

On the Exclusive Licensing of Disease Gene Patents

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Jon F. Merz

Center for Bioethics

University of Pennsylvania

acknowledge collaboration of Mildred Cho,
Debra Leonard, Madeline Robertson,
Anna Schissel, and Antigone Kriss

Overview

- What are disease gene patents?
- Ethical concerns about the monopolization of genetic testing services enabled by disease gene patents
- 3 surveys
- Conclusion

Disease Gene Patents

- A small but rapidly growing subset of “gene patents”
 - Thomas et al showed diagnostics to be the 5th most prevalent class in their summary of patents issued 1981-1994 (Nature 1996; 380:387)
 - Diagnostics was 1st in their review of patents issued in 1995 (Nature 1997; 388:709)
 - Celera intends to patent ~300 SNPs/”gene systems” having diagnostic potential (Science 1998; 280:1540-1542)
 - Celera, Incyte, and Athersys have filed 10s of thousands of provisional applications (The Scientist 2000; 14[5]:8)

Disease Gene Patents

- Claim the observation of an individual's genetic makeup at a disease-associated locus when done for the purpose of diagnosis
 - Based on the discovery of a statistical association or causal connection between genetic variability and disease risk/occurrence
 - Cover all methods of “looking at” that locus
 - May be used to monopolize provision of medical service

Ethical concerns

- Exclusive licensing is being used to monopolize lab services
 - ability to prescribe nationwide medical standard of care
 - may restrict access by requiring prepayment, charging higher prices, refusing Medicaid reimbursement
 - may subvert education, counseling of providers/patients
 - potential lack of adequate quality control
 - may limit types of “permissible” testing

More ethical concerns

- conflict of interest
 - inappropriate (over)use of tests
 - direct to consumer marketing
 - human subjects concerns
 - monopolization of samples/research resource
 - aggressive solicitation
 - undermines objectivity in performing/publishing research

More ethical concerns

- Exclusive providers may inhibit research
 - external study/validation
 - may inhibit widespread clinical use and observation
 - impose stifling reach-through conditions (e.g., rights of first refusal, compulsory licensing of related discoveries)
 - may impose unethical constraints (e.g., limits on clinical uses of research results)
 - right to royalties/control downstream research using the claimed gene sequences is a disincentive to development of therapeutics

Study 1: Licensing of DGPs

- Identified 37 US Patents containing extremely broad claims for all methods of diagnosing particular genetic mutations
 - search of Lexis and Genetic Medicine databases; examined first claim for over 600 patents
 - less 2 patents with non-US assignees
 - less 2 patents that lapsed for nonpayment of fees
- 33 patents, issued from 1991 thru 1997:
 - assigned to 16 universities and 3 companies
 - 22 (67%) funded in part by federal gov't
 - cover:
 - neurological diseases (13)
 - metabolic disorders (6)
 - immunological disorders (3)
 - cardiovascular diseases (6)
 - cancers (5)
- Schissel A, Merz JF, Cho MK. Nature 1999; 402:118.

Study 1: Survey

- Summer 1998, IRB-approved survey of patent holders about licensing efforts, marketing of the patent/genetic test, known uses of the test, and enforcement
- held 17 (89% of institutions) interviews, covering 27 (82%) patents in our sample
- 9 of 14 patents (64%) issued more than 2 years prior to our survey were licensed, contrasted with 5 licensed patents of 13 issued more recently (1-sided Fisher's exact $p=0.17$)
- tests for which respondents reported known clinical uses were more likely to be licensed (OR=14.7, $z=2.3$, $p=0.02$)

Study 1: Survey results

Patents covered by survey 27

Licensing:		Require license for research activities:	
exclusive licenses granted	14 (52)	yes, without exception	
nonexclusive licenses granted (22)	0 (0)	yes, except academic researchers	6 (22)
no known interest to take license	9 (33)	yes, royalty-free	3 (11)
license in process	2 (7)	no	12 (44)
will not be licensed	2 (7)		
Promotion and development of patented test:		Known uses of test:	
active marketing effort	25 (92)	clinical	9 (33)
not worth effort	1 (4)	research	15 (56)
not being promoted, no reason	1 (4)	don't know	8 (30)
test in commercial development	7 (26)		
Enforcement of patents:			
intend to enforce	18 (67)		
no, too troublesome/expensive	9 (33)		
suspected infringement	5 (18)		
mailed notices of infringement	3 (11)		
brought lawsuit	1 (4)		

Study 1: Conclusions

- Many institutions are granting exclusive licenses on disease gene patents
 - not all: Michigan is broadly licensing the $\Delta F508$ CF patent, which issued July 1998
 - but: broad patenting strains university resources
- Exclusive licenses are being used by various parties to restrict clinical (and clinical research) uses of patented tests
- NIH should not grant exclusive licenses, and universities should limit exclusive licensees to nonexclusive performance and sublicensing

Study 2: Pilot Survey of Laboratorians

- with Mildred Cho and Debra Leonard
- IRB-approved anonymous survey of attendees of AACC Forum on Genetic Testing and AMP Annual Meeting, Nov. 1998
- convenience sample: surveys mentioned and available to attendees outside meeting room
- 15-question, 2 page survey addressed:
 - lab setting and position of respondent
 - types of testing performed
 - licenses held on procedures, devices, or reagents
 - whether the lab had not developed or stopped offering a patented test
 - respondents' perceptions of the effects of patents on clinical/research testing services

Study 2: survey responses

- 74 responses (22/~100 AACCC, 52/~300 AMP attendees)
- 52 respondents (70%) were lab directors
 - remainder were supervisors, staff, technologists/tech managers, or other
- 46 (62%) worked in university laboratories
- 71 labs (96%) perform genetic or hematopathology testing
- 55 respondents (74%) reported holding licenses on patents
 - 54 hold PCR licenses
 - 7 hold licenses on disease genes, including:
 - Factor V Leiden, Apo-E, DMD, BRCA, FrX, others
- 61 (82%) reported paying royalties
 - range: 9% (PCR) to 75% (hCG)

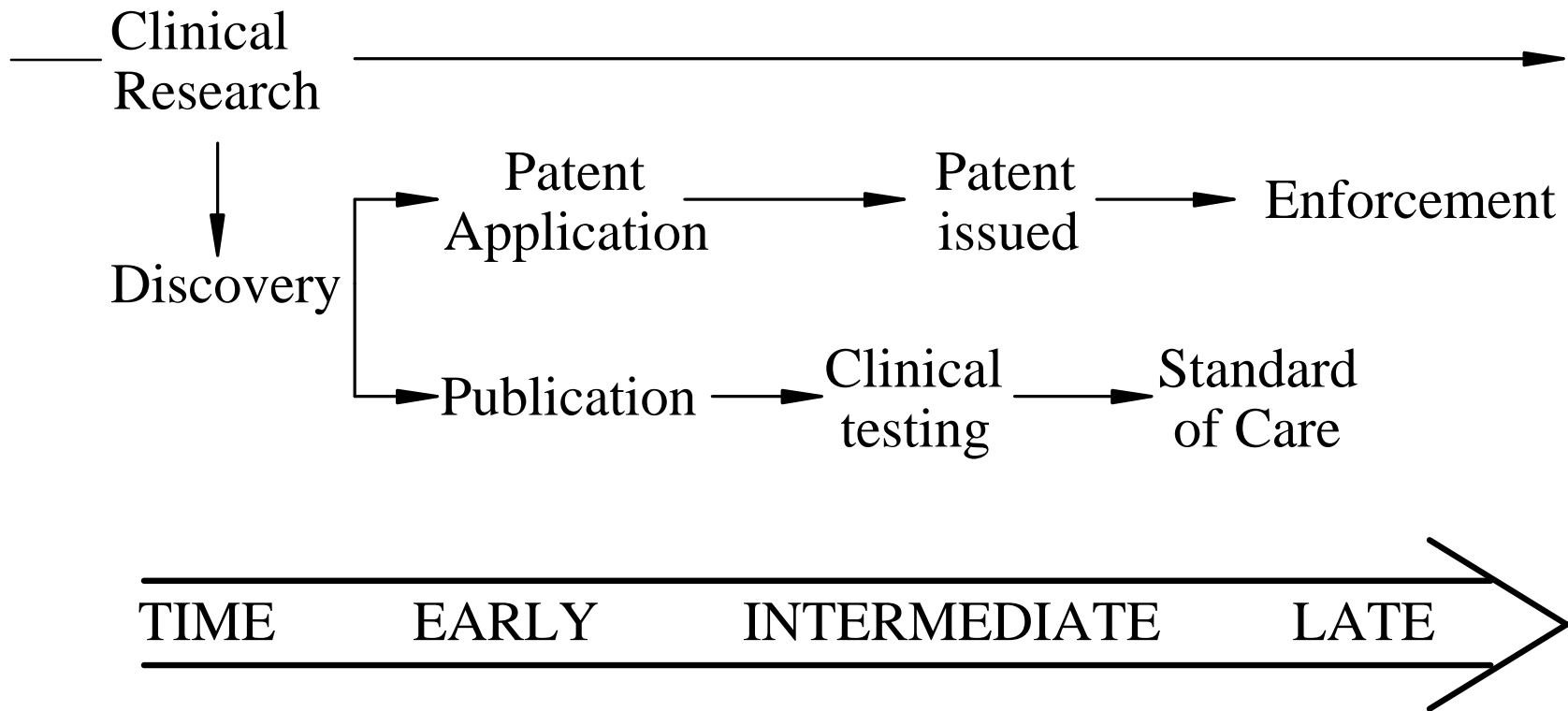
Study 2: survey results

- 18 respondents (25%) reported that their lab had been prevented from continuing to offer or perform a clinical test that they had developed and validated
- 35 respondents (48%) reported they had decided not to develop or perform at least 1 test because of a known patent:
 - HFE; Apo-E; BRCA; hCG; CMT; Factor V Leiden; Fragile X; CF, SMA; SCA; Gaucher's Disease; HNPCC; others.
 - lab directors more likely to report they had not developed a test than other respondents
- despite the nonrepresentative, self-selected sample, this suggests that many labs are being affected by disease gene patents
- suggests need for more systematic study

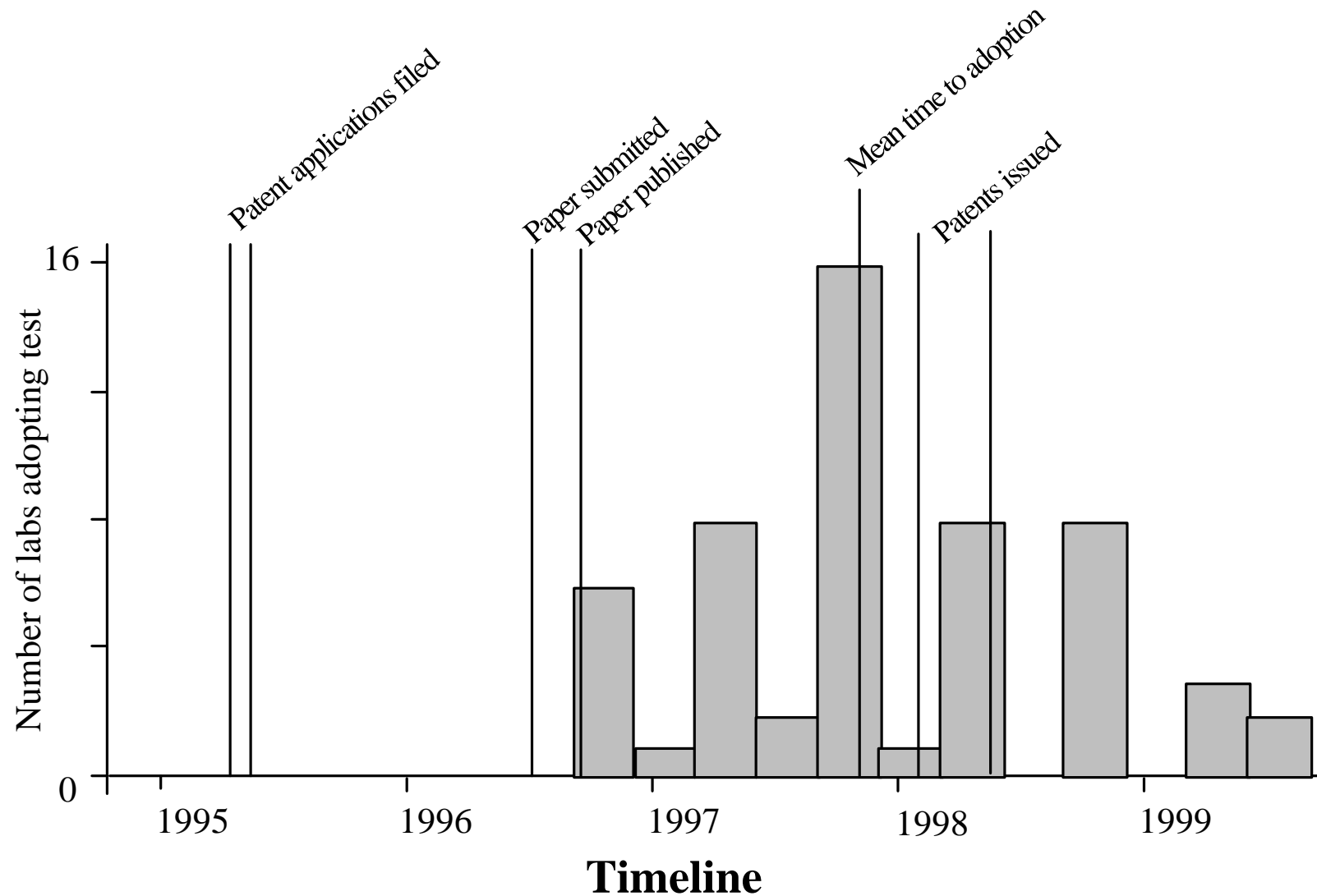
Study 3: Survey of Labs re. HFE testing

- with Antigone Kriss, Debra Leonard, and Mildred Cho, summer 1999
- IRB-approved survey of US-based laboratories capable of performing HFE testing
 - identified 117 labs in GeneTests database and AMP Test Directory
 - snowball sampling yielded 11 additional labs, for total sample of 128 labs
- of 128 labs, AK contacted by phone 121, and completed 112 surveys (87.5%), with 9 refusals
- 86 respondents (77%) were lab directors, 11 were supervisors (10%), and the remaining other types of staff.
- current hemochromatosis testing:
 - 18 (16%) perform biochemical tests only
 - 54 (48%) perform HFE testing only
 - 14 (12%) perform both

Patenting May Influence Test Dissemination/Adoption



Study 3: Survey results - time to adoption



Study 3: Results

- 104 respondents (93%) stated they were aware of the HFE patents
 - 56 heard about it from colleagues/meetings
 - 30 reported first learning upon receipt of SkB letter
- 50 respondents reported receiving the SkB letter
 - those receiving the letter were more likely to say the patent influenced their decision not to develop or to drop the test (p<0.001)
- 21 (19%) stated they had not developed the test at least in part because of the patent
- 5 (4%) stated they had ceased performing the test

Study 3: Conclusion

- As of August 1999; at least 20% of labs nationwide had refrained from performing hemochromatosis genetic testing because of the HFE patents and exclusive license
 - the patents create uncertainty for laboratorians regarding the expenditure of resources to develop and validate tests
- This case is still evolving: SkB sold its clinical laboratories business, and while many labs reported signing confidentiality agreements to begin negotiations for sublicenses, no one reported having completed such negotiations.
 - a follow-up survey may yield valuable insight to the process by which the patented test moved into the market

Conclusions

- Numerous questions have been raised about the relative benefits and burdens of genetic testing patents
- Because of the ethical concerns about the risks to patients and public health, to the practice of medicine, and to medical science, perhaps we should shift the burden of proof to show that genetic testing patents are “worth it”
- Should consider policies/law that prohibit exclusive licensing or require licensing of physicians/laboratories at reasonable royalties
 - can maintain the putative incentive/reward of patents while limiting potential negative effects