International Reports and Recommendations Regarding Gene Patents, Licensing Strategies, and Genetic Tests
John Barton, J.D.

DR. EVANS: And the last portion of the international roundtable from today is going to focus on several recent international reports that address gene patents, licensing and genetic technologies, and how intellectual property affects genetic testing.

Our first speaker is John Barton. He's an Emeritus Professor of Law at Stanford University and co-founder of the Stanford Law School Center for Law and Technology. He specializes in international and high technology issues. He serves as a member of the Nuffield Council's study of gene patenting and was chairman of the U.K. Commission on Intellectual Property Rights and Developing Countries.

He looks far too young to be a Professor Emeritus, but I'll turn it over to you, Mr. Barton.

MR. BARTON: Thank you very much. First of all, I must own up that I'm going to deviate somewhat from the international focus, if that's acceptable. I'm going to spend some time on precisely the international focus based on work with the Nuffield Council, and then, because it seemed eminently appropriate, tell a little bit about a real-world experiment, a factual experiment that I have not published but that seemed particularly important, and then come back over to the recent Supreme Court cases because they really are producing a very fundamental change in patent law.

I don't think I need to tell you about - well, I do want to say one thing about gene patents. I think it's extremely important to remember when we talk about patents that we're talking really about particular claims, and the question is what is claimed? It's easy to say that a particular gene sequence is patented, but what does that actually mean? It usually means something like I claim the isolated sequence; in other words, in essence, so to speak, a very long oligonucleotide that has been cut off from the rest of the DNA. I claim constructs like a production organism that has those sequences put into it so you can produce a particular protein easily. I claim the proteins. Maybe I claim the research use. It's very important to distinguish between these because that really affects the effective scope of the patent.

Now, the reports that I'm prepared to talk about, and I'm going to concentrate on just the first of these, are the Nuffield Council on Bioethics, one which I was involved in about five years ago now, but note that many of the same things were said in other recent studies.

Let me say just a little bit about the Nuffield group. It was very heavily an academic group. There is an academic geneticist on it, there's an academic philosopher on it, there was a retired eminent person from the pharmaceutical industry. There was nobody who had had background in the diagnostic industry, and I think it's important to recognize that in evaluating the conclusions. We really had three themes that we were trying to put together. One was we figured it was absolutely crucial for Genentech to be able to produce TPA; i.e., a natural human protein that has a therapeutic purpose but wouldn't be practically available unless made through genetic engineering. It's absolutely important to have that kind of product.

Then at the other end, because that obviously argues for broad patenting, but then arguing in the opposite direction for some of us is the question of the research tool use, the relationship between the biotech industry, which would like to have lots of things patented in terms of research theories, genes, receptors, everything like that in order to be in a good bargaining position for

raising capital with the pharmaceutical industry and then produce its products for the pharmaceutical industry. So there's a big split in the industry on that set of issues, as well as between the academic scientists and the industry.

Then, obviously, the diagnostic testing question where the tension which you've seen all through today. The tension is clearly very significant. To what extent do I want to preserve (inaudible) for preserving these diagnostic tests by expanding patentability, and to what extent do I want to preserve access by narrowing patentability?

Now, what we did was attempt to fundamentally recognize - and I'm going to read a conclusion in a moment - fundamentally state legal principles firmly and severely in order to try to reduce the problem as much as possible. In a sense, looking at the numbers which my colleague Joseph Straus showed, looking at the numbers to a great extent, clearly Europe has done that. The number of patented gene sequences in Europe is obviously - I calculated no more than 10 percent of the number in the United States. So there is a difference there.

But then I think what was in some sense our most important insight was that we wanted, to the extent possible - and we talked about this, although it appears more as a theme than as a conclusion - we wanted to distinguish between a DNA sequence as information, which we want to keep in the public domain and useable as broadly as possible, from that sequence as a chemical, which is legitimately patentable, because that's fundamentally the distinction we tried to push. You can see immediately why I want to make sure that we emphasize what do we mean when we patent a gene, and I want to talk a little bit about claims.

So in a sense, if we could make that distinction effectively, and obviously doing so was extremely difficult, then we would have solved some of the problems. To the extent that we do make that distinction, we effectively say diagnostic tests are unpatentable when the claim is in the form I have identified this mutation as associated with that disease and I claim the use of the mutation to detect the disease. We would leave patentability - and this is the kind of direction we went in the analysis - we would leave patentability for I have a particular gene sequence which if you use it in a particular probe will be good at identifying whether or not that mutation is there, but we have left it possible for others to try to find the mutation in other ways, as for example by sequencing the genome, and that would avoid infringing the patent. So that was the clear implication of where we were going, and to give you a sense of how far this went, let me quote from the conclusions.

"We recommend that the criteria already in place within existing patent systems for the granting of patents be stringently applied to applications for product patents which assert inter alia rights over DNA sequences for use in diagnosis. If this recommendation is implemented, we expect the granting of product patents which assert rights over DNA sequences for use in diagnosis will become the rare exception rather than the norm." We conclude that the protection by use patents for specific diagnostic tests - i.e., my patent on the particular chemical, the particular sequence which you use to find the mutation - we consider the grant of use patents as a way to provide an effective means of rewarding the inventor while providing an incentive for others to develop alternative tests. We then went on and you can see clearly a strong bias towards public access to tests.

We considered that in the case of patents that had been granted for diagnostic tests based on genes, compulsory licensing may be required. Now, this is something which I think the committee would probably find quite useful. It's available at www.nuffieldbioethics.org. Obviously, it's now five years old. Nevertheless, I think we had some very good insights in it,

and I think it's well worth your review, recognizing that it has to be brought up to date. I think I'll pass this given where we're going.

With that background on the Nuffield Council, I would say it was well accepted within the British community. The way a commission works in the British community is a little bit different from the way a commission works in this society, and it's a small enough society that you get feedback from all kinds of different directions on a personal basis. The feedback was quite positive.

The second point I want to talk about is the real-world experiment which I had done, and I did it in significant part while I was at NIH two or three years ago. It's unpublished, but I thought it was so relevant to you. I talked with the Duke people and I'm going to give them all my data. I felt concerned because all the critiques I'd seen of diagnostic patents take the bad side. They take the side of saying here are the cases in which access has been denied. None of them look at the other side of it, to what extent is there an incentive. So I attempted to say in order to try to solve that problem, instead of looking at all the patents and diagnostic tests for which there are complaints or concerns, I would choose as best I could an unbiased sample of diagnostic tests, and I called up GeneTests up in Seattle and got their 10 most commonly chosen tests and their 10 most common gene review access tests and put those 10 together. There was some overlap. So based on that, I got 17 gene tests that I attempted to look at, and I looked at in each case to the extent I could what kinds of patents covered those tests, and it was clearly a nightmare. I mean, it was clearly not random. I put that forward in big, bright letters because it was an interesting game in itself in which in some cases I had essentially to go to the scientific articles that I found from the gene test area, find out whether or not their names appeared on patent applications. I mean, it was not an easy thing to do, and I found all kinds of patents. You can see again all the different kinds of focuses of these.

But what came out very interesting when I looked at them is that although the number of patents were divided roughly evenly between what I called the private world - i.e., the Myriads of the world - and the public sector - i.e., the University of California, et cetera - there was a significant focus. The private emphasis was heavily focused on hereditary hemachromatosis, on BRCA, and on spinomuscular atrophy, and almost everything else was public sector. The obvious implication, and it's kind of obvious when you step back from it, is that for what looked like the most popular, biggest market kinds of tests, patents and diagnostics work. They encourage private sector innovation. For everything else, it's done under NIH funding or Howard Hughes funding or what-have-you, and we don't really need a patent to encourage the innovation - maybe. I'm going to give a critique of that.

So the implication is the incentive effect works strong for the most common genetic diseases. For the others, we are assuming - and this is a point which I haven't heard mentioned at all today and I think is extremely crucial - we are assuming it is an easy leap from detecting the gene sequence to having an effective diagnostic test. That depends, in fact, on what the FDA does about the regulation of diagnostic tests. If the FDA makes it harder to bring a diagnostic test to market, then maybe we need a patent. I mean, I'm sure you've all heard the story which is accurate that if a university invents a new pharmaceutical product and puts it in the public domain and writes an article on it, the market product will never see the light of day. You need a period of exclusivity in order to justify the elaborate tests that are necessary in order to bring the product to market, in order to justify investing in the clinical trials. Clearly there is an interplay between the value or not of genetic patents and the regulatory standards we apply to them, and I think that's an extremely important issue which should be considered.

I might also note a couple of other nuanced differences between the old world and the new world. I mean, this study was two or three years ago. The Myriad controversy, which has taken a fair chunk of the day, was essentially five years ago. Let's look at today's issues. I actually published an article last summer in Nature Biotechnology on patents and pharmacogenomics, basically. Consider the interplay between the company which has intellectual property rights on a pharmaceutical product and the company which has IP rights on the diagnostic test which you use to decide whether or not that particular pharmaceutical is appropriately used on a particular patient. In fact, my article talks about the Herceptin example. It turns out that in the Herceptin example, a Genentech product, Genentech went and, in essence, sponsored the encouragement of some diagnostic companies. It won't necessarily go that way in the future.

There are, for example, a host of companies which are trying to claim fairly broad patent rights on P450, which is one of the key enzymes in metabolizing a variety of different drugs, and it's probably going to be very crucial in the future of pharmacogenomics. So that case might go quite differently.

I might note also that we're going to see more and more sophisticated kinds of intellectual property that come from the big pharmacogenetic studies. We're going to see essentially the drug company finds my drug works well for this category of patients and not so well for that category of patients, and here is the elaborate mathematical function which is based on a zillion different mutations found or SNPs, depending on how the study has been done. Here's the elaborate mathematical function which is going to draw the line between the effective and the ineffective cases, and we're going to see people obviously claiming intellectual property on that. Is that a diagnostic test? That's part of the future.

I should admit a conflict of interest here because I've done some work for Affymetrix. The question of arrays in which you have a zillion different diagnostic tests based on one chip, clearly horrible problems if the marketing of a chip to, let us say, detect different sub-forms of cancer or different sub-forms of HIV which can be treated with which drugs and so forth, if some of those can be held up by patents on the use of individual sequences, it's going to be a very complicated life. So I simply kind of want to suggest as part of your thinking, make sure you look at these problems as well as at the other ones you've talked about.

Now, the final point, and I think I feel appropriate bringing this one in, is a little bit further data on how the law has changed since 2005. There are several major law-changing centers in this city within a very few blocks of where we sit, and the Supreme Court has really decided - and I think I may as well put it straightforwardly - the Supreme Court has really decided that it does not like the direction that the Court of Appeals for the Federal Circuit has taken patent law in. I think that's pretty clearly what has happened. I think every one of these cases that I'm listing, plus a couple more - and I'll have to drop the second one from the list, as will be clear in a minute - are cases in which the Supreme Court has reversed the Court of Appeals for the Federal Circuit. Every one of them makes a major change in patent law, and we're talking within the last two or three years. Let me just kind of walk through them very quickly, spending most time on coming back to LabCorp, which I think is the crucial one for our discussions here.

Merck v. Integra, this said, in essence, that the statutory research exemption can be applied very, very broadly. In my judgment, although I think there are people who disagree with me, in my judgment it has radically changed the balance between the pharmaceutical industry and the biotech industry. It has told the pharmaceutical industry you can infringe a lot of biotech industry patents as long as you are doing so as part of a regulatory process. That's extremely significant

for the research tool set of questions, which are of course another part of this genomic patent issue but clearly is not your focus.

eBay v. Mercantile Exchange decided last year that the standards for deciding when an injunction should be issued should be a lot more narrow than the Court of Appeals for the Federal Circuit had had it, and the clear implication is no longer is an injunction automatic. There are now two sides to that debate, and to take a serious example, suppose my gene chip has your patented test on it along with a zillion others that are important to a particular diagnosis. Can you get an injunction to keep my chip off the market? It's not crystal clear at all, but very likely that since eBay, you cannot. You can get a right (inaudible) for damages, but obviously that doesn't bring you nearly the bargaining power that the injunction does. But I do note that there was a case interpreting this one in Texas just about three weeks ago in which the question was can CSI Arrow, which is the Australian analog of the National Science Foundation or the Indian Council for Science and Industrial Research, can it get an injunction prohibiting use of, in this case, a technology involved in a standard for the wireless phones or something like that, some electronic standard? Can it get an injunction in that context, and the trial court said yes. It hasn't worked up the ladder, but the trial court said yes, even though obviously this company's only interest is in - the Canadian research institute's ultimate interest is not in producing a product but in obtaining a royalty. So there are some questions about that one.

Then the KSR International case just this last term has radically changed and radically tightened the standards of non-obviousness in the United States, making us look very different from where we were.

But now I want to come back to LabCorp, and here again I own up to the conflict of interest. I co-authored a brief here and co-filed it together with Affymetrix, and I think the briefs for this case are something which you all may want to look at, as are the decisions. The case fundamentally involved a correlation, and I must admit I always forget what the two compounds are involved in the correlation, but it involved a correlation between two chemicals in the human body and use of that correlation for diagnostic purposes. One of the components was folic acid.

So it said, in essence, if you measure compound X and use it to infer that there is a deficiency of compound Y in the body, you're infringing my patent. The initial trial case was brought literally on the grounds that said doctors were infringing the patent every time they did this analysis, and then the company which provided the diagnostic test to help the doctors was a contributory infringer and should therefore be sued. That's a fairly standard kind of game in terms of how you find a defendant in the patent business.

Well, this was something which under today's law, as interpreted by the courts for probably the last 20 years, was clearly patentable. This was anything under the sun, to go back to Chakrabarty. This was clearly patentable, but on the other hand this was very close, going back to my Nuffield Council report, this was very close to the information. This was very close to a discovery rather than an invention, and that point had just kind of been passed over in the law of the past 20 years. We had assumed that it had been conceded, and the case was being appealed to the Supreme Court on other grounds, and the Supreme Court issued a very surprising memo that said we aren't interested in those grounds; we want to hear about subject matter grounds. I'm paraphrasing, of course, but isn't this really a discovery, not an invention? Please tell us about that. That's what we really want to hear about.

Now, first of all, it's very odd and unusual for the Supreme Court to do anything like that. Second, this issue hadn't been discussed at all at the lower court level because everyone assumed

that the law had been settled. As a sense of how much everyone assumed that the law had been settled, the Department of Justice or the Solicitor General, whoever it was, the U.S. government came in with one of its amicus curiae briefs saying, look, you change this body of law and you're going to upset zillions of existing patents and settled expectations based on those patents. Obviously, the government didn't go on to say that. This may or may not have been an invoking interpretation of law 25 years ago, but the law has kind of crept in this direction and we don't think you should go to bat quite so dramatically given how much people relied on the old law.

The Supreme Court went ahead, heard the case, and then it came down with a very cryptic opinion. First, the majority opinion was we granted cert improvidently. In other words, we shouldn't have heard the case, we're not deciding it. Three judges dissented and said this invention should have been struck down as non-patentable. This is really a discovery. It is abundantly clear - and this is why it's crucial for you all - that if those three judges prevail, gene diagnostic patents are toast. They're gone.

So the real question, then, is what this bizarre situation means, and let me give you three possible interpretations. First, the hornbook interpretation. You are not supposed to draw any conclusions at all from the fact that the Supreme Court has not granted cert in a case. That's simply a procedural thing and you're not supposed to pay any attention to it, and therefore the law remains what it has been for the last 20 or 25 years, and the diagnostic test is patentable. Alternative 2, at least six judges didn't want to hear the case. Maybe they all felt gene tests with diagnostic correlations were patentable, and therefore gene patents stand. Version 3, three judges expressed this position. The other five judges decided that in this very bizarre and unusual patent, it wasn't appropriate to go ahead and bring the case to judgment. Let there come up a case in which the issue has been debated at the trial level and we get all the arguments and so forth, so that at least some of those six judges were coming out the other way on procedural grounds rather than on substantive grounds. We have no idea, of course, which of these versions is right.

But the net result is, I would say, the amount of money that I can obtain as a royalty for a diagnostic patent has shrunk radically. Clearly, these patents are in question. Maybe, in essence, the court has sent a signal saying the next time we get one of these cases, we're going to come down the other way. But precisely because this amounts to such a change in the law, we want to do it with a little bit of warning.

Now, before you go on to say whether or not that warning will really work or anything, consider the incentives for people to bring the litigation. I am a company which has some diagnostic patents. You infringe them. How much do I want to bring the issue to the U.S. Supreme Court? Probably only a little more than you do, and neither of us wants to spend the money doing it. So what I want to suggest is that it may well be that the effective business implication of this will be to leave diagnostic gene patents in a kind of limbo which may last forever. We may never get a Supreme Court decision on it, but in a kind of limbo where they're clearly a lot less valuable than they were not too long ago. And then even if I won the case, if I'm suing you on a gene patent, pretty clearly the extent to which I can get a remedy is going to be cut down by the eBay case, whether or not I can get an injunction, and whether I can get an injunction against you on the research tool context is going to be cut down by the Merck case, and whether or not the invention was obvious in the first place is going to be cut down by the KSR case. In other words, there is a very good chance that in its (inaudible) reform program, the Supreme Court has changed the law in exactly the direction that the Nuffield Council report wanted to go.

Thank you.