U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY

Twelfth Meeting

Tuesday,
March 27, 2007

Founders Room
Inn and Conference Center
University of Maryland
3501 University Boulevard East
Adelphi, Maryland

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (8:05 a.m.)

DR. TUCKSON: Good morning. They turned the Reedster bunny outward because, quote, "they wanted him to have web time."

(Laughter.)

DR. TUCKSON: A little product placement here. Some lawyer for the government is running around going inappropriate advertising, and I'm going to have to send them some conflict of interest form which says I have no stock in the Reese's company. I'm going to move it even more front and center just to cause that trouble, because I don't have any stock in the Reese's company.

But we want to thank Hunt, by the way, for leading our Task Force on Large Population Studies and for guiding the development of our report to fruition.

Hunt, by the way, the report does look terrific, and I want to commend you and the task force for a job well done. As I mentioned yesterday, I handed a copy of it to the Secretary in his private office, and that was fun to do, so thank you.

Yesterday we accomplished a great deal. I am really pleased about the task force that has been created. I think it's a really good one. The challenge now for that task force -- and Andrea and I and the staff have always thought it's a plan -- is timing and timeline. So we're going to ask Greg Downing if he comes today -- if not, we'll call him on the phone.

Oh, there you are.

Let me just be explicit here. What we need is to get with you guys after our meeting adjourns, in the next couple of days, and get a real sense of the timeline for the Department in terms of what it needs. Then we'll piece up and put out the committee's work based on deliverables to try to meet you all's timelines. I think the message that we would appreciate you taking back to Sheila and to Greg and to the Secretary is that we got the clock, the 664 days, I guess, left in the Secretary's tenure. Is it 665?

DR. PAREKH: I think it's 665.

DR. TUCKSON: Are they taking that Wednesday off?

(Laughter.)

DR. TUCKSON: He forgot about the Wednesday he's taking off.

So we want to make sure we're responsive to that.

DR. PAREKH: That sounds fine. Thanks, Reed.

DR. TUCKSON: Good. Thank you. So we'll get that done.

But what I would like, by the way, is what we are going to do before we leave today -- and I'm going to (inaudible) as we go along, but if anybody during a spare intellectual moment wants to take a white piece of paper and draw out what you think is the map, if you sort of take in your mind's eye molecule creating reagent, molecule beget reagent, reagent beget test kit, test kit beget laboratory, Laboratory A super-high-powered pharmaceutical company Laboratory B academic center with a zillion billion resources, academic Lab 3, a little teeny one in a corner somewhere barely turning out one thing for one particular disease or condition, and then from there it goes to doctor and genetic counselor decide to do something with this or not, FDA does something. So if anybody's got in their mind the map, to write on one page that just puts it right there, and then, Muin --

(Laughter.)

DR. TUCKSON: Muin has the map.

Then, Muin, because you're good, you take one color or check mark, like CLIA got it nailed, then another one, CLIA not so sure, FDA nailed, something else. Who knows? Here are the unmet things, and then just across the board so you can sort of see where the holes are.

So if anybody's got those kinds of things in their head and wants to give it to Andrea to fast-forward the committee, that would be just wonderful. So we're taking all comers. Thank you.

Moving on, don't do like I did yesterday. There were a lot of things I didn't do, but one thing I didn't do was I didn't order lunch, and they don't care. So you either get it in by 10:00 or 9:30, by 9:30 if you don't order your lunch on the form, they don't care.

Welcome again to Debra Leonard.

PARTICIPANT: She's not here. She'll be back later.

DR. TUCKSON: When you see Debra, tell her we welcomed her. Although she rotated off the committee, you never get to leave. She's now serving on our Gene Patents Task Force, and we want to thank her for being there.

In our June meetings, in the (inaudible) meetings, we decided to proceed with the study of the impact of gene patents and licensing practices on patient access to genetic technologies. We approved a broad study scope and discussed an investigational approach consisting of several elements: data gathering and analysis, gathering public perspectives, exploring international perspectives, and then ultimately preparing a report for the Secretary. The task force has been very active since we last met, and our friend Jim Evans, M.D., Ph.D., will provide you with all of the details.

James?

DR. EVANS: Great. Well, welcome everybody. It should be a great session. We have some excellent people here to help us understand this very complex and somewhat fraught topic. In the interest of full disclosure, I want you to know that the DNA sequence on my tie is not a patented sequence. Since this is a public meeting, I won't show you my DNA boxer shorts.

(Laughter.)

DR. EVANS: Gene patenting, we've been talking about addressing gene patenting now for about three years on the committee, since before I got to the committee. It is a topic that I think, perhaps second only to genetic discrimination, raises and evokes very strong passions. Unlike genetic discrimination, those passions are from all ends of the spectrum. In genetic discrimination, it was rare for somebody to get up and support it wholeheartedly. But gene patents people have strong feelings about, and in addition to being something that evokes strong feelings, it's a highly complex topic, one that many of us need a lot of education on.

So the cornerstone of today's session for this morning really is a series of educational talks from leaders in the field who are going to help us understand the topics that are out there. I want to just briefly review how we got to where we are and where we're going.

The Task Force on Gene Patents and Licensing Practices consists of five of the SACGHS members, although Andrea, because of other obligations that you heard about yesterday, is going to be rotating off. We have a number of extraordinarily helpful ad hoc members and ex officio members as well.

We realized early on in this process that we, again, needed a lot of help in understanding these issues and in dissecting the current landscape and the changing landscape of patents, law, practices, licensing, et cetera, and we were fortunate enough to persuade several people to help us. I'll be doing formal introductions later, but Bob Cook-Deegan at Duke, as well as Christopher Conover and Subha Chandrasekharan, who will henceforth be known as Dr. C. in keeping with yesterday -- we were also very fortunate last night to meet with these folks in a special session of the task force here in this room after our nine hours of meeting during the day, and we got to hear from a number of individuals all listed here who had looked at specific aspects of patent law, of patent and licensing practices, with obvious reference to genetics and gene tests. That was extremely helpful.

The history of this endeavor dates back to March of '04 when gene patents and licensing was identified as a priority issue for this committee. It was deferred given the fact that the National Academy of Sciences at that point had an ongoing study that they had yet to report on. By

October of 2005, the NAS report had just been released and a small group was formed to review that report, and our thinking at that time was that it was entirely possible that the NAS report would have done our work for us and that we really wouldn't need to pursue anything.

However, in full committee in March of '06, the NAS report was summarized and reviewed and it was felt that more information was needed with regard to the specific charge and mandates of this committee. Specifically, the NAS report spent virtually all of their time looking at the basic science landscape and how patents and patent practices and licensing were having an effect and might have an effect on basic research. That, of course, differs from the charge of this committee, which is more associated with the public's health, clinical access and those types of things. Since the NAS report did not really address those in any detail at all, we felt that there was more work to be done.

In June of '06, we held an information session and at that point decided to move forward with an in-depth study. We began long and rather agonizing discussions about the study scope and work plan. We established the task force, and by that time there was somebody foolish enough to take on the chairmanship of that task force.

In October of '06 we held our first task force meeting. We again kind of hammered out what the scope was and we began to develop approaches for addressing that scope.

In November of '06 we decided at the full meeting to move ahead with an in-depth study. We again discussed the scope. That's been kind of a recurrent theme, and in December of '06 we refined the proposed scope and developed an approach for study.

In February we were still working on the scope, and we decided at that point we needed some new blood, and we were again lucky enough to get Bob Cook-Deegan and other members of Duke University's Center for Genome Ethics, Law and Policy to develop a literature review, relevant case studies, and help us tackle this rather daunting topic.

Then just last night in this room we held a special task force meeting where we heard some great presentations by the Duke CGE that addressed some of these issues, and we discussed next steps in the bar afterwards.

We wanted to review with you the current scope. So this is just to review with you the scope. We're done wordsmithing and deliberating on the scope. One of the things that I would emphasize that we've been very, very conscious of in this whole procedure -- and, in fact, the various stakeholders would appropriately insist that we do so -- is that we need to maintain a level of neutrality and openness about both the positive and the negative effects of current gene patenting. If one reads the popular press and the media, one might think mistakenly that there are only negative things about patents. That couldn't be farther from the truth. We need to look at both the positive and the negative effects of both patenting, and I would really emphasize licensing practices on, again, our core concern, patient access to genetic testing, ultimately.

I emphasize licensing practices because I think there's a great deal of feeling that if there are problems with the current landscape of patents, law and application and practice, that where the remedies lie are in how these things are licensed and how they are applied. We want to focus on gene patents for health-related tests, and that includes diagnostic, predictive or other clinical purposes. This encompasses both clinical access and patient access. Just to fill you in on the perhaps somewhat obscure nuances between those, what we mean by clinical access would encompass, for example, a provider's ability to order a test, to get that test for that patients, which in a way is an intermediary step to our ultimate concern, which is patient and public access to these technologies and these tests. We're also interested in considering the effects on translational research; that is, if there are things that enable or block the ability of such new technologies to reach the clinic and reach the bedside.

This is a diagram of our study plan, of how we would like to go about this process. In

part 1, we will concentrate on data gathering and analysis, again to get a view on where we stand at this point. That will consist of literature review, expert consultations, case studies, and perhaps additional research. I would emphasize that if gaps are identified in the current body of literature and answers that are out there, and -- this is a big if -- there are tractable types of things that can be done in an expedient fashion, we would consider funding something on a modest scale to try to fill those gaps. Again, it would have to be very practical, it would have to be timely. We don't have three years to wait for new answers to come in.

In part 2 -- and again, these are divided conceptually into parts, but there's no reason they have to be done serially; they can at least in part be addressed in a parallel fashion -- we want to gather public perspectives. This is obviously a topic that is more and more in the news. It's something that the public has concerns about, has probably more uncertainty than they have concerns, but we would like to solicit public perspectives, compile and summarize those comments, have a roundtable and public hearing about gene patents, and then analyze those public perspectives.

Part 3 is to try to gain some insight from international perspectives. Obviously, this is not a subject that the U.S. alone has grappled with, and although we are obviously in an extraordinarily different policy and governmental framework than other countries, that doesn't mean that we might not be able to learn important lessons about how other countries have addressed these types of thorny issues. So we would like to gather data from that perspective, identify experts, address those things at a roundtable, and ultimately analyze and summarize those international perspectives, all of this, of course, with the intent of a final report to the Secretary.

Again, I would emphasize that I don't think any of us are interested in a quixotic and completely impractical set of recommendations. What we would like to do, if possible and if they're out there, would be to identify practical things that we could recommend that would enhance the benefits of patent practice and licensing practice, and if identified, surmount some of the obstacles and problems.

The goals of today's session, then, are basically educational. We want to provide the committee and everybody attending with a primer on gene patents and licensing practices that then will assist in the development of the study. We want to overview various forms of intellectual property, the use of gene licenses by federal and private sectors, and then the history and the current very much changing landscape of gene patent policies.

So at this point I'd like to recognize our first educator, our first speaker, and that's Jorge Goldstein. He's going to delve into various forms of intellectual property and the rights conferred by each.

Dr. Goldstein is the director of the Biotechnology Chemical Group at Stern, Kessler, Goldstein and Fox. He has prepared and prosecuted patent applications before the U.S. and foreign patent offices in the areas of genomics, molecular and cell biology, recombinant DNA technology, immunology, transgenics, therapeutic methods, organic synthesis, pharmaceuticals and polymers. He's also an expert on intellectual property strategy, trade secrets licensing, research, contracts, university-industry relations, federal licensing due diligence, and acquisitions. Obviously, the man to ask if we have any questions.

He'll be providing us with background on the laws, legal decisions and policies that have influenced what is deemed patentable with respect to genetic material, and I'd like to turn the floor over to you, Dr. Goldstein.

DR. GOLDSTEIN: Thank you, Jim.

Can everybody hear me? Good.

Thank you for inviting me to give this primer on intellectual property. I'm a practicing attorney. I do this in my spare time as a hobby. But what I'm involved in day in and day out is representing the diverse parties before the patent office, before the courts, before international tribunals,

each of them arguing their case. I do then take a very passionate and strong belief in whatever party I am representing.

(Laughter.)

DR. GOLDSTEIN: That doesn't always represent my views on things, and I have learned to write articles and give lectures like this disclaiming, of course, that anything I say here has nothing to do with the positions I take in court, and vice versa.

I have given a great deal of thought and written a fair amount, including some debates with people who are present here, directly or indirectly, about gene patents, and I have been involved in the field since the last '70s/early '80s, when the Cohen-Boyer patent was first allowed and issued, and when Cesar Milstein failed to get a patent for his (inaudible), which was one of the biggest patent mistakes the British government ever made.

So I have sort of put together a combination set of slides which includes an introduction to intellectual property, very quickly, and then some higher-level thinking, if you can call it that, about gene patents and the different types of gene patents and so on.

So what forms of intellectual property are there? What is a patent? How can there be patents on genes? Who owns your genes? That's an interesting question that really isn't that interesting to a patent lawyer or to an intellectual property lawyer, but the press is all over this stuff, and Michael Crichton just wrote an article in the New York Times, on the op-ed page about a month ago in which he actually went further and started talking about who owns your disease. So I have some strong ideas about who owns your genes and who doesn't.

Obtaining and enforcing patents, the patent system and how it fits with gene patents, and then some conclusions and recommendations from my perspective at a high level, including things like patent pools, for example.

So why do we have intellectual property? Well, there are a number of discussions and theories. Historically, patents originated in Venice in the 15th Century to attract and retain artisans who were coming from the Middle East so they would stay in Venice and teach the Venetians the art of canal building and ammunitions and silk weaving and so on, and wouldn't go on to somewhere else. So the Venetians cooked up this idea called the patent in which they would give them exclusive rights to canal building as long as they stayed and taught. Full disclosure, enablement, written description, all of that was in there already, and it worked.

So the idea was to protect ideas, expressions, promote investments, encourage disclosure, and some forms of intellectual property are forms of information and source identification, such as trademarks.

The source of intellectual property in the United States is the Constitution. Article 1, Section 8 talks about promoting the progress of science and the useful arts by securing for limited times -- that's pretty critical, limited times, 20 years from filing these days in the United States and pretty much the rest of the world -- the exclusive right to the respective writings and discoveries. This includes the right to have copyrights and the right to have patents.

So just a general introduction to intellectual property from trade secrets all the way to patents, and I will very briefly, very quickly give you specific examples so you can walk away with a sense of what the difference is between a trade secret, a trademark, a copyright and the different forms of patents.

A classic example of a trade secret which everybody talks about at dinnertime is the formula for Coca Cola. Believe it or not, it's still a trade secret. There are presently industrial espionage litigations going on given that the secretary at the Coca Cola company tried to sell some secret that she thought was the secret, although it's pretty clear that it wasn't, to some friend of hers, and she's being

prosecuted under various different statutes and so on, including misappropriation of trade secrets. The formula for Coke, and I mean Coca Cola, is indeed secret, and it is in a vault in Atlanta and only two or three people know it, apparently.

What is a trade secret? Well, it is knowledge that confers advantages to an entity, say the Coca Cola company. The advantage is that it lasts as long as the knowledge is kept a secret. The disadvantage is that secrets are hard to keep, although Coca Cola has done very well. But they are hard to keep, and you need to make sure when you go to court that you can demonstrate to the judge that you've done the best you could to keep it. You can't stop someone else from independently discovering it or inventing it, and in fact it has happened, much to the chagrin of people, that independent invention or independent rediscovery results in the loss of the secrecy. The disadvantage to the public is that the knowledge of the formula for Coca Cola is not placed in the public domain. So it stays in the vaults of Coca Cola and nobody knows about it, and they have a right to exploit it.

DR. LICINIO: So if Coca Cola keeps it for 300 years as a secret, it's there for 300 years, as long as they can keep it? There's no limit?

DR. GOLDSTEIN: Yes.

So that's a trade secret. Trade secrets are enforced in state court. They're not federal. There is a federal espionage act that protects the stealing of them, but trade secrets are in fact state-created causes of action.

The next piece of intellectual property, trademarks. A classical trademark that I will talk about here is, let's say for example, in the health sciences, the trademarks for erythropoietin. A trademark is something, something. It need not be a word. It could be a building, like McDonald's, for example. It's something that distinguishes the goods and services of one company from those of another. So the same erythropoietin is called EPOGEN by Amgen, and in Europe J&J had been selling erythropoietin under license, and they called it EPREX. So the association of EPOGEN apparently immediately causes everybody to know that this is coming from the reliable source that they've taken EPOGEN from for the last 10 years, and it's Amgen, and it's not some other drug. It's not a different source. It's the same drug, but it's the source that they have relied on. So it's a source identification. That's what it is, versus EPREX, which is the same drug but it comes from J&J.

What can be trademarked? Certainly, the name of a product, like I just showed, a building, like the Golden Arches is a trademark. What's not always clear to people is that a sound can be a trademark, right? If you think about "Intel Inside," that little sound that Intel has, four notes, that's a trademark of Intel. It's registered as a sound trademark at the Patent and Trademark Office. A color can be a trademark, brown for UPS, or pink for that insulation that you put in your attic for the winter. It is a color, and color is in fact trademark-able.

So trademarks give you a sense for a source. The advantages are that, again, they last for as long as you use them. You can prevent others from using similar marks. It makes it quick, and there's an advantage to the public to connect the source with a product. If you don't use it, you lose it.

The next intellectual property section, copyrights. Now, copyrights are --

DR. LICINIO: Just a second. Is a trademark forever?

DR. GOLDSTEIN: A trademark is forever as long as you use it and you do not abandon it and you don't let it become generic. If the trademark becomes the generic word, you lose it. For example, Xerox is a trademark for copying using xerographic methods. But when people say I want to Xerox something, they're using it generically, and the Xerox company is constantly reminding people not to use the word "Xerox" generically because they're going to lose it as a trademark.

To Hoover in England, I'm told, is a generic word for vacuuming. The Hoover company doesn't like that, and one of the dangers with a trademark

becoming very famous is that you can lose it if you don't protect it as a trademark.

Copyrights. Now, copyrights are in a different form of intellectual property. I'll give you an example here. If you think about Jim Watson's "Molecular Biology of the Gene," a copyright is a legal expression. It's a protection for an expression. It is not the idea, but it's the style, the format in which the idea is presented. So if you think about Watson's book, there are obviously an infinite number of ways of describing and writing a book on molecular biology. You can write a book on molecular biology without copying Watson's book, without copying his style, his chapter organization, his titles, his subtitles, where he puts the figures, the phrases that he uses, and you're fine. You can write your own book. You can write as many books as you want on molecular biology. But if you photocopy any page of Watson's book, you're violating the publisher's copyright.

So the idea is not to protect the concept of writing about molecular biology. It's the particular way, it's the format, it's the style that is protectable by copyright, and the copyright is owned initially by the author and then by the publisher if the author is writing on behalf of. The expression can be independently created and not unique, and it has to be capable of being fixed in a tangible medium.

What can be copyrighted? A whole bunch of stuff can be copyrighted, and we're talking again about expression and not ideas, literary works, musical works, sound recordings, dramatic works, including choreography, including the NFL games, for example, which are pretty dramatic. Pictorial graphic sculptures, motion pictures, architectural works. How about outside of these classical fields of literature or art, what can be copyrighted? Well, the best example of a sort of quasi-utilitarian application of copyrights is the software industry. The problem with software copyrights is that while you can protect the form in which a particular flow of ideas is created so you or your publisher own the copyright on the code, on the lines of code and how you have interpreted the flow of information, I can look at your code, reverse engineer it, figure out what it is that you're trying to protect, and then write my own code different than yours, and I am not violating your copyright. That's why protecting software by copyright is a limited proposition. The best way to protect software is to protect the ideas, the flow of information, and that is done by patents. Also, of course, the particular way in which you interpret the flow is done by copyrights.

In the late '70s, early '80s, there were papers that came out on the possibility of copyrighting genetic sequences, and my only answer is what I say there, I don't think so. The problem with copyrighting utilitarian objects is that the law does not allow you to use copyright to protect the function of the object. So you need to be keenly aware of the limitations of copyright to just protect the style or the particular mode of expression and not the underlying idea.

So let's turn to patents. What's a patent?

DR. LICINIO: About copyright, is there a time for it? There is 50 years, right?

DR. GOLDSTEIN: Well, it can be extended. It's very long. It can be for the life of the author, plus. So it's pretty long.

DR. LICINIO: Why did the Mickey Mouse copyright last forever? It's over 50 years now and Walt Disney is long dead, and yet the copyright is still in place. It's past any legal limit.

DR. GOLDSTEIN: I don't know, but I can look it up.

So what's a patent? A patent is the right to exclude, okay? It is not the right to do anything. It's not the right to make anything. It's the right to exclude others for a limited period of time from a number of things that are in the statute, such as making use and selling, offering, importing, exporting, and so on. It's a right granted by the government, and the quid pro quo is the government gives you the right to exclude and you need to disclose fully the invention that you want to patent. If the quid pro quo is not met, if you do not fully disclose or if you disclose it fraudulently, or if what you disclose is inoperative, the patent is invalid. Even though the Patent Office may have granted it, it doesn't mean the

patent will hold up in court. So litigators like me go into court all the time trying to prove that a particular patent was granted by mistake, that the Patent Office missed some piece of prior art or believed that this thing is reproducible and it's not reproducible at all.

So the quid pro quo is private disclosure, especially disclosure that would otherwise not become public, like the disclosure of a corporation. I mean, academicians who live for doing basic research and making it available to the public don't always understand the concept that the alternative is to keep it secret. For academicians, keeping things secret is sort of anathema. The point of doing academic research is to make it available. But for industrial scientists, for corporate scientists, secrecy is the norm. It's their daily life. So the concept of disclosing it to the public fully and enabling is a very strange concept for corporate research, and the patent sort of says to them, okay, look, if you disclose it, I'll give you 20 years exclusivity, you'll be the only one who will be able to do this. This is the Venetian concept again. You can talk about Dupont or the Grand Canal, it's basically the same idea.

So what kinds of patents do we have? Well, the classic patents that you all talk about are so-called utility patents, 20 years from filing. It takes about three years to prosecute, so it's about 70 years from issuance. The invention must be useful, novel, not obvious. There are design patents which protect the design, the look of something, again very similar to copyrights in some ways in the sense that there are probably many, many ways of designing a speaker, a microphone like this, for example, right? And if I have a particularly fancy one, I could probably protect it through design patents. There are multiple ways of designing a utilitarian object. Any one of those that is fancy can be protected by a design patent. It's for decorative designs or articles of manufacture.

Then there are plant patents, which you don't have to worry about too much, 20 years from filing and for asexually reproduced plants.

So we talk primarily about utility patents. We're not going to talk about copyrights, trademarks, trade secrets, primarily utility patents. What can be patented through a utility patent? Certainly processes, methods of producing compounds, methods of using them in therapy and diagnosis, instrumentation, machines, manufactures, things like plastics and paper, a particular chemical entity or genetic entities. Software can be patented, as I just described. Methods of doing business is a relatively new one, and it's causing a great deal of consternation, especially in the financial industry that is getting sued by all kinds of sole inventors that have patented methods of calculating bond fund balances at the end of the day, for example.

Abstract ideas cannot be patented. Mathematical equations, algorithms without any use whatsoever cannot be patented, and laws of nature cannot be patented. This has become a controversial issue recently in the sense that it's being brought in to try to capture within the concept of a law of nature things like correlations between metabolites and diagnosis. There was a case that went up to the Supreme Court called the Metabolite case in which that was tested, but the Supreme Court said we shouldn't have granted cert, go away, there's another issue that you want to deal with before you come back here. So the whole biotech patent bar was sort of left holding their breath as to what's going to happen with diagnostic correlation patents.

DR. TUCKSON: Excuse me. Could you make a distinction on the copyright that you can't copyright --

DR. GOLDSTEIN: Where is the question?

DR. TUCKSON: Over here.

Copyright does not protect the function of an object. Can you patent the function?

DR. GOLDSTEIN: Yes.

DR. TUCKSON: So you can patent the function?

DR. GOLDSTEIN: Yes, right. The patent covers the function, the utilitarian aspects

of what the object does, whereas the copyright protects the form, the style, the look of it. That's why patents are, I think, more powerful to protect the ideas than copyrights. If I can patent the basic concept or idea that I developed, then you could embody that in many different ways, and yet if you appropriate my idea, I got you.

MS. CHEN: How about something that is functional, like an object or something like a gene, that is happening in nature?

DR. GOLDSTEIN: Bear with me for a minute. I'm almost there. As long as you take it out of nature and introduce some sort of intervention and make it separate from nature, you can patent it.

Patents encourage disclosure. They encourage investments. They can prevent others from using the invention as a trade secret. That's interesting. If I were to rediscover the formula for Coca Cola, and it's not public, and I got a patent, Coca Cola would have to stop using the formula. Now, if Coca Cola wanted to patent it now, it would be too late. There's case law that says you have to choose either trade secrecy or patents. You cannot keep your inventions or discoveries a secret for 25 years and then, when it's about to be discovered, you patent it. That's a no-no. That's called an estoppel in law. It means you can't do it. Whereas if I rediscover it by myself and I patent it, the fact that it's secret in the vaults in Atlanta is not prior art against me. So there's a risk in keeping things secret, especially if they're going to leak out.

If I was Coca Cola's patent lawyer 65 or 70 years ago when that pharmacist discovered the formula, and he came to me and said should I keep it a secret, I would have said no, don't keep it a secret; and he said but I swear I'll be able to keep this a secret for 65 years, I would have given him bad advice. Thank god he didn't come to me, right? He did much better.

(Laughter.)

DR. GOLDSTEIN: I just don't believe that secrets can be kept for 65 to 70 years, especially in a product that's going to be drunk by billions of people over those 65 years. There's got to be some chemist that can figure out what's in there, right? But, hey, common sense doesn't always win.

Disadvantages of patents. Well, to the corporate scientist, the patent needs to pretty much lay out a blueprint of what the invention is, the formula, the Coca Cola formula for example, the process of making it, what goes into it, et cetera. It's expensive to obtain. It's even more expensive to litigate. Litigating a patent even before trial can cost $2 to $3 million. It could easily be about a million a year. When people say to me how much is it going to cost me to litigate this, my rule of thumb is about a million a year. How many years? Two to three years, and then trial, and trial, you can multiply that by two or three. So it's a multi-million dollar business to litigate patents.

You may need to seek patents in many countries, because if you've got a patent in the U.S., for example, people could go abroad and do a lot of things abroad, bring the data in. There's case law that says that you could, for example, do drug screening internationally and send the data in by Internet, and bringing in data is not importation of a screening patent.

If the technology is developing very quickly, patents are limited. So in consumer products, patents are of limited use many, many times.

So now we'll talk about patents on genes. Patents on genes, as patents on proteins, as patents on naturally occurring materials, claim isolated and purified molecules, not the natural molecules, and there's lots of legal precedent for this. Adrenaline in purified form, practically free from gland tissue, was patented in 1912. Prostaglandin in sufficiently pure form, that was the word of the patent claim in 1970. In 1977, in a case called in re Burge, there was a patent of biologically pure cultures of Streptomyces.

I'm highlighting in yellow the critical words that need to go into the patent claim.

In 1979, strawberry flavoring compositions were patented where 2-methyl-2-pentanoic acid derivatives were the one set of compounds that were found to give strawberry flavor to the strawberry, and they were isolated and purified, and then compositions containing them. Now, a composition containing 2-methyl-2-pentanoic acid reads on a strawberry, right? But if you put in substantially pure 2-methyl-2-pentanoic acid, and that is interpreted to mean you need to purify it first, crystallize it, and then you add it to the composition and that's the way it's construed, then it doesn't read on a strawberry because a strawberry as a composition of matter is natural and the flavoring compound was not isolated and purified and put in there.

In 1980, the famous Chakrabarty case, in which an Chakrabarty from GE made a recombinant bacteria that was able to grow and metabolize a whole set of hydrocarbon fractions, tried to patent it, the thing went up to the Supreme Court, and the Supreme Court said, in a very famous statement that's always reproduced by patent lawyers in the biological sciences, "Anything under the sun made by man" can be patented. I'm sure that today the Court might say anything under the sun made by a person, or made by a man or a woman, but those were the days, 1980.

So that is used by patent attorneys a lot, anything under the sun, meaning if it's made by man, if the hand of man has intervened, like purifying the strawberry extract, then it's patentable, even if it came from nature. So let's look at what a gene patent actually looks like.

A gene patent ultimately is a gene claim. A patent contains a whole bunch of disclosure at the beginning, and then there are a number of numbered claims at the end of the patent, and Claim 1 of Kirin Amgen's erythropoietin patent is reproduced in this slide. That's the 008 patent. It issued in '87, and that patent has actually expired. So the DNA patent for EPO is gone, although Amgen has played lots of games and has filed subsequent filings and has patents on all sorts of other things beyond this gene. But this patent did them very well. This is still a $4 or $5 billion market, and they've held tight. They've let no one in because of these patents.

So what is claimed is -- I'm going to use this one -- purified and isolated DNA sequence. That's the critical wording that I just mentioned. It has to be purified and isolated. That's the statutory requirement. The sequence encodes EPO. It's selected from two subparts of this claim. The first one is a DNA sequence that's actually set out in the patent. It's Figures 5 and 6 for the complementary strands. That happens to be the human EPO gene sequence. But Amgen, as all biotech patent lawyers, doesn't just want to protect the particular human gene sequence or its complementary strands. It wants to protect orthologous genes, genes that come from other species, genes that have been modified in some way from the human gene. Otherwise the patent is very narrow and could easily be voided. It is not that difficult to envision the possibility of changing a few bases here or there, or maybe a neutral non-impacting mutation, and develop an alternative, and if you've got a patent that's limited to just the one sequence that you have, the patent could easily be voided. So what is really critical in this claim is Part B, DNA sequences which hybridize under stringent conditions to the DNA sequences defined in A. This expands the human gene to a family of similar isolated orthologous EPO genes, and also to mutational variants of the basic human genes.

It's interesting how this is defined. It's basically defined by hybridization under stringent conditions, which are defined in the patent, and it's a test to see what infringes and what doesn't.

So with this little primer, question: Who owns your genes? I would like everybody to walk away from here and go back and read Michael Crichton's op-ed page and find out how wrong he is about all the stuff that he's talking about. He's a great novelist and I love his books, but as far as policy is concerned I think he should just keep writing fiction.

So who owns your genes? Well, from a legal point of view it depends on whether they're in your body or they're not in your body. If they're in your body, the genes are yours, you can rest

assured. On the other hand, if you are in the hospital or in your doctor's office and blood has been taken, the law has been pretty clear for many, many years, and there was a case that confirmed it in 1990 at the University of California, the famous Moore cell line case, that once your genes are extracted from your body, they belong to the hospital. So the act of extraction changes legal ownership of the genes, of the genetic material.

Now, let's say you do a deal with a lab. You say, look, before you pull my blood, I want to own my genes. They'll say, what, are you crazy? Well, fine, but this is not crazy, because in fact what happened in the Moore case is that this man discovered that his genes and his cells had been isolated, purified and used commercially to produce cytokines or some other biological material, and he got pretty upset that people were exploiting the biological material of his. So let's assume that you do a deal with a lab. If you do a deal with a lab, you can change by contract the operation of law, which is what the Moore case said. They could, in fact, belong to you. You could walk home with your test tube, with your genes.

If I have a patent on your isolated genes, and you have the little test tube that you go home with, they're yours, there's no question that they're yours. But if I got a patent on them because they're now isolated, can you commercialize them? And the answer is no. You own your genes, but I own the intellectual property on your genes, just like if you own a copy of Harrison's "Principles of Internal Medicine," and I am Houghton Mifflin, I own the intellectual property, the book is yours but the copyright is mine. You can go to your grave with that book as far as I'm concerned, but you cannot reproduce it, sell it, distribute it, make copies of it, a fair number of copies. So there's a big difference between owning the book and owning the copyright, owning the genes and owning the patent. So you own your genes, but I may own the right to exploit them.

Can I use my patent on the isolated genes to stop you from metabolizing? That's a trick question.

(Laughter.)

DR. GOLDSTEIN: I hope you know the answer, right? Of course not, because patents are on the isolated genes. They're not the patents in your body, in your chromosomes.

So how easy is it to obtain gene patents? By this I mean isolated genes, right? Well, there are a number of standards in the Patent Office that go from the genetic sequence that you disclose, and utility is one of the most difficult parts to overcome when you're trying to obtain a gene patent. It has to be substantial, credible and specific. You need to have a written description of the gene and variants of the gene in order to get generic scope, like we were talking about before. You need to be able to reproduce the invention. You need for the gene to be novel; namely, it has not been published in isolated form, the sequence, in another publication before you filed. And it cannot be obvious.

Now, the standards, roughly speaking, are much higher to overcome at the utility written description end of things than at the obviousness end of things. In the United States, pretty much if I come up with a new sequence for a gene that's well known, for example, but I've modified the sequence or I have found an allele or I have a variant of it, I can get it. There is no really very high, very strict obviousness standard in order to obtain gene sequence patents in the U.S. In Europe, it's very different. The Europeans took an entirely different turn early on in the development of the law, and they can demonstrate that if there are methods and incentives to make these variants, the gene is obvious. In the U.S., the Patent Office is not allowed to present evidence that there were methods available to isolate this new gene. The protein was known, genes in other species had been isolated, there were methods to isolate it from humans, therefore it's obvious. That does not work in the U.S. It works very well in Europe, and it demonstrates very clearly how both in the U.S. and in Europe we went in very different directions. The Europeans are not happy with the direction that we took, and there's a lot of criticism in

the academic literature, in law review articles about the direction that our court took.

Now, as I said, the essence of a patent right is the right to exclude, and the right to exclude, which is the essence of the patent, includes the right to an injunction. Namely, I can go to court and I can get the court to stop you from making, using, selling, importing, exporting, offering, et cetera. I have the right to extract damages. If I have been hurt in my marketing of erythropoietin, for example, by your copy that infringes my claim, and I can demonstrate that I lost profits or the market was diluted, then I can get either my lost profits or I can get reasonable royalties, and I can leverage the ability to get an injunction to be able to obtain licenses.

Now, the right to enjoin in the U.S. has historically been very, very strong, and the interesting news for this group, I think, is that there's been a recent Supreme Court case called MercExchange v. eBay where the right to enjoin has been cut back from what it's been historically. But until very recently, until this case, this eBay case, any activity that furthers the institution's legitimate business objectives is an infringement and can be enjoined, and this applied even to Duke University. Those of you from Duke know this case like the palm of your hand, Madey v. Duke.

Madey was a professor at Duke. He had a laser that he had patented when he was at another university. He was using the laser at Duke to teach postdocs and graduate courses and so on, and then he got unhappy. He left Duke, and he found out that Duke was continuing to use this patented laser of his. He sued Duke, said you've got to stop, and Duke said stop? What are you talking about? I'm an academic institution. You can't tell me to stop. What are these patent injunctions against me? And the court said yes, against you; sorry, Duke. As long as your institutional legitimate business objectives are supported by this infringement -- namely, you teach; that's your legitimate business objective. If you're a private university, you're not a state university, you're not even immune from suit like many state universities are -- it's an infringement and you may have to stop. Well, you can't imagine the brouhaha this caused. I mean, academic institutions went to Congress and they were stunned. They still are stunned. When I talk to university tech transfer officers, they still don't want to talk about Duke.

(Laughter.)

DR. GOLDSTEIN: They don't want to talk. It's something that we really don't want to deal with.

The experimental use defense is essentially non-existent in the United States. That's another thing to note here.

Clinical use of a drug that is generating data that will go to the FDA under this statute, 271(e)(1), and a Supreme Court case called Integra v. Merck, said clinical research is, in fact, exempt from patent infringement. So if a pharmaceutical company is doing clinical work and they're using a patented drug, they are free to do so until the clinical work ends and they're going to the market. At that point it becomes an infringement. The question in Integra v. Merck is how early does clinical work start? Is preclinical work still covered? Is only experimental research covered by this immunity?

Now, the right to exclude has recently been cut back. It used to be that if you proved that there was an infringement and the patent was still valid at the end of litigation, an injunction came in and automatically you got an injunction if you asked for it. It's no longer automatic. It's pretty clear from the Supreme Court case and from lower court cases interpreting the Supreme Court case in the last six months to a year that, for example, a patent holder that does not manufacture -- in other words, is not in the marketplace with the infringer -- may not readily get an injunction.

Health is a major public policy concern, and the courts have noted that over and over again in injunction litigation. So a patent holder in the health sciences -- this is pretty critical, I think, for this group -- who does not work the invention, has a patent, frames it, puts it on the wall, likes looking at the patent, and maybe offers licenses every now and then, maybe not -- there's no obligation to license a

patent in the United States. It's not an anti-trust violation to not license a patent right. But nowadays, patent holders who are not working the invention, who are not perhaps licensing the invention -- that's a test case that has not yet come up, but it's coming for sure -- may not be able to get injunctions. That actually opens the door in the U.S. for the first time to serious thinking about compulsory licenses, licenses which are forced on the patent holder against his or her will by order the court. Compulsory licenses have been anathema to big corporate interests in the U.S. for decades and decades. The eBay case has sort of opened the door a little bit, and it is now possible to at least write academic articles on the fact that compulsory licenses are coming, and I've already seen a few cases.

DR. EVANS: Dr. Goldstein, I think we're running short on time. This is so great and I want to make sure we get as much as possible from you, Dr. Goldstein. So if you could, within the next 10 minutes or so, finish up, then what we'll do is we'll bring back Dr. Goldstein with Ms. Driscoll and Dr. Sun-Hoffman for questions.

DR. GOLDSTEIN: Okay. So the door has opened, and I think the next few years are going to be very interesting, especially in health care patent litigation.

I've already talked about full disclosure, time-limited exclusivity, capital formation for technologies of risky outlook. The idea of privatizing technology that would otherwise be in the public domain helps promote investment in them. If the technology stays in the commons, the basic idea is nobody will put in money to protect it, and so maybe it will just sort of die in the commons and it will not make it into the markets.

But there are patents, and there are patents, and the patent system is actually created as a one-size-fits-all system, and I think careful thinkers of the system and of the law always sort of distinguish, even though the law doesn't, between different industrial sectors.

The synthetic drug sector, like the pharmaceutical industry and the biopharmaceutical industry, is the classic poster child for a good, strong patent system. Major investments are needed; long delays; there's a high risk of failure, and the products have very long life. This is not like the consumer products industry where products have short lives, no major investments are necessary. At the end of the spectrum is business methods. Business methods don't require high-risk investments, the product lives are relatively short. A lot of the investments and the inventions in developing a new business method like a computerized method of calculating fund balances at the end of every day, like in the State Street case, don't need patents, and the application of patents to business methods is sort of an afterthought. It's like the Supreme Court said, well, we don't see why not, but it's not like a patent is necessary to promote good, smart, Wall Street financiers from inventing a new way of calculating balance funds, whereas you can contrast that with the pharmaceutical industry.

In the middle is usually placed the semi-conductor industry. Investments are needed, no question about it. Copying is still a risk, but there is a thicket problem in the semi-conductor industry. It is estimated that if you want to put a new DVD on the market or a CD player or an iPod or whatever -- iPod is a registered trademark of Apple Computer, and I'm not trying to use it generically. I am so paranoid about using iPod.

Anyway, if you want to put a DVD player or one of these miniature MP3 players on the market, it's estimated that you need thousands of patent licenses, thousands. We're not just talking a thousand, two thousand. There is an estimate that for a complicated, high-definition television set, you may need 19,000 or 20,000 licenses. Now, there is a real thicket in there, and this is the industry where patent pools have come out of, because people cannot move without patent pools. Nobody can put a product on the market.

So are isolated human genes like synthetic drugs, or are they like business methods? What role do patents play in genetic patents? The answer, which is what lawyers always have as an

answer when everything else fails, is it depends. It depends on the function and the use of the gene and who are the potential defendants, whose ox is going to get gored here.

So let's sort of think about gene patents in three different categories, because I think it's useful to put some taxonomy on gene patents. There are DNA patents that encode protein drugs, like TPA and EPO and interferon beta. The defendants tend to be in the biopharmaceutical companies. At the other end are DNAs encoding targets and receptors, like the CCR5, like Tralar-2, like DNAs encoding molecular receptors that are used for drug screening. The potential defendants in this category tend to be academic institutions and small research companies that are doing high-throughput screening, for example, with these receptors. In the middle, just like the semi-conductors, are diagnostic probes. These are not DNAs that encode any protein. They're used as probes. They're used per se. It's the product that's being used; for example, the BRCA1 gene. The potential defendants are a mixed bag. They include diagnostic companies that are putting kits on the market, and they also include the medical community, which is doing clinical work, maybe doing research.

So if you think about gene patents in these three different categories, things become a little clearer as to whether they are more like synthetic drugs or they're more like business methods.

The TPA gene. If you said to Genentech or Amgen that they cannot get a patent on the TPA gene or the EPO gene or the interferon gene that encodes a protein that's being used as a therapy, as a drug that needs FDA approval that has long obligation times and high risk, they would probably not spend any money on this stuff, and it could very well be that the TPA gene would be discovered, published, and there probably wouldn't be much TPA in the pharmacies of the United States, and therefore DNA encoding drugs, protein drugs like TPA or EPO, I think are a lot more like synthetic drugs than business methods. Patenting the gene, not the protein, rewards the innovator of large-scale production. The risk is high. I've mentioned this factor already. In fact, there's case law that suggests that the patent on TPA has already been construed pretty narrowly so that subsequent generations of TPA, second and third and fourth generations, are not covered by the original TPA patent.

Now, at the other end is, for example, the erythropoietin receptor. If I isolate the DNA for the EPO receptor, I can get a patent on it, but the research obligations are the most important obligations here. We're not talking about the EPO receptor as a protein being sold as a drug in the marketplace. We're talking about the receptor being used as a high-throughput screening tool, as a research tool. So the commercial application is much lower than for erythropoietin itself. Development risk and costs are not very high. These are used primarily as research tools.

Enforceability is iffy for these research tool patents. You can use it abroad. You can bring in the data. Preclinical may be exempt, as I described before. It's very difficult to ascertain what the damages are. If you're infringing one of my patents on a research tool, how much money can I get from you if I take you to court? What is it worth for you to be doing research? Can I tie in your eventual discovery of some blockbuster 10 years from now and say if you discover that blockbuster because you used my receptor in vitro to do high-throughput screening, even though you're 10 generations away as far as designing drugs, I still want a cut of that blockbuster. That's called a reach-through royalty, and needless to say there's lots of controversy about this.

Certainly, if the NIH had anything to say about this and they put money into the research, they don't like research tool patents being licensed exclusively and hold up research, and there is a clear sense that patents in the research tool field tend to impede the dissemination of research tools. Big pharma does not like them.

Now, that is very important, because when big pharma steps into a debate, they carry a lot of weight. So a lot of people may talk a lot about research tool patents and whether they're good and they're not good, and then big pharma says research tool patents are no good, and then everybody listens.

Merck, Lilly, I represent them, and I'm also fighting with them all the time.

So in the middle, I think, sort of like semi-conductors, are genes that encode diagnostic probes. The commercial and the research obligations are in tension. There are still manufacturers who put kits on the market, and they want patent protection. They don't want people copying their kits. But the receiving end of these patents doesn't just include the manufacturers, as with protein drugs, but also end users. There's a lot of debate in the literature, and I think lots of evidence, that developing improvements in genetic tests has led to large fragmentation of the patent field, just like with semi-conductors, and there is a clear sense that who can perform the genetic tests may very well interfere with good medical practice and may inhibit others from finding mutations.

So in my taxonomy, diagnostic DNA patents are like semi-conductors, and I think there's a problem with them that needs to be solved the way semi-conductors have solved their problems. The perceived value in patents, therefore, in human genes depends a bit on who is talking. Academia, which is the sort of middle one, feels that as far as DNA-encoding protein drugs, they like patents. If they discover the gene for EPO, you can be sure that they want to have an exclusive right to license this exclusively to some pharmaceutical company that's going to make them a lot of money.

On the other hand, as far as DNA-encoding receptors, they sort of feel for research tools that they like to patent them, but they're having a lot of trouble licensing them. There are not that many takers. Reach-through royalties don't always work very well. On the other hand, if you're talking to big pharma, big pharma loves DNA patents that encode therapy drugs, EPO and TPA, but they hate receptor patents. They don't like them. They don't want to have to pay stock royalties. They don't want to have to pay for the use of research tools. There are small startups who, of course -- I mean, everybody agrees that DNA-encoding therapy drugs are good things to have. The patents should be there. Where the big difference is is in the research tool end of things, and there are startups that make their living from isolating research tool genes and patenting them. If you say to them that research tool DNA patents should not exist, they're not going to like it, because they may very well not exist themselves.

So in thinking about diagnostic patents as semi-conductors, I have together with others thought -- and there are a number of academic research groups and law groups that have thought about this in great detail, about patent pools, and in '05 I published a paper in Nature Biotech that said that following the model of consumer electronics one could think of creating in the diagnostic field, not in the other fields, pools that use internationally recognized medical standards, like the ACMG standard for cystic fibrosis, to define what patents belong in the pool and which ones don't, which ones are essential patents and which ones are not, which is always a problem with pools. You'll hear pools being discussed as the panacea for solving all these problems. It's not. They have to be thought through very, very carefully.

In the biotech industry -- and I will leave you with the final conclusions -- no one other than you owns your genes. Don't worry about it. But they may own patents on the isolated versions of your genes. They provide commercial exclusivity. Not all gene patents are created equal. There are different categories, and they need to be thought of in a different way, and whatever you recommend, do not throw the baby out with the bath water.

So post-eBay, I think there are real possibilities for compulsory licenses, health-based compulsory licenses coming down.

Patent pools. I believe that in the diagnostic field, they can be worked, but you may have to start working with international health organizations to create standards. Just like diagnostic standards are applied in health, they could be applied in the legal field also, universal standards for diagnostic genetics.

Define experimental and preclinical research better without undermining all research

tool patents.

There was an issue of Academic Medicine four years ago that had a lot of this that I recommend for an excellent survey on gene patents, human gene patents, although so much has happened in the last four years that it's already out of date. But as an introduction, it's a pretty good set of articles on it.

Thank you. Sorry I took too long.

DR. EVANS: Oh, no. Thank you. That was wonderful.

(Applause.)

DR. EVANS: I really want to thank you. That was a fantastic primer. It's exactly what we needed.

We're going to wait for questions until the next two speakers have gone ahead and spoken.

I want to turn now to Ms. Claire Driscoll. We're going to hear from two speakers representing on the one hand the federal sector role, on the other hand the private sector role. Claire Driscoll is from the Office of Technology Transfer at NHGRI, and she's going to begin by describing the federal perspective. She's responsible for the oversight of NHGRI's Intramural Patent and Licensing portfolio and advises the institute on technology transfer policy and related matters.

Claire?

MS. DRISCOLL: I'll try to be fairly brief. I know we have a long morning ahead of us.

Today I'm going to talk about how the NIH handles patent and licensing of genomic inventions, including specifically the licensing of gene patents. Not unlike many in the medical community, NIH is definitely concerned about the possibly negative health repercussions of certain licensing practices, namely broad, exclusive licensing of gene patents for diagnostic applications. So I'll give you my bottom line right up front. The bottom line is if there are real problems, and there do seem to be some at least examples of problems in this field, I think the focus as far as interventions should be definitely at the level of licensing and not at the level of patents. So I think that will be my take-home message.

So here's the reality. We all know this. We are in the age of Homo economicus. So this is where we're at. We have to realize that and start from there.

A little bit about the NIH, and what I want to emphasize here in this slide is that, one, we're big, but we spend 10 percent of our $26, $27 billion budget internally on campus in what we call the intramural program. So a lot of the policies I'll be discussing today only apply to the intramural program. So some of my views, what I'll say is why aren't we doing this in the extramural program? And the simple answer is because the grantees don't like us telling them what to do. But I think the time has come to consider taking some of the policies that have proven to be effective in the intramural program and perhaps having the grantee community at least -- right now they can voluntarily adhere to it, but there's no mandate that they must follow some of these policies. So I'll start by discussing some of the NIH policies.

Here are our patent principles. They're fairly simple. No further R&D is needed. The research tools example is a great example. We don't patent. If there's a low public health priority, a low commercial interest, we don't patent. We will patent if there's a high public health priority even if there's low commercial interest. So we have a large portfolio in neglected and rare diseases, for example. So what we try to achieve is a careful balancing act between providing IP protection and fostering biomedical innovation. If you have too much IP or restrictive licensing monopolies, you'll hinder future research. But if you don't patent important inventions such as the genes that encode for proteins that

could have therapeutic use, you're not going to get appropriate commercialization of important technology. So we try to achieve this balance.

Here are, again, our intramural, focusing on the word "intramural." This is what we do on campus at NIH. We focus always, always, always on the public health benefits first, and the royalty income and financial benefits to us is our last concern. That all sounds great. We can afford to be altruistic. We have a big budget. We don't get financed based on royalty income. This is not the reality for the universities, so you have to be aware of that.

We try very hard to never give a license for more, as far as the field of use, for more than the company realistically needs to develop that invention. So we do preferential non-exclusive licensing or narrow exclusive licensing, and we try to optimize the number of new products that hit the market. The best way to do that is to do multiple licenses.

The other thing we insist on is that the availability of the technology for research -- and maybe we should extend that to research and clinical. Right now it just says research. But we make (inaudible) must allow us to do research ourselves with the technology, but we also want other non-profits and governmental institutions to be able to do research.

So what are the mechanisms we use? We use very standard mechanisms. I won't spend a lot of time on them, but one anomaly is the Cooperative Research and Development Agreement. Under this agreement, we actually give our CRADA collaborator an option to exclusively license any inventions. So that's an anomaly. Most of the time we do non-exclusives, but if you work with us under a CRADA, you get an exclusive option. But even in that case, we're very careful to make sure the scope of the license matches the scope of the research plan. So again, we don't give people more than they really need to commercialize. We kind of do the opposite of academia. We give mostly non-exclusives, occasionally co-exclusives, a few exclusives when it comes to therapeutics or vaccines. Again, even those can be quite narrow by field of use, by disease indication, by technology platform. We try to really parse it out so that we can give multiple licenses. We very rarely give a broad license.

So here are our statistics. Again, we're diametrically opposite of what academia does. We do over 80 percent of our licenses as non-exclusive. If you look at the AUTM, the Association of University Technology Managers, survey data, you'll see that in academia it's mostly exclusive licenses. To be fair, we don't know really the nature of all of those exclusive licenses. Some of them may be narrow. But the way AUTM does the survey, you can't really tell. But again, we're a little bit different, and so I want to emphasize that difference.

The difference is extramural folks, our grantees, can really do as they wish when it comes to patent and licensing. Under Bayh-Dole, they can really control their own inventions, commercialize them as they see fit. We sometimes put restrictions on them. There's the famous research tools policy that NIH put in place a few years ago. We sometimes ask for acceptable intellectual property sharing plans, and we had a new policy -- not a policy. I have to be very careful. A guidance document came out a few years ago called "NIH Best Practices for the Licensing of Genomic Inventions." This we sometimes ask our grantees to seriously consider adhering to, but it's not a requirement for the grants. This document, I should add, came out of the Genome Institute. It was really Francis Collins', the director of the NHGRI, idea. He felt that we were actually doing all of these practices for over a decade, but nobody on the outside knew that that's how we were handling the licensing of gene patents. So we tried to put everything down in writing and just distribute it to the community.

We also sometimes do a declaration of exceptional circumstances, a DEC, where we essentially tell our grantees you have no Bayh-Dole rights. As you can imagine, the universities hate these and they fight against this every time, but in some projects it's very necessary that the end products, such as full-length cDNAs from human, rat and mouse are all available without any restrictions, or in the

case of creating a library of knockout mice. If there were patents attached to each and every knockout mouse, we couldn't really get them out there to the research community. So occasionally we'll completely take away Bayh-Dole rights, but that's very rare.

So the academic research enterprise really is the source of many of the platform technologies and the new products commercialized by industry. I think people have to remember that. The companies are in licensing from academia, so that means who controls the licenses, who is writing the license agreements. The universities are writing them. Companies can ask for certain things, but it's the universities in many cases who control how the licensing is done. So if genetic inventions, for example, were no longer patentable, or patent owners of these inventions had to sub-license or give a license to all interested parties, that would affect the viability and profitability of the industry. So it would be in no one's interest to put diagnostic companies out of interest. That's not what we're saying. What we're saying is there are probably ways to be more thoughtful and careful in licensing so that you don't create monopolies or problems with pricing because one company has a lock.

As an example, other than Myriad Genetics, probably the most hated diagnostics company, is Athena. Here's a list of patents just from Athena's website. What Athena has done is they have created a large collection of patents for various neurological disease conditions. But if you take a closer look and see where these patents come from, what you'll see -- and by the way, this slide is from my friend David Ledbetter at Emory. I want to give him credit for this set of slides.

They end license these. If you look at the patent assignee, take a look. Do you recognize those? Are those mostly companies? No. They're academic institutions. There is one for Athena. Keep going down the patents that Athena owns or has licensed; again, mostly academic entities. Keep going; academic entities. There's one, another one from Athena. Keep going, another one from Athena. Everybody else, universities, and so on. Universities, universities. A few companies; mostly universities. So out of those dozens and dozens of patents end licensed by Athena, only three did they develop in-house. The rest they end-licensed. They have mostly exclusive licenses. Nobody else can do these genetic tests except Athena, and they have a policy just like Myriad Genetics of not sub-licensing. So if you want that test done, you have to go to Athena. It's probably not a great public health situation.

I'm going to use some data from Bob Cook-Deegan and his colleagues. As you know, the Duke group published a couple of years ago or last year in Nature Biotech. They did a licensing survey, and they were specifically looking at DNA patents and who owns those patents. Again, who is number one? The University of California. Who is number two? The U.S. government. That's NIH, actually. The NIH owns the second most number of gene patents. That's good that we're non-exclusively licensing those. The ones circled in red are universities who are top-30 DNA patent holders, but they've also signed a new white paper, which I'll talk about in a minute, that's come out from the premier technology transfer organization. AUTM, the Association of University Technology Managers, has come out with three weeks ago a very nice white paper which is actually technology neutral but does mention specifically the case of gene patents and diagnostics, and a number of the universities who hold the largest number of these patents have actually signed on.

Now, it's kind of like in the future. You really can't do anything about the legacy patents they've already signed, but I think it's a good start. Are they doing this because they're altruistic? No. They're doing it because the universities are getting terrible press now. There's a lot of push to change Bayh-Dole. There's a lot of criticism for how universities are licensing these patents. So I think their thought was, well, gosh, let's voluntarily do something proactive before the NIH or these pieces of legislation are going to force us to change how we do business.

I should also mention that 40 to 65 percent of all of the DNA-based patents filed by the universities were made using government funding. So in other words, by their own disclosure in their

patent applications or disclosure to the iEdison reporting system, over half of the DNA patents discovered or gene patents discovered by universities were funded by government funds. So what does that mean? That means that the NIH or government had a policy telling them how to license. You would catch about half of these.

As evidence that the issue of gene patents has gone mainstream, I'm embarrassed to admit that I sometimes read this very flimsy publication that comes in the Sunday paper called Parade Magazine. I about choked on my coffee back in November when I saw this. I mean, "Gene Patents are Putting Your Health at Risk," in mainstream Parade Magazine. That's as mainstream as it gets. So we have to have an intelligent discussion about this.

And then, as has already been mentioned, Michael Crichton's book, where he has at the back of the book his author's notes. Author notes. Awful.

(Laughter.)

MS. DRISCOLL: Number one, stop patenting of human genes. Number five, rescind the Bayh-Dole Act.

Again, the Bayh-Dole Act is the 1980 piece of legislation that gave universities the right to own and commercialize their own inventions even if those inventions were made using government funds. So that's extreme. I mean, that would just put a complete halt on many industries that are basing their businesses on inventions coming from universities.

I'll go quick through some of this, but just to point out that gene patenting really came to the fore once the Human Genome Project got going, and since then there have been a lot of reports. I just want to point them out.

Also something to realize is how sensitive the biotech industry is to perceptions or concerns about not being able to have sufficient patent protection. When Bill Clinton and Tony Blair announced the working draft of the Human Genome Project back in 2000, somebody, one of their spokespeople answered a question in a way that made it sound like there would no longer be any ability to patent genes, and the stock market that day, all the biotech stocks took a 20 or 30 percent plunge in one day just based on that statement. So it's important to realize.

There have also been some proposed pieces of legislation. I want to point out this one from 2002 because I actually think it was pretty good, and I'll talk about it in a minute. There was also a Nuffield Council report, and then finally in 2003 we finished the Human Genome Project. So the good news is that by the time we figured this all out, there are not genes left to patent and all of the early genes that were patented will actually be coming off patent because it's taken so long. So, in fact, pretty soon the problem will just take care of itself, but it will take another five or ten years.

Then we have the MSA study, which you know about. There's the NIH best practices, which I think is really a very good document. Coincidentally, we didn't coordinate with OECD. They called their guidelines Licensing of Genetic Inventions; we call ours Genomic Inventions. But essentially the recommendations are identical. They emphasize non-exclusive licensing, paying attention to fields of use, making sure you retain a research use provision for everybody, not just yourselves, and these sorts of things. They're very much in line with each other. So there's a real convergence of opinion where everyone seems to be agreeing. Then the tech transfer professional association, AUTM, came out with a white paper this month which is not specifically about gene patents but the recommendations are almost identical to some of the other reports.

So again, my bottom line, stop worrying about gene patents. Focus on access. It's the licensing that really matters. It is unlikely, I think, that patents on genetic sequences will be revoked or prohibited from being patented even though there's a bill to try to do just that, and I think it will be very important to develop alternative, feasible strategies to ensure maximum access and use of these inventions

by everyone, including clinical labs, research labs and companies. As Dr. Goldstein already pointed out, it's actually pretty tough now to get a gene patent, very tough in Europe and Japan, but still fairly tough in the U.S. So there is at least a higher bar now for getting these patents, and they tend to be more narrow. So I think if we focus on licensing, we'll do a lot better.

I'll just take a minute on this old bill because I think it's a far better proposal than Dr. Weldon, who is an M.D. and a representative from Florida. His new bill actually proposes a complete ban on human gene patenting, but it's not retroactive, so really it doesn't matter. But anyway, his previous bill was kind of nice. What they did was they did an analogy to the surgical technique exemption from 10 years ago. They proposed to exempt from patent infringement individuals who use patented genetic sequence information for non-commercial research purposes. Again, if you add clinical in here, you pretty much cover everything, and they specifically said we should exempt medical practitioners. So this was kind of a good idea. It didn't go anywhere, but I thought the concept was good.

Unfortunately, Dr. Weldon then decided to propose a new bill in 2007 where they prohibited completely the patenting of human genetic material. Again, this is silly because there's really nothing left. I mean, it would be very hard to find a new human gene that hasn't been published on, and it doesn't address the key public health concerns of what's already been licensed. People are concerned about the same examples, and that's my other point. I think there does need to be more data. In my 10 or 15 years of doing this, I hear the same five examples or six examples repeated over and over. We can all name them by heart: BRCA1 and 2, Myriad Genetics; hemochromatosis; Canavan's disease. It's the same ones. Are there any new ones? Is it getting worse, or is it just these few that are exceptional? Then, of course, Athena Diagnostics. I really think there are only a few, and I think it's the same ones over and over again. So we have to look at that and see what the data is. If 99 percent of the people are playing by the rules, that's a good thing. But I haven't heard any new examples recently.

So again, this is just to show you that a lot of other societies are coming along. The American College of Medical Genetics came on board in '99 on this issue, again all in line with all the other policy documents I mentioned.

So here's our strategy in summary. We publish a lot, we execute primarily non-exclusive licenses, especially for diagnostic applications, we give very limited fields of use, we have mandatory sublicensing in our licenses, very important, and we have evolved this best practices guidance for use by ourselves and by our grantees. But again, it's not required by our grantees. So this isn't new. We've been doing this for 15 years. Our grantees are not required to follow these. Imagine if they were. And we always include provisions to ensure continuing availability for all others for research purposes, not just ourselves.

So here's a summary of the licensing of genomic inventions policy document. I won't go through it in detail. You get the gist. It's the same concepts over and over again in all of these documents. The one thing they do emphasize is to have commercial development and to monitor and enforce terms. Most of the time, once a license is signed, everybody is happy, and nobody pays it any mind anymore. So you have to go back, you have to follow. If the company is not appropriately commercializing, you need to take back the license. You need to force them to sublicense if they're not appropriately developing the tests in a timely manner. This all requires staff up front, but it's very important. The NIH is finally doing this in a very rigorous way. Many universities are not.

Here's the white paper from AUTM. Again, I think it's very sensible and balanced. It's technology neutral, and I kind of like that. Although they mention diagnostic tests, it just deals with licensing of inventions in general, how to best serve the public, and how to make sure you're still encouraging commercialization. It's signed by many big-name universities. They're not afraid to lose a little money by saying that they're willing to do non-exclusive licensing. It's been endorsed by several

different groups, and we're hoping to get more folks in there, and it definitely is in response to some negative press, but so what? It's still a good thing.

Again, licensees in this document they emphasize should not hinder clinical research, professional education and training, and you should be able to do independent validation of the test even if there's patent coverage. So they say very clearly licensing of a single gene for a diagnostic may be counter-productive. We know that, but they're finally saying it and putting it out there.

Some remedies. I'll finish up with some proposed remedies. Some of them have already been mentioned. We could pass legislation to have compulsory licensing. That's not a terrible idea. We could also work on a true research exemption. Who would write that and what it would say would be very challenging, but that's possible. You could also try a non-infringement provision for people who use DNA tests for non-commercial purposes. Patent pools, as Jorge mentioned. I think these are difficult, but it's also an option. There's some anti-trust issues that will be hard to solve. You could encourage cross-licensing, and there's a new open source movement, adopting some open source provisions from the IT industry which are kind of interesting as well.

But I think the best possible remedy, and I'd like to emphasize that this is my personal view -- very important, not the view of NIH -- is that I think as a start you can ask government grantees to follow some of these guidelines, and if they have a chance to renegotiate some licenses that come up for renewal, they should really think about it. They're going to hate it, we're going to get a lot of letters from COGA, but still it's not a bad idea. Again, you need some data to see how big the problem is. But if the problem is there, you might have to have the grantees at least adhere to some of these practices, which I think now a large number of entities agree is the way to go. But again, you do need some data. I would say the problems are both NIH grantees and definitely a lot of companies as well.

So again, here are your options. You could follow our best practices or the AUTM white paper. They're nearly identical, and I think we go very far.

So to conclude, the good news is that there's been policy development which is moving ahead, and there have been some common principles which have emerged. The bad news is that this is taking about 20 years. It's a great start. I like the idea of being a bit broader than the NIH best practices policy, but I do worry that by the time these policy or legislative fixes are put in place, many of the gene patents that were licensed out will have expired or that the proposals are only going to be for licensing going forward and they're not going to be retroactive and deal with the legacy problems, which is probably where the significant problems lie.

And I'll stop there. Thank you.

(Applause.)

DR. EVANS: Thanks. That was really wonderful, extraordinarily practical kinds of things we need to hear and consider.

Next I'd like to introduce Dr. Lin Sun-Hoffman. She's a senior patent attorney from Applied Biosystems, where she provides intellectual property counseling and research tool products. Previously she worked at Celera Genomics managing patent preparation and prosecution on gene patents, as well as other gene-related diagnostic and therapeutic patents. She also worked as a patent examiner at USPTO in the biopharmaceutical group, and she's here today to enlighten us about the private sector side of this equation.

It's great to hear from you.

DR. SUN-HOFFMAN: Thank you. Thank you for the invitation.

Can you hear me? Yes, okay.

I'm from the industry, unlike most of you, and work with academia or work with NIH government. I spent the last seven years as an in-house counsel. First I worked for Celera Genomics,

which is a genomic company, and we did a lot of gene patent filings. Then recently I moved to another division in the company Applied Biosystems, which is a research tool company. So I see both aspects of the gene patents. So before I start, there's a little disclaimer here that it's my personal view and does not represent the company's view.

First, as Dr. Goldstein already gave you a broad introduction of gene patents, just from my aspect the typical gene patent claims are nucleic acid, protein, method for detecting a gene, method for making a protein and for screening, and also you claim antibodies based on this gene, making an antibody. In addition, with a gene patent, you also have a method for diagnosing a disease by monitoring a gene expression, a protein expression, and also a method for treating a disease by targeting that gene with an antibody or small molecule. So that's a typical claim in the patent.

Why do companies use gene patents? You probably know this background for pharmaceutical companies. Many of them need a protein target, and to screen the small molecule they have libraries, just to screen the compound. For biotech companies like Genentech, Celera is actually developing the proteomics platform, working on using a target to develop antibody treatment. So you have all different proteins that express in different disease stage, so you will develop hopefully the target for treatment by antibodies. Here are a couple of examples of the treatment: erythropoietin and human growth hormone, Rituxan and Herceptin. These are targets to specific gene proteins.

For diagnostic companies -- and Celera also has this diagnostic with mutations that are associated with certain genes. So this is another type of use for the gene. Both speakers also talked about the BRCA1 and 2. That's also for the diagnostic purpose with gene. For the research company like Applied Biosystems, we use them as probes, primers, and putting arrays for the assay.

The gene patent holders, academic and U.S. patent, they are the majority holders, and there is some industry, biotech companies. People are probably familiar with Incyte, Celera, Genentech and HGS. These all have a lot of patents issued to them, assigned to them. I used Claire's slide. That's the survey to reiterate that the majority of gene patent holders are academic and government.

So from the companies' point of view, we want access to a patent, especially like a research tool company. What we first do is a freedom to operate. We do a big search, try to search whether those genes have patents issued, and actually the majority of the gene patents are either patented or in the public domain. In the earlier ones, they're already in the public domain. No one can patent. We found a bunch of them also in the public domain.

Once you do a search and if there's no freedom to operate, that's the patent counsel's rule in the company, if there's no freedom to operate, we just either seek a license or design around, or try to negotiate some kind of other deal with the patent owner.

Again, with academic and U.S. government, they are the majority owner of the gene patents. So the licenser is usually a downstream developer. They try to obtain a license to get more steady -- just like Claire stated, that the majority of biotech companies, research company getting their first research information from the academic or NIH. From my experience, we usually get the licenses that are non-exclusive from academic and from U.S. But as Claire stated, now more and more academics, they want to have exclusive license. So they need to make more money off that. But because we're in the more research tool area, so it's more tend to be the non-exclusive license.

For the biotech company who is a patent owner, from where we stand here, we either own the company, just like Genentech -- they're the owner of the gene patent -- they either out-license them or they develop themselves. Genentech does out-license. It's like Incyte. Celera also does out-license of the gene patent, and also internal develop those genes themselves. Some of those only develop exclusively. That's the BRCA1. But I was told Myriad, they do license to the academic for studying the BRCA genes, but not to the other industry.

The type of agreement we have is straight license agreement. From the industry point of view, it's license out. We prefer non-exclusive, unless the target has some huge development value. In the early stage, it's really non-exclusive, or if there is some more internal development, we also have a collaboration agreement with big pharmaceutical company or biotech companies.

In what situation we do the exclusive or non-exclusive? Here in the diagnostic area, typically we have non-exclusive license, but non-exclusive can be licensed for different indications, for certain type of disease. We restrict them to one type of disease, not other type of disease, or you can license to different companies with a certain type of disease.

In the therapeutic area, we tend to prefer the exclusive license and to multiple different areas of disease.

The payment, what we do is like royalty and also annual licensing fee. There's a different type of payment, payment milestone and up-front payment, a combination of payment. This all depends on where the product is developed, at the stage of the product. If it's a small company, we tend to have less up-front pay and more royalty.

So it's kind of complicated in determining the royalties. That depends on the stage of development, whether this is in the early stage or it's in the late stage. Some companies just want to do the screening part, and the royalty might be lower. Also, the type of technology, whether you use it as a probe or you use it as a drug development. The strength of the IP, that's always an issue, and also how big the market is for this gene.

In the diagnostic field, we usually look at about 2 to 3 percent of royalties, and the issue of diagnostic, there's a bunch of multiple licenses required to enable one technology. It's like royalty stacking. I guess I will explain a little bit about royalty stacking. For example, we have a PCR assay. That's the ABI technology. For enabling this technology, you have to get not only the PCI itself, the method, and also you have to find all the primers. If the primers is patented, you have to license those primers, and the dyes of this technology you have to license from different company. So multiple license adding together, the cumulative royalty can get up to 30 percent.

In the therapeutic area, it's usually the revenue is high. So at the front they usually ask for 5 to 8 percent. It's much higher than the diagnostic for the royalty.

This is just like a summary of the royalty determination. When you're in license, what are you looking at? IP position, whether the claim scope is big or its narrow, as Dr. Goldstein already explained to you. The patent has a lot of different scope. Also the royalty stacking issue, how many license they have to get to enable this kind of technology, and the potential revenue. There's financial modeling in the company to look at how much they can make, whether they want to make this kind of payment, and again whether this is diagnostic or this is therapeutic area.

For out-licensing, they also look at the company size. With big company, they're probably looking for more money, if it's Genentech, versus if it's a small company. They also look at the market size, look at the disease, if it's orphan drug or it's a big oncology field; and also the terms of use, how you use it for the commercial or just for the research, the same as diagnostic versus therapeutic. So that's all the fact we look at to determine the royalties.

So from the gene patent owner, since I've been on both sides, I'm just looking at it from my personal view. We all feel we have a right to own a gene, but it's really hard from the company point of view to find who is using my gene. That's a special force you have to hire to look for that. Usually the gene patent user are in the early stage. They just want to screen it or do something. It's not in the late stage. That's our concern. It's really hard to find who is using it. The company don't worry about academic using a gene. It's not very common for a company to sue an academic, very few cases. Also for gene patent, the revenue is very low. If you only license gene inside Celera, it's not a very high licensing

fee we're asking for. It depends on the product you're using, too.

Then from the non-patent owner there's another concern, the strength of the IP, whether the scope that happen cover the scope, because a lot of patents in the earlier stage -- I was an examiner in the Patent Office, and the standard was developed at a different stage. So different time when patent was issued has different scope. If you look at early patent that was issued and use it now, many of those can be invalidated because the standard was so different.

So that's to the next point, the inconsistency of the PTO standard, because PTO has at a different time also evolving their standard. Another issue is when we do the search, some of the patents are difficult to search. You really couldn't find a sequence because in the earlier time there's no sequencing database. So that would be another concern from the non-patent owner.

One thing here we have an issue is the patent scope, recently we get a letter from a company, another company, from a university actually, asking us to get a license from them, and we believe that patent -- first, we did not infringe. Second, this patent was invalid. We explained to them. The second letter was a cease and desist letter saying you cannot use it. That was kind of concern for us. The tech transfer office should really look through their patents because the patent was so broad. It's too broad and there was no support. We did our analysis internally, and we just saw there's no way that our product was covered by that patent. But it's like the disconnection between the academic field with the industry. How can we talk to them to convince them? Instead we just keep getting the letter saying if you don't do that, we can take action. So it costs money for the company, because we calculate how much do we pay them, the royalty, and it's only $8.00. Do we need to go find a lawyer to pay $50,000 to get an opinion, or should we go to the court and spend $1 million to fight for this patent? It's all these issues.

We say, okay, let's just pay the money, $8.00. We feel like this patent is invalid. Why should we encourage this kind of behavior? So that's all the issues we need to think about.

So the reality check. This is my last slide. The majority of genes are patented. What can we do? It's already there in the public domain, and also licensing a gene is possible. You can get either exclusively or non-exclusively. For the companies with research tool, diagnostic company needs to consider royalty stacking. The issue is if I'm using one other product and the other company comes to us, we usually resolve this through the cross-licensing. Company to company we found it's easier to deal with. The difficult part is company to academic, and sometimes with NIH we had some issues too, because they just come to us and say yes, you have to pay this, you have to pay this. Let's sit down and talk.

One time we get a threat from one party is either academic or government saying if you don't get a license, we're going to tell all your customers that this patent, you're infringing the patent. So this is kind of scary for a company point of view, say how can we find a way to resolve the issue, especially with those genetic patents, because the patent itself is not as strong.

Again, enforcement of gene patents is difficult until the product is developed. Before the product is developed, really we cannot even find out. It's hard for us to find out whether they're using this gene. You have to search other websites. That's what university people do. They search the website and look for everything to see whether you're infringing.

Thank you. That's my talk.

(Applause.)

DR. EVANS: Thank you very much.

If we could get Ms. Driscoll back up, the three speakers will field questions now. I think, since I cut Kevin off before, he should get to be the first one.

DR. FITZGERALD: I just had a quick question that might lead, unfortunately, to

long answers. So if we could just get one insight from all of you as to where you think the Metabolife case might go. I mean, I know it was kicked back downstairs by the Supreme Court for another reason, but I presume it's going to be once again looked at, this idea of being able to patent or control a correlation, and then how that will impact the field. So just a quick insight from all of you might be good at this point.

DR. GOLDSTEIN: If I was a Zen master, I'd give you a quick insight.

(Laughter.)

DR. GOLDSTEIN: But I am not.

I think the Metabolife case was -- again, for those who do not follow what happens in patent law in the Supreme Court, which is probably most of you, the Metabolife case was a case that tested the validity of a claim that had a correlation at the core of the claim that basically said you test for a certain metabolite and if certain levels of the metabolite are found, you correlate that with a particular disease, although the particular disease was not mentioned and it was simply a very basic correlation.

The Supreme Court was asked to review the case and discovered that a critical issue to it was whether this was closer to a law of nature than they wanted it to be, and whether it was in fact so close to a law of nature that it was unpatentable subject matter. This was something that had not been addressed at the lower court level, nor had it been briefed, and the Supreme Court doesn't, like a lower court, say to the parties please brief this issue so that I can decide it. If they don't like the status of the case, they send it back. Go away, it's too early.

My sense is that what will happen is there is a particular technical difficulty with the claim, and if I was in charge of that case I would probably try to redraft the claim, reissue the patent so that it actually isn't just a correlation, like a law of nature, and it becomes a real diagnosis of a real disease, in which case the Supreme Court would have had nothing to say about it.

So the problem was a bit claim drafting. It was not the right claim to be taking up to the Supreme Court, and it may be a while before you see another case like this. I don't think that case is going to go back up to the Supreme Court. I think people who are drafting claims these days have read in between the lines of what happened in this case and are no longer going to draft pure correlation claims.

MS. DRISCOLL: I would just say the NIH probably internally would probably not file on that type of patent. In fact, we're having a lot of trouble just dealing with proteomics and microarray where you're trying to look at dozens or hundreds of genes, and where do you put the boundaries on this is upregulated, downregulated, and it gives you a signature? Those are impossible to enforce, and they're very expensive to try to prosecute. So in most cases we wouldn't even file.

DR. SUN-HOFFMAN: This case actually looks through the claims. The rest of the claims are addressed. It's the assay of detecting the correlation. But just this claim they're making very broad. So the impact is really on the physicians or patient who wants to use it at home, and it's like Claire said, it's hard to detect those kind of infringement. How can you sue everyone like that? It's not practical.

DR. EVANS: Marc was next.

DR. WILLIAMS: I'm cognizant of the fact that Mark Twain said that it's better to remain silent and be thought a fool than to open your mouth and remove all doubt.

(Laughter.)

DR. WILLIAMS: But I had a couple of issues that I'm confused on, and particularly in Claire's presentation when she said that basically everything is public domain and this is a temporary problem that's going to be going away. In my mind, it seems that what's public domain is sort of the reference sequence, and many times when we're dealing with diseases we're talking about variations from the reference sequence mutations or whatever, and these are the things that people are developing tests to detect and targets to treat.

So the general question is how will patent law treat those variations from published reference sequence? And then depending on the answer, I have a couple of follow-ups.

MS. DRISCOLL: Well, there was a study, I think it was 2005, Murray et al., and they showed that 18 percent of the known human genes that are in GenBank are associated with issued patents. So that means 82 percent are not. But most patents, as Jorge pointed out, you're getting not just the gene but you're getting a certain homology to all other known genes. So that's going to pretty much cover most known mutations. Maybe it won't cover mutations in the regulatory sequence, but you're getting most of the known genes even if you're adding information on new mutations. It's either in the public domain or it's already covered in current applications, because based on all the bioinformatics work, there's really probably no genes left that are completely unknown that will be newly discovered. That's what I meant.

So they're either in the public domain or they're already covered, and different variations are already covered in issued patents or pending patents.

DR. SUN-HOFFMAN: I just want to add something. The gene patents are pretty much covered, as Claire said, but there's a new development of association that's still coming.

MS. DRISCOLL: That's still coming, epigenetics, regulatory.

DR. SUN-HOFFMAN: Especially association with certain diseases.

MS. DRISCOLL: Full-length cDNAs of human genes. That's done. But other stuff definitely is still coming down the pike.

DR. WILLIAMS: Okay. The second question then relates to what we were talking about yesterday on oversight of testing. One of the things we were talking about is raising the bar in new tests and the oversight that's going to be applied to those.

So looking at Dr. Goldstein's list of major to minor and where these things fall, if we greatly increase oversight and the costs associated with development and oversight of testing, is that going to raise the bar to push more people towards patenting as opposed to being more open? Is that a concern, or are we really not talking about the types of dollars that would make that change at all?

DR. GOLDSTEIN: Maybe I'm not the best one. I wasn't here yesterday, so I don't know the details of the concept of oversight and what that's going to push people to do. Maybe if you could clarify that a little bit.

MS. DRISCOLL: You're worried about pricing? So in other words, you're making it more attractive to have a standardized test?

DR. WILLIAMS: In other words, people are developing in-house tests, and there's a certain cost associated with the development of the test. But right now, I think of it akin to developing a drug where there would be no regulation, where you could just then release the drug into the market. But we're talking about applying more oversight for drugs before they come into the market, which is going to raise the cost of the test development. I don't know what the magnitude of that cost will be. It's almost certainly not going to be of the magnitude of what the pharma companies are experiencing with their drug development. But if we do push up the cost where it's going to cost more for a company to develop a test, is that going to push them more to say let's exclusively patent that to recover costs?

DR. GOLDSTEIN: Yes. Now that I understand what you're saying, no question about it. Clearly in this taxonomy that I showed, from synthetic drugs to business methods, clearly the most patent intensive industry of all is the pharmaceutical industry, and that's because they have these long oversight times. Their patent rights are getting cut back. They're constantly lobbying for extending the patent rights, and it costs them $700, $800, $900 million per drug, counting all the failures and everything else in there.

If, in fact, the diagnostic industry goes in that direction, the value of patents is going to go up. People will be much more involved in patenting and exclusive licenses.

DR. WILLIAMS: The last point I wish to make is you noted that there are differences between the U.S. and the international approaches to patenting these things. I'm also aware that there are now, at least in the ultra-rare disease testing area, foreign laboratories that are going through the CLIA certification process to be able to run these tests offshore but under U.S. regulation.

If that becomes more widespread, how do you envision that would impact enforcement of the U.S. patent versus an international patent that may be, say, more user friendly for somebody who wants to develop the sequence into a test?

MS. DRISCOLL: Well, they can certainly ship the data back and that's not an infringement, so it's very attractive. I mean, there have been several biotech companies that have been founded on that principle. Nimblegen, which is a microarray company, that's what they do. They have facilities offsite. You must send the samples to them and they email back the data, and that way it's not infringement. So I think it's just people taking advantage of the loopholes. If they were going to produce it in the U.S., they would be infringing or they have to pay a license. So I think it means it goes abroad. It's just a practical response.

DR. SUN-HOFFMAN: Just in addition to that, the gene patent has higher standard in other countries, in Japan and in Europe. As a matter of fact, like a BRCA1, they didn't make a single penny off that in Europe. The standard is different, so it's easier to attract people to use those methods offshore.

DR. EVANS: I have Hunt, and then Debra, and then Julio.

DR. WILLARD: Thank you, Jim.

I want to follow up a little bit on Marc's question, because I think the area of concern, it seems to me, and the potential battlefield for some is not the issue of gene patenting per se. That's a shorthand that people use. What they really mean is it's a gene involved in a disease and there's a claim, and this dates back to cystic fibrosis in 1989, and there are going to be thousands more of those associations and patents that will come down the pike, and that's where the concern is. So I think focusing on the fact that gene sequences are in the public domain and that patents issued 15 years ago only have five more years to run, I don't think anyone cares about that anymore. The issue is cystic fibrosis, breast cancer, and a thousand other disease gene associations that are likely to come forward over time, and the protection given to either an academic researcher and/or a for-profit institution for finding that and thus protecting that association.

DR. FERREIRA-GONZALEZ: I would just like to add a specific example. In the last six months our laboratory has received letters to cease testing for three different targets, but this is in the oncology area. It's not monogenic disorders but it's related to the association. As I said, three letters have been received in the last six months for EGFR, for Jac2, and for BRCA mutations in CML patients for lack of response to (inaudible), and this is just in the last six months.

DR. GOLDSTEIN: I know something about cystic fibrosis because I wrote and obtained the patents for (inaudible) and the Hospital for Sick Children in Toronto. The delta 508 mutation is very well known to me.

The problem is not so much that patents to correlations are going to disappear. They're not going to disappear. The Metabolife case raised the possibility, but patent lawyers are drafting claims differently after they read what the Metabolife case had to do. So those patents are going to keep coming. You're absolutely correct. It's not so much that the patents are going to stop, unless some of this legislation passes and stops it, like the 2002 legislation that you were talking about. It has to do more with how are they enforced, how are they exploited, how are they licensed. I mean, it's a back step. That's why I'm worried about not throwing the baby out with the bath water.

There are patents and patents, and I think there are lots of gene sequences that can be

used, for example, as research tools, that can be used as diagnostics. So even my taxonomy fails if you get to the edges between them. The sense that there are continuously going to be an increasing number of correlations between particular sequences and particular diseases or SNPs or RFLPs and diseases is going to continue, and people are going to continue patenting them. I think the battlefield is between the parties, for example, that are doing this in some sort of a commercial context who are probably going to continue receiving these letters and parties who are doing it primarily for basic research or just to advance knowledge who are probably not, although it's a very iffy proposition.

What's little known, for example, about the Integra v. Merck case was that Scripps was a defendant in that case. Scripps is an academic institution, and they got dragged into the litigation even though they were "doing research." But they were doing research with Merck's money. So Integra dragged them into the litigation. Given the number of academic institutions that are receiving corporate money, it's very easy for somebody to say that the institution is just the research arm of Merck, and Merck is just outsourcing the research to Scripps.

So I think a lot of these lines that we're hoping to draw between academic research versus non-academic research versus commercial research are all very fuzzy anyway. My view that I described a little bit in the talk is that ultimately if you're dealing with microarray diagnostics or if you're dealing with multiple mutations or multiple SNPs for a particular disease, the ultimate solution is not just any old patent pools, which have problems because of anti-trust issues, as Claire mentioned, and other such issues, but carefully defined patent pools where international health organizations like WHO or PAHO or the ACMG, the American College of Medical Genetics, step in and say a pan-ethnic panel for cystic fibrosis needs to have the following seven mutations. These mutations need to be in every universal test that works pan-ethnically for cystic fibrosis, and then the patent owners, which in our field -- I mean, the patent owners in the consumer products, electronics, know that they cannot put a product on the market unless they talk to each other. It's impossible. They depend on each other. One has the patents on the chips, the other one has the patents on the CDs, the other one has the patents on the electronics. There is no product unless they talk to each other, and they are used to talking to each other.

In our field, companies don't talk to each other. There is this long history and tradition of exclusivity in the biopharmaceutical industry, and I find this over and over and over again. So for them to sit down and start talking about cross-licensing or forming a pool for diagnostics is way out in left field. If some international organization were to come in and say this is the test, you need these five mutations, and it's too bad that three of them are patented by three different people, but any one of those is not the standard of care, I think it's going to force -- that's my proposal -- people in this industry that don't talk to each other to start talking to each other and to start to cooperate a little more. That's my view.

MS. DRISCOLL: And the other solution is either compulsory licensing or exempting clinical practitioners from patent infringement. So there is a dichotomy because the very same universities that have a clinical lab at their hospital that are getting these letters, their tech transfer office is busy patenting these things and going for licenses. So you can't say don't sue our clinical lab but, by the way, we'd like a lot of money on this. So it's a real problem.

The other issue with cystic fibrosis is you had an inventor and some people back there in Michigan who actually said to the tech transfer office please license this non-exclusively, and that's how it was handled. I've seen Debra Leonard's presentations, and if everybody did it the way CF was handled, we wouldn't be here.

DR. WILLARD: The other point I wanted to make, and then I'll yield the microphone, is I think it's relatively easy in your position at NIH and at NHGRI to suggest that academic institutions follow the NIH's guidance document, and I think that's a little bit disingenuous because the

NIH plays by a different set of rules. You don't have a mandate to try to make money, and your bills are paid by the taxpayers. Private institutions especially live under these perhaps unrealistic but nonetheless expectations that tech transfer will potentially make money for the institution, and that's the motivation for doing this. So you can't tell them to adopt a different set of standards that say don't worry about the profit motive, simply give everything away as much as you can and be reasonable about it, because that's just a different game.

MS. DRISCOLL: But to be fair, the university in California non-exclusively licensed the Cohen-Boyer recombinant DNA patents and they made a fortune because they did hundreds of licenses. So it's not always unprofitable to license in this manner. A lot of people just don't realize that.

It's also unrealistic for every tech transfer office to cover its costs or to be a profit center. So universities have to learn that.

DR. WILLARD: But these are not controlled experiments, obviously.

MS. DRISCOLL: No, they're not.

DR. WILLARD: And reasonable minds and reasonable institutions can differ on their strategies.

MS. DRISCOLL: I agree with you. Absolutely.

DR. EVANS: Okay, we have a little bit of time left. I have three more people on the list. Debra, then Julio, then Sherrie.

DR. LEONARD: Mine are more comments because Andrea and Hunt and Marc basically raised one of my concerns.

I'm a little skeptical of patent pools because there's that word "voluntary" in there, and academia doesn't know how to play nice in the sandbox like industry cooperating with each other because they need each other. Academia tends to be these "all for me" and "all for me." So I'm a little skeptical of the patent pools and how long it would take to get a patent pool together for one disease even if you eventually could.

The second point is what was raised by Andrea and Hunt, that this is not going to be a problem that goes away. It's not that everything is out there and it's going to go away because I'm aware of the older ones that you were mentioning, but the last two and a half years I've moved up to a higher level. I'm not directly running a laboratory, but Andrea mentions that in the last six months there have been three cease and desist letters. It's not stopping and it's having a very large impact on diagnostics. So while we talk here and we have, you have as SACGHS, a mandate to look at research issues related to genomics, this task force has decided to look at clinical access and patient access. So I think you need to focus the discussions on those aspects of the impact of gene patents on clinical access and patient access to the use of this information for health care. The conclusion of the evaluation of the NAS report was that much of the research issues had been addressed, and so I think maybe we should focus the discussion more on the clinical and patient access issues.

DR. EVANS: Okay. Julio, and then Sherrie.

DR. LICINIO: I had a comment about the microarray stuff, because when you do a microarray, you put all genes there, and many of them are already covered by existing patents. So how are people handling this? Because now as you do high-throughput stuff, if you do a microarray, you can't possibly go to every single gene and look at every patent and application for that. So how are people balancing these two things, the need to do things in a high-throughput manner, and all existing patents that are behind all of the genes that are in a microarray?

DR. SUN-HOFFMAN: I can put two cents in there. With those microarrays, we do a freedom to operate search and then go to the companies to talk to them. Usually the license fee is pretty low, but sometimes we cannot find the genes. I mean, it's impossible to search every single gene. So far

we've only gotten letters from universities. They have time to go through all these websites to find out which genes are there. But it's hard to detect most of the time. Affymetrix has not got any lawsuit for their microarray. That's really not a big issue in the industry at this time.

DR. GOLDSTEIN: But you're right in the sense that every one of the gene sequences in one of those microarrays, if they happen to be a DNA microarray, needs to be cleared to be used commercially, and if you've got a million different sequences up there and even one of them is patented, you've got to either take it out of that array or you go get a license, or you stop the whole project. All three of those have happened. People many times will proceed towards developing a microarray and find out that two or three of the genes that they want to use are exclusively licensed somewhere else and either they take them out or the whole project stops.

MS. DRISCOLL: And Sherrie.

DR. HANS: Ms. Driscoll, you indicated earlier that one suggestion is for the NIH guidelines for liberal licensing to be made mandatory for grantees. I wondered if you could explain the legal authority that NIH has to do that and what mechanism would be used, like a regulation. Let me just tell you what I'm struggling with by using a parallel example.

In the area of research with animals, NIH clearly has the authority to regulate what happens with animals while the research is being conducted, but what if there was a lucrative market for post-research animal petting zoos or something? How could NIH control that after the research is finished and it's a commercial activity that no longer involves the research?

MS. DRISCOLL: That's an excellent question. I mean, we essentially would probably make it a condition to grant. In other words, we would say you can't take the money unless you say that you'll at least do narrow exclusives or non-exclusives, and we'd probably have to write in some reasonable exceptions or some sort of a vetting process so that we don't scoop up too much. But as far as legal authority, we probably don't really have -- it would mean a change to Bayh-Dole to really be able to do it, but what we could do is make it a condition of the grant. So essentially we're not making you do it; it's just if you want our money you have to do it.

DR. HANS: Has a legal analysis been done to answer the question whether you have the authority or not?

MS. DRISCOLL: I think we could get the authority. I don't think we have the authority right now, but I don't know that definitively. As far as the research tools policy, we were able to make that a policy. We didn't have to change any laws. We were able to just institute that as a condition of grant. So that was the kind of analogy I was thinking of, unpopular though it would be.

DR. EVANS: Okay. Well, we're already behind a bit, and I'm going to pull a Reed on you and curtail part of the break. Let's meet back in five minutes.

Again, I want to thank the speakers very much.

(Applause.)

DR. TUCKSON: Reed would never do that. I don't understand.

(Laughter.)

(Recess.)

DR. TUCKSON: So here's the situation. I'm buying time so people come in. Now they're here.

I've got a couple quick little things I've got to do. Number one, if you want a ride to the airport or need transportation, you need to go to Abbe or you will be walking, because they don't care. Like I didn't get any lunch yesterday, I'm telling you. They don't care.

Oh, I'm just teasing her. Now she feels bad. I'm sorry. They care. They love everybody. I'm sorry. They're going to take my money away.

Number two, congratulations. She's not here now. Okay, we'll do it later.

Debra Leonard, we're so pleased that you're here and you're going to do public testimony. Because you have to go to the train, we're going to do public testimony, and because one of the things you're going to publicly testimony on is the topic du jour, among other things. We're happy to have your public testimony.

DR. LEONARD: Up there?

DR. TUCKSON: Of course.

DR. LEONARD: I forgot my hats.

DR. TUCKSON: Oh. For those who don't know, depending on what she's talking about, she'll put on one hat or another, and she's got a whole collection of them.

DR. LEONARD: And just in case you're confused, I'm not Bob Cook-Deegan.

Dear Dr. R., members of the committee, good morning. I'm Debra Leonard and I'm speaking to you now as a member of the Association for Molecular Pathology. I'll forego the explanation of the mission and membership of AMP since we've provided comments to SACGHS on numerous occasions in the past.

The purpose of these comments is to provide AMP's perspective on three issues relevant to the charge to the SACGHS and of concern to AMP. The first is the proposed federal legislation related to oversight of genetic testing. As you've heard in other public comments yesterday, recently two bills have been introduced into the U.S. Senate relating to the regulation of laboratory-developed tests. Senator Kennedy has introduced a bill entitled "The Laboratory Test Improvement Act," and Senator Obama has introduced a bill entitled "The Genomics and Personalized Medicine Act." AMP agrees with the intended goal of these bills, which is to protect the public health by ensuring safe and effective diagnostic tests to inform clinical decisionmaking. However, we are deeply concerned that these bills, if enacted into law, would have unintended negative consequences, including severely restricted access to genetic testing services by the public, as well as decreased innovation and implementation of novel genetic tests.

As in other areas of medical practice, laboratory medicine advanced by incremental steps as new information about clinical targets and test performance become available. AMP strongly believes that the same intended goals of these bills can be achieved by strengthening existing laboratory oversight mechanisms and a strong collaboration with the private sector.

The purpose of raising these issues with SACGHS today is to ensure that this advisory committee is aware of these bills and the potential negative impact that may result for genetic testing services. Furthermore, AMP asks SACGHS to request that the Secretary of Health and Human Services convene a meeting to engage key stakeholders who may be affected by these bills with members of Congress and relevant regulatory officials to reach a common understanding of the purpose of the legislation and the best ways of achieving these goals without unintended harmful outcomes.

The second point of concern is assessment of coverage and reimbursement for genetic testing services, and I feel like a broken record here. That wasn't in the official comments. AMP members perform genetic tests and other types of molecular tests for the management of patient care. We continue to struggle with the economic reality that the reimbursement level set for the CPT codes used for genetic testing are less than the cost to perform these tests. While the SACGHS report on coverage and reimbursement issues made recommendations to the Secretary that CMS develop a plan to address this issue, AMP is not aware of any action taken to date. AMP applauds SACGHS for its report and recommendation and asks that SACGHS follow up to determine if action will be taken to correct the inadequate payment levels for these CPT codes.

Finally, the third point is on gene patents and patient access. AMP asks that

SACGHS continue to give full consideration to the negative impact of gene patent exclusive licensing and enforcement practices on genetic testing. We are encouraged by the approach that SACGHS has taken to investigate the impact of gene patents on patient access to genetic tests. AMP wants to assure SACGHS that gene patent enforcement continues to limit the tests clinical molecular pathology laboratories can perform for their patients. We encourage SACGHS to thoughtfully consider and develop recommendations to the Secretary of Health and Human Services that will address the clinical impact of these practices.

AMP remains available to SACGHS to assist with or provide additional information for your thoughtful deliberations and important work. On behalf of AMP, I thank the committee for your time and for listening to the concerns of AMP.

DR. TUCKSON: Well, thank you very much. Those are comments that are well received.

Are there comments? There's one comment from Andrea.

Let me just say at the outset that we will add the CMS comment. We have had a number of items that are moving to CMS in an organized way as a result of the terrific staff that are here not only from CMS but also from the Director's Office. So I feel pretty confident that that will be added to the list of things that CMS will be responding to, and I feel that there's a pretty good pathway to try to get CMS comments back to us on your matter as well as the other ones that came up yesterday.

DR. FERREIRA-GONZALEZ: Let me bring the microphone closer so I can project.

One thing that strikes me about today's comments, and actually two comments from yesterday, the different organizations that represent not only the laboratories but also advocate groups and interested individuals that brought to our attention the legislation that is being introduced at the Senate right now, the Obama bill and Kennedy bill. We also have received a chart from the Secretary to look at the issues of oversight, and what we heard yesterday also is that the Secretary's office is looking at issues of oversight.

So it seems to me that what these groups are asking us to maybe look at these issues and ask the Secretary to engage the stakeholders, then maybe some kind of coordination among the different groups to make sure that what is done at the level of Congress versus the level of the Secretary, and even our group, and we hear from the stakeholders are not better coordinated.

So I would think that maybe what we want to consider as this committee is writing a letter to the Secretary asking these specific questions, asking him this specific issue of the coordination and including the stakeholders during the deliberation of these issues.

DR. TUCKSON: First of all, it's a great suggestion, and we could certainly write that letter. I think we had Kris Bradsher yesterday, who was representing the assistant secretary for legislation, who couldn't be on the call with us. Who is the person who couldn't be on the call?

MS. CARR: Craig Burton.

DR. TUCKSON: Craig Burton. So I think that what we might want to do is sort of say to Anand that maybe if you could take back to Craig Burton this point.

Could I get a sense of the committee that essentially what we're looking at is just that we want to be assured that the administration is doing everything that it possibly can in terms of its coordinated activity between the various bills that are in play to try to give us the best calculus for success in solving this equation.

DR. FERREIRA-GONZALEZ: And make sure the stakeholders are also involved in these discussions to make sure that there are no unintended consequences to the development or implementation of these issues.

DR. TUCKSON: So unless the committee would like to guide me in a different way,

given that we had a conference call yesterday with the senior person representing that office of HHS for legislation, with the two key congressional staff people who clearly all knew each other and who are all talking, if we could give a strong sense, Anand, back to what you heard here, I think that would sort of be faster than trying to write the letter and have it go through whatever the heck process it has to go through.

DR. FERREIRA-GONZALEZ: Would it drive the message stronger of our feeling if we write a letter?

DR. PAREKH: It will.

DR. TUCKSON: All right. Then we'll follow up with a letter. Then Andrea will draft the first draft of the letter and get that draft to Sarah, who will then expeditiously get it to me, and we will forward it to whom? To the Secretary, correct?

PARTICIPANT: Should we get it to the members first?

DR. TUCKSON: No, we don't have time. If you want in on this, you'd better get to Andrea and help her to draft it.

Look what you sparked.

DR. FITZGERALD: Before you leave, Debra, just a quick question. Preliminary to having perhaps a meeting of the various stakeholders on the Obama or the Kennedy bills, do you have somewhere your specific questions or concerns about the two bills broken down to each one?

DR. LEONARD: The Kennedy bill has very broad implications for all of clinical laboratory practice. So they don't restrict it to genetic tests. Any laboratory-developed test is included in this process. So what you need to understand is that's far-reaching, way beyond genetic testing. The breadth of that is very scary to clinical practice.

The Obama bill actually incorporates much of what this committee has been deliberating on in the various sections. It is much more reasonable in allowing a process to be developed on oversight of laboratory-developed tests specifically, but there are many other sections to the Obama bill. But looking at the laboratory-developed test process or oversight of those tests, it's much more to look and develop a process which would allow stakeholders' input. So the Obama bill is probably more reasonable of the two. I think that reflects AMP's analysis and other clinical laboratory organizations.

DR. TUCKSON: So I think, Kevin, it's important, and your comments are respected. I want to be clear about the committee's sense of expectations in terms of what we can do. As I understand it, I think that what the Andrea recommendation is is that we are encouraging the Secretary's office to continue the process of collaboration between the two bills' sponsors and the stakeholders so as to advance the chances of a bill going by. I think we are being studied in not trying to get into which bill is better, although Kevin's question is more than appropriate. I just want to make sure that there's no sense from the committee that you would be disappointed if we did not weigh in as to which bill had greater merit or another. I think that's probably not our role as the advisory committee to the Secretary. Okay, good. Thank you.

DR. EVANS: I assume you've turned it over to me?

DR. TUCKSON: With glee and to the committee's great relief.

(Laughter.)

DR. EVANS: I want to introduce now Bob Cook-Deegan, and it's really very much a pleasure. The Secretary's committee is very fortunate to have gotten the services of Bob and his group in trying to help us grapple with these issues. His team is working on the patient access study. Bob is the director of the Center for Genome Ethics, Law and Policy at the Duke University Institute for Genome Sciences and Policy. Previously he was director of the Robert Wood Johnson Foundation Health Policy Fellowship program at the Institute of Medicine.

I'll turn things over to Bob.

DR. COOK-DEEGAN: Thanks, Jim.

So I'm going to mainly walk you through a primer on intellectual property. I'm going to try because Jorge and Claire and others have covered a lot of this territory. I'm going to try to just pull out some lessons. But before I do that, I wanted to acknowledge the students who did so much work. They gave a presentation to a subset of your task force last night. Three of them are still here: Melissa; Julia, who is actually a postdoc/legal scholar; and Patrick are here; and Chris Conover, the actual teacher of the course that presented last night, is here. The students are on the left, and Subha and Julia and I have been helping out with that project. Subha is the postdoc who had to leave early this morning to get back so she and I can teach at 6 o'clock tonight, and she's running the class tonight.

Basically, what we were asked to do by your committee is to turn the data and the resources that we have at Duke on the question that's facing your committee, which is about access, and I think one reason that Sarah and your committee turned to us is because we have a research group that has been funded by the National Institutes of Health, the National Human Genome Research Institute, and the Department of Energy to study the role of intellectual property and information flow in the innovation process in genomics, and it funds a center called the Center for Public Genomics. It's called that because we are in particular looking at what's the distinctive role of having lots of information about genetics and genomics available to large numbers of people all over the planet through the Internet at relatively low cost? What does that do for the innovation system, and how does that interact with the intellectual property system? So this is a sub-class of things that we've been looking at, although we had really not looked specifically at genetic diagnostics until you asked us to a couple of days before Christmas in a flurry of emails.

So here are the factors that you're obviously contending with. What are the mediating variables that affect access that might relate to intellectual property? One is price, right? The whole idea of a patent is that you get more control over your price because you can prevent other people from making, using and, most importantly, selling the thing that you made, your invention, on the market. It can also be associated with control of the invention, and you will see some examples of that in the diagnostics arena. That is, you can actually impose conditions on the people that are doing the tests because you have sole control over that invention. So, for example, in diagnostic testing for Alzheimer's disease, there was a big controversy in the beginning, was it a screening test or a diagnostic test? Well, Athena Diagnostics said we'll only do the test if the clinician sends a signed statement that says this person as far as I'm concerned has dementia, and therefore this is a diagnostic test. That was to prevent screening. They could do that because they have the exclusive rights to the three Duke patents that govern ApoE testing for Alzheimer's disease.

Another factor that interacts with intellectual property is regulatory approval. I gather you heard about that yesterday. But obviously, if FDA gets heavier into this game of either testing in Mendelian tests or for these more complex microarray and multiplex tests, then obviously that has an influence on the overall market, and the intellectual property interacts with the Food and Drug Administration in ways that I'll explain in a few of the cases.

Finally, reimbursement and coverage is a big deal, right? I mean, you just heard about that, right? Who pays? How much a payer pays for a service matters a lot, and in some of the examples we're going to walk through, depending on how the rules fall out, if those developing tests are expected to prove the equivalent of safety and efficacy for a genetic test before they get paid for it -- that is, if CMS starts saying we aren't going to pay for your test until you've proven clinical utility and you have to pay for it -- then it's going to cost more to develop these tests, and there's going to be a higher demand for having intellectual property protection before you take the step down the road towards getting a new test on that particular condition.

I'm going to mention some of the case studies. This is not data that's available to you yet. The students are working on these right now, but these are the cases, and I really am not going to go too deeply into them, but we are doing a comparison of breast and colon cancer testing because they are kind of clinically similar, but the patent landscape is completely different because, for the most part, Myriad Genetics has control of the patents that are relevant to BRCA testing, whereas the intellectual property for colon cancer testing is more diffuse and it's mainly owned by academic institutions, and it's available through a much larger number of laboratories.

I won't go through each of these cases because it's going to take too much time, but we will be sending you information on these that describes the conditions, describes the clinical decision trees, and looks explicitly at the role of intellectual property on access to the degree that we can find it. I will say one summary, that it's going to be very, very hard to give you crisp, clean information that keys in only on the question of access. Usually, maybe the best we're going to be able to do in some cases is to look at utilization, which is how many people actually use a test, which is only a loose proxy for access. What you really want to know is how many people who should be getting access to something are as a fraction, and how many people who shouldn't be using a test because it's overutilization are using it. It's very hard to do that, but we're going to go as far as we can with these case studies.

I'm now going to shift gears and I'm really not going to cover those case studies because you're going to get more information about that. This is the team that has pulled together a lot of the data that I'm going to be displaying. There's going to be a lot of data. I apologize for that, but the slides are going to be available to you, and I think we've got references for most of the data so you can recover it and look at it at greater length when you need to.

Just to reiterate some of what happened this morning, basically a patent is this ability to prevent others from making, using or selling your invention. You have to disclose your invention in sufficient detail that somebody else can use it, and the patent system works because the court system of national governments becomes a tool for defending your rights. You get a patent right and the courts will defend your right. So they're subsidizing your exercise of that right.

Why are patents called patents? It's because the idea is that you have to disclose a lot of information in order to get that right. That was the tit for tat that was set up in the Constitution of the United States.

So we have actually, in our project, mainly been looking at technologies. So none of the things that you see on this list here -- these are things where we're trying to pull together what is the story. I have coded them into things that are unpatented, things that are patented by academic institutions, and things that are patented by private sector interests, usually firms. Most of these are patented entities, small start-up firms. We have pretty good stories for some of these. Some of them we're just getting started on, like Perlagem, Illumina, 454 Piracy Quincing, and Selexa, the things we're going to start this summer. But let me step back and say why were we doing these studies in the first place, and let me step back even one step beyond that, which is what are we going in the first place.

Everything you heard about this morning was all the hassles, all the transaction costs, and all the price increases that are associated with patenting. So why are we doing this in the first place? Well, there are basically two justifications for having patents. One is because if you do something that's useful for the world, you should get a reward for it. It's the just desserts theory. Therefore, if you're contributing something valuable to society, you should make a little bit of money off of it. This idea actually goes back to John Locke. It was John Locke's idea that Thomas Jefferson kind of stole and put into our U.S. Constitution, and that's where the idea of progress in science and the useful arts came from. It was a very straightforward translation of Lockian ideas.

In the area that we're talking about, there are basically three things that patents do in

the biomedical research domain. One is that it does what I just said. It ensures that somebody who contributed some new invention that's quite useful gets a little bit of money out of it, and there are examples of that in our stories.

Kary Mollis, who is working at Cetus, discovered PCR. Cetus patented it, and they patented a bunch of other technologies that were related to polymerase chain reaction. They made about $300 million off of the invention when they were sold, when Cetus was sold in parts to Hoffman-LaRoche. The PCR part went to Hoffman-LaRoche, and the rest of Cetus went to Chiron. That deal went through in part because the $300 million for PCR enabled the deal to happen. Then Hoffman-LaRoche made about $2 billion off of PCR. Now, how have they done that? Because your reagents for doing PCR are a little more expensive. Every time you buy one of those thermal cycling machines, you're paying for licenses that are feeding money back through Hoffman-LaRoche indirectly.

So why are we doing that? Well, because somebody did something really useful. PCR is an awfully cool piece of analytical -- it's a fantastic method, and everybody uses it everywhere. So $2 billion sounds like a lot, but if you spread it out over many years and you bundle it with all sorts of other things, the system kind of accommodates it.

The same thing for Cohen-Boyer. I know that you've heard about that case, but that was a discovery at Stanford and the University of California. They made about a quarter of a billion dollars that was split between the universities and I don't think had any impact on the end price of any of the products that generated most of the income for those two universities.

So that's one thing that the patent system does. You do something useful, you get some money out of it. So it's a fairness doctrine.

There's another thing that the courts have tended to focus on more recently, and that is that if you have patents or you have the prospects of getting patents in the future, that induces investment in companies. So, for example, when investors were deciding back in 1991, 1992 should we invest in this thing called Myriad Genetics, well, probably those investors were thinking if Myriad can get some patents on some useful commercially valuable things, then we'll get some money back from our investment. So this is an induced investment theory of patenting. It is contingent on being able to carve out some intellectual property and sell it for a profit. The same thing was going on at Incyte and Human Genome Sciences when they started doing cDNA sequencing. So we have stories like that going on, and in the chart that Claire showed you'll see that Incyte and Human Genome Sciences have a highly disproportionate share of the gene patents, U.S. gene patents. The reason for that is because they did the sequencing. They did that because, in part, they were expecting to get patents that they could sell on the market. Either they would make products based on those patents or they would get revenues when other people made products based on the stuff that they discovered.

There's a third thing that patents do that does a lot of work in drugs in particular, and we have case examples of that in biotech. That is, if a product, after you've discovered it and you've made an important discovery, if it still costs a lot of money to take it to the market -- so say you have to prove safety and efficacy of your product -- you have to patent the thing up front, but then you have to prove that it works and it's safe, that costs tens of millions of dollars, sometimes hundreds of millions of dollars. If you're going to make that investment in proving that it's safe before you can get it onto market, you need something that protects your investment in the discovery in the first place, and that's the work that the patent is doing. It's solving what economists call the free rider problem.

So what happens if you didn't have patents in those situations? You spend the money to prove that something is safe and effective, and a generic manufacturer walks in and says the day that you put this thing on the market, they can remanufacture your product at cost of production without having to do the R&D expenditure to prove that it's safe and effective. Therefore, it's not fair, and

therefore those products are in theory not ever going to happen unless there is some other way to pay for safety and efficacy testing. But the way we've constructed the system, where those costs are borne by the inventor or by the company that's going to market the product, then that's the way it's going to be. You need something that will protect that investment.

Patents are not the only way to do that. Data exclusivity is another way that FDA can do that, and it has done that increasingly.

Some background numbers, and then I'm going to shoot through a bunch of data slides just to give you a flavor. I'm not going to make you memorize it, no quizzes at the end. But here are some numbers, and these numbers are as current as I could make them. There are about 44,000 U.S. DNA patents. So that's in the United States, and I'm sure you'll understand this, but patent law is national law. You can get a worldwide patent, but that means basically you have to go country by country. In places like Europe, you can get a Europe-wide patent, but if you ever have to defend it, you have to go country by country. It's litigated in each national court system.

So the U.S., as we'll see, has a whole lot more out of this activity than other systems. There are about 44,000 DNA patents. Now, what do I mean by a DNA patent? A DNA patent is something that at least mentions DNA or RNA in its claims. In a patent you describe your invention, and then you say claims. The claims are what Jorge was talking about. Those are the picket fences that define the boundaries of your invention, that say if you walk onto my territory, we're going to hit you. The claims are what define that boundary zone, and if you mention nucleic acids in a claim, then we're pulling it into a data set that's called the DNA Patent Database, and it's just a collection of terms that are specific to nucleic acids. It's about 25 or 30 terms that we tested one at a time for sensitivity and specificity, and we think it works pretty well for capturing DNA patents.

There's a subset of those patents that are sequence patents that mention DNA sequence specifically, and the number drops from 44,000 down to something on the order of 16,000. These numbers are very inexact, but it gives you at least an order of magnitude. So what's the difference? The difference is things like recombinant DNA, like PCR, like methods, like bioinformatics patents, many things, promoters, enhancers. They might be sequence-based or they might be too short to trigger the sequence category that other groups are studying.

Then finally, within sequence patents, there's a subset that is a gene patent. A gene patent is usually for a complete DNA that's the full length of a messenger RNA, the vector that contains that DNA and the cell line that would produce the thing that that gene makes. So that's usually a package, and that's the prototype gene patent. There's a little bit of wobble in these terms. Of those, you've heard the figure of 4,000 stated from the Jensen and Murray paper. Actually, of those 4,000, about 1,000 of them are only on microarrays and stuff like that. So your classic gene patents actually account for about 3,000 of those.

Now, the thing to notice on this slide is that of the 16,000 sequence patents that exist worldwide, most of those are only in the United States, and I'll show you a graph in a minute, but here are the raw numbers. There are only about 750 of those that have been issued in Europe, and only 500 of those have issued in Japan. Those are the three big markets. So this is actually kind of a real strange situation.

DR. LEONARD: Bob, do you have any idea how many of those gene patents are disease gene association patents?

DR. COOK-DEEGAN: No, nobody has looked at that. Actually, maybe I'll come back to that at the very end, because it's one of the things that we're thinking about doing as a technical thing as a next step.

So just to summarize what I think is a fair summary of what most scholars -- I mean,

we're academics, so we don't agree about anything, but here are some things that most people who study this business would say we kind of agree that these are generally true.

We think that patents do induce investment in private sector activity. That is, there is more R&D going on because of the prospect of having a patent. These companies exist precisely because they expect to make money. One of the ways they expect to make money is by having patented things.

It does create assets for start-up firms. It does solve the free rider problem, at least in some situations. We have many examples of the patent system generating income for universities, like the Cohen-Boyer patents, where the Axel patents generated $790 million for Columbia. So the universities are making streams of revenues off of the patented materials.

There are some other things that we agree are inherent in having a patent system. They make it more expensive because you're charging more and because there are hassle costs. There are transaction costs that are associated with it. There's more of a bureaucracy. If you're going to keep track of things and account for them, it's going to cost more money and it's going to create friction in the system because any time you're counting things and have to account for them, there's going to be friction. In a way, it's a tax on innovation. The real question, I think, that has been looming under the surface of a lot of the exchange this morning is does it really gum up the efficiency of the R&D system if you have too much clutter?

If you have to clear out the brush before you can do any real work, well, then, we've got a problem, and it's an efficiency problem. There are some things that do not happen in the real world because of these encumbrances. So if we look at the example of PCR, it seems fairly clear that some environmental uses of PCR didn't happen because EPA and environmental researchers don't have NIH budgets, so they couldn't afford to go out and use PCR for looking at zillions of plants in many, many ecosystems. They just couldn't do it, and the difference between patented and unpatented technology may have meant that certain areas of research just didn't happen.

That said, though, what happens if you look at some inventions that were patented versus some that were not? What we've got here is three examples. This is polymerase chain reaction, which again was patented by Cetus. This is PBR 322. This is the cloning vector that was second generation that was developed at the University of California at San Francisco, unpatented but absolutely could have been patented. It's a beautiful piece of engineering, and it is a widget. Then we have Maxam and Gilbert sequencing that absolutely could have been patented. How do we know that? Because there was a DNA sequencing method that was patented in 1973 that was a lot less clever than this. So it could have been patented. It wasn't. This is by a guy who went on to form Genome Corp. or wanted to form Genome Corp. He's not a guy who hated patents, although at the time that this was discovered they just didn't think about doing things that way, and so it wasn't patented.

The question here, though, is does the fact that something is unpatented, like these two inventions, affect the adoption curve? To a first approximation, you'll see that the curves look pretty similar. So what can we conclude from that? Not a whole lot, because we don't know how much use of PCR there would have been if there weren't a patent. What we can say is that at least it wasn't catastrophic. There was a lot of PCR going on. It was a little bit more expensive than it otherwise would have been, but it doesn't seem to have completely driven the nation's system to a halt.

Now, one of the things that is distinctive to genomics is that it was a very compressed period of very rapid investment in a lot of companies, and this is their market capitalization. So these are the publicly traded firms. These are the firms that not only got started but actually went to the public markets and put their stock out for trade so you can count what they do, and one of the things you can count is how much are they worth, and here's the 2000-2001 bubble. It peaked about three months after the announcement of the draft sequence in June of 2000, and then it went down by a factor of five, and it's

beginning to build back up. But what you'll see is there was at one point almost $100 billion in value in these companies. That's what investors thought they were worth, but, in fact, that dropped precipitously, and it shows you the volatility.

This shows you the big 15 firms on that list. There are about 75 firms on that list, 77 firms on that list. But of the big 15, what you see is they have continued to increase their R&D despite these fluctuations in their overall market value. You'll see that what they're spending their money on is R&D, but they're also spending their money on plant and equipment, and the fact that this curve is going up faster suggests that they're also spending money, grabbing new talent from the pharmaceutical industry and other places. They're beginning to pull people into their businesses that get paid more than the R&D people do, so the curve is a little bit steeper. They have to pay more money for that kind of talent.

This is the general landscape of DNA patents. This is the most general category that I gave you, and it shows you the very rapid slow rise from the Diamond v. Chakrabarty, which is right here. This is when it became okay to patent a living thing, but you'll see that there are some DNA and RNA patents that happened before then without any controversy. But it really took off, kind of a steady rise during the early '90s, late '80s, early '90s, and then it took off exponentially for a while from '94 to '99. For three years in a row it dropped, and then last year it went back up again. I haven't shown you those figures. The figures for this year so far are that we're a little bit ahead of where we were last year. So we may have a 2007 that's a little bit higher than the numbers were for 2006. This is not a permanent drop-off. It looks like it's beginning to reverse.

This is a striking slide. This is how many sequence patents. This is the subcategory of those patents that are for sequences that have been issued by the different patenting offices around the world at different times. You see that the U.S. was always a little bit higher. There were a fair number of them in the United States that were not being issued. Japan is black and Europe is white. They always wear the white hats in the patent game. What you see here, though, is since 1996, after that exponential rise that you saw in the previous graph, there are a lot of patents that are being issued in the United States and no place else, not in the other two major markets. This is what that looks like year by year. So you see the slow and steady increase. The reason that they're dropping at the end is not because it's going away but rather because those are probably things that are still under examination in the patent offices around the world, and therefore those curves will probably come up to some level that's higher than it is right now but it just hasn't happened yet.

Who owns these things? The only really definitive data on this came from reading all of the patents that were issued in the United States from 1980 to 1993. Steve McCormack and I read these by hand and coded them, and one of the things we coded was who owned them. What you see here is a very anomalous pattern of about 39 percent of these patents are owned by academic institutions and a little bit, over half of them, are owned by for-profit firms of one sort or another. Usually it's 3 percent academic ownership of a patent or less in other domains, telecommunications, widgets, instruments. So this is an anomalously high representation, and here are the data from the European group, a really nice piece of analysis that came out last November by the Science Policy Research Unit at the University of Sussex here. You can get this on the Web. But what you see is the fraction of patents going to private sector interests -- that is, private firms -- has been going up with each successive time period, which is what you expect to happen. So if you add up these things at the bottom, which are the private sector interests, you'll see that their fraction of these patents is going up.

Now, this is a slide taken from the Jensen and Murray paper. I apologize for the low quality. It's from Science magazine. I just pulled it right out. The news here is that this fraction, this is the fraction of genes that Claire alluded to. These are gene patents. So how did they define that? They found all the patents they could find that had sequence information in them and then they married it to the

database at the NIH, the National Library of Medicine, that is the best curated gene database. So this is the stuff that biologists do to characterize their gene. They dump the information at the National Library of Medicine, and they compared the sequences in patents to the sequences in well characterized genes and they said where do they match, and that's how they came up with this collection of 4,000-some genes that are patented and the 82 percent or so that are not patented.

Now, that unpatented set is a combination of things that will never be patented and things that are not yet patented, and we don't know the relative proportion of those. Nobody on the planet knows that.

Claire showed one of the slides, so I took it out, of who owns the academic institutions that own the most DNA patents. This shows you what they do with those patents. The first two bars are things that -- we didn't know what was going on. The universities actually don't administer a certain number of patents that they own. They give them to somebody else to administer, so we don't have any data on those. Zero licenses for about 30 percent of the patents. That means somebody paid to get a patent and then they've never licensed it. That happened about 30 percent on average. Most of the patents were licensed once. Does that mean it's exclusive? No. You can have a non-exclusive license to a single licensee, but there's a lot of overlap with exclusive licensing here, and there are a lot of really interesting patents in this collection of these 45 patents that have been licensed more than nine times. That's the Axel patents on co-transformation on production of a protein out of a cell. It's the Cohen-Boyer patents. It's being able to detect fluorescently labeled cells that Lubert Stryer developed at Stanford. So that's a bunch of really classic patents that have been non-exclusively licensed, usually as a source of income that has not really gotten in the way of the innovation process, very much like the PCR story except a little bit cheaper.

Now, what Sarah asked me to do is to say, okay, so what are patents doing, and then what could government or other stakeholders do about this? What are the policy levers that are at your disposal? So here I'm going to walk through some things that are going on, some things that you might think about that you could do, just to give you an idea of what's going on in the real world that your report is going to interact with.

One is that there is patent reform that's being contemplated in both the House and the Senate. A bill that made it, there were hearings in both the House and the Senate last year. It sounds like there's even more energy behind this because the intellectual property interests of the telecomm, computing and software businesses are fed up and they're putting a lot of muscle behind trying to get patent reform, and that's really what's driving the patent reform.

The biotech and pharmaceutical constituencies have for the most part been very happy with the way things are. It's oversimplification to say that they -- I think they would be happy if there were no reform, but I think they may have accepted that there might be reform, and therefore if there's going to be reform there are certain things that they want to see happen. But this patent bill is going to probably be going through over the next year or two, during this Congress, the 110th Congress, and this is something where there might be provisions that would be relevant to your work.

A bill was dropped in about a month ago by Javier Becerra from Los Angeles and Representative Weldon, who is a physician from Florida. This is a bill that would say from here forward -- Claire alluded to this -- from here forward there will be no sequence-based patents. So that bill has been introduced. There's one co-sponsor, Pete Stark, and we don't know what's going to happen with that beyond what I just said. You saw a mention in Claire's talk of the Rivers bill. Lynn Rivers was from Michigan. She was squeezed out because she got forced into the same district with John Dingell. He won the primary and she was out of Congress, so her bills died with her candidacy and nothing happened in the 108th Congress, but that idea is still perking in the background. It could be brought to life again.

There are also examination practices in the patent offices, and you know what? That's doing a lot of work. That's doing a lot of work. If you look at the difference between the U.S. and Europe, most of that is not the rules, because we have the same patent criteria for the most part on both sides of the Atlantic. So something is going on in the way the patent offices are handling these inventions that's quite remarkable. That tells you that there are levers to pull in that domain.

You heard mention of a research exemption. There is no research exemption under U.S. law. Madey v. Duke started its history about 100 yards from where I park my car every day, the free electron laser facility. That case is now over. We gave him back his electron laser, so this case you won't be hearing about anymore. We've already done our damage. But there is talk in the wake of Madey v. Duke of creating a statutory research exemption under U.S. law. There were some proposals. It is not currently on the table for patent reform in the United States, but you will see that in Belgium and in France they actually passed research exemptions that are pretty substantial, and there are many research exemptions in other countries that allow you to do research on the invention. These are actually exemptions that allow you to use the invention, as well as do research on it, much broader exemptions.

Finally, you heard Jorge and Claire both allude to compulsory licensing. What does that look like? Basically, in Belgium, if the King of Belgium decides our health would be better off if we could use this wonderful invention that somebody made, it doesn't take away all of the rights, but it takes the exclusive right away from the patent holder and basically says as the King of Belgium, I'm acting on behalf of the people and we're better off. We will pay you, but we'll pay you what we damn well please, not what you want. It reduces the price leverage that a patent holder has, so patent holders tend not to like this stuff. But that's what has happened in Belgium and France, and it's under hot dispute because India passed a new patent law that went into effect last January. It's being actively litigated right now.

One of the issues is compulsory licensing. Many developing countries that have to adopt the new Western rules of patenting have built compulsory licensing into their statutes precisely because they want to keep public health at the forefront of their governments' activities. So those are problems that exist in the real world.

DR. LEONARD: And that compulsory licensing you're implying comes with reasonable royalties?

DR. COOK-DEEGAN: Yes. Well, yes. It's supposed to come with reasonable royalties. That's one of the issues. The Thai government, for example, I don't know if you're following it. The Thai government just stepped in on some AIDS drugs and said we're going to force a compulsory license. The royalty rate was 0.5 percent, which most of the scholars in this field think is too low, and if it's challenged, and it's going to be challenged in the World Court system, it may be too low. But if it had been 5 percent, I don't think there would be have much of a squabble about it. So, yes, it's supposed to be fair and reasonable, but what that means to the court system depends. But, yes, it is not an absolute right to override the patent rights. Rather you're supposed to still give the inventor some return for their invention.

In the patent reform system, this is probably more detail than you really need to know, but these are the two things that have gotten the most attention in the patent reform bill in the U.S. One is that the U.S. is the only major country in the world that has this rule that in the U.S. if there is a dispute between two people who file patents at the same time, the courts are supposed to figure out through what we call an interference proceeding who actually invented it first, whereas in other countries the patent offices just say, okay, you have to prove that you invented it, which is much easier to do; that is, you can't steal something and patent it. But if you invented it yourself and you can prove that you didn't steal the idea from somebody else, meaning they can't prove that you did, then it's the first person to file a patent application. It's just an administrative simplification. So for the software and computer people, this is

driving them batty because they have patents all over the world, and they want the U.S. to shift to the same rules that other countries have. These interference proceedings are extremely expensive and you have to hire very specialized lawyers. There are only a few people in the world who do this stuff. If you break any of the rules about evidence, your case blows up in your face, so you hire these people at very high prices. So everybody would like to get rid of those transaction costs, except for the lawyers, so the U.S. might switch to a first inventor to file system.

Interestingly, universities are kind of in love with the first inventor criteria. They love the U.S. law as it is, so there's been some hostility to this change within the university community.

Finally, probably most importantly, as illustrated in the case study that Julia Carbone will be presenting to you when she finishes her case study of BRCA, there's an opposition process in Europe that does not exist in the U.S. What does that mean? It means when a patent comes out, somebody else can say we don't like that patent, we think it's too broad, and you guys in the patent office forgot to consider this other stuff when you gave out those claims. You have to do that within a certain time, and once that has happened it starts a proceeding to basically look at the patent again in light of the new information that's been contributed by outside parties, and this is what happened to the BRCA patents and led to the dramatic narrowing of the BRCA1 patent from the entire gene to just the mutation that is highly prevalent in some Ashkenazi Jewish families. That's how it was discovered and that's how the claim is structured in the European Union now. It's a very, very narrow patent compared to the patents in the United States.

One little sidebar here is that the Cohen-Boyer patent kind of went through this kind of process, not completely unprecedented, but that was because Stanford brought that on itself by openly prosecuting their own patent. Why did they do that? Because they thought that they were going to get sued. They thought that they were going to have trouble keeping the cats herded, and therefore they openly prosecuted the patent. So a lot of prior art was brought to the attention of the patent examiners by a flurry of articles that happened just before the decision was going to be made, and the patent office issued the patent anyway. So a court looking at that case would say, hey, they did consider that stuff, and this is not just a patent, this is a patent that withstood some scrutiny that was much more serious than it normally is.

So what are the tools at your disposal? What could you do? Well, there are all sorts of stories in the scientific community of things being patented, scientists not liking it and beginning to push back and say, hey, you know what? We're just not going to get those licenses. Initially, PCR licenses were going to come with some restrictions, and Cetus scientists would not sign up. They made a lot of noise. They complained in Science and Nature. They wrote nasty articles. They would yell at the officers of Cetus Corporation when they went to cocktail parties, and you know what? It changed. Their policy changed. They loosened up their licensing restrictions.

Oncomouse and cre-lox, Dupont, held those patents. Harold Varmus as director of NIH took an active interest in this, negotiated much more liberal licensing strategies from Dupont, which then became the template for other universities to use as their licensing strategies. It gave the scientific community access to very valuable technologies, and it didn't require a law being passed. It just required some open negotiations, some people yelling at each other in public, and lo and behold the policy changes.

Moreover, Harold Varmus and Francis Collins, as well as Bruce Alberts when he was the head of the National Academy, wrote letters to the patent office saying you guys are being too sloppy, you're issuing too many gene patents; stop it. They made a lot of noise and, lo and behold, in conjunction with a very important court decision, U.C. v. Lilly, the patent office began to increase the level of scrutiny of gene patents specifically. You wouldn't know that from the patent numbers, but the fact is that there

are a lot of patents that might have come through otherwise that did not come through.

Finally, there are all sorts of rules that have been alluded to. These are where most of these guidelines that Claire is alluding to, the OECD licensing guidelines, the AUTM guidelines, the NIH best practices document, and the research tool guidelines are all in this category, but there are also some rules that the scientific community has imposed on itself about sharing of data and materials that interact with intellectual property. So the large throughput sequencing centers agreed in 1996, when we've sequenced a length of DNA of more than 1,000 base pairs, we're going to dump that on the Internet every night. They just bound themselves to an informal contract saying they would do that. That mattered.

What does that do? It means that information is out there and if you discover a gene that's based on that sequence and that's the only thing you've done is sequence that stuff, then you're going to have a hard time getting a patent on it because that's now in the public domain. It doesn't make it impossible, but you have to do something beyond just the sequencing.

The SNP Consortium, this is the group that was trying to find variations in the human genome. They sat down and said the only way that we can make sure that this stays in the public domain is we're going to file patent applications, we're going to characterize each spelling difference in the human genome long enough that we're sure nobody else can patent it, and then we will walk away from the patent. So it was expensive, laborious, but it was crafted as a strategy for keeping things in the public domain.

Then we're already mentioned the research tool guidelines from 1999 that NIH put out and basically folded into its grant-making cycle. So if you get a grant now from NIH, you say we're going to play by those rules. There's the best practices document that came out a couple of years ago, and the OECD licensing guidelines were just officially sanctioned last year. There's the university statement that Claire directed you towards and that was in your packet for the meeting here this week. This came out mainly from Stanford, and Arnie Bienenstock and Kathy Ku at Stanford I think did most of the work in getting these universities together.

But a lot of the problems that you're addressing would not exist if those guidelines were being followed. It's really that simple. If you could get norms and practices to adopt those guidelines, you have a legacy problem. You have all these patents and all these licenses that have already been assigned. Those aren't going to go away, but moving forward a lot of those problems would be solved if those guidelines were being followed.

Finally, when you get a grant of a certain size from NIH, you have to have a data sharing plan. We had to have one for our grant. Well, we make certain promises in there. We've signed a piece of paper that if we don't do it, somebody could do something about it. So that's a tool that could in theory be used to make sure that information is out there, it's flowing freely, and that it's being used for the purposes for which it was generated. The problem with that, of course, is enforcement. How does anybody actually know? Well, they don't, but that is a tool that is out there. Right now we only have informal mechanisms. How would we know? We do know if somebody is a really, really bad actor or if they're stupid enough to say in public what they're doing, which sometimes they do. But most of the time you don't know unless you have a very systematic way of monitoring what information is being shared.

Now, Sarah did ask me to review some of the empirical data. You got one of the experts on probably the single most important study on this list, the survey that Mildred Cho, John Merz, Debra Leonard and their colleagues did of what clinical labs were doing, and what they demonstrated is that some folks have stopped offering tests that they used to offer or have decided never to offer in the first place tests that they might otherwise have agreed to offer but for the patent situation. That tells you that at the provider level there are certain folks who have backed away from certain kinds of diagnostic testing. It doesn't necessarily tell you about access because in the case of Myriad, for example, if the

same patients that would have sent their samples to U-Penn or the IVF clinic in Virginia or to Oncoremed when it was operating, if instead they're sending them to Myriad, there might not be an access problem. It might just be that they're paying more money but it's not really an access problem. It's a pricing problem. We don't know that, and it's very, very hard to get data that are sufficiently refined to be able to tell that.

There are two poster children that do almost all of the work. It's probably the reason that this committee exists. In the survey of the literature that was done by the Alberta group, Julia's colleagues at the University of Alberta, Tim Caulfield and Tania Bubela have done a really nice survey of who said what about the BRCA and all these other cases that are on the poster children of bad behavior in DNA licensing. BRCA is way, way, way far and ahead the case that mattered the most, had the most negative publicity, and is mentioned in almost every policy report. You saw some of those policy reports from the U.K., from the U.S., from Ontario. There's a compendious report from the Australia Law Reform Commission. They all mention BRCA. They may mention Canavan's, they may mention ApoE Alzheimer's testing, but they will all mention the BRCA case.

Now, a few things that will come out, I think, in Julia's case study when she's done with it. The thing you need to understand about BRCA is that the patent story is what carried the day in the United States. BRCA essentially is only offered as a genetic test by Myriad, and the reason for that is because they did have very strong patent positions and they drove the other providers out of the market using their patent position. That is not what has happened in any other jurisdiction.

In the U.K., the national health system pushed back. They said we're not going to play by those rules. In Canada, one province, one health minister in one province very publicly said we're not going to play by your rules, and over time, since Myriad has not sued and has not won, has not prevailed, the other provinces have pretty much followed that province, Ontario, in not paying attention to the patent. For all intents and purposes, they are being ignored, and it's testing, as usual, in most of these other jurisdictions. In Australia, Myriad licensed to an Australian firm that said, hey, health systems in the provinces, you can use this, we will non-exclusively license to you. So it's a very different patent situation in the United States compared to any place else.

The Canavan's case is a very unusual case. Again, it was a relatively inexperienced licensing office. This is my interpretation of the story. It was some combination of secrecy, betrayal and overpricing that led to the bad outcome. I think it was a bad outcome and it led to an out-of-court settlement that I hope all the parties are happy with. We don't know the details of what the settlement was because that's what happens when you settle out of court. It's secret.

Now, here are some things that are going on that are actually a very big deal, and I think maybe these are even more powerful than patents in predicting access to tools in the future. One is coverage and reimbursement. The key question here is if it becomes a rule that you have to prove that your test is actually useful in a clinical decision path that's going to be part of a clinical guideline, for example, if you have to prove that as a company before you can put something on the market or before you get paid for it by the payers in the U.S. system, that's going to be a pretty heavy burden. That's going to be a lot of money that has to be spent demonstrating that clinical utility, and it does mean that patents are going to be a more important part of the game, and it's going to get even worse if you not only have to prove that it works but you have to prove that it's worth paying for, and yet that may be the direction that things go.

If the FDA gets in the game, either for the single gene Mendelian tests or for the multiplex tests, that is a regulatory hurdle that everyone would have to go through, and that would increase costs and would also increase the importance of the intellectual property associated with those tests, because then you have to solve this free rider problem that you talked about before. You would have to prove your thing is useful before you can make any money off of it, and that means that it's going

to cost more to develop these tests.

Finally, the push-back is one of the themes of what I'm talking about today. The biggest push-back in the BRCA cases came from the monopoly power of a patent holder bumping up against the monopsony. Economists have this term, monopsony, which is when you're the only buyer. So monopoly works against people when they're atomized buyers, but when there's only one other buyer, they can negotiate as hard as you can because they control the market. When monopoly meets monopsony, the dynamics are completely different. That may be what happens in some diagnostic tests if the national governments decide they're going to play hardball.

So a few things to say about the examples I've given here is that many of them are irrelevant. That's the thing to notice here. The technology is moving very rapidly in the direction of many genes being associated with any given condition, many alleles for each gene, and needing to be able to have technologies for looking at what's happening to those genes. It's not just measuring inheritance, it's also measuring something in a tissue or a state variable. Is this cancer or is it non-cancer? That's the direction that an awful lot of DNA analysis is going. That's a completely different game, as you've already talked about.

The technologies there are chip technologies, microarray technologies, analytical algorithms. This is a much more complicated thing, and it begins to feel a little bit more like making DVD machines or making really complicated cumulative technologies that require multiple components that Jorge Goldstein alluded to at the end of his talk. It's a completely different game from the BRCA/Canavan's case. So those could prove to be outlier cases rather than the norm.

We've already said enough, I think, about Myriad and Athena to indicate that those are the two cases in the gene patenting game that have the biggest effect on diagnostics that I'm aware of. Mike Watson might know of some cases that I don't know about, but these are the two that we keep bumping into in our work.

Now finally, what's going on in the big picture about gene patenting that might influence your thinking as you make this report? There are a bunch of opportunities that, even given the current patenting situation, might have led to different outcomes if behaviors had changed among the stakeholders. One is if some of these patents began to be challenged. If instead of just paying license fees -- we heard the dynamic of how a company thinks about should we actually pay for this license or not, right? If it's $8, you're going to pay the license because you don't want to spend a million dollars on a lawsuit.

Now, what's the dynamic that's going on there? We've got a prisoner's dilemma. You've got one very big stakeholder who has a very strong stake in defending their intellectual property, and you have a lot of other players who have a much lower stake in seeing the friction go away, and you're willing to tolerate a certain amount of friction especially if you have to take a big risk to solve the problem for everybody else.

But it seems possible that there could be push-back that would happen from time to time, and there are several cases that I could think of. For example, I mentioned ApoE because these are patents that are held by my own university. In doing the clinical trials under federal funding, if the universities that decided to do that clinical trial stuff had said no, we're not going to play by your rules, they could have in theory taken this to court. I don't want to predict how a judge would look at a federally-funded invention, funded by NIA, being licensed to a company that then goes back and is being used primarily by a clinical trial being paid for by NHGRI and other parts of NIH and saying you absolutely have to honor this patent, because there is that little provision in Bayh-Dole that says the government has certain rights and interests in these inventions. It's not clear to me that this is out of bounds. It's arguable. You'd get lawyers to line up on either side, which is why nobody pushes back,

because the risk is that you might lose. You might spend a couple of million dollars and in the end you're still going to have to buy the license. You're still going to have to pay that $8 per test.

Debra had this experience with Myriad. It actually wasn't Debra. It was the University of Pennsylvania, her institution, where it became a bone of contention whether providing BRCA testing under NCI studies was considered research or not. Could there have been push-back against Myriad on that case? I think there might have been. It's arguable that the outcome might have gone the direction of saying that is research, and it's not under the research exemption, it's under Bayh-Dole, because there were federal inventors associated with the original invention.

It looks like, as Jorge alluded to, the Supreme Court is kind of itching for a case to reign in the Court of Appeals for the federal circuit in its broad interpretation of what's patentable. It looks like Justice Breyer would just love to have a case to chew on, and if that happens, then suddenly the rules are very different. That's how we got into this game. Diamond v. Chakrabarty was a 5-4 decision. One vote changes and then the rules change tectonically. It's an earthquake.

Finally, as I've already illustrated, the stories for BRCA in Canada and the U.K. suggest that patents are not necessarily the most important thing to be paying attention to. When you're dealing with a health system, which we don't really have in the U.S. -- we have atomized buyers and sellers and payers. But in other systems that have a more coherent policymaking framework, it turns out that maybe the patent situation is not going to be the thing that determines the outcome nearly so much as what gets paid for and under what conditions.

Finally, stay tuned, because we're doing this gigantic experiment with domains of intellectual property that are owned on this side of the Atlantic and are unowned on the other side of the Atlantic and in Asia, and I have no idea -- this is a game that is just beginning to play out, because there's a 20- to 30-year litigation cycle.

Insulin was cloned in 1977. The case that finally decided that took place in 1997. So it was 20 years of fights going on before we knew what the answer was to the original cloning case. So there's a 20-year cycle. Most of these patents began to issue in '94, so what does that tell us? It tells us that in about seven or eight years from now we're going to begin to see whatever litigation. That's likely to be the time when this stuff hits the fan.

So I've already hit all these points, and I have a bunch of data slides if you have questions, but I'm not going to hit you with all those slides. It's just a bunch of information that I wanted to make sure is available to you in your deliberations.

Debra, you've already got a question.

DR. LEONARD: Can you clarify under Bayh-Dole the government's march-in rights? Does that require going to the courts and through litigation for the government to do that, or can they just say we're going to allow the use of this in these situations?

DR. COOK-DEEGAN: Let me be clear about Bayh-Dole. There are three aspects of Bayh-Dole that are related that are completely different, and they've got three different procedures. One is the rights that I alluded to. Basically, if your invention derived from federal funding, the government very clearly -- so, for example, the NIH intramural labs can make, use and sell the invention from any university that takes grants. You discover something is valuable, you patent it. NIH intramural labs unquestionably could use that for free because they are the government. They are part of the very department that sponsored the research. They can use it for free. That's built into the statute. They don't have to do anything for that. It's a royalty-free paid license to use that invention if one dollar of it went through federal funding. That is just built into it.

There are two other provisions in Bayh-Dole. Claire alluded to one of these. So if NIH, like it did with the mammalian gene collection and with the mouse knockout collection -- NIH did

this declaration of exceptional circumstances and it said this is a special case. We're funding this work in order to create a resource that's going to be freely available. That's what we're trying to do, and patenting is just getting in the way here.

NIH makes that determination, but it actually has to go through the Department of Commerce for permission to do that because Bayh-Dole is officially administered by the Department of Commerce. So there has to be an extra layer, and that's one of the things that some of us have talked about for reform. If NSF and NIH and DOE and the Department of Defense had a little bit more flexibility in how they could go about doing that, you might see more use of that kind of provision. The universities hate that because that's a reduction of their autonomy to decide what they would do with their own inventions, but that is a possible angle.

The third thing you alluded to is march-in. March-in is something where there were four provisions that were written into the bill that said if any of these four conditions are met, then the government can step in even though we gave you your patent rights. The government has decided that this is a really weird case, and one of those provisions is public health. NIH can at that point march in and grab back the intellectual property they gave away. That's very different from these other two situations.

March-in has been invoked, to my knowledge, three times. It has never been acted upon. That is, NIH has never actually done it. The procedure for that is for NIH to make a determination. If they decide they're going to march in, then the patent holder has an appeals right that's built into the Bayh-Dole statute. It's never gotten to that level because NIH has always decided no, we're not going to march in.

DR. LEONARD: What are the four conditions? You mentioned one is public health.

DR. COOK-DEEGAN: I don't want to quote them off the top of my head. Public health is the one that has done all the work in all of the cases that I'm aware of, but there are three other provisions. I think one of them is probably that they're not working the patent aggressively enough.

Do you remember, Claire?

MS. DRISCOLL: I think that's one, that they're not actively commercializing.

DR. COOK-DEEGAN: Debra, I don't want to quote that off the top of my head because I didn't read the Bayh-Dole statute yesterday, and I try not to every day.

Kevin?

DR. FITZGERALD: First of all, thanks, Bob. That was great, as always. But I just want to follow up on that last point because with the SNP Consortium, the idea was to go get the patents and then walk away, and what you just said is if you don't pursue the patent, then you can lose the right to have that protection. So is that now a non-viable strategy?

DR. COOK-DEEGAN: It's somewhat different, Kevin. The reason the SNP Consortium was doing what it was doing was let's say that they were doing something and it was a matter of dispute whether they were the first to come across this SNP or some other company was, right? Or some university or something, but some other group files a patent application. If they have not filed a patent application, if it's been published and it's really clear to the world that everything about that invention has been published in a single publication -- these are very stringent standards -- then they wouldn't have to do anything. It would be public domain and you can't get a patent. It would defeat the patent. But there's a good chance that there might be a little piece of your invention that you didn't include in a single publication, in which case somebody can patent it. You can't block that unless you yourself have standing as an inventor. So they wanted to be able, if somebody came in, they wanted to throw it into interference, and they were pretty confident they would be the first to win most of those interferences because they were spending money faster than anybody else and they would find most of

the SNPs first.

So what they were doing was characterizing them. They were not losing their patent rights because they never got the patents. They were filing patent applications. These are really bizarre patent applications that go on for pages and pages. They're phonebook-sized patent applications where the last 600 pages are sequences of stuff that they have no idea what it does, but they wanted to dump it into the patent system so that they could keep somebody else from patenting it. So then they would abandon the patents. So they had standing as inventors for long enough to prevent anybody else from patenting, and then they would just dump it into the public domain. It's a very sophisticated, expensive strategy that can only be used every once in a while.

DR. RANDHAWA: A question to clarify. You had mentioned briefly the FDA. So one of the benefits of patenting to an inventor is awarding the free rider, and you had mentioned exclusivity by the FDA could be used for the same ends. Could you elaborate on that?

DR. COOK-DEEGAN: Yes. So what FDA can do sometimes, and it's being built into our trade agreements -- those are very hotly contested provisions. But basically what you can do is FDA can in certain circumstances say we will only consider data that are contributed by the party that was testing this product or service, which means that if somebody else later wants to make that product or service, they cannot use the data from the first party. So somebody gets approved by the FDA and they get a diagnostic test on the market. Let's use a diagnostic test on the market. Let's assume that it's a Mendelian test or something like that. They show that they can measure what they're measuring, that it's accurate, that it does what they say it does. It gets approved by FDA. It's on the market, and then somebody else comes along and says we want to do that same test, and FDA is saying we have to prove these things to you.

Well, we just want to use the data that they contributed and we'll show that we're testing the same thing they are. FDA can say no, you can't use those data at all, you have to recreate all the data that they produced as the first approved entity, and therefore you get rid of the free rider problem by forcing everybody to generate the data de novo. It's very wasteful. Economists hate that kind of a system, but the fact is it does solve the free rider problem in very much the same way as a patent does.

DR. WILLIAMS: So is that through the 510(k) thing?

DR. COOK-DEEGAN: That's specific to devices. Jorge would probably know a whole lot more about it. In the trade agreements, basically what is being done is if you introduce a new drug into a new domain, a new jurisdiction, what we're now building into our trade agreements is basically after their approval by the equivalent of our FDA, you've got five years of data exclusivity, or seven years, or fifteen years or whatever, whatever is negotiated into that agreement. So it's another form of exclusivity, but it doesn't depend on patents. It depends on an administrative decision by an FDA or FDA equivalent, and I don't know what triggers it in the FDA.

DR. GUTMAN: I'm from FDA.

DR. COOK-DEEGAN: Oh, okay.

(Laughter.)

DR. GUTMAN: And I must tell you I've never heard of this provision. I've been operating at FDA for 15 years without knowledge of this provision.

(Laughter.)

DR. GUTMAN: The 510(k) program doesn't lend itself well to this construct at all. The PMA program I think does to a certain extent lend itself. One of the advantages to sponsors to fielding a Class 3 product is it does put more burden on their competitors. It makes it more difficult, although not always impossible, to do product to product comparisons. So I must tell you the construct is not familiar at the working level outside of the usual way we do business, which is to bifurcate the data

requirements for a Class 2 versus a Class 3 product.

DR. COOK-DEEGAN: The person who has written probably the most about this is Becky Eisenberg, and if you guys want to go down this pathway, she wrote a piece a couple of years ago. This is the mechanism that was used to get Tacrin on the market because it was an unpatented drug, and they had a period of data exclusivity for Warner-Lambert to test out Tacrin for treatment of Alzheimer's disease. It's not a common thing, but in theory it exists.

In a way, the pediatric extension is a data exclusivity situation. So it's an idea that's floating around out there. If you wanted to go down that path, I'd get Becky in here and ask her to talk about what she's found out about it.

DR. EVANS: Okay, great. Thank you very much.

(Applause.)

DR. EVANS: In the next few minutes we're going to have an update on the progress status of the SACGHS study, and that's going to be by Bob Cook-Deegan and his colleague, Christopher Conover.

Just before doing that, I just wanted to review for you all the structure of the study plan. You've seen this slide before. Again, Part 1, the items in red are things that are being pursued by the institute there at Duke, literature review, consultations, case studies, the conceivable need for additional research if very tractable and identifiable; Part 2, the public perspectives that the staff here is beginning to put the nuts and bolts together for; and then Part 3, gaining some international perspectives.

So I'd like to introduce Chris Conover, who works closely with Bob. Chris is an assistant research professor of public policy studies at the Terry Sanford Institute on Public Policy at Duke University. So Chris and Bob will give us an update, and then we'll have committee discussion of the study plan.

DR. COOK-DEEGAN: I'm going to be really brief, and you'll be really happy to know that I don't have any slides.

I gave you the backdrop for the work that's been going on at our center, which has been looking at the innovation process in general, and this flurry of emails that I alluded to is Sarah sent me an email just before Christmas basically saying could you guys help out, take the information that you have, the kinds of study tools that you have, and could you apply them to this problem that we're facing for the advisory committee.

So I fired off an email, and I'm not going to say anything more than that except to say it seemed like a really great opportunity to do two things. One is to actually show that our research is relevant for real-world decisions. A federal advisory committee is a pretty good proxy for somebody who is trying to make a decision about something because you're spending a lot of time and energy trying to figure out something, and I figured, well, we'd better make our stuff available to that group. Sarah also cc'ed Francis Collins and Jean McEwen, who was here earlier, who is the staff officer. So I knew what the right answer was.

(Laughter.)

DR. COOK-DEEGAN: So we were very happy to help out. One of the mechanisms that I thought of immediately is the mechanism that Chris is going to talk about, which is what happens at wonderful universities is you have access to students who are really bright and have energy, and they also have to take courses, and one of the courses that we teach is going to be described by Chris.

DR. CONOVER: I'm the director for the Health Policy Certificate Program at Duke, and as part of that certificate, the certificate basically is like an interdisciplinary major that any Duke graduate student can wrap around whatever degree they're pursuing. In the Capstone seminar that's the last course they take as part of their certificate sequence, they're supposed to bring everything together

and do a first-rate policy analysis, the way we put it in the syllabus.

This was a great opportunity, as Bob said, for all the reasons that he's described, but let me just describe the group of students who take this class. It's very interdisciplinary. This year we've got students that are representing the business school, the law school, the medical school, and even the school of the environment. We also have mid-career people who are pursuing a Master's of arts and liberal studies. So it's a very diverse mix of people and it leads to very interesting discussions when we talk about policy issues.

So we're doing this study in basically two tracks. We're doing a literature review where we've --

DR. COOK-DEEGAN: We didn't show that one.

DR. CONOVER: Oh, you didn't show that one. Okay. So are you going to describe the process?

DR. COOK-DEEGAN: I was just going to describe a little bit about the case studies. That's all.

DR. CONOVER: Okay. So we have a conceptual model of the process of innovation starting from basic research and going all the way down to testing actual patients. As Bob said earlier, the issue in terms of access is trying to figure out who should be getting these tests and are they actually getting these tests in the real world, and are there either price issues or other delays, time issues that result in decrements to access.

But we're looking at both the issue of underutilization as well as overutilization in going through this model.

DR. COOK-DEEGAN: And just a little update on what we're doing. This is kind of a foretaste of what you'll be getting later.

So there's this conceptual model of how does a genetic test develop. We're relying very heavily on a report that was done by the Lewin Group on the development of diagnostics a couple of years ago. Lewin is a Beltway bandit that does terrific work in health policy and health technologies, and they did a report on how does a new diagnostic happen a couple of years ago. So we're following their model, applying it to the more specific case of genetic tests, and the students are doing literature reviews on what can we say about genetic tests specifically at each of these stages.

The other thing that we wanted to do is what usually drives policy is you collect and count things when you can, and you usually can't get any of the numbers that you really care about because people don't collect them in the way you need to interpret them. The other thing you do is collect stories. So we're trying to do systematic stories called case histories that would be things that we think would be discussed in the literature -- for example, BRCA -- and give you a little bit of an insight into how those stories came about.

So these are the case studies that the students converged on. We got some help on this from Mike Watson, who gave us a heads-up, particularly in the last two cases. We wanted to find squeaky wheels in some cases, we wanted to be sure we had a representation of different kinds of diseases, and we wanted to do comparisons where we might get some insight. There's no perfect controlled experiment where patents are the only variable that changes between Story A and Story B, but we can get some approximations where patents are one of the important things that is a difference between Case A and Case B, and we think we have some of these up here.

Breast cancer versus colon cancer. These are roughly equal prevalence. The genetic test falls in more or less the same place in the clinical decision nodes, and the fraction of cases accounted for by familial cancers that could be tested for is roughly 5 to 10 percent in both cases. So genetic testing is kind of similar in those respects. In one case we have Myriad that has secured access, exclusive rights

to most of the patents in the United States but not abroad, as I pointed out. In some cases they got the patent rights but not the authority to use them for any useful purpose. But in the United States, they have both. They have the patents and they shut down the alternative providers of BRCA testing, and that contrasts with colon cancer where the ownership of the different genes is mainly by academic institutions, with a few companies thrown in as either assignees or co-assignees, and there's licensing and many, many more providers of the test. Therefore, we can look at prices, and the students, Chris DeRienzo, who is a medical student at Duke who is getting his public policy degree, has actually called up the labs that offer colon cancer testing and breast cancer testing and said what do you charge, a very simple methodology.

The next case is Tay-Sachs versus Canavan's. This is a set of tests, two tests done in more or less the same population, both with very dire outcomes, clinical outcomes, where the intellectual property is in both cases, actually, to non-profit institutions, but the licensing was quite different. Canavan's was a controversy. Tay-Sachs, we're trying to figure out exactly what the intellectual property landscape is. We discovered the seminal gene patent, but it doesn't appear to have been licensed, but there are some other patents that might be relevant to that. We're trying to track those down and figure out what the story is.

Cystic fibrosis you all know about. Generally, oversimplifying, this is generally a case of relatively liberal licensing mainly by academic institutions that did the gene discoveries. It hasn't been terribly controversial.

Hemochromatosis. Debra and John Merz and Mildred Cho wrote a whole article on this that I suspect you've read. They wrote it up in Nature. It was discovered in a baby biotech. It was discovered at Mercatur. Mercatur went belly-up and sold its IP to Progenitor, which in turn went belly-up and sold its IP to a large firm. That's an oversimplification. "Belly-up" is not a technical term.

(Laughter.)

DR. COOK-DEEGAN: Basically, what happened is it started at a genomic start-up from the first generation and has been subsequently sold up the food chain and is an interesting story. It's a fairly common Mendelian trait.

Then the last two cases are ones that, in fact, Mike Watson had a big say in helping us think about. These are cases where there are many genes where there is intellectual property, some of which is being liberally licensed, some of which isn't, where maybe a pool might emerge or might not if the world were a perfect place. The funny thing about people as compared to DVD machines is that the frequency of the alleles differs. The frequency at a particular gene test is going to be different. They're going to have different powers, so not all patents are going to be equally valuable. If you've got a patent on a gene that accounts for most cases of a particular condition, you're going to think that's more valuable than the other patents that are less frequent in the population. Therefore, you might hold out for a patent. Usually in a patent pool, the easiest thing is to just throw it into the pool and you just count patents and give out the money according to that. If you've got a holdout who thinks that their patent is particularly valuable, it complicates the formation of the patent pool. So this is what's going on.

Moreover, these are the kinds of cases where if what you wanted to do was make the world a wonderful place where everybody could get access to technologies at a very low cost, these are the places where you would have to have lots of genes and lots of alleles of those genes on a single diagnostic test, and you would just use one blood sample and test it all. That would require aggregating all the IP. So if you're going to have an aggregation problem, these are cases where that might show up.

Where we are in these cases is right now we've started to gather the patents. It sounds easy, and sometimes it's easy to identify the patents. Making sense of how they actually do work in the real world is really complicated, and that's where we are right now. We're trying to identify the patents and then actually read the claims and figure out which piece is absolutely essential and which piece could

you throw away without worrying about it. We're hoping to go as far down that path as we can and feed that back to your committee in the next couple of months.

DR. LEONARD: It's very disturbing, and almost refreshing in a way, to hear you say how complex looking at the patents related to a disease are, because that's what every physician has to do at every academic institution if they want to do testing, and it's not what physicians should be doing. So it's actually kind of interesting to hear that an expert has problems doing this.

DR. COOK-DEEGAN: I'm not an expert. Jorge might be an expert. I'm not an expert. I'm a scholar. That's the opposite of an expert.

(Laughter.)

DR. EVANS: Are there other specific questions about these case studies before we move on to the committee discussion for the last 20 minutes or so?

(No response.)

DR. EVANS: Okay, thank you very much again.

(Applause.)

DR. EVANS: We have four specific questions to go over with regard to this morning's session to get committee input on the first one, again remembering this was essentially an educational session. Did the session this morning provide sufficient background information on the basics of gene patents and licensing practices? Are there gaps that you all feel that you can identify that we need to fill at the next session? Are we deficient in our background at this point?

I'll take no comments as a lack of deficiency. Going once, going twice, okay.

PARTICIPANT: You could debate scope.

DR. EVANS: Well, I'd really rather not debate scope, but we do have a debate coming up. Actually, we do have a debate that gets to scope, but it's the last thing.

The next one. This is similar to the first question. Did this session provide sufficient background information on the key policy developments related to patenting and licensing practices? Again, would you identify any specific pieces of information or gaps that we need to fill before going on?

(No response.)

DR. EVANS: Great. I mean, I for one feel much better after this session. I feel like we've really had a series of speakers who were able to lay these things out for us.

The study methodology is difficult, and I think Bob really summed up nicely the challenges in this type of thing and broadly in the policy realm. We're interested ultimately in patient and public access. We even use physician access as a rough proxy for that. That said, it's problematic if not impossible to really get at that specific question of patient access. Therefore, what has been identified through the task force meetings, through consultation with Bob's group and all really is trying to get at the best types of information that are out there, but also the types of case studies that might allow us to distill some data out of it on the impact of patents.

So we've focused on performing these case studies via the Duke collaborators, getting public perspectives and public comment, and then trying to also glean some lessons from the international perspective. Is there a sense among the committee that we're on the right target with regard to this methodology?

DR. WILLARD: Pursuant to the questions that came up in the earlier morning session, it seems to me that a piece of information we're lacking -- and it seems like a finite challenge, although I know Bob would scream at me for suggesting that -- is if there are only 3,000 or 4,000 gene patents, it seems like the question we don't know, and Debra asked it earlier, is what percentage of those patents actually relate to a disease association and how many of them recloned a gene for such and such a protein. At least my thinking about all of this would waiver significantly if there were 200 patents related

to human disease versus 2,800 patents related to genes and human disease. It is finite. Someone would have to go through all 3,000 and you wouldn't have to read the whole patent. You'd just have to look at the claims. The claims either claim a method for diagnosing disease whatever, or they don't. I think we're missing that kind of information.

DR. EVANS: And I guess what you postulate, then, is if it's actually a very small percentage, then there's less evidence that patents are having much impact.

Debra?

DR. LEONARD: Except that your own point earlier was that this is where science is going, to make these gene-disease associations, and that's what's going to be patented more and more in the future. So even if it is a small percentage, I don't know that knowing the percentage of those 3,000 is going to influence what this committee does because it could be a small tip of the iceberg or a larger tip of the iceberg, but it's still a tip of the iceberg I would argue.

DR. EVANS: And I would think it would be kind of a cost/benefit situation here. If it were something that could be done in an afternoon, it would be very interesting and I think it would be useful information. The question is how costly would it be, and that's something we can take up with Bob in a task force meeting and explore that if the committee wants us to do that.

Debra?

DR. LEONARD: When Bob put his slide up about factors affecting access, Sarah and I had a little discussion because there was price, there was hassle, there was regulatory approval, but Sarah and I were talking and there's also, I think, to some extent availability, because availability of tests, which gets to some of the stuff that John and Mildred and I did about how broadly is a test available, which gets to the sole provider of a medical service, how many of those really are there if you take into account all the Athena patents and the Myriad. I'm not aware of too many sole provider situations, but that's the worst way of looking at availability. I mean, that's the worst examples of availability.

Then there's also the issue of how a patent holder restricts the use of the patented information. So with the example of CMT1A, the exclusive licensee of that patent would not do prenatal testing. So they were deciding medical practice. So are there examples of access because of the way the patent is being utilized or licensed or available for medical use in various ways? These are all exactly proxies, but these are some additional proxies that you may want to take into consideration as you're looking at these various cases.

DR. COOK-DEEGAN: Debra, I think it's worth having availability as a separate thing. I tend to think of that as related to the hassle factor of having to ship off to a thing, but it's absolutely a different thing, and maybe we should use that word, certainly one of the classic words of the IOM definition of access. So we should fold it in.

DR. LEONARD: I think of hassle as the laboratory director getting a cease and desist letter and having to spend hours and hours and hours with their university lawyer and the patent lawyer that they're bringing in to consult with. I mean, that, to me, is hassle, or being proactive and having to look up who the patent holders are and whether they're going to enforce against you before you do a medically relevant test.

DR. COOK-DEEGAN: That actually isn't what we thought of. I mean, that's true. All those things are true. Those are in the category of transaction costs before you can even start doing business. I was actually thinking of what has led to the outcomes in the U.K. and Canada as much as anything else, when Myriad says you have to send the samples to us, it perturbs the system of genetic services, the relationship from physician or counselor to proband, and if you have to ship it off to someplace and then handle the situation, you have to create a new data structure, you have to create new relationships, you have to put it in the mail. That's what I was thinking of, that it perturbs that system,

and that, as much as anything else, as much or more than the price, has driven the behaviors of some of the buyers of these services, saying we don't want to play that way, we're not going to make an exception just because you got a patent on it. So that's what I was thinking of as the hassle factor.

DR. LEONARD: I think there may be a lot of definitions, then, of "hassle," and maybe you need to refine that.

DR. COOK-DEEGAN: I got it. I got it. We'll have to do that.

Could I comment just for a second on Hunt's thing? It's actually something that I think it would be good to have a discussion of your whole committee about at some point, after the dust has settled a little bit.

It would be possible -- and I showed the list of 1,000 patents where we went through and actually hand-coded them. It took us about a year, and I'm never going to do that again. It's a fair amount of work, but it is an enumerated set of things. We actually coded all of those patents, and one of the things we're thinking of doing is for those sets, from 1980 to 1993, there are 38 categories. So is it a cDNA? Is it a mammal? Is it in humans? And diagnostic method, probe -- there were three or four categories that have something to do with diagnostics, and we have those boxes in there, and we could go back to those original 1,000 patents and say was this a diagnostic or not, and get the pioneer cases.

But the other thing that we're thinking about doing, and I don't know if it's possible or not but we could explore this, is once you've got a set of patents like that, there are new semantic Web computer technologies that we might be able to say, okay, computer, here are 60 or 80 patents, all of which we know have diagnostics in them because we hand-coded them, so go find out in these 44,000 patents in the DNA patent database, go find the other patents that kind of look like these, and then we'll pull those and look at those and see if that's doing a good job, because it will just look for words that show up and do a lot of work in those patent claims that would allow us to do that. So we don't know if that's technically possible, but if it is, it might be possible to very quickly do the sort of thing that Hunt is talking about.

The problem with that, though, is if you look at, for example, this European study, there were actually 1.9 million sequences that were claimed at one level or another that resulted in the 16,000 sequence-based patents. Now, how do you go from 1.9 million to 16,000? Well, because there are a lot, a lot, a lot, a lot of things that show up early in the process and never actually get issued as claims; and number two, a lot of those things are things like probes, SNPs, and all that, some of which are diagnostically relevant but aren't genes. So you would miss all of that if you only look at gene patents that meet certain criteria, and that actually could be a pretty big deal for microarray testing and stuff like that. We just don't know.

DR. EVANS: I think what we can do if we have the permission of the full committee is discuss that in a task force meeting and decide on the cost/benefit of pursuing that.

Marc, do you have a question?

DR. WILLIAMS: Yes, one more comment related to that. If there are going to be policy changes that are considered, it might be useful to know what the legacy would be. In other words, what are the ones that would already be out there and would not be considered? That could make a tipping point in terms of how the policy might be crafted.

The other thing in terms of looking at access issues that I didn't hear is that I know that there are a lot of payers that are dealing with issues of contracting with specific reference laboratories, and then how things are happening relating to tests such as BRCA that are available as a sole source. I know that, at least anecdotally, there are some of those companies, payers that have written benefits to basically say this is excluded because it's not covered, and that would be another way to look and see what would be the impact, at least in a captured population, on access.

DR. COOK-DEEGAN: That reminds me of one data resource that I should have mentioned as we did our summary that I forgot. Out of doing these case studies, we are trying to think about what data could we mine to get this, and Alexandra Shields at Harvard is an incredibly good health services researcher, and she has been trying to come up with algorithms that would map to -- for a lot of the tests you would care about, there aren't specific CPT codes, but you might be able to take ancillary data and narrow down to the situations where it's kind of the equivalent of you get the BRCA test or you don't, and she thinks that she might have developed some algorithms, in fact using the UnitedHealth Care data set, where they might be able to at least get utilization data, which again is a loose proxy for access, but it might allow us to, for example -- we don't know, but suppose that they had data from Denver and Atlanta, and we could time sequence that according to the months after the direct-to-consumer ads happened and we saw an uptake in utilization for the CPT codes that look like they're likely to be BRCA testing. That would be a piece of information about the impact of an intervention. We don't know if we can do that, again.

DR. EVANS: Or if you could compare the colon and breast, for example.

DR. COOK-DEEGAN: Yes, right. So we're trying to explore what we can do with what data sets exist out there. A lot of that expertise is going to be well outside our group. Alexandra has all sorts of expertise that we don't have in our group, but I think she'd be available to you all.

DR. WILLIAMS: Yes. If that algorithm is put out there, I hope it's not copyrighted or patented because we'd love to use it.

DR. EVANS: Two more. We do have one more potentially controversial issue to address between you and lunch.

Kevin, and then Debra.

DR. FITZGERALD: Just a quick question. Maybe, Bob, you could give us a sense of this.

I know this has come up a couple of different times with all the speakers, the idea of the differences in the international arena as compared to the United States. What I'm curious to know is that granted, in the patent landscape nations tend to operate somewhat individually, but still there's got to be international pressures that are there, or tendencies or dynamics or something that somebody might have the pulse of, to give us a sense of where things might go, because granted we advise the Secretary of this country, but obviously, as you've all pointed out, things are not going to be happening in isolation or in a vacuum, and if something is available overseas that is going to be cheaper -- I mean, I presume that's where the market is going to go. So we won't be able to make decisions in a vacuum because it will just potentially put us in some kind of very uncomfortable position.

So can we get a better sense of the international trajectories and what's going to happen?

DR. COOK-DEEGAN: Let me make two generalizations about that, Kevin. Number one, you've seen the data that show that we're an outlier case in terms of what intellectual property is out there. What can we interpret from that? Well, what I'm about to say is blindingly obvious but may overwhelm that difference, which is if we're talking about access to care, we're also an outlier, right? So what is it that's causing that? I doubt that it's patenting that's causing that. What we already have is limited access to all sorts of goods and services in the United States for certain subpopulations.

Teasing the specific stuff that's relevant to intellectual property is going to be really, really hard when you're dealing with systems of care whose dominant value is fairness of access, whereas ours has been access to innovation. That's how we've structured our system. So there's a really profound problem of interpretation that we're going to confront when we're dealing with access, because the fact is for many, many U.S. citizens, access is a very complicated problem here. The bottom and the top in our

economic system have pretty good access. It's the people right above the working poor category where most of the access problems arise, and we don't have data on those populations that are very specific. We're trying to mine that out, and we are going to see if we can do that with existing data sets, but I'm not sure how important intellectual property is when you've got a profoundly unfair system that you're starting with.

DR. EVANS: Okay, one last question from Debra before our last item.

DR. LEONARD: Actually, you think you're going to move to the last item. I want to go back to the previous one. Can you go back to the policy? I know that all the speakers today have brought up a lot of different policy options, but I don't have a clear sense of all of them in my head. So I think something the task force needs to do is make a list of NIH USPTO legislation, patent pools, diagnostic, medical exemptions and tech transfer, and who would do those.

DR. EVANS: Absolutely. Policy options, yes. That's on my agenda. That's something that I could completely agree that as we move forward here we have to keep in mind all of the different possible remedies to issues that might come up as problems.

Chira?

MS. CHEN: From the data that you have given, Bob, you have given the source of how much it costs in the U.S. Could you also give some pricing information, how much it costs like in Canada or in Europe? Maybe that might help to understand if a patient could get outsourcing to get their test done somewhere else.

DR. COOK-DEEGAN: Yes, I think we can get those data in some cases. I hadn't thought about the Athena stuff. We're doing it on BRCA. It's going to be easy to get that because you can find out. It's not always easy for health systems to know how much it costs them to do it, because in other places it's a completely different model of how the test gets done. But you can get kind of an idea of how much a lab needs to get paid in order to do a service, and that gives you some idea of what they would charge. So you can get very rough -- we're talking about one significant digit kinds of estimates, which is better than we usually do in the patent business. So we may be able to give you some limited information there.

DR. EVANS: Great. Okay.

I'm going to move on. We have four full minutes to discuss this controversial issue, and this does indeed have to do with scope. Should the scope of our study be broadened to include the impact of pathogens in gene patenting and licensing practices on patient access?

Let me just review for you briefly what the scope says, that we're undertaking a study of the positive and negative effects of current gene patenting and licensing practices on patient access to genetic technologies, and ultimately on the public's health. I'll give you my view. My view is that it's very difficult to address that scope without also addressing the effect of gene patents on human pathogens. If there are patents on hepatitis C, if there are patents on pathogens that have a profound impact on human health, and there are genetic tests that are useful and employed by physicians that will help the public health, it's hard for me to exclude those from our scope. Not everybody feels that way.

Debra?

DR. LEONARD: Is it possible not to include pathogens as the focus of everything that we're doing but consider always when we're looking at the policy options whether or not pathogens would be covered by whatever options we're looking at? Because we will have to consider the broader impact of whatever policy suggestions or recommendations we're making to the Secretary. So we could always keep that as a back question in our heads without actually asking Bob and those students to take on another case study or something like that.

DR. EVANS: No, I agree. I'm not interested at all in expanding the amount of work.

I think that keeping that, though, on the table is, to me, legitimate.

Marc?

DR. WILLIAMS: Yes, I was just going to say a couple of things. I mean, in the rapid diagnostic area, I would look at this as similar to other types of rapid diagnosis for pathogens. It's really probably not that dissimilar. The targeting area is probably going to go through the typical pharmaceutical type of approach in terms of can we use gene targets and pathogens to effect therapy. Where I think it will get tricky and where we need to, maybe as Debra says, keep it on the back burner is what's going to emerge relating to pathogen-host interactions, how does the pathogen genome interact with the host genome, and then will that really get into issues that are going to prevent moving knowledge forward that way.

DR. EVANS: Any other comments?

(No response.)

DR. EVANS: Hunt?

DR. WILLARD: I was just going to concur. I just reread the charter. I mean, it's very hard to exclude it given that we're focusing on technologies, not on genetic disease per se.

DR. EVANS: Right. So then if the committee approves, what we'll do is we will keep that within our scope, within our purview. However, I also agree that we don't want to derail our deliberations by focusing on that exclusively. Agreed? All right.

I think we can adjourn to lunch, then. I don't know where Reed is.

MS. CARR: You're acting chair.

DR. EVANS: Oh, great. Well, I've got some other changes I want to make.

(Laughter.)

DR. EVANS: Let's have lunch.

(Whereupon, at 12:45 p.m., the meeting was recessed for lunch, to reconvene at 1:45 p.m.)

AFTERNOON SESSION (1:45 p.m.)

DR. TUCKSON: The session is now back in order. Thank you all very much. I don't think we have any more public testimony because Dr. Leonard has already presented. So we will be able to move forward.

Can we at some point, if our ace team could put up on the board at some point soon our strategic agenda, because that's really what the rest of the afternoon is all about. It's really all about the strategic plan.

In June, I asked the members and the ex officios to identify new study topics for the committee to consider, and a couple of our colleagues have actually been really thoughtful about that and have made some suggestions. By the way, by saying we are revisiting the strategic plan, that does not mean you have to change it or do anything. I mean, you've got a lot on your plate, so don't feel compelled

simply because the idea was on the agenda. It's just a matter of a normal review. I'm not trying to downplay Steven's or the doctor formally known as G or Muin's presentation, but I do want you to know that you don't have to change anything if you don't want to.

We are now going to hear two proposals, and let me start with Steve, who will speak first on the importance of analyzing the economic consequences of the genomic innovations.

Steve?

DR. TEUTSCH: Thank you, Reed.

This proposal actually links very closely with what you'll be hearing from Gurvaneet and Muin. So although they were developed a little bit separately, we may want to, as we go on, figure out how they may fit together.

You have the proposal in Tab 7. I'm not going to read the whole thing, and some of it restates the obvious, that we know that only innovations that we've been talking about have the potential to improve the health of Americans and are likely to have a fairly broad impact on not only the health care system but all of the commercial enterprise that supports it.

But one of the major problems that we face in this country today, of course, is just the extraordinarily rapid rise in the overall cost of health care, which now consumes some 16 percent of GDP, about twice what it is in the rest of the world, and one of the major drivers of that increasing cost is technological innovation. Today, genomics is probably a tiny part of that increase but has the potential for playing a much larger role in being a cost driver in the future. As I looked at the charge that we have on the advisory committee, it seemed like the economics is one of the major social consequences that we probably should be looking at as within our charge.

So looking at our technological innovation and its impact on the health care system, although we have a robust environment, we know that almost all of the technologies that are out there in the aggregate increase costs. There are just very, very few that in the aggregate really save money, and many of these new technological innovations provide great value, and we as Americans have embraced them. But nonetheless, there are just very few that actually save money in the aggregate. We hope that genomics will be one of those that lead to prevention and avoidance of huge amounts of health care cost, but that may not be the case if what we have is a plethora of new therapies that get targeted, and so we have the costs of the diagnostics, the management, and then of course the potential for costly drug therapy or other kinds of interventions.

So if we think about or try to imagine what the future is, it's important to think about how that process potentially is going to get managed so that we have rules of the road going forward. Even if you take the premise as correct that the costs are likely to increase in terms of health care costs, that's not necessarily all a bad thing because the technological innovation has lots of other benefits at a societal level as well. We can go through a long list, but it obviously can support a vibrant research and development enterprise, commercial enterprises, to the extent that we're healthier there's more productivity, Americans have a better quality of life. So there are many aspects of the economics that bear thinking about.

I think one of the reasons to bring this up is that the economic consequences of research in general and of genomics in particular haven't really been put in the broadest economic context for policymaking, and we have the opportunity to do that. Now, that's a big topic, and in fact the economic consequences of the research enterprise go way beyond the mandate of our group, but on a quick scan of who is doing this, we couldn't find any other groups that were really taking this on. We could be more thorough in the future to look, but it's not a problem that's being addressed very systematically in informing the dialogue.

So what I was going to propose to the group is to examine the issue first on a fairly

preliminary basis, sort of to do a scan of the, if you will, the economic consequences environment and look at a number of issues, but we should explore what are the issues that we think really should be addressed, and I identified a few that at least occurred to me.

Who will and should pay for innovation and the downstream costs, and how are we going to afford that? Who is going to benefit? Industry? Public health? Employers? Academia? Individuals? Health care payers? And how can these costs be anticipated and managed appropriately so that we optimize the use of the available resources and allocate them wisely? How are these technologies going to be paid for when they are developed?

What are the rules of the road, particularly for insurers as they come forward, so if one is going to be investing in the development of the technologies, what's the assurance that they'll actually get covered? Is this going to be based on some level of certainty if there are net benefits and incremental benefit cost or cost-effectiveness or some other contextual issues? There are a lot of issues here where I think we could elicit some of the stakeholders' perspectives and help them form a better perspective on how we can go forward.

There are just a lot of ways to use the research monies that are available, and we can talk about how they should be allocated to basic versus applied research, the better use of technology and the translation into practice, establishing proof of concept, more for prevention or more for therapeutics, and begin to think about if there isn't some advice that we can provide along those lines as well.

So as a first step, what I proposed was the creation of just a very small exploratory group from those of us on the advisory committee and our colleagues to begin to prepare an issue brief that we can bring back in July that will flesh out this domain a little bit more broadly, and also then to talk about where it is that we have the greatest opportunity to contribute, and if there's agreement then to proceed to some type of white paper that we would put together as a product of the committee itself.

DR. TUCKSON: Thank you, Steve. What we'll do is why don't we try to keep our notes squared away, and then we'll come back to that one and we'll discuss both of them together. That's terrific. Thank you.

Now if we could sort of hear from Gurvaneet Randhawa.

DR. RANDHAWA: Thank you, Reed. That was perfect.

(Laughter.)

(Applause.)

DR. TUCKSON: Thank you.

And Muin Whoever.

(Laughter.)

DR. RANDHAWA: Thank you. Muin and I are in the unenviable position of being the last people that are holding you up in this room, so we'll try and make it brief.

I only have one slide in front, and although the formal title is "Integrating Genomics in Clinical Practice," one can call it the slide from Dr. G. and the world of genomics from him.

What I've done in this slide is just to highlight maybe not at the 30,000-foot level in a slide that you saw yesterday from Wylie Burke of the different phases from discovery to outcomes and impact on outcomes. In this slide, from more of a 10,000-foot above-the-ground view, we're moving from the top-left corner, which is the initial discovery that's done in the biomedical research labs, and also with the genetic epidemiologists, largely in academia, largely funded by NIH, and of course with the CDC's program of HuGENet, where the first link is made between a gene and a disease. Sometimes it's a causative link. Usually it's just a correlation. This can be done through in vitro experiments, animal data from animal models, and from humans.

Now we move from the phase of academia and federally-funded research to more of

the phase where products get developed, and this is more the private sector, the pharmaceutical industry, the diagnostics industry. Just for convenience, I've put only two pathways here, the research and development of therapeutics and the research and development of diagnostics. One can also add vaccines here, and of course if you're talking about pharmacogenetics it would look a little bit different, but this covers most of the applications.

So for the therapeutics research and development, we have a fairly well-defined path of Phase I, II and III trials. For the diagnostics, it's not as well defined, and it's more a combination of observational studies which, as we heard in many cases, like the BRCA example of the oncogene example, haven't gone through the FDA regulatory approval. But for the most part, things do undergo regulatory approval and then are available for clinical use. Now, that's actually where most of the things need to happen before we can start thinking of using this routinely in clinical practice.

So the next box that I have down below is what I've called a small box of outcomes research. This is actually a huge number of both study designs, all the way from randomized clinical controlled trials to cohort studies and case-control studies, and this group of study designs can also come from different databases. We have health plan databases, we have Medicare and Medicaid claims databases, we have electronic health records as another source, and of course we can launch new prospective studies.

What I have below the box is three different mechanisms at AHRQ that we can use to fund these kinds of outcomes research. One is, of course, the traditional grant mechanism that is closely modeled on the NIH, which is the R01/R03 grant mechanism. We also have a program co-administered with the FDA, the CERT program, the Centers for Educational Research on Therapeutics, which is a cooperative agreement program. Then we have the newly-started contract-based program called the DEcIDE network, which means developing evidence to inform decisions about effectiveness. This is a contract-based program newly created in the agency as part of our effective health care program, which was started to look at the comparative effectiveness of drugs and devices and diagnostic tests.

So the next phase after we have all of the data from different studies is to actually synthesize the data. One process of doing that is through our evidence-based practice center, the EPC program. Yesterday we heard Dr. Berg, who is chairing the EGAPP panel, about an evidence-based decisionmaking process through the clinical guidelines, and we are working very closely with the CDC's EGAPP program to have evidence reported through our EPC program. Some of the examples were genomic testing in ovarian cancer, cytochrome P450 testing in depression for SSRI use, and the other two reports we have are on HNPCC testing and the breast cancer expression profiling. This is just with the EGAPP program. We also have other collaborations. HER2 Nu testing is another evidence report that is still ongoing; family history testing through another part of CDC, the Division of Cancer Prevention Control.

So although we have mechanisms to look at many different topics, the theme is still the same; that is, there's not much evidence. That came clearly through yesterday, and I think the challenge we have is not how we handle the evidence, which of course is a daunting task by itself, but how to get the evidence in the first place, which is where outcomes research comes in.

But just to go through this whole process, the evidence synthesis or these evidence reports are very closely paired to decisionmaking. So that is the DM in the next box. So decisionmaking can be for guideline development, which is the GD in the initials above the box, or coverage decisionmaking, be it through the Medicare program, the Medicaid program, the health plans, and insurers. That's just ascertaining whether there's enough net benefit of introducing something into clinical practice. So there's a whole slew of questions here that need to be addressed.

What are the benefits of this new test or therapy? What are the harms? What are the

net benefits? What is the added value? Most of the time, things are not done in a vacuum. You already have an existing test, an existing therapy. What is the added value of this new test and new therapy to what we already have here? Finally, what are the costs and the cost effectiveness?

Once the decisionmakers look at all these aspects, then a decision gets made to either cover the test or to recommend using the test, and then we have the next set of challenges, which is how to implement these decisions. You've already heard issues about access to care, we heard issues about changing behaviors from early adopters to late adopters, and finally we move into the final phase of routine clinical use.

So although I kind of simplified the diagram, there are some other steps one can think of. For example, there could be a feedback loop from the routine clinical use to see, as part of post-marketing surveillance, are we achieving the intended benefits or not. Then there are also the public health dimensions that Muin will address which are not part of this slide.

The only reason to have this slide is just so that we can focus on what is the discussion about right now, and it's on outcomes research, just that small box right after availability for clinical use.

I think it will be useful for us, and I'm grateful that this coincided with the Secretary's charge to develop evidence, and that could be part of what this work group, if the committee decides to have a work group, could be doing, to give guidance on what are the current gaps that we have in evidence that can be used to make decisions, what are the mechanisms of creating the new evidence needed to make these decisions. If the existing mechanisms are good enough, how can we better link them? So if you're already collecting enough data for diagnostic tests, health outcomes, therapies, and the problem is they just reside in different databases with different entities, can we better link them, or do we need to modify databases or create new ones? How would we adopt electronic medical records or health records in this process? There are some advantages to using them, and there are some limitations to using them.

So I think there is a whole set of issues here that could be teased out, and it will be useful for us as we go into the future to think of this as a cross-cutting issue that can be started with genomics as our beginning point, but it can be adopted in other non-genomic settings, to use the same processes to identify what the outcomes are.

In terms of piggybacking on ongoing initiatives, we are collaborating very closely with the National Office of Public Health Genomics at CDC on a DEcIDE project, which is evaluating the strengths and weaknesses of existing databases to obtain outcomes of genetic tests. So we could use that ongoing project as a leverage point and build off of that to perhaps come up with a set of recommendations or next steps that can feasibly be adopted by federal agencies and potentially improve our public/private partnerships.

So that was the essence of my message here, and I'll turn it over to Muin.

DR. KHOURY: Thank you, Gurvaneet.

I didn't want to have any slides at first, but then I couldn't help it. I saw the translation highway in front of me.

Thank you, Gurvaneet, for laying it out very nicely. I mean, there are many variants of this that we have seen over time, but basically there are three things I want to say before I lay over the public health perspective to this, because I think it's crucial.

The first thing, coming back to this, this is a genetic translation highway. It starts with any scientific discovery, goes all the way down to routine clinical use, and I think genomics is but one of the many, many technologies that are upon us now. This translation highway reminds me of what Claude L'Enfant wrote in an article in 2003 in the New England Journal of Medicine, a sounding-board piece called "Lost in Translation." The idea is that there are so many things that come down the pike, but

there are constrictions on the translation highway. Things stop, and he used many examples, like why aren't people using aspirin for occurrence of heart attacks, et cetera. Then he ended up his article by saying if we can't do it with aspirin, how can we do it with DNA? I mean, probably you can use proteomics and RNA and everything, but the idea is that this highway is going to be overwhelmed with a lot of cars.

Coming back to Steve Teutsch's analogy -- not analogy, but the proposal to look at the economics, because all of these things are expensive, and they're coming down the pike, and there is a constriction. There are millions and billions of dollars spent on the upper half to find genes, to develop diagnostics and therapeutics, and very little going on on the outside, the descending path down below.

In December I attended a meeting sponsored by NCI, the extramural division, to look at outcomes research in the field of cancer genomics, and there were many presentations, including Catherine Phillips, who is an economist, who presented some economic data in cancer genomics and showed that in spite of hundreds of thousands of articles published in cancer genetic disease associations, there are only three or four economic analyses in the field of cancer genomics. You can almost find them.

Now, economic analyses depend on data. In the absence of data, you model it. You can develop cost estimates, but where is the effectiveness data? If you want to develop cost effectiveness analyses, you need to be able to do this.

So one of the things we've done at CDC over the last 10 years is to try to develop a population health model for this translation highway, and I'd like to highlight five boxes there, not to overrun the highway with more cars, but basically starting with the upper left-hand side, which is sort of to put in a big focus the role of the public health sciences and genetic epidemiology, biobanks, large cohort studies. These are where the action starts to accelerate the gene discovery. We don't need to sell that in this session.

The second box is the Human Genome Epidemiology Network, which was designed as a collaborative global movement to make sense of gene-disease associations, because for every association you find, there are three negative results, and then it becomes so chaotic that you need a systematic review and meta-analysis of the field. So I think we made a lot of progress in highlighting what we know and what we don't know about gene-disease relationships from a public health perspective.

The third process, which you've heard about ad nauseum over the last few months, is the EGAPP process, which kind of sits in the middle of the FDA, the outcomes research. It's sort of a synthetic process to figure out what we know and what we don't know about the various outcomes and the characteristics of genomic technologies from analytic validity of tests to clinical validity, clinical utility, the ELSI stuff, utilization. You've heard a lot about this, so I don't want to belabor the point, but it's a structure that was designed to be a public/private partnership to highlight what we know and what we don't know, to move things along the translation highway, so to speak.

The fourth box down below is sort of the infrastructure over which the clinical pathway of drugs and therapeutics and genomics will have to go. You heard from Ann Willey about state regulations and policies which may or may not supersede FDA and CLIA, but clinical practice is very state specific. I mean, the example of newborn screening is one example of what are the policies around the use of genetic information that actually all newborns will have to go through. This is a very weak base right now in genetics at the state level, at the community level, because people are trying to figure out what it all means. But public health will have to play a role when things begin to move down that translation highway.

Then finally, when things become part of routine clinical use, people always ask the question, so what is the impact? Who is using it? Do we have disparities? Is it costing more? Are people's health outcomes being affected by all of this?

So right now, it's very sad to say from my perspective that the bulk of the investment in genomics and population health is in the upper half, really big studies, big science, big therapeutics, and then it becomes atrophied as we round the corner and we move towards real translation. This reminds me, actually, of a recent article that was published in JAMA not too long ago. There were two articles published at the time. One is about community-based research and the other about practice-based research. Westfall and his co-workers talked about the blue highways. He talked about the usual meaning of translation and the NIH lingo is to move it from the bench to the bedside, which is a T1 translation. That's sort of the usual term in translation, but really that only covers part of the translation. You need to move it from the bedside to the practice, which is a post-T1 loop.

In this paper they talked about T2 and T3. T2 essentially is that translation step that leads to guideline development, meta-analysis and systematic reviews, and this is kind of what we've done with EGAPP, is to develop that infrastructure and the model process that tries to tackle T2. T3 is actually doing the research that disseminates, implements, looks at outcomes, looks at utilization rate. That's T3, and nobody really has a handle on T3 right now. It's scattered all around. There are very few studies, and far in between, and we've kind of done a preliminary analysis of some of the cancer genomics that includes the economic analysis that Steve Teutsch mentioned earlier. The number of articles published, let's say, on BRCA1 and colorectal cancer genes really drops significantly as you move from the BRCA1 and HNPCC gene discovery down to utilization rates and outcomes on patients and families and populations. There is no data because there is no funding behind it, basically.

So I think to finish up this joint proposal, Steve and us didn't coordinate our approaches, but it really talks to the overarching concern about the evidence of genomic applications, the implications for economics, and outcomes research broadly defined to include a number of parameters that are really crucial to measure to have a really good translation of this technology into improving the population's health.

So what we'd like to do is open this up for discussion to see whether or not this committee wants to weigh in, in a good way like you've weighed in on many other topics. Thank you.

DR. TUCKSON: Thank you all, the three of you. Appreciate it.

Steve, I think from the earlier conversation, sort of sees the synergy of these as well. So we might want to entertain this as a bundled cabal, the people who have gotten together and are trying to move this forward. Of course, I'll ask each of them individually.

But I think what we are beginning to see, as I engage in this strategy here and try to tie it back to what the Secretary is pushing through, and what the whole health care system is pushing through -- so if we look at the major paradigm -- and again, I'm just restating what's obvious to everybody, but if we look at the major paradigm in health care delivery today, it really is this sense that no one can afford to continue to pay for everything coming down the pike just used willy-nilly. So it's a very clear momentum around transparency, and transparency of what is the performance of the delivery system both in quality and in efficient use of health care assets. That's what's really there.

So outside of the field of genetics, where we have more history and where you have larger numbers of patients in the population, we have been able to begin in health care the revolution, as it were, to translate science into guidelines, guidelines into performance measures, performance measures that lead you to be able to evaluate both quality and efficiency in the use of assets, make that information available to the public for more informed choices about where they go for their health care to meet individual need, the ultimate personalization of medicine.

So I think what I see, if I understand what's happening here, is to say okay, we recognize in genomics, particularly in diagnostics, but also in therapeutics, that this has not had the benefit yet because it's still a newer field of having the level of research that allows the specificity of

clinical guideline development that then is translated into real outcome measures for performance, that then allows us all to know whether or not these precious health care assets are being used in a way that advances the performance of the health care system both in terms of quality and cost effectiveness, and thereby ultimately also makes it more difficult to make sure that individual care is tailored to meet the individual needs of each unique person. That's what I sort of see as the genius of these two sort of coming together. Am I completely off base in that analysis, Steve?

DR. TEUTSCH: No, you're right on target. I think the other side of this is that understanding the value proposition, if you will, on the health care delivery side and what it's likely to be should inform the R&D process as well so that there is some better expectation that we allocate those resources where we are going to be best able to use them to benefit the health of the population given the resources we have both on the R&D side as well as on the health care side.

DR. TUCKSON: So Marc is raising the next question, and as he does, Muin, I want you -- because you used the word "population-based" stuff a couple of times, and I think that given what Steve just said, I'm particularly, as one observer, curious about the level of analysis that you are thinking about here, is it the level of analysis of effectiveness of this at the level of the community, the state, the city, the county, the community, or is it the level of analysis of the relationship between the patient and their physician?

DR. WILLIAMS: I just used the analogy of the road. This is where my tires hit the road as far as I'm concerned, about where things are going.

First of all, it's axiomatic with quality improvement that medical outcomes and cost outcomes are two sides of the same coin, that they're inseparable. So to separate into two working groups I think would be an artifice. So I would concur with the idea of bringing them together.

The second point I would make is that in addition to the R&D that Steve just mentioned, I think that this is also an opportunity to really work around other identified priorities within the health care system to find out where we can make our biggest impact. As an example, I'd like to just mention something that we're doing at our place around pharmacogenomic dosing of Coumadin. This has obviously been a fairly hot topic, and we just completed enrollment of an RCT looking at genomically informed Warfarin dosing to see if it makes a difference in medical outcomes. We built in parallel with that a cost outcome study so we're able to capture all costs along with the medical outcomes so we can really comment on both aspects of that.

But the reason to choose that is that if you look from a patient safety perspective, which is a huge initiative within the health care system, you've got 2 million adverse events a year that are related to the use of Coumadin and Warfarin. So it's a huge target where there would really be a lot of synergy to work around understanding all of the different aspects of this, and those are the types of targets that I think we need to identify.

The one thing, if we were to go back to the first slide, is we've talked about things kind of emerging out and then being translated into practice, but the example that Muin used of aspirin is an excellent one. We've known that aspirin works for 30 years. We still can't get people to use it. There's a lot of medications that are already out there in use that would probably benefit dramatically from applying this type of genomic information to inform their use.

So it shouldn't just be thinking forward to new things that are being developed, but it's also thinking about what are the targets that are already existing that we can go after, if you will, retrospectively.

DR. TUCKSON: That's a terrific comment, terrific comment.

Muin, in terms of that --

DR. KHOURY: I think to use the term "population health" instead of either

"medicine" or "public health," because population health is a concept that embodies the health of the population. When people talk about public health, they typically think about public health agencies and state health departments. The IOM had a series of nice treaties on the future of the public's health, one of them not too long ago, in which they talk about a population health umbrella is the one with medicine and public health agencies and others in the private sector coming together to improve the translation from science to actual applications and improvements of the population's health.

Now, there are very few things in genomics or in general that are under the public health system in terms of delivery of services, newborn screening and some of the genetic services, but I see the implementation of genomics and genome-based technologies will be in our fragmented health care delivery system. But if we develop a population health umbrella to measure outcomes, whether you measure them in primary care or you measure them in a well-defined community, which could be an HMO-based organization or groups of them that can develop the actual measures that we've used in other areas of public health, this is a new area. But other areas of public health or the public's health have developed indicators of success and failure --

DR. TUCKSON: Let me ask you a little bit, because obviously you've thought about this stuff, but it's fine not to have the answers to these dumb questions of mine, and that's where the committee may start to grapple with it, so it's terrific. If you take what Marc said and use the example of Coumadin, it is very easy to get your arms around something that says at the end of the day we know that there are X number of preventable hospitalizations or extra lengths of stay in hospitals that result from misadventures with Coumadin dosing, that more specific information about which tests work, better guidelines, and better performance by the clinical community in using that information in making therapeutic decisions would ultimately result in savings. You can pretty well get your arms around that and it has a benefit.

If you try to take not a public health system but a prevention or a health-enhancing initiative, maybe it might be something in the area of newborn screening. I don't know. I'm trying to think of what would be the analogous example that would help us to look at it beyond the level of the clinical intervention.

DR. KHOURY: Well, prevention is the key that ties both medicine and public health, because we're hoping this technology will have a promise for developing earlier, faster and more personalized intervention, whether at the therapeutic level or at the diagnostic or health promotion level, things like the use of family history, for example, early diagnostic tests, whether they're done in a screening model or not. They could still be part of the health care delivery system is what we're talking about here, and I think developing an approach that says we're going to introduce these things using the best available evidence, we're going to measure success, we're going to measure how much it costs, we're going to figure out the best way to introduce them, and at the end we're going to measure their impact and their utilization by the population, keeping in mind that there are large health disparities in the United States population between the haves and the have-nots, and that's a very strong impetus for public health to step in because what I'm afraid of is that at the end, when we start measuring successes and failures, we'll see that the gap in health disparities may enlarge rather than narrow, which is what we want to have happen.

DR. TUCKSON: I've got Steve, G., and K.

DR. TEUTSCH: Even at the population health level, which outcomes research can bring, we've used some of the tools of outcomes research for priority-setting at a population level based on what the effectiveness is, safety and the cost-effectiveness to set rankings, as you know, for preventive services, because they're not all created equal. Those get not only into guidelines but then into benefits designs. They get used in metrics and quality improvement that are meant for population-based change.

So even when we're talking about things that are pretty clinical, the outcomes research approaches and the economics approaches really help us deal with things at a population level so that we can make sure that the things that do provide the most value have a greater likelihood of getting done.

DR. TUCKSON: So the order is Dr. Randhawa, and it then will be the terrific Fitzgerald, and then Hans. But let me just ask, Gurvaneet, whatever you were going to say, would you also say, at least at this level of your thinking, are you more focused on the committee trying to find and identify priority examples for which there ought be outcome measures that are informed by guidelines that are whatever, so that you start to introduce those things into the system? Or are you arguing more for an analysis that starts to look at the robustness of the research enterprise that allows whatever comes down the pike to happen? It's the question of what is your level of specificity of engaging this topic.

DR. RANDHAWA: I'll start with your question for us, and I'll give the comment that I was going to give. I think the short answer is yes, both. On the one hand, we do need to focus on the infrastructure and the research enterprise and the health care-oriented enterprise and see how we can build a more robust infrastructure to get outcomes data.

But it's hard to do this in the abstract without having some concrete examples and say here are four or five different kinds of examples which give us a spectrum of what kind of challenges we are facing currently and how we think the next steps will help to overcome these challenges.

Now, the comment that I was going to make is that I think there is, again as an example of where clinical health and public health kind of intersect, is obesity. One can screen for BMI in a clinician's office, but a clinician is fairly ill-equipped to give the counseling and the time, as well as deal with the community kind of interventions that may be available to an obese person to lose weight, whether it's access to better exercise in the community, if there are counselors and nutritionists who will advise and help improve the nutritional intake. So I think there are especially prevention examples where it's not solely in the clinical domain, and there needs to be an interface with the broader public health community.

DR. TUCKSON: So before Kevin, Dr. Fitzgerald, come on, philosophically I embrace what you are saying. I think it makes sense. I'm struggling a little bit on that last comment to get down to the level of granularity around the research-informed guidance that leads you to a guideline, that leads you to a performance measure, that leads you to being able to detect the outcome of some of what you did. I mean, if I was concerned about fighting the obesity fight and I wanted to worry about, as we were talking about offline, the availability of food in the grocery stores in minority communities and there are only fast food restaurants, I don't think that gets at this particular domain.

Can you say a little more about where you see the focus of the science in the prevention of obesity?

DR. RANDHAWA: Well, I'll defer to my companion here, Muin, who offers to take this on. But I'll also add something later.

DR. TUCKSON: Kevin, you're in the queue.

DR. KHOURY: Gurvaneet mentioned the example of obesity. That's a great example. Last year or a few months ago there were a number of genes discovered where some variants may increase your risk of obesity. The same thing for Type 2 diabetes, actually. There are three or four genes. People are rushing to develop a diagnostic test to try to offer people, because based on that test you're going to reduce the risk of obesity. So you go from that T1, you found the gene, you start doing the clinical trial, and then you round the corner and you say, okay, what's the added value of this diagnostic test? Are there any specific gene-based interventions that we should give? So you do the EGAPP process, so to speak, and you find out, well, we haven't done the clinical trials, we don't know the parameters of the test. If we do this in a community, it will take away from that. You do the economics,

and then suppose it meets all these standard tests of evidence-based, and then you have a test that you're now beginning to deploy in the population? So you move to T3.

Then you say, okay, who is using it? Is it helping people? Is it contributing? Because a genetic test for obesity doesn't stand alone because of the gene-environment interaction that goes along with obesity. So the manner in which a genetic test for obesity is introduced on this translation highway is very complicated, and it doesn't just stop at T1 or T2 regardless of whether or not you offer the test as a screening test for the whole population or you offer it in a primary care or a medical geneticist's office. So there is a translational process with outcome research that goes along with it, and I think that's what we're asking the committee to grapple with, to round the corner with us and help us move along.

DR. TUCKSON: Gurvaneet, do you want to just comment, and then we'll go to Kevin.

DR. RANDHAWA: Just to give the specific example of the obesity example where this might be helpful, when the Preventive Services Task Force took this topic on in terms of the interventions in people with high BMI, it found that you needed to have medium- to high-intensity counseling. So in terms of the evidence base of where the public health is going to come in, if you can identify genetic populations that will need more intensive interventions than the average risk population, those kinds of studies can feasibly be done in the public health community setting, and that's where the evidence would come in, not from a clinical individual patient provider.

DR. TUCKSON: Kevin, is yours exactly on this point?

DR. FITZGERALD: No.

DR. TUCKSON: Then let me let Chira just jump in real quick. We'll come right back to you.

MS. CHEN: I think something like that could be done right now for BRCA1 and BRCA2. There is a test, and there are some outcomes for patients. They either did the test, followed the rule, did the counseling, and I think we probably could go through some of those data first and see how it goes.

DR. KHOURY: Actually, we know very little. This was what happened at the NCI meeting that I attended in December. People were asking for these kinds of data, outcome research, utilization research, economics.

MS. CHEN: From where I work, I know there's a database, and they have that kind of information.

DR. KHOURY: Which database?

MS. CHEN: Within the institution database.

PARTICIPANT: Muin wants it.

(Laughter.)

MS. CHEN: I could talk to them, you know.

DR. TUCKSON: This is great. This is the direction right on the money. So clearly what we are hearing here is that currently it appears that there is an inadequate database that is not yet fully translated into effective guidelines by which we are able to evaluate performance and to hold clinicians accountable for how they use BRCA1/BRCA2 tests. What we are hearing, though, on the encouraging side is there may be nodes of information that might be used to try to play this game out, and you can sort of use that and then talk about what happened and what would it take to scale that up, and what would be the benefit. So that may be a possibility.

MS. CHEN: I mean, if there's a mechanism for these people to write it, I think that that would benefit for what they're doing, then they probably will publish it. But right now it's just sitting

in a database in somebody's office.

DR. TUCKSON: By the way, as we go to Sherrie and then Jim, Kevin got lost.

Sherrie, are you on this point exactly? If not, then I'm going to go to Kevin, and then you. So we'll do Kevin.

By the way, I want to keep some of these balls clearly in front of us. So one of the things that I think I want to continue to get you to concretize around is what you mean and what you don't mean. If we did this, it will be a long-term initiative, obviously, and there's a lot going on. That's why I keep asking the question about the entire research database. You talk about carving out a lot of money from NIH and putting it into this. What are you talking about in terms of the research infrastructure of the country?

Part of it is that you've got a Secretary who is down to 665, and he is putting his eggs in a personalized health care basket. So the question is in some ways -- and I'm not trying to push you in a direction in terms of multiple ways of dealing with this. Do you say to the Secretary we want to participate in delivering to you on your watch a few low-hanging fruit efforts where at least you can claim credit for having pushed forward the evidence-based, guidance-based performance assessment that allows transparency of individualized, appropriate decisionmaking for some diagnostic, some particular intervention, and that that is the beginning of now moving this field into the mainstream of day in and day out fundamental clinical care delivery, just like everything else is being dealt with?

So I just want you to keep that concrete thing in your head and whether or not you want to embrace it. I'm not advocating it. I'm just trying to see where you're trying to embrace it.

So let's go to Kevin, and then we'll go to Sherrie.

DR. FITZGERALD: Just to answer that point exactly, and to give it some granularity, in the pharmacogenomics struggles that we had in looking at the recommendations and trying to come up with recommendations that were not only broad but also in some ways concrete, I think these were two areas or the one area where we continually sort of butted up against a lack, a chasm where there just wasn't any. So in a sense, too, we can say that this is a very logical next step in this committee's development and movement along, and go back to the Secretary and say this is leading us to where we want to go, which is development of best practices, which is what we call for anyway.

DR. TUCKSON: Makes sense.

Dr. Hans?

DR. HANS: I think I'm struggling with the same thing that you are, Reed, with what can this committee do, what can this committee get their arms around that would be useful and helpful to the kinds of questions and concerns that have been laid on the table. There are levels of analysis that could be done on these questions, and this group tends to do its best work around the policy analysis and at that level, not the research questions, which really gets to various agencies and the large panels of research experts that they have. I know we have sprinkled in the group research experts, but we tend to pull to the policy level as a committee.

So the suggestion that I want to lay on the table based on the discussion that we have had thus far is really a study with four points for consideration. The first point is that the group would make the case for why T3 analysis is critically important for public health, clinical care, and for the economics of public health and clinical care, and there I think you could use the specific examples like Gurvaneet was talking about to illustrate those points. So you can get into some specific analyses of some specific cases and make it come alive for the audience, but do it in such a way that you're really making the case for why these kinds of analyses are important and what's currently missing.

And that's the second point, to do the needs analysis of what databases and information is out there and what's missing, what is not available to the community to be able to do these

kinds of T3 analyses; and then to lay on the table for the Department based on that needs analysis what are the kinds of questions that the Department really needs to address, what kinds of questions do they need to invest in to ensure that you are doing the kind of research so that you can ask and answer these kinds of questions.

Then the final piece is how do you get the different components of the Department to work together in order to accomplish and answer those questions. So CMS has a role here, NIH has a role, AHRQ has a role, CDC has a role, I think you could argue that VA might have a role, and I think that this group has been very good at helping the Department see how the different pieces and components can play together to try to look at some very big questions.

DR. TUCKSON: We're coming to Jim, and then we'll come to Muin.

So let's just review those as issues. I think, first of all, where we are, based on Kevin's comment as well, is that I think we're starting to get to a consistency or consensus of understanding what we want to achieve at a conceptual level and some of the pieces. So now we've been advanced here by saying, okay, maybe our role is to make the case for why this is important, why T3 level of analysis is important, find some representative cases to make it come alive and make it dramatic. That's a legitimate role, shining a bright light on this. Then secondly, do the needs assessment for what do we have that can answer these questions and what don't we have. So it's, oh, by the way, there is a database in an institution like yours, but there's not a lot of data that Muin feels comfortable about. So we sort of say here's what's there and here's what's not there to be able to answer the question.

Then we raise the questions that DHHS needs to be able to answer, and then say concomitantly that DHHS needs to invest in to be able to answer, these are the things that you've got to resolve and solve. Then lastly, to identify the major players in the Department and external to the Department who need to be a part of this effort and try to create some template that helps facilitate interagency coordination that allows them to get at it.

Did I sort of get your points? All right, that's terrific. So why don't we have, as people comment and make their comments, whatever they were going to say, say what you were going to say but react to the specific proposal that's there.

Jim?

DR. ROLLINS: My discussion is not necessarily -- well, it's sort of related to T3, but after listening to Gurvaneet, Steve and Muin, there are two things that struck me. One is cost effectiveness; the second thing is probability.

In terms of cost effectiveness, CMS, when we look at technology, we don't take cost into consideration. It could cost billions. We don't take cost into consideration. A lot of insurance companies also don't take cost into consideration. But once that technology has been recommended to a second committee, they do, and they may say even though it's great, it costs too much and we're not going to cover it. So if there's some way that that could play, I think that would really propel the issue.

The second one is probability. Now, CMS, as I said, when we look at genetic testing, one of our concerns is a specific test may show that a person has an increased propensity or an increased probability of a particular genetic disorder. How much of that is in terms of quantifiable amount? For example, based on a family history, based on a population of a thousand patients, there may be a 20 percent chance based on a family history that the person has that particular disease because of their forebears. A specific genetic test might increase that from 20 percent to maybe 22 percent, or maybe 30 percent, or maybe 70 percent. Where does that patient fall in terms of that spectrum? Are they going to stay at 1 percent, or is it going to move up to 99 percent? If there was some quantifiable way you could add the increased probability, as well as the family history in terms of a particular disorder, I think that might help to push the issue of trying to get an insurer to cover a specific genetic test.

DR. TUCKSON: So if we take the Sherrie outline and you sort of say -- again, I think this is an important point. So the Sherrie outline, you might say that the probability example is one that you could use to make the case for why the T3 is important. You might take your cost effectiveness deal and answer the second point that she made, which is do we have enough information as we do our needs assessment to actually answer the cost effectiveness question? And if we don't, then we need to identify that. That would pop up as a need for information and research. So I think both of your points fit into the four points that have been laid out.

We have Muin, then we have Alan.

DR. KHOURY: I just wanted to comment, and I'm not sure who raised it first. I think, Reed, you talked about the tight timeline for HHS given that it's two years or less. You know, the Secretary's initiative right now with personalized health care fits very nicely with that. I haven't talked to him in particular, but I don't think he wants to stop at T1. He wants to move this technology to improve the population's health, and I think the methods of electronic health records and all his approaches are tools that could be used to develop a T2 and T3 research agenda that could use the available technologies to measure and link records together so that you can do delivery research, intervention research in the real world, and then outcomes research when it's all done.

The second point I wanted to mention is don't forget T2. You'll never get to T3 unless you do T2. T2 is very crucial, and this is where EGAPP is right now. I mean, moving things into guideline development, using systematic base processes is a huge constriction, and right now people go around it without the evidence of effectiveness. They just go around it. I think T2 and T3, what I'm advocating for is a post-T1 translation agenda, not only T3. So if you think about T1 as transcription, post-T1 is really translation, and that's what we're talking about, the real translation.

DR. TUCKSON: Thank you, sir.

Alan?

DR. GUTTMACHER: Maybe we can change the terminology, because it sounds like tumor staging.

(Laughter.)

DR. GUTTMACHER: From genetic oncology.

I think clearly, Steve and Muin and Gurvaneet have identified what's really an important issue and I think one that is appropriate for this group to be looking into. I very much liked Sherrie's statement, refinement of where we're headed.

I would add to that what I think was implicit in Sherrie's comments, but I guess I would make explicit, which is that while probably all of us around this table would like to completely remake the nation's research and clinical care systems, that may be a little bit beyond the scope of the committee, and we will be most successful, as I think is implicit, when we focus on the genetics/genomics part of this, that if we try to overreach, we'll get into trouble.

There's plenty we can do in this area while focusing on that, and perhaps we can somehow get our way into the rest of the nation's health care and research as well. But I think that's our entry to it.

DR. TUCKSON: All right. Let me do this. I think we could be coming into violent agreement with each other on this, and I think we think this is important. I feel confident enough as your chair to suggest that there is a worthy effort for people to go and think through. What I would suggest, at least what I would hope that the committee would do as it sits down, and we'll populate that committee in just a moment, would be that, first of all, I think using Sherrie's four points are very useful as a point of departure for organizing some of this.

I think that you need to give some group thought to whether or not we're trying to find

-- as you look at your illustrative cases to make the case, being specific about those which get to the level of prioritized specificity, like hemoglobin A1C3. Is Dr. Smith ordering hemoglobin A1C3 or not? Is the diabetic care delivered consistent with the best possible standards? That's a level that you can get your arms around. It's real clear, it's real specific, and that's where the momentum is moving today, ACE inhibitors, beta blockers, really nuts and bolts. In trying to find examples that move this field into that level of granularity on the clinical care delivery side, I think you have to be pretty explicit about trying to grapple with some of the larger, more population-based issues that are outside of the relationship between a patient and their physician, and who is the accountable unit for these outcome measures when you move beyond patient-physician decisionmaking. I think you want to be thinking about where that is. I think you want to be giving some good thought to whether you are -- and I think the way that Sherrie solved it, it probably makes this question less important -- whether we are trying to identify, again, or urging some specific things to get translated, or just finding examples that illustrate what we want to do that speak to the question of whether it really is requiring a different or some kind of an investment in the research dollars in the infrastructure that allows you to answer these kinds of questions.

I think it's really that if you're identifying need, somewhere or other you've got to have the science that gets at that need, and that's not a simple issue, obviously, you all know, but I don't think you should be cowed by that challenge.

MS. CHEN: Under the cancer point of view, there's more funding. They are doing it comprehensively from translational, from the research to clinic and back again, and they should have a lot of this information.

DR. TUCKSON: Good, so that's homework to do, and I think I'd like you to be on the committee, quite frankly.

But again, I would want you to consider as a subcommittee, I'd want you to consider the point that while our committee hopefully will transcend and have transcended any particular administration and/or Secretaries, I think we owe it to our Secretary of the moment to try our best, especially when we have one who has reached into us in such a dramatic way and said I care this much about personalized medicine to sort of try to tie the theoretical construct of this to his effort that says I want things that allow individual human beings in America to have care that's delivered cost-effectively with quality that is reported transparently so that they can match their care delivery infrastructure to meet their individual human needs, their personalized medicine thing.

So I think we want to couch it in that sense, given that's where his head is and what he's putting his efforts in. We want to try to speak to that to the greatest extent possible. I would urge you to do that.

So now we have co-chairs of the committee. We have three co-chairs, and we'll need one out of the three. So Steven gets to be the chair of the committee. Muin and Gurvaneet Randhawa --

DR. KHOURY: Are ex officios.

DR. TUCKSON: -- are ex officios, so they are part of the committee, and they are co-conveners with you.

You are on the committee? Marc, are you sure?

DR. WILLIAMS: I do it every day. This is what I do every day.

DR. TUCKSON: Well, then, there you are. Marc is there.

(Laughter.)

DR. TUCKSON: Oh, the other piece I forgot. I would like you to consider drawing a dotted line to this neuronal outreach into a receptor site on Andrea's committee. Andrea has a part on her committee that says oversight for how guidance is made in terms of whether the right test was chosen, so clearly there is a neuronal connection here, and we want to make that explicit link.

DR. WILLIAMS: That's exactly what I was thinking, and since I'm already on Andrea's committee, and since my role on that committee is from the perspective of the health care delivery, that would be the natural link.

DR. TUCKSON: Of course, because of the Tucksonian rule that no good deed goes unpunished, Sherrie, of course, has to be on the committee too.

(Laughter.)

DR. TUCKSON: So we've got that. This is exciting.

DR. GUTTMACHER: Are you looking for other ex officios?

DR. TUCKSON: Unless you're about to volunteer somebody other than you, I am.

DR. GUTTMACHER: Greg Feero, F-E-E-R-O, of our staff.

DR. TUCKSON: It looks like Greg's got unanimous consent.

DR. GUTTMACHER: I'll break it to him.

(Laughter.)

DR. TUCKSON: You're such a nice guy.

To the self-starting initiative people, a round of applause. That's terrific, just terrific.

(Applause.)

DR. TUCKSON: Can I get staff to put up the strategic plan? I think you've already now busted the bank on energy. I want to just review with you briefly your strategic plan and make sure that you as a committee are comfortable now. So the vision statement is pretty straight away. Genetic discrimination, there's not much more we can do other than that we've made a terrific recommendation, and we will be following up. Anand is not here but he's supposed to call in, and we're going to send a letter too. What did I do? What did I combine?

DR. WILLIAMS: You're talking about GINA, and we were talking about the Kennedy and the Obama bills.

DR. TUCKSON: Oh, I see. You're right.

DR. FERREIRA-GONZALEZ: The Kennedy and the Obama go in the oversight.

DR. TUCKSON: My fault. My bad.

Education and training. We did ask somebody to do something on that, and I think it was the nursing people. So the nursing people were supposed to give us -- oh, how are you doing? You're going to send us something, right?

DR. CASHION: Yes, we're going to send it.

DR. TUCKSON: I think what we need to do, then -- so you'll do that, we'll do that, and then we'll have -- let's invite NCHPEG leadership to the table and let's really say to them we're not interested in 1959, 1970, who did what. The bottom line, one question, straightforward, no fooling around, a reasoned, informed assessment of the quality of the level of preparedness of the professions in being able to handle the genetic information that's coming forward, and we should probably pick a third somebody or another. We'll figure that out. If anybody has somebody smart in terms of who else would know this stuff, the American College of Medical Genetics.

MS. CARR: Reed, do you also want not only that very broad question answered but some sort of update since our resolution was put forward in 2004? Do you want to know are we in a better place, have we made some progress?

DR. TUCKSON: Yes. Maybe the AAMC, or if you figure somebody who kind of gets a sense of what's going on. Maybe the AAMC is too upstream. Maybe if you could think of somebody who does CME.

DR. WILLIAMS: Bruce (inaudible) would be the one to talk to about that. He's done a lot of the work with AAMC and a lot of other groups around the education thing. He published the

piece in Genetics and Medicine about the readiness of the curricula.

DR. TUCKSON: Let's take that name, and let's get somebody from the American Board of Medical Specialties. That's the way to do it. Let's do it through the boards. We've got the nursing. She's going to come.

You're going to come, aren't you? Yes. You're going to be there, NCHPEG is going to be there, we'll get the boards. So what we'll do is we'll ask the ABMS to send us a representative who happens to be from the American Board of Obstetrics and Gynecology who can speak to it from an obstetrics/gynecology point of view, but also an ABMS-wide point of view.

DR. FERREIRA-GONZALEZ: You want to include also from the laboratories?

DR. TUCKSON: To be considered, a laboratorian who basically says let me tell you something, we're getting nothing but crap in here and you need to know it. So we'll think about that. That's actually a very good idea.

You know what would be good? To get a laboratorian, like one of the major laboratories, one of the big players who sees this stuff, and then sort of ask them to draw the curve, if they could make a curve of level of crap year over year.

PARTICIPANT: Do you want a commercial lab, or do you want an academic lab?

DR. TUCKSON: Commercial. Lab Corp, Quest, somebody like that. Billings, let's bring Billings back in. Paul, right? He knows this stuff, doesn't he? Okay, we'll figure it out.

Next, coverage and reimbursement. We will have a CMS briefing on where they are on this, or someone representing CMS at a superior organizational level. But somebody is going to come in here and tell us something about coverage and reimbursement, because we just can't keep hearing that this stuff went nowhere and died on us. So I'm not concerned about that. That will be an easy one to do.

All right, direct-to-consumer marketing. Do you have an update?

DR. KHOURY: We have data. Next time.

DR. TUCKSON: All right. By the way, we're going to be doing a lot of these things, so these are obviously going to have to be short, no fooling around. One of the things that I think we do well, and we've done it to death, is long presentations. Basically, we're going to change up a little bit, with your permission, and staff and I will work hard with the presenters to say we want you to answer a question. We don't need to know about the history of your field. Just answer the question, okay? So we can fly faster.

DR. KHOURY: Are we becoming a court of law here? You want a yes/no answer?

(Laughter.)

DR. WILLIAMS: No, it's "Dragnet."

DR. TUCKSON: This is the Dragnet rule. "Nothing but the facts, ma'am."

But that means the challenge is on us, and we need to know why we're asking these things. We need to sort of say to ourselves and to people who come to us that based on our responsibility to the public, what is it that really is the most important thing, and basically being clear about what it is that we think we want to know, and then being very specific. That's what I think we've got to do. So we've got to raise our game.

Large pop studies? Done. Done.

Pharmacogenomics?

DR. FITZGERALD: Hello, public. Make your comments by June 1st.

DR. TUCKSON: Thank you. So we'll have an update on that, Kevin. That's moving forward.

Gene patenting?

DR. EVANS: We're moving along.

MS. CARR: Would we want to start part 2 for July, if we can?

DR. EVANS: Absolutely.

MS. CARR: So that will be public comments solicitation and maybe a roundtable of some sort.

DR. TUCKSON: So just think about it for a minute. The things on the left side are bang, bang, bang, bang, bang, updates, we're on it, we're doing our job not by having to create subcommittees but to be using our role and responsibility. The pharmacogenomics is ongoing, and that's going to be with us. So the people who are on subcommittees are going to be using their time on that. The gene patenting is ongoing, so there's a lot of work that's going to be happening there. Oversight has been reinvigorated and now is gangbusters, lots of time, lots of energy on that, will take up lots of our bandwidth. So that's there. Then we created the new one today, so that's a fourth one. We don't know where it's going to take us, but it's there to be discussed.

What are we going to call it?

DR. KHOURY: I have an idea. Outcomes could be construed as narrow because there is implementation research, delivery research, economic research. Why don't we call it translation?

DR. TUCKSON: Let me see. No, no, you can't say translation. No. You've got to say --

MS. CARR: T3?

(Laughter.)

DR. TUCKSON: No. It needs to be self-evident to the public, because you're not talking about just translation. You're talking about measurement, outcome evaluation. I think you're talking about evaluation of -- let's just call it the evaluation committee for the moment. We'll try to find out something that makes sense. It's more than translation, Muin.

All right. Now, is there any member of the committee who feels like they don't see their face in the class picture? Is there anybody who feels like their issues are not being addressed? I came on this committee and I'm willing to travel all the way to College Park because I've been tearing about thus and so, and they keep ignoring me, and I'm furious with the chairman. So everybody is okay?

(No response.)

DR. TUCKSON: Okay. You can still be furious with the chairman.

(Laughter.)

DR. TUCKSON: I want to do one last thing before we close out. I would like the staff to stand up, please. Stand up. Stand up. Come on, come on, you've got to go. You have to stand up, all the staff. We're going to stay here until you stand up. We just want to thank you all very much.

(Applause.)

DR. TUCKSON: And to all the ex officios, we really do appreciate it.

And to the committee members, thank you all. It's been a really good meeting.

You all take care.

(Whereupon, at 3:06 p.m., the meeting was adjourned.)