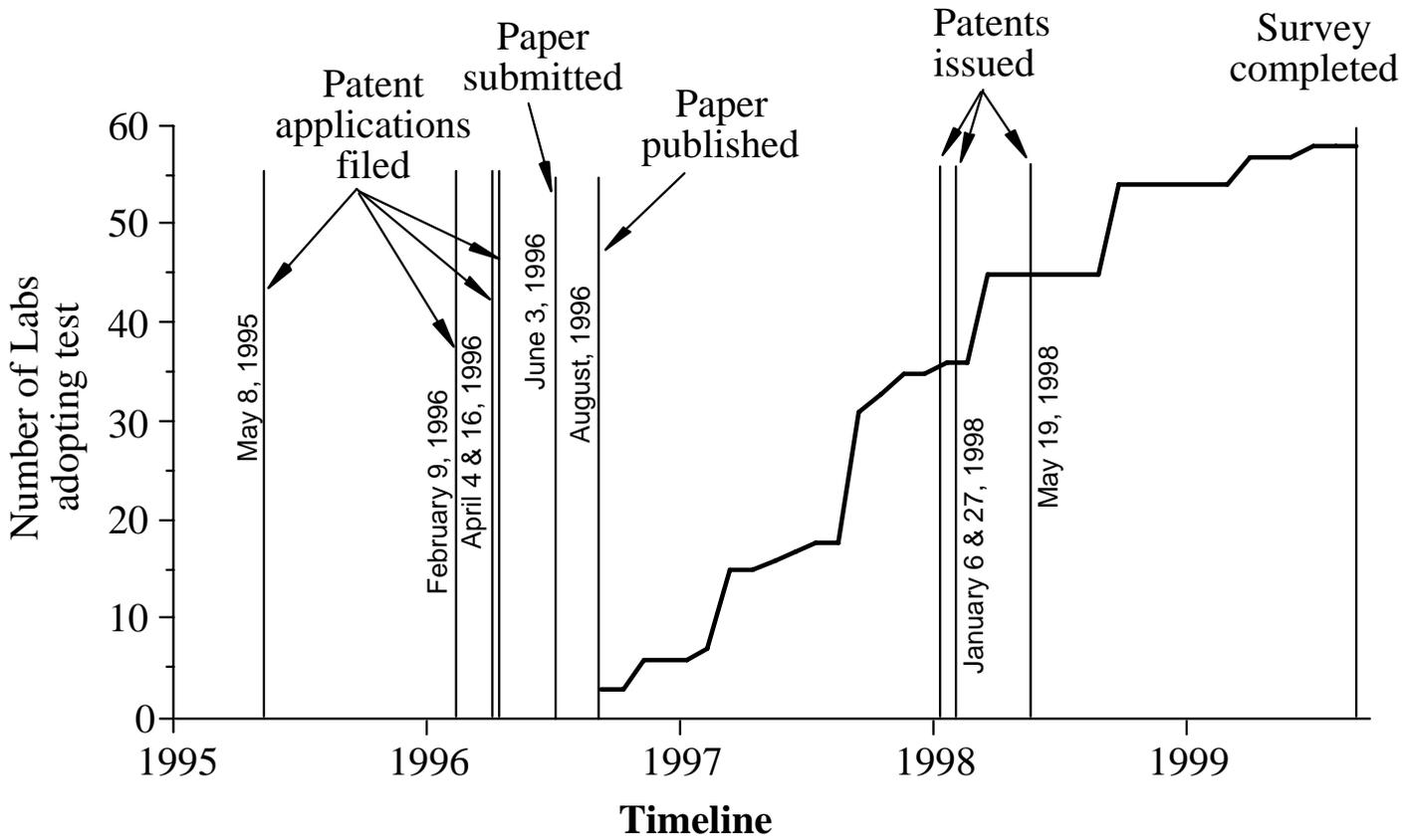


Figure 1 Timeline showing HFE patent applications, publication, patent grants and the cumulative number of laboratories at the times they began offering the clinical test following publication of the gene discovery in ref. 8.