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Special Article

Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services

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The growth of patents that include genetic sequences has been accompanied by concern about their impact on the ability of physicians to provide clinical genetic testing services and to perform research. Therefore, we conducted a survey of clinical laboratory directors that perform DNA-based genetic tests to examine potential effects. We performed a telephone survey between July and September in 2001 of all laboratory directors in the United States who were members of the Association for Molecular Pathology or who were listed on the *GeneTests.org* website. One hundred thirty-two of 211 (63%) laboratory directors were interviewed. Ten of these were excluded because they did not conduct DNA-based genetic tests. Almost all performed genetic tests for clinical purposes. Half performed tests for research purposes as well. Twenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories. We found 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68%) are held by universities or research institutes, and 13 of the 22 patents (59%) were based on research funded by the United States Government. Overall, respondents reported that their perceptions of the effects of patents on the cost, access, and development of genetic tests, or data sharing among researchers, were negative. In contrast, most respondents felt that patents did not have an effect on the quality of testing. We conclude that patents and licenses have had a significant effect on the ability of clinical laboratories to develop and provide genetic tests. Furthermore, our findings suggest that clinical geneticists feel that their research is inhibited by patents. The effects of patents and licenses on patients' access to tests, and the costs and quality thereof, remains to be determined. *(J Mol Diagn 2003, 5:3–8)*

Patents were created to provide incentives for the production of innovative products that could benefit the public. It is argued that patents have been critical to the growth and maintenance of the pharmaceutical industry.[1,2] In this industry particularly, patents are seen as necessary to enhance an inventor's ability to recoup the substantial investments of many years and hundreds of millions of dollars necessary to bring a new drug or device to market. However, it has been proposed that patents are not necessarily an effective incentive for the development of clinical genetic diagnostic tests.[3] For example, it may only take weeks or months to go from a research finding that a particular genetic variant is associated with a disease to a clinically validated genetic test.[4] Furthermore, the need to license multiple patents for the development of a multigenic genetic test may inhibit the development of such tests. Thus, some have suggested that patents and their associated licenses may be inhibitory to the translation of genetic findings into diagnostic tests.[3]

An increase in the number of patents that cover genetic sequences has raised concerns about the impact of these patents on the ability of physicians to provide clinical genetic testing services and perform research necessary to refine or develop new tests or therapeutics.[4,5] Some of the concerns are that patents and restrictive licensing practices for genetic tests may decrease access to testing services, increase test costs, or decrease the quality of testing. On the other hand, others are concerned that, without intellectual property protection, re-

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search would not be done to make the discoveries on which genetic tests are based, and the test would not be developed after the discovery was made.

Previously, we conducted a pilot study to examine the effects of patents and licenses on the practice of clinical genetic testing.[5] To conduct a more comprehensive study and update our previous findings, we conducted a systematic survey of clinical laboratory directors in the United States that perform DNA-based genetic tests to examine the impact of patents and licenses on the provision of clinical genetic testing services.

Materials and Methods

Sampling

Our sampling frame was all laboratories in the United States who were members of the Association for Molecular Pathology or who were listed on the *GeneTests.org* website. We identified directors or the representative of each laboratory most knowledgeable about impacts of patents and licenses on the laboratory's practice. Laboratory directors were identified from the 1998 printed Association for Molecular Pathology Test Directory (the most recent directory available), and from the *GeneTests.org* website on June 18, 2001. (GeneTests is a website maintained by the University of Washington and funded by the National Institutes of Health, the United States Department of Energy, and the Health Resources and Services Administration. The website lists laboratories in North America and elsewhere that perform genetic tests if they request inclusion on the website.) The Association for Molecular Pathology Directory identified 95 laboratory directors who perform genetic tests. The search of *GeneTests.org* identified 127 laboratory directors. An additional 6 laboratory directors were added from a comprehensive updated listing of clinical laboratory directors provided by GeneTests, for a total of 133. We combined this sample of 133 directors from GeneTests with the sample of 95 from Association for Molecular Pathology and eliminated 17 duplicates for a final sample of 211 laboratory directors.

Survey

We conducted a telephone survey of the selected laboratory directors between July and September in 2001. We attempted to contact each director by phone up to approximately three times, followed by one e-mail contact to establish an interview time. A small proportion (~10 people) was contacted by e-mail because their staff indicated this as their preferred method of communication.

The survey consisted of 95 closed-ended questions that addressed the following topics: the setting in which the respondent worked; the categories of tests performed by the respondent's laboratory (eg, genetic, paternity, infectious diseases, and so forth); whether the respondent held any patents or licenses for procedures, devices, or reagents used in clinical testing; whether the laboratory had been prevented from performing or had decided not to develop a clinical test because of a patent or license; and the respondent's perception of how strongly patents had affected access to, quality, and costs of testing, or the ability to do research. The survey included one open-ended question asking whether participants thought there were any ethical issues raised by patents on genetic tests and another to allow participants to add any additional comments. For the purposes of the survey, respondents were told that we defined genetics tests as DNA-based tests to predict or diagnose disease (not including tests to detect infectious agents).

Table 1. Institutional Affiliation of Respondents*

Institutional affiliation	*n* (%)
Company	19 (16)
University	73 (60)
Federal	16 (13)
Nonprofit	80 (66)
Private hospital	64 (52)
Other	10 (8.2)

*Totals do not add up to 100% because response options were not mutually exclusive.

Analysis

Our analysis included descriptive summary statistics on respondent characteristics (eg, role in the laboratory, type of testing performed) and proportion of respondents reporting particular effects of patenting on the laboratory.

Results

Response Rate and Respondent Characteristics

Of 211 laboratory directors contacted, 132 responded, yielding a total response rate of 63%. Of these, 10 were not included for further analysis because they reported that they did not perform DNA-based genetic tests. The final number of responses analyzed was 122 (58%). Respondents did not differ significantly from nonrespondents in the likelihood of being from a for-profit or nonprofit institution (chi-square test, $P = 0.37$).

The majority of respondents were directors of university laboratories. The institutional affiliation of respondents is shown in Table 1. Sixty-one respondents (50%) were from laboratories that conducted clinical laboratory tests only, 60 (50%) were from laboratories that conducted laboratory tests for both research and clinical purposes, and 1 laboratory conducted tests for research purposes only. One hundred fourteen respondents (93%) were laboratory directors, and the remainder were laboratory supervisors, technologists, or other laboratory staff.

Licensing Practices

Ninety-one respondents (75%) said that their laboratories held a license to use a patented method, device, or reagent, and 90 of the 91 said that they had a license to

conduct the polymerase chain reaction. Twenty-five laboratories (27%) had a license to perform a genetic test. These licenses were for tests to detect a wide variety of conditions, including hereditary breast and ovarian cancer (BRCA1/BRCA2), Canavan disease, hereditary hemochromatosis, and fragile X syndrome, among others. Eighty-four respondents (69%) said that they paid royalties to use a patented method or reagent.

Effects of Patents and Licenses on Clinical Genetic Testing Services

Seventy-nine respondents (65%) said that their laboratories had been contacted by a patent or license holder regarding the laboratory's potential infringement of a patent by performance of a genetic test. These notifications were for several different genetic tests, including Apolipoprotein E genotyping, hereditary hemochromatosis, fragile X syndrome, BRCA1/BRCA2, Canavan disease, Charcot-Marie-Tooth disease, spinocerebellar ataxia, and Duchenne muscular dystrophy, among others. Twenty laboratories had received notification for one test, and 51 had received notifications for up to three tests, but 26 labs had received notifications for four or more tests.

Thirty respondents (25%) answered yes to the question, "Has notification from a patent holder or licensee ever prevented you from continuing to perform any clinical test or service that you had developed and were offering?" The 12 tests that laboratories had reported ceasing to perform are shown in Table 2. In searching the US Patent and Trademark database of patents on January 15, 2002, we found 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68%) are held by universities or research institutes, one by an individual, and the rest by for-profit companies. Thirteen of the 22 patents (59%) were based on research funded by the United States Government. The patents were issued from October 1994 to June 2001. The research leading to these patents was published between December 1988 and August 1996 in research articles that we found in *MEDLINE*.

To put these 12 tests into context, we searched the GeneTests database and found that, in June 2001, 461 genetic tests were offered as a clinical service. The vast majority of the tests was for rare disorders and not performed by many laboratories; 394 of the tests were performed by 10 or fewer laboratories, whereas 67 of the tests were done by 11 or more laboratories. However, all of the 12 tests that laboratories had stopped performing were performed by 11 or more laboratories, as reported by GeneTests in June 2001. The number of laboratories performing these tests ranged from 11 (for Charcot-Marie-Tooth disease) to 97 (for fragile X syndrome).

Of the 30 laboratories that reported being prevented from performing a test, 17 reported being prevented from performing one test and 12 laboratories had been prevented from performing more than one test (one laboratory director did not respond to this question). Of those who had reported being contacted by patent or license holders, laboratory directors at companies were significantly more likely to report being prevented from providing a test (10 of 14, 71%) than laboratory directors at universities (12 of 50, 24%) ($P = 0.001$).

Sixty-four (53%) respondents answered yes to the question, "Have you ever decided not to develop or perform a test/service for clinical or research purposes because of a patent?" Laboratory directors at companies were slightly more likely to report that they had decided not to develop or perform a test (12 of 19, 63%) than those at universities (36of 73, 49%) but this difference was not statistically significant ($P = 0.28$).

Opinions about Effects of Patents on Genetic Testing

Respondents were asked to rate the effect of gene patents on various aspects of clinical genetic tests. They were asked to provide these ratings based on their perceptions of clinical laboratories in the Unite States that provide genetic testing. Means and distributions of ratings for their perceptions of laboratories in general are shown in Table 3. Mean ratings indicate that respondents thought that patients access to testing had been decreased by patenting, costs of testing for laboratories had increased, and costs of testing for patients had increased. Respondents thought that the laboratory's ability to develop tests had been decreased, but that test quality had only been modestly affected. Respondents reported on average that information sharing between laboratories had decreased and that the ability of laboratories to do research had been decreased modestly by patents. However, analysis of the distribution of ratings (Table 3) shows that virtually all laboratory directors felt that patents have had a negative effect on all aspects of clinical testing, except on the quality of testing. A few respondents felt that patents were beneficial to test development more generally. For example, one respondent said, "I don't think that the argument that we can't research or do more testing because of patents is valid. Without patents, people wouldn't be able to test because the technology would just be published and sitting in someone's lab book. People shouldn't be complaining that they can't run tests. They should just pay." There were no significant differences between average responses of laboratory directors from companies compared to those from universities.

Discussion

Effects of Patents and Licenses on Clinical Genetic Testing Services

Our findings suggest that a substantial fraction of laboratories in the United States that provide genetic tests have been affected by patents and licenses. Almost two-thirds of the laboratory directors in our sample had been contacted by a patent- or license-holder about the labo-

Table 2. Genetic Tests that Some Laboratories Stopped Performing Because of Patents

Genetic test	No. of respondents that stopped performing this test	U.S. patent no.*	Patent filing date	Patent issue date	Patent holder	Gov't funded work leading to invention†
Apolipoprotein E (Apo E)	9	US5508167	4/13/94	4/16/96	Duke University	X
		US6027896	4/15/98	2/22/00	Duke University	X
		US5716828	2/10/98	5/15/95	Duke University	X
Hereditary breast/ovarian cancer (BRCA1/BRCA2)	9	US5753441 (BRCA1)	1/5/96	5/19/98	Myriad Genetics, Inc. (BRCA1)	
		US6051379 (BRCA2)	12/2/97	4/18/00	Oncormed, Inc. (BRCA2)	
Duchenne/Becker muscular dystrophy	5	US5541074	11/21/94	7/30/96	The Children's Medical Center Corporation	X
Hereditary hemochromatosis (HFE)	5	US5705343	2/9/96	1/6/98	Mercator Genetics, Inc.	
		US5712098	4/16/96	1/27/98	Mercator Genetics, Inc.	
		US5753438	5/8/95	5/19/98	Mercator Genetics, Inc.	
Myotonic dystrophy	4	US5955265	4/14/95	9/21/99	Massachusetts Institute of Technology; University of Wales College of Medicine	X
		US5977333	4/14/95	11/2/99	Massachusetts Institute of Technology; University of Wales College of Medicine	X
Canavan disease	4	US5679635	9/9/94	10/21/97	Miami Children's Hospital Research Institute	
Spinocerebellar ataxia (SCA1, SCA2, SCA3, SCA6)	4	US5834183 (SCA1)	6/28/94	11/10/98	Regents of the University of Minnesota (SCA1)	X (SCA1)
		US5741645 (SCA1)	6/6/95	4/21/98	Regents of the University of Minnesota (SCA1)	X (SCA1)
		US6251589 (SCA2)	5/18/98	6/26/01	SRL, Inc. (SCA2)	
		US5840491 (SCA3)			Kakizuka, A.	
		US5853995 (SCA6)	1/7/97	12/29/98	Research Development Foundation (SCA6)	X (SCA6)
Adenomatous polyposis of the colon	2	US5352775	8/8/91	10/4/94	Johns Hopkins University	X
Charcot-Marie Tooth type 1A (CMT-1A, CMT-X)	1	US5780223 (CMT-1A)	6/6/91	4/26/94	Baylor College of Medicine (CMT-1A)	X
		US5691144	6/5/96	11/25/97	Athena Diagnostics, Inc.	
Fragile X syndrome	1	US6107025	5/24/91	8/22/00	Baylor College of Medicine	X
Huntington disease	1	US4666828	8/15/84	5/19/87	The General Hospital Corporation	X
Factor V Leiden (activated protein C for thrombophilia)	1	US5874256	2/21/97	2/23/99	Rijks Universiteit	

*For patents filed with the U.S. Patent and Trademark office that were most relevant to the performance of the clinical genetic test of interest.
†As indicated in the U.S. patent.

ratory's potential infringement of a patent by performance of a genetic test. The majority of the patent holders enforcing their patents were universities or research institutes, and more than half of their patents resulted from government-sponsored research. If these patents are inhibiting commercialization of genetic tests, our findings would suggest that the Bayh-Dole Act may not enhance technology transfer of this kind of invention in the intended manner.

Table 3. Opinions about Effects of Patents on Genetic Testing

Patents have:	No. (%) indicating negative effect*	No. (%) indicating no effect*	No. (%) indicating positive effect*	Mean rating (*n*)†
Made testing more or less accessible to patients, or no effect? (less access to testing) (no effect) (more access to testing) −3 −2 −1 0 1 2 3	107 (89)	10 (8.3)	3 (2.5)	−1.8 (120)
Decreased or increased the cost of testing to labs, or no effect? (increased cost) (no effect) (decreased cost) −3 −2 −1 0 1 2 3	115 (96)	4 (3.3)	1 (0.83)	−2.2 (120)
Decreased or increased the cost of testing to the patient, or had no effect? (increased cost) (no effect) (decreased cost) −3 −2 −1 0 1 2 3	107 (91)	10 (8.5)	1 (0.85)	−2.0 (118)
Increased or decreased the ability to develop a test, or no effect? (decreased ability) (no effect) (increased ability) −3 −2 −1 0 1 2 3	105 (91)	10 (8.6)	1 (0.86)	−2.0 (116)
Increased or decreased the quality of testing services in labs, or no effect? (decreased quality) (no effect) (increased quality) −3 −2 −1 0 1 2 3	53 (45)	61 (51)	5 (4.2)	−0.8 (119)
Resulted in more or less sharing of information among researchers, or no effect? (less sharing) (no effect) (more sharing) −3 −2 −1 0 1 2 3	98 (85)	16 (14)	1 (0.87)	−1.7 (115)
Has resulted in an increased or decreased ability to do research, or no effect? (decreased ability) (no effect) (increased ability) −3 −2 −1 0 1 2 3	79 (67)	35 (30)	4 (3.4)	−1.1 (118)

*Percentages do not always add up to 100 because of rounding error.
†Not all respondents answered all questions.

As a result of patent- or license-holders exercising their intellectual property rights, one-quarter of the laboratory directors in our sample stopped performing a genetic test that they had been offering. In addition, just more than half of the laboratory directors had decided not to develop or perform a test specifically because of intellectual property considerations (eg, knowledge of the existence or possible future existence of a patent or license).

All but one of our respondents represented laboratories that performed genetic testing for clinical, as opposed to research, purposes. Thus, the implications of these results are fully applicable to the availability of genetic testing in clinical settings. These results also suggest an impact on hospital budgets, to the extent that hospitals are forced to send laboratory tests out to a licensed laboratory at a higher cost to the institution than if they were to perform the tests in-house. Although the absolute number of genetic tests that the laboratories in our sample stopped performing is not large, and the proportion of all tests offered is not high, the tests that laboratories have stopped performing seem to have high clinical relevance because they detect common alleles and/or are relatively commonly used in clinical practice.

Laboratories at companies seem to be more affected than university laboratories in their ability to continue to perform tests that they had been offering, but not necessarily more affected in their decision to develop new tests. This may indicate that companies are more likely to be challenged for patent infringement activities than universities.

These findings are virtually identical to those we obtained in a pilot study of laboratory directors conducted in November 1998,[5] suggesting that patenting and licensing practices affecting genetic tests has not changed dramatically in the last 3 years.[5] They are also generally consistent with a 1999 laboratory survey concerning testing for hemochromatosis.[4] However, with the explosion in the discovery of new genes and the likely development of many commercially viable genetic tests (including those designed to predict susceptibility to prevalent conditions and those to predict responses to drugs), these practices may change. One reason may be that intellectual property could be perceived to be more important for niche markets created by pharmacogenomics research.

Opinions about Effects of Patents and Licenses on Genetic Testing

It was striking that virtually no respondents, including those from commercial laboratories, thought that the effects of patents and licenses on the cost, access, and development of genetic tests have been positive. In contrast, most respondents thought that patents did not have a significant impact on the quality of testing (although nearly half stated that the effects were somewhat negative). Our data indicate that United States laboratory directors performing genetic tests think that gene patents hinder rather than facilitate clinical genetic testing. In addition, our data suggest that laboratory directors may feel more strongly than genetics researchers that patents have a negative effect on research; a recent survey of the members of the American Society of Human Genetics found that 46% of the respondents feel that patents have delayed or limited their research, whereas two thirds of laboratory directors in our survey felt that patents inhibit research.[6] This may point to a more pronounced effect of

patents on clinical genetic testing research than other kinds of research.

Conclusion and Limitations of the Study

We conclude that patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already developed genetic tests, and that these effects have not changed substantially throughout the past 3 years. Furthermore, the development of new genetic tests for clinical use, based on published data on disease-gene associations, and information sharing between laboratories, seemed to be inhibited. Our study does not address the issue of whether patents provided a major incentive for the initial research that led to the patent and development of the genetic tests that the laboratories subsequently stopped providing. However, our findings here and elsewhere[4] demonstrate that laboratories are able to quickly translate published data into clinical tests without the incentives provided by patents, and that laboratories are stopped from performing tests after patents issue. This suggests that patents are not critical for the development of an invention into a commercially viable service when the invention is the finding of an association between a genetic variant and a particular condition.

Despite the reduced number of clinical laboratories offering specific clinical genetic tests, we do not know whether patients who were denied access to these tests had testing performed by another laboratory. Furthermore, our data do not directly address the question of whether patents and restrictive licensing practices have affected the cost and quality of genetic tests, or hindered new research. Nevertheless, the practitioners in the United States who perform these tests on a daily basis overwhelmingly feel that costs, both to laboratories and to patients, have been increased. Such increases can only lead to limited access. In addition, a lower number of laboratories performing the tests could lead to lower test quality, less test method innovation, and less clinical research. Although patents may have provided incentives to conduct the basic research underlying the genetic tests, the reported inhibition of clinical testing and research does not bode well for our ability to fully and efficiently use the results of the Human Genome Project and related work.

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