Data and Analysis of the Impact of DNA-based Patents on Access to Genetic Technologies and Services
Mildred K. Cho, Ph.D.

DR. LEONARD: So I'm very pleased to introduce Mildred Cho. Dr. Mildred Cho from Stanford University.

Mildred, take it away.

DR. CHO: Thank you.

(Slide.)

Thank you for inviting me here. It has already been very exciting even before I got here like the taxi ride getting here from Dulles but I don't think it was exciting as some of your trips here. I didn't have to ford any streams or anything like that but here I am.

So thank you for inviting me. I'm just going to go through the results of some studies that I did—that I started at the University of Pennsylvania when I was there when Deb Leonard was there and actually the reason why these studies were done was because of Deb Leonard.

When I was at the Center for Biomedical Ethics, she came over to the center to visit me and my colleague, John Merz, when we were over there. John Merz having some background in intellectual property and me having an interest in genetic testing. And she came over with one of those letters in her hand. She said, "You have to study this." So as a result—those of you who know Deb from having been on the committee with her, she didn't go away until we had gotten a grant to go to study this and she was a co-investigator on that grant.

So I'm just going to through the results of some of those studies very quickly and they have—at least the part that I'm presenting has been published. We're doing a little bit more analysis on some of the data but most of it has been published and I think you probably received those papers. So I'm just going to kind of go through the summary of those studies.

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So, as Deb already described to you, what we were interested in is looking at sort of the impact of the patenting activity on both the practice of clinical genetic testing as well as the research and development that went into that. I know you're interested in sort of access issues and issues of clinical genetic testing but, as you probably also know, it's hard to draw a very clear distinction between the research activities that go into developing a clinical genetic test and the actual provision of clinical genetic testing services. And the people who do those activities are often one in the same and it's very difficult to sort of say when you've moved from research to clinical activity. So in a sense we were sort of studying both of those.

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Some of the concerns that Deb had already described to you are what we ended up looking at, including issues about the cost and access to testing services, as well as the ability to conduct research and development to improve clinical genetic testing services. As well as possible concerns about whether intellectual property protections might actually be insufficient in some cases and perhaps provide not enough incentive for development of new genetic tests.

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So I'm just going to go right into describing some of the studies. There were two studies that we did which were studies of laboratories like Deb Leonard's in the United States where we were looking at the impact of patents on those laboratories and their ability to provide clinical genetic testing services. This is one of them.

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And one of those two was a particular case study looking at the provision of one genetic test in particular and the case was on the provision of hemochromatosis.

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And then finally I'll just go very briefly at the end into a couple of studies we did looking at how patents related to DNA based inventions have been licensed.

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So for the two surveys we had similar methods. They were both done as telephone surveys of laboratories providing clinical genetic tests in the United States as ascertained by gene tests and the membership in the Association for Molecular Pathology in the United States.

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And as it turns out there's actually not that many labs in the United States doing clinical genetic testing. As far as we could tell, about 200 or so. Just over 200. So we could actually try to sample the universe of that sample. And so we—for the first study where we were going to ask questions about clinical genetic tests performed by—all the clinical genetic tests performed by these laboratories, we were able to get 60 percent of the labs to respond.

And of those respondents—we included 122 laboratories who conducted clinical genetic tests. Some of them were eliminated because they did not perform the kind of tests we were interested in, not performing DNA based genetic tests. And of those 122 that we included in the sample, all but one conducted testing for clinical purposes. That one said that they were just doing testing for research purposes.

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So of those testing labs, the majority of them had been contacted by a patent or license holder with a letter like those that you saw from Deb. So this was back in 2000-2001. So this is a few years ago and so most of the labs had received a letter like the ones Deb showed you.

And a significant proportion of those 122 laboratories said that a patent or license holder had prevented the lab from continuing at least one test service. So that's a quarter of the labs and that again was a few years ago.

Seventeen of the 30 labs that had reported being prevented from continuing a test service had been prevented from providing one test but 12 had been prevented from providing more than one test.

And, interestingly, the for profit testing companies were more likely to report being prevented than university laboratories and that may have something to do with the volume of testing that Deb mentioned.

(Slide.)

So if we look at the tests that they said they had been stopped from being performed, you'll recognize many of these from the talk that Deb had so I think that many labs had gotten the same letters about the same kinds of genetic tests so you'll recognize BRCA1, ApoE, canavan disease, SCA, Fragile X and so there were very specific tests that were being prevented from being performed.

(Slide.)

And so when we looked—we went and decided to look a little bit more at the characteristics of those tests and how many labs were doing those particular tests because we were thinking, well, maybe these are tests that more labs do because they are of more clinical interest or there's higher volumes or more reason to do these kinds of tests. So we did look at how many tests that were being done by over 10 labs and all 11 of those tests that I had on that previous slide were being done by a large number of tests.

Many of the genetic tests that you know about are done very—on very rare conditions and so there may only be one or two clinical laboratories in the whole United States doing those tests because there's maybe only ten people in the country at any given time that have the condition that is indicated. So all the—but in contrast all the things on the list on the previous slide there were things that were done by a larger number of labs.

(Slide.)

And there were 14 patents relevant to the 11 tests that you saw on the previous slide. Most of those were held by universities, not for profit companies, and seven of those or half of them were—the patents or the inventions were made as a result of research funded by the government.

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So, as I said a couple of slides ago, a quarter of the labs said that they had been stopped from using—performing a test that they had previously been performing as a result of the patent enforcement. Half of those labs had decided not to develop or—well, not half of those labs but half of the labs in the sample decided not to develop or perform a clinical genetic test because of a patent. So in addition to labs stopping performance of a test they also halt their development of new tests because of the possibility of patent performance. And there was no significant difference between companies and university labs in their response to this question.

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We were not able to look directly at issues of cost and access on a per test basis because some of that information is very difficult to get. As you saw from Deb's presentation, sometimes or almost always the licensing agreements that are struck between patent holders and the licensees are confidential. So it's very difficult if not impossible to get the actual terms of licensing agreements because of these confidentiality restrictions. So we tried to get information as best we could from laboratory directors about how they had personally been affected in the performance

of their laboratory testing both on their own ability to provide tests, develop tests and also provide those tests to their patients.

(Slide.)

So we asked about their opinions on the effects of patents on their ability to—the patient's ability to access testing, whether the costs had been—had gone up or down, whether they felt there was any impact of patents on the quality of testing, their ability to develop new tests, to share information with other laboratories on how best to do these tests, or to do research.

And, as you can see from the responses here, these are the absolute numbers of lab directors responding to these questions. Their responses were on the whole overwhelmingly on the negative side, meaning in terms of access lower access, higher costs, lower quality. Zero in the middle here means neutral. So lab directors were more neutral on the issue of whether patents had an effect on the quality of testing but again negative in terms of their ability to develop tests, share information with other labs or do research. So we think there has been—at least on the basis of this information, it looks like lab directors are not—are not happy about the effect of patents on their ability to perform and develop new tests.

(Slide.)

And, furthermore, it looks like the patents and licenses have affected tests that are most commonly performed. At the end I'll show you a little bit of data from other people who seem to have found similar things.

(Slide.)

And some of these patented tests have resulted from government funded research, although not all, so there may be some reasons, which I'll go into after the next slide, that may impact in terms of the policy options that we might want to think of on the basis of this kind of information.

(Slide.)

The second study was looking at the patents on the—the effect of patents on the HFE gene, which is associated with hemochromatosis, and this gene was being researched by a company called Mercator Genetics, which spent a lot of money developing its own method and discovering the association between HFE mutations and hemochromatosis.

Three patents were issued to Mercator in early 1998 for genetic testing of two of the more common variants but Mercator went out of business and Progenitor merged and was with Mercator and was assigned its patents. So it took over these patents for the hemochromatosis testing.

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Progenitor then licensed those exclusively to SmithKline Beecham for an up front payment and this exclusivity and payment guarantees were continued until a kit became available for use by clinical laboratories.

So SmithKline Beecham began enforcing those patent rights in 1998 and you can see the terms that were offered to other labs were similar to those that were offered to Deb Leonard in her lab.

In the fall of 1999 this diagnostic test was sold to Quest and during that time and for some years afterwards there was not active enforcement of these patents.

(Slide.)

A couple of years later Bio-Rad began offering a test kit for these two mutations and was offering to license this to perform testing without its kits but at a fairly high cost. And so again up front payments and per test fees were involved if you required a license for this.

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So at this point we were already contacting laboratory directors to survey them so we asked them specifically about this particular set of patents and almost half the labs that we had contacted were performing the HFE testing at that time. There actually had been more labs performing the tests but some of them had discontinued that because of the possibility of patent enforcement.

As you can see, almost half the labs had received a letter of patent enforcement from SmithKline Beecham at that point.

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So as I said a quarter of the labs had not developed and were not performing the HFE test because of that patent enforcement and only four percent had stopped performing the test at that point but more had stopped performing it afterwards.

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So over half of the labs, 60 percent of the labs that were performing that HFE test had introduced performing the test before the first patent issued in 1998 but after the critical paper about the association between the mutations and the disease had been published in 1996.

So you can see that this is a very rapid adoption of this test after the publication. So almost immediately after publication and with a mean time from publication to adoption this test was adopted in an average of 14 months after publication. This is very rapid compared to if you think about drug development, for example, from the time of finding something that is a patentable invention, some kind of discovery, to go from discovery to clinical adoption. A drug would probably take more like 14 years than 14 months.

This is very rapid and very different from the sort of pharmaceutical development model where—if you think about the—when you think about the policy options, again this is something that should be taken into account as a major difference in diagnostic testing between this and drug development and the impact of patents or even the necessity for patents in that procedure.

(Slide.)

So this is just a graphic to illustrate some of the major time points in the development in the patenting and the most important things to look at are you can see where the paper was published here at this time and this line indicating the number of labs starting to use the test and where the patents were issued. So many of the labs had already adopted the test before the patents were issued.

(Slide.)

So on the basis of these studies we do think that patents and licenses have had a significant test on provision of clinical genetic testing services at least as ascertained by surveying lab directors. We are not able to get data directly on the provision of individual clinical tests as they get passed down from reference lab to reference lab. So we don't know whether the total volume of tests has decreased or the total price of those tests as experienced by patients has been increased, decreased or has prevented individual patients from getting testing because from the patient's perspective this process may not be apparent to them. They may not realize that their tests have been referred from one lab that doesn't have a license to another one that does and so forth.

But as seen from the laboratory directors' perspective, it does appear that the impacts on costs, quality, access and further research on these tests have been largely negative for patients from their perspective.

(Slide.)

At least for some tests labs don't appear to require patents as an incentive to develop findings into clinical practice on a rapid basis. Again this is in contrast to, for example, drug development.

However, patents may provide incentives to conduct research necessary to identify genes associated with disease and so, I think, in this—what this illustrates is a sort of difference in providing incentive for research to get to the invention as opposed to the necessity for patents to provide incentive to do post invention research. So if you think about sort of the finding of an association of a disease with a gene as the invention, it may be necessary to provide incentives to get to that point but for clinical genetic testing to get from that point of discovery to providing clinical services is something that does not necessarily have to require lots of investment to get to from R&D to the—to get through the R&D process.

Part of that is obviously because if you're developing a drug, the regulatory hoops that you have to jump through compared to providing a clinical genetic testing service are very different. If you're providing a kit there's more regulatory burden and more development that you have to go through and more costs but it's still quite different from drug development.

(Slide.)

I'll just talk very briefly about some of the licensing studies that we did. These were not done as a study of laboratory directors. Here what we did was identify in the patent database institutions that held patents in particular—in a particular class that was relevant to DNA tests. So what we did was select the class 435/6, which is a class of inventions that were—that are considered molecular biology inventions that involve nucleic acids. And then we selected the subset of those that had sequence identifiers included in the claims where DNA sequence is provided.

Then we identified all the institutions that held—that were assigned three or more patents in that class and it turns out there aren't—at least at the time that we did the study there weren't that many of them. There are many more now but we identified approximately 100 institutions holding patents in this class at that time.

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So we interviewed 27 non-profit institutions and 19 for profit institutions of those and people at NIH.

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And asked them about licensing practices of the patents that they held in that class. Interestingly, when you look and analyze these institutions broken down by nonprofit and for profit institutions, the behavior of the patent holders is very different when analyzed this way. A very small proportion of the disclosures that are received by nonprofit institutions are actually filed as patents. Whereas in for profit institutions almost all of those possible inventions—inventions that are possibly patented are actually filed.

On the other hand, the behavior in terms of licensing is the reverse. So the nonprofits tend to license exclusively once they have a patent. Whereas, the for profit institutions tended not to provide exclusive licenses.

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There was also very little agreement among our license holders and there wasn't a difference between nonprofits and for profits about what constituted a research tool versus a target. So some of the quotes that we got in these interviews are here. One person said that a drug target or disease diagnostic is not generally considered a research tool. Another one said that genes are drug targets—that genes that are drug targets are viewed by large companies as research tools but small companies feel that they are not research tools.

So this is just a couple of quotes out of a whole number where it was clear that one person's research tool is another person's target basically. This is also a reflection again of the difficulty with creating a clear distinction between sort of clinical practice and research especially in the area of DNA diagnostics.

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So overall from this and other kinds of studies that we've done on patent holders of those that have DNA based patents, these inventions may not be controlled by—most DNA inventions may not be controlled by a patent and an exclusive license, especially in the nonprofit sector. So there may be many things that are inventions that could be patented but perhaps are not. But if those are—inventions are patented at a nonprofit university, for example, they are likely to be exclusively licensed.

And clinically important patents on diagnostics may be more likely to be subject to patents than those that are not and you could kind of see that from both Deb's information and from what we found in our surveys.

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There haven't been—as far as I can tell in the literature—other studies of the impact of patents and licenses on clinical practice per se but many others have looked at DNA based patents and the impacts of those. One recent study was looking at patents on the human genome overall. That was published in Science last year. And they found that nearly 20 percent of human genes are claimed as U.S. intellectual property.

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And they found that 63 percent of these are held by private firms and 28 percent by public entities but the distribution across the genome—so if you actually map the patents to the genome you could see that the distribution is, as you would expect, uneven. So, for example, of 291 cancer genes that they located throughout the genome, 131 of those are patented. These three genes here, BRCA1, et cetera, were in the sort of highest list for number of patents. So you can see that the patents tend to cluster around things that are of clinical significance as one might expect.

(Slide.)

So those are—that's the end of my presentation. I think we're going on to other questions later.

DR. TUCKSON: We'll get to the questions. Thank you by the way. Well done.

DR. CHO: Okay.

DR. LEONARD: So it is—thank you, Mildred.