SECRETARY'S ADVISORY COMMITTEE
ON
GENETIC TESTING

FIFTH MEETING

Wednesday, June 7, 2000
The Governor's House Hotel
1615 Rhode Island Avenue, N.W.
Washington, DC

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P R O C E E D I N G S

DR. McCABE: Good morning, everyone. This morning or today, most of today, we are going to devote to an exploration of current issues in gene patents and licensing. The Human Genome Project and rapid developments in diagnostic technologies provide many important new tools for enhancing patient care.

As with any rapid technological change, however, these developments also raise new questions. We have heard concerns from members of the public that gene patenting and licensing practices are having an adverse impact on cost, accessibility, and quality of genetic tests. Everybody turn off your mikes, please. We need to learn more about these concerns. We are also aware that patents are an important part of the commercialization process and that they lead to the development of many beneficial products.

Our session today brings together a range of perspectives on the issue. Our presenters will help us learn about how patents and licenses work, how they enhance the public good, and along with understanding the benefits they provide, we will also hear more about the concerns they raise. We want to come away with an understanding of the issues and a clearer idea of whether further study of the issues is warranted.

We have organized the session into three panels. The first panel will provide us with a foundation of basic information about gene patents and licensing policies and practices. In the second panel we will hear some concerns from clinical, ethics, and patient communities about the impact of gene patenting and restrictive licensing practices on access, quality, and cost of genetic tests.

Our third panel will provide perspectives from gene-based companies about the benefits of patents and licenses.

Before I introduce the presenters in the first panel, I want to ask all of the four presenters to please try to keep within the time allotted for your presentations, and all of the presenters today. We have much to accomplish in this session, and we want to have time for follow-up questions from the committee members after each presentation.

So our panel this morning, the first panel, is entitled "The Basics of Gene Patenting, Licensing, Technology Transfer, and Commercialization," and I will give you the bios now on the individuals all together.

Ms. Lila Feisee is the Quality Administrator for the Technology Center, 1600-2900, at the Patent and Trademark Office. Ms. Feisee started working in PTO in 1990 as a biotechnology patent examiner in the area of recombinant antibody engineering, cancer immunology, therapeutic compositions, and methods employing antibodies, proteins, and DNA. In 1996 Ms. Feisee became a supervisory patent examiner for units examining patent applications directed to antibody engineering, cancer immunology, cytokines, receptors, growth factors, hormones, and related therapeutics and diagnostic methods.

Prior to joining the PTO, she was with the National Cancer Institute. Ms. Feisee is a graduate of the University of Virginia and has a Master's degree in molecular biology from George Washington University.

Our second speaker will be Mr. Charles E. Ludlam. Chuck Ludlam has been Vice President for Government Relations of the Biotechnology Industry Organization or BIO since 1993. BIO is the trade association of 830 biotechnology companies, state biotechnology centers, and suppliers to the biotechnology industry.

Before joining BIO, Mr. Ludlam was legal counsel to the House and Senate Committees for many years. He has also been a trial attorney for a regulatory agency. His areas of expertise are in

issues affecting international competitiveness of the high technology sector, including regulation, intellectual property, and capital formation.

Our third speaker will be Mr. Stephen A. Bent. Stephen Bent is a partner in the Washington office of Foley and Lardner, a member of the firm's intellectual property department. Mr. Bent counsels and represents clients in the legal issues associated with biotechnology asset valuation and management, venture capital, licensing and technology transfer, corporate acquisitions, and actions between parties involving rights in biotechnology patents.

Mr. Bent is the author of a number of publications on biotechnology intellectual property law in both scientific and legal journals. He is a graduate of Earlham College, and he earned a Master's degree from the University of Connecticut and a law degree from George Washington University Law School.

Our fourth speaker for this panel is Mr. Jack Turner, who is Associate Director of the Technology Licensing Office at MIT. He joined the MIT Technology Licensing Office in February, 1993 after working for more than 25 years in engineering and senior management positions at three high tech companies in the Boston area. He has been involved with product design, manufacturing and marketing throughout his career. A graduate from MIT, he has a degree in electrical engineering.

So we will start off with Ms. Feisee.

MS. FEISEE: Good morning. First I wanted to thank everyone for allowing me the opportunity to come here and give you a little bit of information about what we do at the patent and trademark office. I know this is an area, gene patenting is an area which has created a great deal of concern and interest in the past few years. It is a brand new area. Biotechnology is fascinating in all aspects, and I hope that what I can tell you today about the patent system will provide you with some information about where to go in the future.

I am the Quality Administrator for the Biotechnology Examining Group. My director, John Doll, was to speak before you today. However, he was asked to speak on behalf of the Under Secretary of Commerce, Q. Todd Dickinson, in Cambridge, England for the Wellcome Trust Foundation, so I am speaking on his behalf. He is one of two directors in our Technology Center, and they are both accessible via e-mail and via telephone. You do have handouts in front of you which give you the information that I have, that I will be speaking on today.

It is very difficult to distill what has taken over 200 years to develop in 15 minutes, but I will try my best. First of all, we do have a mission statement at the Patent and Trademark Office. It is our job to help applicants get a patent. Before I start with my talk on the patent system and how it is involved in gene patenting, I would like to do some shameless advertising. I am sure my director would appreciate that.

If anything that I say today piques your interest, you are welcome to attend one of two different types of customer outreach programs that we do have. One of them is the open house that we hold annually in conjunction with BIO. This year's open house will be held October the 18th. In general, what we do in these fora is discuss the current policies with respect to biotechnology patenting. This includes genetic materials as well as other areas of biotechnology.

Another forum, if you are interested in coming, on a quarterly basis we do have a Biotechnology Customer Partnership and a Chemical/Pharmaceutical Customer Partnership. Our next meeting will be August 2000. I am happy to give you any information on this after the meeting, if you are interested.

Okay, U.S. patent practice. Like I said, it is going to be a little difficult to do this in 15 minutes but I will do my best.

First of all, the patent system gets its basis in the United States Constitution. In Article I, Section 8, Clause 8, the federal government is given the mandate to promote the progress of science in the useful arts by securing for limited times authors' and inventors' exclusive rights to their respective writings and discoveries. The term "discovery" is explicitly recited in this direction from our founding fathers. In 35 U.S.C. 100, the definition of the term "invention" is "invention or discovery." You will note here that the distinction between these two terms has been explicitly removed.

The patent system provides a balance between the public and private interests. It is a quid pro quo. In exchange for full disclosure of their invention that is sufficient to place the invention in the hands of the public, an individual is granted the right to exclude others from making, using, offering to sell, or selling their invention within the United States, or from importing into the United States any patented invention during the term of the patent.

The Patent Act of 1952 by Congress provided four basic statutory requirements that must be met in order to obtain a patent. The requirements are that the claimed invention be statutory subject matter and be useful; that the claimed invention or discovery be novel, that it has not been discovered or invented before; that it would not have been obvious to a person having ordinary skill in the art at the time that the invention or discovery was made; and that it be fully and unambiguously disclosed in the text of the patent itself, so that someone practiced in the art would be able to practice the claimed invention.

There are major areas of patentability consideration covered by statutes: 35 U.S.C. 101, which determines statutory subject matter and utility; 35 U.S.C. 102, which addresses anticipation; 35 U.S.C. 103, which addresses obviousness; 35 U.S.C. 112, first paragraph, which addresses enablement and written description; and 35 U.S.C. 112, second paragraph, which addresses definiteness.

Patent eligibility is determined on a case-by-case basis, and appropriate scope of patent protection is granted based upon the nature and the extent of the information thus provided to the public by the applicant.

In 35 U.S.C. 101, I have given you the statute here, it says "Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

In the Patent and Trademark Office we are governed not only by the statutes but also by the interpretation of the courts with respect to these statutes. In a court decision, and it is a Court of Appeals for the 4th Federal Circuit, Merck v. Olin Mathieson, the court ruled that there is nothing in the 1952 act which precludes issuance of a patent upon product of nature when it is a new and useful composition of matter. It also held that all tangible things for which patent protection is granted are products of nature in the sense that nature provides the source materials.

In Merck the compounds at issue were Vitamin B12 compounds. In this instance, the fact that the composition was a naturally occurring vitamin, that is, that it was isolated from nature, it did not preclude patent eligibility.

You should note that in order for an invention to be distinguished from the product found in nature, the invention must be distinct in form or content from that which is found in nature. Products of nature in their naturally occurring form would not be considered to be statutory subject matter, and therefore not eligible for patenting.

In re Bergy, another court decision, the Court of Customs and Patent Appeals ruled that biologically pure bacterial culture was patentable and not a product of nature, because the culture did not exist in nature in its pure form and could only be produced in a laboratory under very carefully controlled conditions.

Diamond v. Chakrabarti, this is a Supreme Court case that held that genetically engineered bacteria that was useful for cleaning up oil spills was patentable. Many commentators feel that this was the court decision that allowed for the phenomenal growth of the biotechnology industry.

I will touch on the other statutes that we cover. These are basically what allow us to determine patentability. And then I will go into two new guidelines that have been published in December, which were open for comments, for public comments, and I will give you an update on those and a brief overview of those, as well.

35 U.S.C. 102 tells us that "a person shall be entitled to a patent unless"--that is very important. When an inventor submits an application, the burden is on the Patent Office to show that they cannot have a patent. Under U.S. patent laws, a prior disclosure of the claimed invention is said to anticipate the invention and may preclude patentability.

In your handouts I have some examples of different types of situations where possibly rejections could be made. I won't go through those in my talk, in the interest of time.
35 U.S.C. 103 tells us that a patent may not be obtained, though the invention is not identically disclosed or described as set forth in Section 102, if the differences between the subject matter to be patented and that in the prior art are such that the subject matter would have been obvious.

Another key portion of this statute is that patentability shall not be negatived by the manner in which the invention is made. This is critical because the Patent Office is not in a position to determine that a DNA sequence is not patentable merely for the reason that it is routine to sequence a DNA fragment.

Under the U.S. patent laws, a reference that discloses a variation of what is claimed, wherein such variation would have been obvious to one of ordinary skill in the art at the time the invention was made, may render the claimed invention obvious and therefore unpatentable.

In 35 U.S.C. we follow an analysis set forth by the courts in Graham v. John Deere. The examiner must determine the scope and contents of the prior art. The examiner must ascertain the differences between the prior art and the claims at issue, resolve the level of ordinary skill in the pertinent art, and consider objective evidence that is present in the application that indicates obviousness or non-obviousness. The specification should also enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The courts in in re Wands provided factors for an examiner to use in order to determine whether a claimed invention was adequately described or adequately enabled in the specification. The breadth of the claim, the nature of the invention, the state of the prior art, the level of skill in the art, the level of predictability, the amount of direction and guidance provided by the applicant, the presence or the absence of working examples, and the quantity of experimentation are factors that are involved in determining whether this statute is met.

If you are interested in obtaining information about how examination is directed with respect to 35 U.S.C. 112, enablement, we do have a web site. I have it in your handout. You can access it at any time you like.

Now I will touch on some of the guidelines that have issued in the past few months. We have two new guidelines. They relate under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph.

The first area of 101 I have already touched on. That is statutory subject matter. That is that an invention must meet the statutory requirements and not be a product of nature. The other requirement under 101 is utility. Simply purifying a DNA would not allow it patentability, does not make it eligible for patenting. It must have utility. The applicant must tell us how to use what they have given us. That is the quid that the applicant must provide.

The revised utility examination guidelines were published in the Federal Register on December 21, 1999. There are training materials that are also posted on our web site. Our comment period from the public had ended on March 22nd, and we are actually in the process of reviewing those comments and finalizing the guidelines. We hope to finalize them in the very near future.

All right. In order for a claimed invention to have utility, it must meet three tests: It must have a specific utility; it must have a substantial utility; and it must have a credible utility. Unless there is a well established or readily apparent utility for what is claimed, the examiner determines whether the asserted utility is specific, substantial and credible.

And invention has a well established utility if a person that is skilled in the art would immediately appreciate why the invention is useful based on the characteristics of the invention. For example, an antibody to an HIV antigen immediately implies utility. It is important to note that a well established utility must be specific, substantial, and credible.

A utility is specific when it is particular to the subject matter claimed. This is in contrast to a general utility that is applicable to the general class of invention. For example, a polynucleotide that is said to be useful simply as a gene probe or chromosome marker does not have a specific utility in the absence of a disclosure of a particular gene or chromosome target.

A general statement of diagnostic utility would ordinarily be insufficient in the absence of an identification of what condition can be diagnosed. A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context are not substantial utilities.

A probe, a DNA segment with no utility other than the fact that it hybridizes to another piece of piece of DNA, would not be substantial. You would have to do further research in order to identify what to do with that particular piece of DNA.

Therapeutic method of treating a known or newly discovered disease, and an assay method for identifying compounds themselves that have a substantial utility, are considered to have substantial utility because they set forth a real world context of use. On the other hand, uses that require carrying out further research to identify or reasonably confirm a real world context are not substantial utilities. Basic research that uses a claimed nucleic acid simply for studying the properties of the nucleic acid itself is not substantial.

We do have throw-away utilities that are also insubstantial. For example, using a nucleic acid as a carbon source would not be a substantial utility. It's a throw-away utility. Using a transgenic mouse as snake food would not be considered as a substantial utility, or using a protein as a nitrogen source. Throw-away, insubstantial or non-specific utilities don't meet the requirement of 35 U.S.C. 101, even if the specification asserts such a use.

An asserted utility is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with logic underlying an assertion. A credible utility would not violate the laws of nature. Perpetual motion machines would not be considered to be in currently available form. Some nucleic acids may be used as probes, chromosome markers, or forensic or diagnostic markers, but they may not meet the requirements of substantial or specific.

The second set of guidelines--

DR. McCABE: If you could wrap up in the next minute or two.

MS. FEISEE: I am doing it right now. We are getting there.

The second set of guidelines, 35 U.S.C. 112, first paragraph, written description, indicates that the specification shall contain a written description of the invention and the manner and process of

making and using it, in such full, clear, concise and exact terms as to enable a skilled artisan to practice the invention.

The guidelines that were published also concurrently with the utility guidelines were prompted by the Regents of the University of California v. Ely Lily, as the court decision that came up, and they indicate a basic inquiry that states, "Can one skilled in the art reasonably conclude that the inventor had possession of the claimed invention at the time that the application was filed?"

The written description requirement is separate and distinct from what is enablement in the same statute, 35 U.S.C. 112, first paragraph. What the examiner does is compare what the applicant has described and what the applicant is claiming. If a skilled artisan would have understood that the inventor was in possession of the claimed invention, even if everything is not explicitly described in the spec, then the requirement is met.

I won't go through all these, as maybe these are all available in your handouts, but what I would like to conclude with is that the patent deal is a good deal. It is a social contract that is between the public and the inventor. The inventor is protected for 20 years from the time that he or she files his or her application, and after this time the public gets it for free.

The inventor could have chosen to keep what his invention or discovery is as a trade secret, and no one would have ever known what he has invented. In the end, what happens is, the public will benefit from the inventor's disclosure of his invention.

So that is basically my 15-minute talk on the patent system. Thank you very much for your attention.

DR. McCABE: Thank you. Our next speaker is Mr. Ludlam.

MR. LUDLAM: It would be a little more informal to speak from right here at the table.

It is a pleasure to be here. BIO is the representative of the biotechnology industry, but that includes not only all the genomics and gene based companies, but also all the gene therapy companies, the therapeutic companies, the food and ag companies who also actually get gene patents on genes that are in animals and foods, so we represent everybody who has an interest on all sides of this, which means that we represent the people who might be the licensees and pay royalties back to genomics companies or to a gene-based company, as well as those who will take the gene and turn it into a product or turn it into a diagnostic or whatever.

It is particularly an honor to be here because the bioethics issues that you have been dealing with heretofore are very, very important to BIO. We are, I think, the leading trade association at this point working on all of the discrimination, confidentiality issues, and we are proud of our work on that. I know Michael Warner was here on Monday, our bioethics counsel, talking to you about those issues.

It is also an honor to be here with Lila and her colleagues from Group 1600 because they are totally professional. Obviously they are the right people to be working on these issues. Their level of expertise is obviously quite substantial. Many of them have both JDs and Ph.Ds, and we view them as the right people to be working on this issue.

It is a very deliberate process. There have been two rounds of comments now on gene patents. These are the documents that Lila referred to, that we have analyzed every word of basically. These are the guidelines, the training manuals. There are 31 examples of how the PTO would rule on individual cases regarding gene patents, 140 pages of analysis.

This is an unbelievable amount of detail. I think in the end we will know more about the PTO's approach to gene patents than any other type of patent. It will be more predictable in the end than any other type of patent application.

And we think the controversies here will revolve around maybe one or two of those 31 examples, and 25 or 30 footnotes regarding those two. In other words, the debate at some point will become extremely technical, among nerds, and not a matter of wide public interest.

Obviously the PTO is taking this challenge very, very seriously. We need to finalize the guidelines and the training manuals. Then we need to see what is issued in the way of patents from the PTO. There are an awful lot of patent applications pending, and we will see which go forward and are issued, and the ones that are never granted, I guess we will never know about at that point.

Ultimately, we will have to see how the courts will rule on this thing. That is another important part of the process. They won't directly rule on the guidelines, but they will rule indirectly on whether the PTO standards are correct, too high or too low. Obviously the PTO is setting a high standard for these applications, and we will see whether or not that is correct.

This is the normal process. This is what we have seen. Every time we get a new type of invention, electricity, plastics, whatever it was, we went through this kind of process, only in this case it is a more professional process than we have ever seen before.

BIO participated in this comment process, filed comments both on the first round of the guidelines and on the second round on March 22nd. We will not end up agreeing 100 percent with the PTO on their final guidelines, I am sure, though we view it as a totally legitimate process.

We gather that the issue pending today before the SACGT is whether or not you will take up the issue and put it on your agenda items for further review. Just to go to the bottom line, that is what we have to do as entrepreneurs, I guess. We do not think that is appropriate. We do not think it is necessary. We think it could potentially be quite harmful. The agency with jurisdiction here is obviously another department. It is not DHHS, it is the Commerce Department, and that is where we believe the jurisdiction should lie.

We are particularly concerned, I have to say. We have experience about what the debates in this area mean. On March 14th, $55 billion in capitalization for the biotechnology industry evaporated in a day because of some misconstruction of statements of the President and Tony Blair. Not only did the entire biotech center go down, including all of the non-gene based companies, all of NASDAQ went down, and NASDAQ has not come back. I think I would say Al Gore, if he wants a thriving economy in November to get reelected, would regret what happened on March 14th because it obviously has had some fundamental impact in the entire economy.

$55 billion is three times the entire NIH budget. Frankly, we don't know what research has been killed as a result of this. We don't know what patients will go awaiting for pure therapies, let alone diagnostics, because of this collapse in the capital markets. They have come back some. We presume eventually it will come back quite substantially, but a lot of research has been curtailed and killed, and we don't know the consequences of that. So we obviously are sensitive about this issue.

The President, fortunately, on April 5th came back and said that he wanted to defer to the PTO and the Commerce Department, so he is firmly on record as saying that that is the legitimate process for resolving the discussions in this area.

Let me make a few comments on gene EST and SNP patents. If we were referring to cDNA patents, there wouldn't be a public debate. If these were viewed as simply molecules like thousands of other molecules, there wouldn't be public interest. There wouldn't be an emotional content to this debate.

In fact, sometimes these molecules are drugs, so any debate about gene patents is a debate about therapeutics and not just diagnostics. Any debate about these molecules is a debate about gene therapy and not just about diagnostics.

From a patent and a chemical point of view, there is no difference between a gene and a gene patent and another molecule and another molecule patent. These are molecules. They are genes. That gives us, you know, an emotional context for understanding what they are, but they are just another molecule.

We need therapeutics and not just diagnostics. One of the worst traumas, I am sure we all agree, is having a diagnostic for a disease for which we have no therapeutic. So it is critically important that we maintain the incentives to develop therapeutics and not just develop diagnostics.

So we need to be very, very careful on these issues, because the patent law that undermines the development of diagnostics is exactly the same patent law that undermines the development of therapeutics and gene therapy and all of the other technologies, and also gene patents for plants and animals. We are finding genes in plants that code for certain things, and that is critical to the entire bio-ag sector. It is also critical to the entire bio-industrial sector, because they find genes that are relevant to enzymes or whatever.

The patent law is obviously a fundamental tenet of the economy. The new economy that we see all around us, that has had such profound effects on the standard of living in the United States is obviously founded in large extent on the patent system.

The patent system has always been controversial. If you can go back to the time when electricity was first discovered, and the first discovery of plastics or whatever, there was always controversy. The patents were too broad, they would block research. You know, the debate has been exactly the same as we are seeing today.

I think Lila has completely dispelled the notion that the fact that a naturally occurring substance is patented is not in the least bit controversial. Obviously you cannot patent something as you find it in Mother Nature. You patent something that you develop into a product where you understand the utility, so that is what the patent is on.

If you attack patenting of molecules like insulin, we wouldn't have recombinant insulin, or we wouldn't have recombinant human growth hormone. We would not have an industry based around many of the antibiotics which are found in Mother Nature.

The fact that Mother Nature was there first and developed some of the basic concepts, and maybe even the basic molecule, is completely irrelevant to whether or not it is patentable. It is patentable based upon value added by the inventor, who understands the utility and can manufacture the product and whatever. Then you get a patent.

Simply the fact that you find it in Mother Nature is not enough. You have to make it into something, an industrial product, and that could be human insulin, human growth hormone or whatever. And the fact that they are natural products means that they are even more valuable, in the sense that they get less likely to get resistance or rejection or side effects or whatever else.

So you want to use a naturally occurring compound instead of a synthetic compound, and all of the gene patenting is the same concept that applies to all these naturally occurring compounds. In this case the compound happens to be a gene rather than insulin or whatever else.

A patent is obviously not ownership. All it does is prevent a commercial competitor from stealing the invention. It has absolutely no impact on people who do not have a commercial motive or intention or application. The U.S. biotechnology would not exist without the patent system.

And even though we have the patent system, the industry lost $5 billion last year. This is the largest money-losing operation in the history of the free enterprise system so far. Obviously we hope that will not continue to be the case. We need to reassure investors that when they invest this money in a research, whether it be gene research or any other kind of research, that their

invention will not be stolen by a commercial competitor, and that is why they need patents.

The industry obviously arose out of NIH funding initially. The technology transfer system which Steve and Jack will talk about, and obviously they are great experts and MIT is one of the most effective universities in the world in terms of technology transfer, is an incredible strength of our system. It is the envy of Europe and Japan and every other country, is these partnerships that we have between academe and industry, and the technology transfer is based around patents. If you don't have intellectual property, there may be something to collaborate about but there is nothing to transfer.

We now have $10 billion invested in research in the biotech industry, another $25 billion in the farm industry. It is double what NIH spends every year, a phenomenal industry, the most entrepreneurial industry in the history of the free enterprise system, the most capital intensive, the most research intensive, the greatest risk-takers, the greatest entrepreneurs we have ever seen in the free enterprise system.

The genomics sector obviously arose out of the Human Genome Project, and the industry is now pouring billions of dollars into genomics research. So it is a fantastic accomplishment of the Human Genome Project that it has stimulated this doubling and tripling and quadrupling of the investment in the private sector.

We have 100 years of genomics research to do, 200 years of genomics research to do. We have 5,000 genetic diseases. We have billions of mutations. There is enough work that we need billions and billions more invested in the private sector to match whatever the public sector is funding, and that will only happen if those inventions are protected by patents.

Let me put a human face on it. I have a very dear friend, a kid I have known since he was born, who is dying of a genetic disease. He is 14. He has Alexander's disease. It's a version of leukodystrophy. We don't know the gene. We don't have a diagnostic. We don't have a therapeutic. And he will probably be dead by the end of the year.

That is why we need billions of research going into this industry in the private sector and in the public sector, to discover what is going on with these genetic diseases. Obviously, genetic diseases, because they are hard-wired diseases, often are manifested early in kids and are particularly lethal kinds of diseases. Breast cancer that is associated with genetics is particularly lethal, particularly early onset disease.

That is why we need the patent system, to bring the private sector into this, into this research with full force. What you get with the patent system is a race to invent and then, once you get a patent, you must race to develop, because having a patent means nothing. It means you have to have a product with sales. And as soon as you get a patent, the term is running, meaning you get a race to invent and then you get a race to develop. That is exactly what we want for patients. That is exactly what they want. Time is not on their side.

Obviously one of the great prides that we have is that we provide tools to doctors. We give doctors things to use to cure patients, to diagnose them and to cure them. It is a wonderful partnership.

Any action that the SACGT takes that undermines, or any other government agency takes to undermine patent incentives for this research will undermine the incentives for research, potentially undermine research on therapeutics and not just diagnostics, and on gene therapy, and potentially investment in the entire biotech industry. We can say that. We have seen that. This is not hypothetical. We saw that on March 14th.

The patent system is fundamentally consistent with the interest of academic researchers. Obviously we publish the terms of our invention when they are granted. That is exactly what academics want. BIO is a strong supporter of publication at 18 months. We don't even want to

wait until the application is finally granted. We strongly supported that during the consideration of the patent reform bill. Unfortunately, we didn't full publication at 18 months, which would mean that it would be published even if the patent had been granted at 18 months.

As a practical matter, patents are never enforced against academic researchers who are performing academic research. There are proposals around that would limit the issuance of gene patents or limit the enforcement of gene patents or establish a moratorium on gene patents. All of these proposals are inimical to the investment in the private sector in this research. We do not want the government going it alone on this research. We want all the genius and investment and capital of the private sector involved.

If we get a limitation of enforcement of gene patents against academic researchers, who are already as a practical matter not subject to patent infringement actions, basically they are asking for an exemption to pursue commercial applications of genetic tests and to make money on genetic tests, and obviously there is no basis for that.

There is no precedent whatsoever in the Ganske-Frist law. I was the leader on our side in the debate on Ganske-Frist. I know every chapter. I have seen at least 200 drafts of that legislation. That was a case where Ganske and Frist said that they had absolutely no intent to have any impact on the biotechnology industry in any possible way, and the only question was how to draft the statute so that it didn't. It took two years, several hundred drafts, to get to the point where our industry and all of this research that we're doing was completely exempt, which is what they said they wanted.

If an academic group comes in and says that they want an exemption, then that is a direct attack on the biotechnology industry and a direct attack on the incentives for this research.

Finally, we have invited the representatives of many of the pathologist groups and other groups to a meeting which we are going to hold at BIO on June 19th. We are looking forward to that meeting. We want to hear their concerns, particularly on the licensing aspects of this issue but also on the patent questions. We are very happy that so many of them have decided to come. We have a very open session, and we think that should be a very useful learning process in all ways.

So, to conclude, we would recommend that HHS defer to the Commerce Department; that the Commerce Department complete its process; that we work with the markets and with these discussions like we are going to be having on June 19th to look at all the licensing questions.

A blunderbuss approach here, either in the Congress or even here or anywhere else, has the potential of a reaction like we had on March 14th. It is obvious that we are not speaking hypothetically about that. So we look forward to working with you on all of these issues, but especially the bioethics issues that we have worked on with you before, and appreciate your letting me talk today. Thank you.

DR. McCABE: Thank you, Mr. Ludlam.

Mr. Bent?

MR. BENT: It is easier for me to think while I am standing up.

As a lawyer who has been working in this field for about 20 years, I have sort of a vested interest in seeing the sector succeed, and so it has been with some dismay that I have seen over the last few years articles and comments appearing in the media about this issue, the issue that we are talking about here. And I wanted to use as the departure point for my comments to you an article that I saw last fall in the Chicago Tribune by Robert Katulik [ph], who is a staff writer there.

It is a well-written article. I used to be a journalist, and I can appreciate the work that went into that article, but it crystallized for me the issues that bother people and have been aired in the press,

and I wanted to address those more or less seriatim so I could get them out in front of you and have them available for your discussion. That article, by the way, is in the September 12th issue of the Chicago Tribune. If you have a chance, you ought to take a look at it.

In that article, Mr. Katulik* charges that patenting human genes threatens to hamstring research and boost the price of some diagnostic tests. That is a quote. What I hope to demonstrate for you in the few minutes that we have, that his concerns are substantiated neither by basic patent principles as Lila has set them out, nor by the U.S. experience with the patenting of DNA molecules which is my experience.

A patent directed to DNA does not embody a property right in a living organism or in a gene. That building block of chromosomes is found in an organism, and I know Chuck has already made that point. Rather, a DNA patent is based on the inventor's insight regarding the nucleotide sequence of the DNA, which after all is an aspect of its chemical composition, and perhaps regarding the function or dysfunction of a protein encoded by the DNA.

Armed with these insights, the inventor is required by law, as Lila has indicated, to furnish in the patent a description that enables the knowledgeable reader to make and use the invention claimed in the patent. That invention may comprehend an isolated or otherwise artificial form of DNA, as well as a new diagnostic test or a therapeutic approach which is informed by knowledge about the DNA. but it cannot, that is, a DNA patent cannot preempt others from using genetic data per se.

And that is directly contrary to statements that have appeared in Mr. Katulik's* article and in a related editorial in the Chicago Tribune that was entitled, "Should Congress liberate gene data?" That was the same theme that the President and the Prime Minister of England picked up on, and sent the sector into a tailspin, as Chuck has mentioned.

Chemical inventions have been patented in the United States for generations, and worldwide for more than 100 years, and there is no plausible ground for a different treatment of biological molecules, including DNA. Indeed, as Chuck has indicated, the need for effective patent protection to shelter risk capital so critical to ongoing research and development in this sector may well be felt more keenly in biotechnology and biomedicine than in other areas, by virtue of the long product developmental cycles that affect these fields. It is not surprising, therefore, that the patents for DNA have played an integral role in the biotechnology revolution for over two decades.

Private enterprises as well as universities and other non-profit institutions now dedicate a lot of time and substantial resources to exploring the entire DNA complement, the genome, as it is called, of different species, including the human genome. Taking the results of this exploration beyond the academic realm would be slowed to prevented, absent a prospect, afforded by patent protection, of exclusivity in commercializing the fruits of applied genomics research. That is really common sense. It is really beyond dispute.

As a consequence, the availability of DNA patent protection stimulates R&D investment and advances new product development precisely in a way opposite the effects that were posited by critics like Mr. Katulik*. In particular those critics are off the mark when they contend that gene patenting will deprive hospitals and clinical research laboratories of crucial genetic and other diagnostic tests which may employ a patented molecule.

It is also beyond dispute that the health care system must bear and will bear a cost for biomedical innovation. Patents, and this is a critical point, patents simply provide a mechanism for ascertaining and allocating that cost when the patented technology is sold, I mean by that, licensed or assigned, against the backdrop of conventional products and services. That is what we call the prior art.

If the negotiated price for a new technology outweighs its benefits relative to that new technology, then either the price will come down or health care providers will not use it. And of course, as

Chuck has said, a patent gives you nothing unless it is access to a market protected by the patent, and if the patent owner prices the technology out of the reach of users, there is no market and the patent is useless.

That really bears emphasis. The intellectual property right, as we call it, that patenting engenders permits market-driven processes to work effectively, as it has for generations in other fields of endeavor. Conversely, it flies in the face of economic reality to imply, as Mr. Katulik's* article did, that the owner of a DNA patent would price the patented technology beyond the reach of health care providers. Particularly from my perspective, working with both health care providers who buy technology, as it were, and the people who supply it, this possibility is especially remote in your area, that is in the area of biomedicine, where the costs of both diagnostic tests and drugs are heavily influenced by government payment rules for health care services.

Mr. Katulik* and critics of a like mind offer up also a scenario of a frustrated scientist dispossessed of his or her research tools by an overbearing patent holder. That simply doesn't happen. Even in the article I am referring to, Mr. Katulik* acknowledges that companies with patents covering DNA-related technology commonly allow and even encourage academic research based on the protected invention. That is not altruism there, because that research generates scientifically credible reports regarding the patented technology, thereby disseminating information which improves the efficiency of the cost-benefit balance to which I have already alluded.

The issuance of well-crafted, valid DNA patents that meet the requirements that Lila has outlined serves the best interests of the biomedical community, and the general public as a consequence. It is incumbent, therefore, for the U.S. Patent and Trademark Office to receive the financial and logistical support it needs to continue improving the quality of patent examination in this area. When the PTO, Patent and Trademark Office, does its job effectively, the market can play its role in this, too.

Against that background, for me at least the more interesting questioning is not how licensing will proceed with respect to what I will call gene physiology patents, that is, patents that cover innovations based on how a given gene or family of genes works. Such patent rights have been licensed, particularly by academic and non-profit research entities, for many years, more or less in conventional fashion, which isn't to say that problems don't arise.

You have probably seen in the Wall Street Journal a few days ago a lawsuit that Abbott has brought against Boston Children's Hospital and a researcher there, Dr. Judah Folkman, over the inventorship of angiostatin, a protein that a local company, local to the Washington area, has developed in an anti-cancer context. So there certainly are problems that can arise, but these problems are endemic to any patenting endeavor, not specific to this field that we are talking about today.

As I was saying, the more interesting issues for me pertain to so-called genomics patents, with claims that often encompass many, many possible gene sequences and that are illuminated by structural generalities, we would say homologies, that are drawn in silico, that is, outside of the wet biology context, in sites that aren't directly related to how the gene sequence works. In practice, the dividing line between genomics and gene physiology is not always so sharp, but for our discussion today, nevertheless, the extent to which a genomics patent fosters the treatment of genes as a commodity I think could fundamentally alter the calculus of technology transfer in this area, and I know that is a concern of you.

One of the instances that sort of brought this to a head was outlined in a little vignette that appeared in a Science article some years ago. I thought I would read it just quickly. This is a quote from that Science article called "How many genes are there?" It relates to, again, a local fellow here, Craig Venter. It said when Craig Venter was, he was then head of TIGR, The Institute for Genomic Research in Rockville, Maryland, he had co-authored a paper in 1994 in Nature and Genetics, postulating that there are 60,000 or 70,000 genes in the human genome.

He relates, that is, Dr. Venter relates that he had received an irate phone call from one of his biggest supporters. In effect, the caller had yelled, "What the hell do you think you're doing, saying that there are only 60,000 genes?" The caller was the late entrepreneur Wallace Steinberg, who had played an instrumental role in forming TIGR and was its main corporate backer.

According to Venter, Steinberg hollered, "I just sold 100,000 genes to SmithKline Beecham," a reference to the landmark deal he had cut at that time that gave the large pharmaceutical company access to this database of gene fragments, the ESTs that Chuck had mentioned earlier. Steinberg, in other words, was seriously concerned because he was always trying to raise the number of genes, because he saw them as a commodity.

Just looking beyond, I will call it the hucksterism of that vignette, we would do well not to fixate on the large numbers that genomics patent portfolios may implicate, at least in theory. That is what you have heard, and there is a truth to it, but I think we need to understand that genes, for purposes of market evaluation, technology transfer, the licensing aspects of it, are not as readily treated as a commodity as grain or the things that we typically think of when we think about commodities.

Really, to the contrary, the value of genomics inventions, if that is the right word for it, is better understood to be a function of the probability that a patent claim eventually will issue covering one of the short segments, oligos, that say a gene chip manufacturer would want to use, since that is really the frontier for the diagnostics field these days.

This probably, that is, the probability that there will be a claim issuing on such a short oligo, is itself the multiple of several probabilities, each related to some consideration that could affect the trajectory of the claim as it passes through the Patent Office and eventually the courts. All of the factors involved together suggest to me, these factors that affect that trajectory, suggest to me that the prospect that a relevant, valid genomics claim issuing on such a short oligo that you would want to use in this context may be sufficiently small to balance out, in effect, the large number of genes implicated in genomics portfolios.

What are these factors? Well, consider first that before the PTO, as Lila has indicated, the proponent of a genomics patent claim faces many hurdles, key hurdles, under these rubrics of utility and enablement and written description, which in the aggregate tend to constrain claim scope, often very significantly. I know that as well as anybody.

The PTO has vacillated over the years in emphasizing one or the other of these statutory provisions, but all are used today by biotech examiners to fend off DNA claims that are supported by prophetic disclosure and that purport to encompass more than sequences, the gene sequences that are expressly described, which nowadays are typically full length sequences and perhaps certain fragments for which there is a specific and credible, substantial utility.

Under the impact of case law coming from its reviewing court, the Court of Appeals for the Federal Circuit, the PTO has moved away from granting genus claims, that is, broad claims that encompass fragments and partial sequences like ESTs. That was apparent certainly from the revised interim utility guidelines which Lila mentioned.

You will recall from one of her slides that in the context of Section 101, the utility requirement, the guidelines specifically address the situation of short DNA fragments that ostensibly are used as probes or diagnostic markers. While that utility may be credible, as the guidelines say, the guidelines also direct examiners to reject claims to probes as such if the specification doesn't disclose a particular utility for the target DNA.

Essentially the same result pertains with this written description rationale that she mentioned, and that is presently in vogue at the PTO because of some of the case law coming from the federal circuit. In that context, a patent claim reciting some variant or fragment of a full-length sequence

or prescribing hybridization parameters to much the same effect, may be deemed unsupported by the specification if it doesn't evidence the applicant's possession, at least conceptually speaking, of that genus that is covered. By the same token, some examiners will reject such a claim on what we call non-enablement grounds, saying that you couldn't actually practice that invention, and they will cite to an absence of a structure function guidance regarding what portions of the full-length sequence work.

So rejections of this sort that examiners are issuing are much more in evidence than they have been in the past, and their message is clear: A claim that is supported by what I called a minute ago an in silico disclosure, drawn solely from database comparisons and lacking in vivo results, generally will issue only when its express language is restricted to certain sequences, full-length sequences perhaps, and some enumerated sequences, which meet ever more literal standards of written description enablement. Conversely, the very sort of prophetic disclosure that typifies genomics patents, with a reliance on structural homology and a boilerplate narration of speculative or makeweight utilities of the sort Lila mentioned, are the most likely to elicit the PTO rejections of this sort, which with increasing predictability lead to narrowly drawn claims which pose only an incidental risk for the maker or users of gene chips.

Oh, my time is up?

DR. McCABE: The two are unrelated. You have another minute or so. One of our members of the committee is calling in on speakerphone.

MR. BENT: Actually, really in closing, what I am saying is that these forces, the market forces which have always applied if they are given their proper reign, and forces within the legal system reflected in the PTO guidelines and the trends in the courts that have prompted those guidelines, will over the long term bring about a steady rise in what I would call pragmatism. That is, on the part of both patent owners and their licensees, a greater sense of reality with respect to those market forces which are channeled by patenting, not created by patenting but channeled by patenting, and that ultimately dictate the valuation of new diagnostic and other biomedical technology.

So the take-home message is, stay calm, don't fundamentally monkey with a system that has worked well for 200 years. Rather, let it interact effectively with the market forces that have been in play for as long as the system itself has been in place. Thank you.

DR. McCABE: Thank you very much, Mr. Bent, and I apologize for the interruption there at the end, but thank you.

Mr. Turner?

MR. TURNER: Thank you for inviting me. Lita Nelson, the director of the office at MIT, was originally scheduled to be here, but she too is in England working on an initiative between Cambridge University and MIT which we are looking forward to over the next coming years. My background is not biotechnology, it is more the physical sciences, but I think my remarks are still relevant.

First, I want to address some of the myths of university licensing, and I will go through these quickly. Many people think that royalties are a significant source of revenue to the university; especially industrial sponsors think this to be the case.

People think that there is a quick return from the transfer of technology to universities, that companies are eager to take technology from universities, and that universities should put up on their web site all the technologies they have available for licensing so everyone can come and just take it. Others also think that the technology transfer office actually finds licensees for university research.

In reality, with the exception of a few blockbuster licensing situations, the revenue from licensing is very small. MIT's total royalty revenue in 1999 was a little over $14 million, and this is against a research budget of $750 million. You shouldn't expect royalties from university licensing. We don't, because it takes a long time to get from university research to product, so we typically don't expect or see royalties on products for 8 to 10 years. Most companies, on the other hand, want products that are much quicker to market than they can find in university research-based inventions.

We have not found that publishing available technology is effective. It attracts totally unqualified inquiries. The appropriate licensee for a university technology has to be found and convinced that the research is relevant to their business. Companies that come looking for specific technologies, we can help, and almost always the inventor needs to be involved in the technology transfer process. The inventor is our best source of leads for licensing his university-based technology.

MIT's philosophy in licensing is the primary objective of what we do, is to get technology out of the university and into the hands of someone who will do something with it commercially. We do not try to maximize our financial income from any invention.

We do use the patent system. It is our strong feeling that without a patent, it is not that we wouldn't be able to transfer technology. We wouldn't be able to attract the investments of companies in the technology we have unless we had patent protection in play and were able to therefore induce them to make investment, knowing that there would be more in the reward side of the equation than there is in the risk side of the equation.

Simply publishing university research results is not going to induce investment. We license exclusively most of the time. Immature technology is very high-risk, and by licensing it exclusively we are able to induce investment. We don't let the financial opportunities of what we have get in the way of licensing it. If the licensee is successful, it will return some revenue to the university and to the inventors, and that is sufficient.

Success factors in our program are a very targeted marketing approach. We focus on a few companies. We build relationships with our inventors, with potential licensees, with entrepreneurs, and with the investment community. Most of our leads for licensing come from the inventors themselves. The folks in the licensing office, where I work, are responsible for a small fraction of the licensing. Company inquiry is next on the list and, remarkably, the folks who actually sponsor research are not a large percentage of our licensees.

Having found a potential licensee, if people think that we are beating people away or have a bidding war going on between licensees, if we have got a sucker, we are going to do a deal.

We share risk. We have low initial fees. We, in start-up situations, will take equity in lieu of or in partial lieu of royalties. We do have diligence provisions in our license agreement, such that if the technology we have licensed isn't being used, we get it back.

The process I won't spend much time on at all, but when we get an invention disclosure, we look at it for, really on the back of an envelope, does it appear to be patentable? And equally important is, if we had a patent, do we think we might be able to do something in the marketplace with it?

We often do some initial marketing to firm up our gut feeling as to whether the invention is worthwhile, by talking to potential licensees. And then if we think we have an opportunity, we engage outside patent counsel--we don't employ patent attorneys in our office--to work with the inventor to prepare and prosecute a patent application.

We then continue our marketing efforts. The inventor, again, is the best source for leads. We determine which companies hold related patents, read trade press, and if the technology is fundamentally new, we work to find a group of people that will start a company to exploit the technology.

Important is, I think, the fact that at least we view the transfer of the technology developed in the university as a service, not as a profit center, and we recognize that for every dollar of royalty that is paid to the university, the companies that are our licensees are going to invest 20 times that in product research, development, to get to market. The technology we have serves as a powerful economic engine, and I have data that supports that in spades, which we have published and you can find on our web site.

I am going to conclude at that point, and use whatever time there is to permit questions.
DR. McCABE: Thank you very much. If the four of you could gather here, we do have time for questions. And Pat, are you on the phone?

MS. BARR: I am.

DR. McCABE: Okay, great. Good. We weren't sure. So again, to keep from getting feedback on the mikes, we will turn yours on when you need. So just shout at us and we will make sure you have a chance to say something.

Are there questions for any of our panelists? Yes, Reed?

DR. TUCKSON: Yes. First of all, thank you to all the panelists. Very, very well done.

Lila, help me to understand the role of the PTO, in that are you just a technical review group that looks at the submission, sees whether it follows these statutory details?

Because what I am concerned about is, some of our panelists give the impression--I don't know whether I have got it right or not--that let the free market do its thing. If the licenser's fees are too high, people won't buy it, they won't make any money, they will go out of business, so just turn it over to the private sector and everything will be fine.

You are a brake on that. Do you view in any way or review whether or not access to a technology in any way is denied because of how the patent is used, or are you only on the front end and are just purely a technical review?

MS. FEISEE: We are on the front end, and we are a purely technical review. We are basically the gatekeepers. Our philosophy is, anyone can have a patent unless we can prove otherwise, and we let the marketplace decide. We really have no control over licensing or anything that happens after a patent is issued.

DR. HUDSON: I guess I fall into the nerd category, in sort of having questions about the details, and I was wondering maybe, Lila, if you could tell me what the effect of the public disclosure of the genome consensus sequence will have on the patentability of other DNA fragments?

MS. FEISEE: The statute, 35 U.S.C. 102 or 103, are prior art related. That means if there is information out, available, that the examiners have access to, then that could preclude the patentability of an application to a gene fragment.

DR. HUDSON: And then a secondary question: Under your new guidelines, how would you view the patentability of SNPs or groups of SNPs?

MS. FEISEE: I am not clear what you mean by that. We do have two different guidelines that we have out there, utility and written description, and what they basically tell us is, they provide us guidelines on how to analyze specific claims. And it is not necessarily related just to biotechnology, it is all application areas that are impacted by this.

It has raised, the utility requirement has raised the bar on the way we look at gene patents at this point, the way we analyze them, significantly from the past. However, I don't know if that is clear.

DR. HUDSON: In an earlier conversation I think John Dahl said that under the new utility guidelines, that SNPs would not be patentable. And in reflecting on that, I was wondering whether or not he meant groups of SNPs that had been mapped for which there was no disease association, or what exactly? There was no example of SNPs in the--

MS. FEISEE: I am not sure why he would say that they are not patentable. I am not sure, but I think if they meet all the requirements, that they do have a specific target, if they detect a specific disease, if there is nothing out there that is like it or obvious, if the applicant has told us how to make it and how to use it, then SNPs are patentable subject matter.

There may be limited scope, depending on what the applicant has provided in his disclosure. They may have limited scope of protection. However, I am not sure why he would have said they are not patentable.

DR. McCABE: Thank you, and I appreciate everyone keeping your questions and your responses short because we only have a few minutes.

DR. TUCKSON: Let me follow up, then. First, one short question to Lila. I think, based on what your last answer was, one of the questions that the committee is struggling with in a lot of areas is, do we view genetic tests or genetic processes as different from other things in the medical domain, and we have been talking about that issue a lot. I would get the impression, then, from what your last answer is, that you do not at the PTO. There is no difference.

MS. FEISEE: No, there is no difference.

DR. TUCKSON: Thank you. Next, just a short question to Mr. Ludlam. Let me make sure I understand, and I want to hear from you, can you tell me what regulatory mechanisms, if any, exist that deal with the question of denial of access because of prohibitive pricing or prohibitive business practices or monopolies over any one particular lab having control over one particular process? Do any of those things occur? Are there any licensure areas, or is this essentially once a company gets a patent, it is a matter really of the free market economics?

MR. LUDLAM: Well, certainly in terms of the substance of the thing, there could be the tort system, there could be relationships with the patent holder. It could be a university. In fact, I think the fourth and fifth largest holders of gene patents are universities. They might have licensed it but they might still have some say in the license.

I know of some cases in the research tool areas where the company has to deal with another party, be it a university, in terms of the licensing terms. We obviously have cases of negotiations with HMOs, negotiations with federal agencies, Medicare, Medicaid. The largest factor, of course, is the market.

A company, an industry that lost $5 billion last year would like to have some sales. They would like to have as many sales as possible. And the idea that a company would sit on a valuable property and not put it out in the marketplace in the widest possible way is just not plausible in the slightest.

DR. TUCKSON: Have you ever had the experience of any opportunity for BIO to go to any of its members or any person at any organization or company in the industry and relay to them any criticisms or concerns of the public regarding denial of access because of pricing, the licensure fee was too high? Do you at BIO have any role or take any role in dealing with those concerns?

MR. LUDLAM: Well, it would be an antitrust violation for us work with our members on anything to do with pricing and whatever else, but the entire Medicare debate on prescription drugs has been characterized by some as a question of access. We are among the leading players in the debate about what kind of a drug benefit or increased access would be for prescription drugs

under Medicare. That entire debate is a question of whether or not the prices are too high and what would happen to research if the government intervened.

I can tell you very clearly back in 1993 and '94, when price controls were proposed on breakthrough drugs in the context of the Clinton health care reform, the capital markets for the biotech industry completely collapsed. It was impossible to do an offering, it was impossible to do an IPO for the entire pendency of that debate.

And if we have that same approach in terms of compulsory licensing, anti-patent approaches or price controls, or something fundamental regarding FDA approval, I mean, this is a fragile industry. This is an industry that needs a whole combination of things. It needs these relationships with universities on commercially reasonable terms. It needs reasonable FDA regulation, it needs patent protection, and it needs markets, and that is the only way this industry is going to get--

DR. McCABE: Reed, we are going to have to wrap up soon. I just want to follow up on that with one last question to Mr. Turner, and that is sort of a following up of the same point that Reed was making but from the university perspective.

Do you get involved, as an office of MIT, in terms of helping to guide licensure when concerns might be raised about licensure or pricing? Does MIT get involved with that?

MR. TURNER: Not in pricing specifically, but an important element of each of our license agreements are the diligence requirements that we include in a license agreement, which the last thing we want to have happen is to license a valuable technology or an important technology and to have it kept from the marketplace for competitive reasons. So we require the development of a product and the making of it available in all of our licenses, but especially exclusive licenses, and we work with the company to develop these guidelines before and during the licensing.

DR. McCABE: And are the investigators involved in those discussions, typically, at your university?

MR. TURNER: I think virtually without exception they are, because they know most about the technology that we are licensing. There is not a universal policy that requires it, but it only makes sense.

MR. LUDLAM: Can I add two sentences?

DR. McCABE: Yes, very briefly.

MR. LUDLAM: NIH had a "reasonable price" clause attached to licenses between '88 and '95, and found out that these relationships with NIH were voluntary and the companies were not willing to engage with NIH in those licenses under those terms. And Secretary Varmus saw that and repealed it unilaterally.

DR. McCABE: Thank you very much. Thank you to each of the panelists for your presentations.

Our next panel is entitled "Emerging Concerns about the Impact of Gene Patenting and Licensing on Genetic Testing: Clinical, Ethical, and Patient Perspectives."

Our speakers are Michael Watson, who is Director of Clinical Molecular Cytogenetics and Professor of Pediatrics and Genetics at Washington University School of Medicine. He is certified by the American Board of Medical Genetics and Clinical Cytogenetics and Ph.D. Medical Genetics. He served on the Board of Directors of the American College of Medical Genetics from 1992 to 1998. He co-chaired the NIH-DOE Task Force on Genetic Testing. He currently chairs the American College of Medical Genetics Economics Committee and the Patent Subcommittee. Dr. Watson received his Ph.D. in physiology and biophysics from the University of Alabama at Birmingham; received postdoctoral training at Yale University School of Medicine.

Dr. Ellen Wright Clayton is the Rosslyn E. Franklin Professor of Genetics and Health Policy and Professor of Pediatrics and Law at Vanderbilt University, where she also directs the Genetics and Health Policy Center. She has studied the legal, ethical and social impact of new developments on genetics for many years. She was a member of the National Advisory Council for the National Human Genome Research Institute, and chaired a joint CDC-NIH Working Group on the use of stored tissue samples for genetic research. She has served on the Social Issues Committee of the American Society of Human Genetics, and is Past President of the American Society of Law, Medicine and Ethics. Dr. Clayton is a graduate of Yale Law School and Harvard Medical School.

Judith Tsipis has been on the faculty of the Biology Department at Brandeis University since 1976. She also serves as director of the Master's degree program, Genetic Counseling, at Brandeis, a program she helped to found in 1992. Professor Tsipis is Vice President for Education of the National Tay-Sachs and Allied Diseases Association. She is also co-chair of the Canavan Disease Screening Consortium, and an active member of the Association of Genetic Counseling Program Directors, the National Society of Genetic Counselor, and the New England Regional Genetics Group. Her involvement in these issues derives in great measure from her own experience as the parent of a child with Canavan disease.

Jon Merz wears at least three hats at the University of Pennsylvania. He is Assistant Professor of Bioethics in the Department of Molecular and Cellular Engineering, Faculty Associate in the Center for Bioethics, and an Associate Scholar in the Center for Clinical Epidemiology and Biostatistics. His research interests encompass privacy and confidentiality in medicine and research, reproductive rates and policy, research ethics and regulation, conflicts of interest, informed consent, and issues raised by biotechnology. Dr. Merz holds degrees in nuclear engineering, business, law, and has a Ph.D. in engineering and public policy. He is also a registered patent attorney.

I would like each of you to try and hold your comments to the 10 to 12 minute range so we will have plenty of time for discussion at the end. Dr. Watson? (Pause.)

Also, just to remind everyone that you are part of the roundtable at the end, so if you could hang around for that. And the other speakers from the first panel, too, if you can stay around.

DR. WATSON: I want to thank the committee for engaging in this discussion. I think it is very important one, and it is a time when I think, when we need to bring some balance to the law and the practice of medicine that is occurring in genetic medicine these days.

I am not a patent lawyer and I don't intend to go very far down that road. My sense is that it is a work in progress, and I think one of the things that we have to keep in mind is that, and I think it was reasonably well elicited in the prior discussion, that the patent law is really driven to assist people and companies in getting patents, and is not driven by the public interest. That is not a part of the patent law. And that in order to maintain the public interest, we have to maintain the balance between the legislative side of life, the judicial side of life, and I think that is why it is important that we not completely disregard the role of HHS in this process. They do have an interest in the public's interest in health care, and it is something that needs to be balanced against the patent law side of the arguments.

Now I want to try to accomplish a couple of things, because I direct a Clinical Genetics Laboratory and I have been sitting out here where the rubber meets the road in genetic medicine for quite a long time, and have found that the imposition of certain kinds of patents upon our laboratories has caused some difficulty in both access, pricing and competition for various aspects of laboratory services. And what I want to do is really try to take you through a few slides that will try to make two points.

One is that people commonly argue about the fact that patents are not imposed on research, but when we provide a clinical service, we are making a profit, which I think we get reimbursed at the

level of about 20 percent of our actual cost. I wouldn't go so far as to say we are profit-making. So we need to balance this concept of what is research in genetic medicine, because I think there are aspects of genetic medicine that are truly distinct from other areas of laboratory testing.

And then I want to try to talk a little bit about medical procedures and whether or not certain aspects of genetic testing are the procedures of genetic medicine, and that in many ways they are very different than many other kinds of laboratory tests. So I am going to move through this very quickly. Lots of patents on genes, at an ever-increasing rate.

In genetics we have a combination of different types of patents: technology patents, which I don't hear much argument about; and then we have the disease gene relationships which are being patented, and this is just a short example of many of the diseases which are now wrapped up in gene patents themselves. And this is just sort of up through H. This list is rapidly expanding.

Now I want to say a few things about the law in general, because I am not a patent lawyer. I think that the fundamental nature of the information in the human genome is truly, very much fundamental, but I think that the public has other kinds of interests in this information, both societal, legal, and driven by many of the discussions we have already heard.

Certainly we have heard the discussions of novelty and non-obviousness. I think the obviousness side of gene sequencing is rapidly changing. The utility issues I think are going to be dealt with in court for a long time to come, and that is one of the down sides, I think, or at least some evidence that there are some problems in the way we are approaching patent law in the human genome.

Now, moving away from the issue of whether or not genes should be patented, I don't think that is a discussion for either the legal side or the professional side. I think that the implications of gene patenting are a public discussion, because of the fundamental nature of that information, so what I want to do is move away from that discussion and move to the way that the gene patents are being enforced at the present time against the health care system.

One of the most difficult aspects for laboratories and for the practitioners to deal with is the fact that monopolies are developing. There are gene tests for which laboratories all over the country have been sent letters, essentially "cease and desist" letters: "You can no longer do this test, and you now need to establish a relationship with the company or the individual that holds the patent for them to provide that service, as the sole source of the service in the country.

That has serious concerns to me, in that it does not drive the competition for the quality of the service, and that is a critical aspect of genetic testing and has been one of the mainstays by which it has grown and expanded, is this level of competition among laboratories. Similarly, pricing is also a problem, in that a monopoly has no competition for the pricing of the test, and it is not something that, you know, in many genetic diseases it is not really so much a question of the marketplace making this affordable. And people will truly need this test and will go to great extremes to get it, regardless of the cost, and I don't know that cost should necessarily be the measure of whether or not the public accepts the fact that this patent is being enforced. And there is a lot of accessory requirements, reach-through types of requirements in many of the gene patents that give the patent holder access to the research being done.

Now just to take you through a couple of examples of where the rubber really does meet the road in genetic testing, and to give you the sense really that a genetic test is not what you commonly see in the newspaper. I think the sense that people get is that when someone finds a gene, they find specific mutations which essentially are the evidence that that is the gene that is causing the specific disease in which the research was done.

Now if we take cystic fibrosis as an example, we had about six mutations back in 1989, and at that point in time we had a test which, for those individuals who had one of those six mutations, was a highly informative and useful test. So we have a test that is in service. However, there are many individuals who are not informative for those particular mutations, and we go through a long period

of clinical investigation or clinical research. And it is this mid-ground between true service and true research where we are getting trapped right now, I think, and it is one of the major problems in the area.

When you think about CF, we have gone from six mutations or so in the late '80s to now, through a large number of laboratories and consortia, to having over 850 mutations in this single gene. Now, as you begin to think about it, about 90 percent of those mutations are quite rare or quite private, "private" meaning they are only in one individual or one family that has ever been described. So these are not going to be mutations of which there is going to be knowledge already established.

These are the types, this is probably one of the most highly complex aspects of genetic testing and genetic medicine, is going into those families in whom you have identified the gene involved through the disease, but they don't have one of the common changes. And the laboratorian is now looking for sequence variations in a gene, and now practicing a highly complex area of medicine, which is the interpretation of that sequence, and whether or not that variation in sequence is truly pathological or not.

That is quite different than looking for the known mutation, which I think is the way most people think about genetic testing, is going and looking for the knowns. However, as I say here, about 90 percent of these are not the knowns, and we have had about 15 years for this story to develop. Had it been encumbered under patents, these consortia approaches, at least monopolistic approaches to patenting, these consortia approaches would have been greatly compromised.

Now I think if you look at CF as an example, these technologies evolve very, very rapidly and in very iterative nature. We have mentioned the more uncommon diseases and the fact that many of what are now our screening panels really only comprise a very small proportion of the changes known to be disease-causing within that particular gene. However, we have a significant number of changes in that gene which have to be approached in a very different way than is traditionally expected.

Now, another example of the way in which a patent can impact truly the practice of medicine can be seen in the Canavan disease story. The way this particular patent is being enforced is--first, let me just back up and say its uses are multiple. It can be used in testing for this very rare disease, but this is a very rare disease and is largely diagnosed by another method, not by a DNA-based method.

The DNA test allows you to identify those individuals in the family who may be carriers of that mutation which was present in copies in the patient, and therefore have a reproductive risk. And, similarly, one can extend that kind of carrier study out into the general population of those individuals whose ethnicity or other factors place them at high risk of being carriers of that particular gene mutation.

Now, what we have seen happen with the Canavan disease patent is that a test that was running about $50 rapidly moved to a test that was costing $350. A $12.50 royalty was applied to the cost of this test, which didn't make a significant impact. But very much more difficult is this volume cap that was placed upon laboratories. They were only allowed to do a number of tests which were comparable to those that they had historically provided.

Now, obviously, if you have just found a gene, your historical volume of testing is quite low, so you are being constrained by what was a diagnostic use of the test. When the DNA test became available, we moved to a much larger population having access, and these volume caps changed the way that we approach the patient populations. They changed the way medicine was practiced, because now with the volume cap you want to try to keep the numbers of tests that you do down, and to fold these things into the next array, the next kind of technology coming down the road of microarrays and chips, is going to cause great difficulty.

When we study, for instance, in carrier programs for the Ashkenazim Jewish population, these are multiplexed assays of maybe 11 to 15 different mutations and six or seven different genes. Now, when we study those individuals, we may study couples largely who present to us with a specific risk factor, being their ethnicity or whatever.

Now, when a couple comes in to a genetics group to seek this kind of testing, it has been suggested that we have two approaches, and they are both used in different settings in the country. You can study individuals, one of the two members of that couple being an individual approach to this. If that individual doesn't have the mutations you are looking for, then some argue that you don't have to study the other member of that couple because that couple is no longer at risk.

However, in a public health sort of perspective, both of those people have come to you with a very similar risk factor, and by not studying one of those individuals we have missed the opportunity to identify a carrier. In rare genetic diseases of this kind, when you identify a carrier, you have identified a significant number of individuals who account for the prevalence, because that change is segregating through a larger family. So by moving to individual testing, away from testing both people in that couple, to keep your volume down, you are missing the opportunity in a public health sense to identify the carriers in the population.

So our screening algorithms have been changed in a number of locations, based on some of these caps. It also forced the laboratories to split these microarray panels or multiplexed panels that were being used to test for the disease, because we can't do a test, we can't leave that test in there, know the answer, but not provide the result. Because now, if you have passed your cap, that test now has to be separated out of your panel and sent off to another location to have that very individual part of the test done.

Now, gene testing monopolies are causing a significant part of the problems right now. They do allow for the true monopolization of a medical service. We have done a lot of surveys. I am not going to go into these. I think Dr. Merz will talk more about them. But it is not insignificant, the frequency at which these genes are being licensed on an exclusive basis and not sublicensed out to a large array of laboratories who might compete for pricing and quality of services.

There are some new exceptions beginning to show up. SMA is being held by Ohio State University in the public interest and is not being licensed at all. It is being essentially open to the marketplace. Cystic fibrosis is being enforced as a patent now, the CFTR gene, but in a much less aggressive way at the current time.

Now, there is a lot of down sides we have talked about. We have mentioned the competition for pricing and quality as being down sides to the monopolistic control of a gene patent. However, there is a lot of other problems. When one has a monopoly on a gene testing service, one is essentially in the position of establishing national health care service for that particular gene by controlling its testing.

If you step back to any CF as an example, there are significant, highly complex aspects of testing once one moves past that core group of known mutations. That is really concerning, that there might be only one location in the country where that most complex area of testing can be performed.

DR. McCABE: If you could begin to wrap up, please.

DR. WATSON: Yes. Let me move through a couple of these, because I am sure it will come up later.

Another aspect of the academic enterprise, because academics is not just the place where we do research, it is also the place where we train the next generations of laboratorians. And we have significant problems within our training programs for laboratorians, in that when we can't provide

tests within our institutions, we cannot expose the next generation of trainees to those tests and to the issues related to them, and that is a significant problem for academia in the training of laboratorians.

It also causes difficult with our clinical databases that have been developed over time, by which the association between new patients and clinical conditions is established. And by not being able to perform the tests and essentially having to turn over these databases to those providing the tests, causes significant problems.

I am going to move along through these. One quick mention is a survey we recently did of laboratories across the country. Ninety percent of the labs in the country have dropped tests under patent enforcement. The pricing and the administrative aspects have been beyond their ability to deal with. This compromises test development. Trainees don't get exposed. We lose local expertise in the underlying problems with that test and issues related to the test.

About half of the laboratories have avoided research in which testing has been constrained by patents, and about 8 percent of labs have found that patent licensing has enhanced their research opportunities. So it is not very common that we have had improvements in research in laboratories based on these patents.

I think, as Dr. Tsipis will show you soon, that we can even compromise the open participation in gene finding studies by the imposition of patent enforcement. And, lastly, not arguing the question of gene patenting at this stage but actually discussing how these might be enforced more reasonably, licensing I think needs to be compulsory, and it has to be very broad to allow for this competition in quality and pricing and for that investigational stage of research to progress at the pace at which it has progressed in the past. And it has to be affordable, such that access to testing is not compromised.

I will wrap it up there, and move to the next speaker, and take on any questions later.

DR. McCABE: Thank you very much.

Dr. Clayton?

DR. CLAYTON: I, too, am grateful for the opportunity to speak here today. From my perspective, the questions before us in this committee are whether patenting human disease genes ought to be subject to different rules than applied to other areas of patents, and if so, what they might be.

Now, to some extent I do acknowledge that this discussion is academic, in the sense that this committee cannot alter patent policy on its own. Nonetheless, I do believe that this committee does have particular expertise and perspectives that have something to contribute.

I want to begin by saying what I am not going to argue and why I am not going to argue it. I am not going to argue that patent and protection of intellectual property are bad, per se. All of us profit daily from a system that rewards private entrepreneurship. At the same time, I think we have to acknowledge that creating private property rights is not without cost, as has been powerfully argued by Heller and Eisenberg in their article on the tragedy of the anticommons, and also I think by Mike's demonstration about the impact of having to separate out on the Canavan disease testing from other types of testing.

The question of what system of property rights leads to the largest amount of goods and services, or even the largest amount of wealth, is an empirical one and one that I am not equipped to offer. I am, however, going to argue later that the maximum amount of wealth is not the ultimate goal.

Second, unlike the American College of Medical Genetics, I am not going to argue simply that we should forbid patents on human genes simply on the ground that enforcing these patents impairs patients' access. Examples of limitations on access are already occurring, no doubt, but the

problem with that argument is that patients' access is limited every time we charge for health care in general, as well as every time we charge for drugs and numerous other interventions, both diagnostic and therapeutic, and a substantial amount of those fees are due to licensing and royalty fees.

Put another way, I think the argument about impairing access goes too far, because it provides no principal basis for saying why patenting human disease genes is bad but patenting all this other stuff is good.

My goal today, however, is to argue that the way human disease genes are discovered does warrant different treatment in the patent system.

Although numerous research designs can be used, the functions of human disease genes can only be discovered by comparing the DNA of particular people who have a certain trait with the DNA of people who do not have that trait. Now, the DNA that is analyzed can be obtained by active recruitment of affected and unaffected individuals, or by the analysis of already existing samples, but DNA from particular people is always required. They don't have to be identifiable but they have to be specific people.

The necessary use of DNA from specific people, including some who are affected, has led to concerns about bioprospecting; that people are being taken advantage of in some way by the way their DNA is being used to create commercial products. These charges have been made by people who are living in resource-poor countries with regard to the human genome diversity project, and as we have heard today and will hear shortly, by people in this country who have contributed their DNA to permit the discovery of disease genes.

The number of groups who have complained about this sort of exploitation by gene discovery is long indeed, and in my view the concerns of these people need to be heard, both out of respect for the Kantian notion that people ought not to be treated as means, and out of the utilitarian recognition that science will stop if people won't let their DNA be used.

In an article that he published in Science, Mr. Dahl analogized patenting disease genes to patenting complex polymers. I submit that despite the similarity of the market allocation and perfection issues, these are not the same. Defining the level of concern about patenting disease genes and its moral and social relevance resides far more clearly within the province of this committee than in the Patent and Trade Office, which has stated unequivocally that this is not what they care about.

If it is correct that the use of DNA from affected and unaffected individuals to find genes is morally relevant to the appropriateness of granting and protecting patent rights in human disease genes, the next question is how patent policy ought to be altered. Let me suggest that the committee could consider a number of options. Perhaps the most obvious is to give the individuals whose DNA was studied a property or royalty interest in the patent. This is what John Moore sought and failed to obtain in his lawsuit against the University of California.

Among the arguments that are made against providing royalty interests are the absence of sweat equity on the part of the patient, not that that argument is entitled to any, any weight in the patent system. John Doll has been very clear that you don't have to work at all. If the discovery comes in a dream and it meets all the other criteria, you got it. That the likelihood of gain is so remote and so likely to be misjudged by people, that they will participate too readily in research; and of course the idea that you might pay the patient is going to cost too much.

None of these arguments is particularly compelling, in my view, and I would note that the question of property interests was not conclusively settled by the Moore case, which after all applies only in California. A better argument, in my view, against providing royalty interests is that it is not obvious to me why that would improve access or further scientific exploration, instead of simply shifting where the money goes.

But whatever the strength of these arguments, I think the royalty interest issue is not likely to be a viable solution in our current economic and political environment. Happily, other alternatives exist. One is to give the group of affected individuals some say in how the patent is used.

In the meeting that we held in March, Vicky Whittamore of the National Tuberous Sclerosis Association told of one group of patients who became co-holders of the patent of the gene that caused the disease that ran in their families, thereby giving them some control over how the patent would be used. Their espoused goal was to avoid exclusive licensing of the gene.

These two solutions, granting royalty interests and granting some decision-making rights, gives power to affected individuals. Another option is to change the bundle of rights that go with these patents, perhaps by requiring relatively broad licensing. Just because patents generally provide exclusive and unlimited control over the use of the discovery does not mean that they have to provide that in all cases.

Property rights exist not because they came from God but because society permits them to exist. Society can and does limit property rights when warranted by other competing goods. Sometimes maximizing individual property interests is not optimal. All of you can think of examples of socially imposed limits on the use of personal property. Zoning requirements and air pollution limits are some of the ones that come to mind.

But to bring the notion that property rights are not written in stone a little closer to the case at hand, I want to consider the case of human embryos as a possible analogy. In most cases, a couple whose gametes are used to create embryos are free to use the embryos themselves, to donate them to other couples or for certain kinds of research, or to destroy them. They are not free, however, to permit the embryos to be used in experimentation and then implanted, or to sell them, even though they could make such decisions about other property that they own like their TV, their car, their house.

Admittedly, I want to say that the analogy between human embryos and human gene patenting is not perfect. We limit the use of human embryos because of their potential to develop into humans, whereas in the case of patenting disease genes we would be concerned primarily about not exploiting the individuals from whom the DNA was obtained.

Nonetheless, I think this analogy does make clear that property rights are not absolutes, but rather are subject to limitations that permit other social goods. It may be desirable in the case of disease gene patents to require relatively broad licensing at a predetermined fee, in recognition of the individuals whose DNA was studied.

Now, I will acknowledge that mandatory licensing may decrease the total dollars generated by patents, and may even decrease private investment, but this may be a price that we need to pay, particularly because there will be offsetting social benefits. Articulating the pros and cons of the various alternatives that I have mentioned, as well as of options that I have not discussed or even thought of, it strikes me as also well within the purview of this committee.

A final consideration that I would raise for the committee's deliberations about the appropriateness of disease gene patenting is this: Congress has dramatically expanded the funding of NIH in recent years. Scientific advances have occurred at a dizzying rate, but as a result of the Bayh-Dole Act and the philosophy that it embodies, at least one outcome of this massive increase in federal funding has been the creation of enormous private wealth.

And I want to suggest that it may be time to revisit the assumptions of Bayh-Dole, advocating for limits on the issuance and of the use of disease patents would be a highly visible way of acknowledging the public's involvement of their DNA in these discoveries. If there is no scaling back or at least acknowledgement that the transfer of money from the public to private sector is at least potentially problematic, the support of the NIH begins to look like a huge gift to the

pharmaceutical and biotech industries and their shareholders at the expense of the taxpayers.

Thank you very much.

DR. McCABE: Thank you, Dr. Clayton.

Dr. Tsipis?

DR. TSIPIS: Is this still on? I also want to thank the committee for inviting myself and other members of the panel to discuss the issue of gene patenting, and while I do wear many hats, today I am going to be wearing the hat of a consumer, the mother of a child, Andreas, who is on the cover of the brochure for "What is Canavan disease?", who died in 1998 from Canavan disease, and that is the primary hat I am wearing. It has also driven my involvement into National Tay-Sachs and Allied Diseases, as well as my being co-chair of the Canavan Screening Consortium, along with Roz Rosen, my other co-chair from the Canavan Foundation.

The consortium came together really in response to the patenting of the Canavan gene, and I will talk a little bit about that. What I want to focus on mainly today is the Canavan disease patent. That is the one I am clearly most familiar with. However, I think the consequences of patenting the Canavan disease gene can be generalized, and they provide I think a vivid illustration for why the patenting of human disease genes is really contrary to the public interest, particularly the enforcement of the patents but the patents as well.

For background, for those of you who don't know what Canavan disease is, two sentences: It is a relatively rare autosomal recessive genetic disorder that is more common among Ashkenazi Jews. It causes a progressive deterioration of the central nervous system, so that children born with Canavan disease never walk, talk, or eat independently. Most die by the age of 10 to 15 years, so it is a serious progressive neurological disease.

Research on the cause of Canavan disease began as research on many genetic diseases begins, driven by the parents of children with Canavan disease. In 1987, Mr. Dan Greenberg, the father of two young children--and they are the two kids inside the brochure--suffering from Canavan disease, approached Dr. Reuben Matalon, then at the University of Illinois, and urged him to determine the biochemical and molecular basis of this devastating disease. There was no way to diagnose it, other than brain biopsy, and we had no understanding of what caused the disease.

Dan and several other families gave Dr. Matalon their and their children's blood, skin, urine, as well as autopsy samples on children who had already been deceased, in order to develop a carrier test for Canavan disease and a prenatal test for carrier-carrier couples, such as themselves. The initial funding for the research, not only at the human level in terms of tissue but in terms of financial, was two consumer-based organizations, NTSAD and United Leukodystrophy Foundation.

The initial research done at the University of Illinois was successful in elucidating the biochemical basis of the disease, so diagnosis became improved, but it did not lead to the desired genetic testing options. In 1990 Dr. Matalon moved to Miami Children's Hospital, where his work on Canavan disease continued, again depending on more samples from affected families, financial support coming in part from consumer groups, NTSAD, United Leukodystrophy, and now later the Canavan Foundation.

Dr. Matalan's lab isolated the Canavan disease gene in 1993, and identified several of the most common disease-causing mutations in Ashkenazi Jews. The research results, including the cDNA sequence of the gene and several of the disease-causing mutations, were published in Nature Genetics, also in 1993.

So we were ecstatic. This meant that carrier testing could go forth, prenatal diagnosis could occur, and in subsequent months and years the work was picked up by labs all over the country and

around the world, used to develop the DNA-based test which could reliably and with great sensitivity determine whether an individual, particularly someone of Ashkenazi Jewish descent, carries a gene mutation for Canavan and therefore is at risk for having a child. The same test also made prenatal diagnosis possible.

And scientists around the world could develop this test. It didn't require any patents. It didn't require any licenses. They were already carrying out PCR-based tests and things like that, really based on their own scientific know-how and the published sequence.

Now, given the carrier frequency of Canavan in the Jewish community and the accuracy and sensitivity of the DNA test, both the American College of Medical Genetics and the American College of Obstetricians and Gynecologists, ACOG, issued position statements recommending that all couples of Ashkenazi Jewish background, either contemplating a pregnancy or already pregnant, be offered Canavan disease mutation testing to see if one or both of them carried a Canavan disease mutation. These became new standard of care statements, and it resulted in a dramatic increase in the number of couples being tested for Canavan disease.

It also set the stage for new population-based carrier screening programs in the Jewish community, and I think most of you know that the most successful carrier screening program to date was mounted in the early '70s and continues for Tay-Sachs disease. More than 1 million people have been tested. The incidence of Tay-Sachs, which is an even, if one can say it, more devastating neurological disease than Canavan, dropped by more than 90 percent in the Jewish community. Let me point out, testing for Tay-Sachs, there was no patent, there was no restriction. Lots and lots of labs carried out the test, and it is really the gold standard for carrier screening in the population.

So the early research, as I have described it to date, and obviously something changed, is the ideal model of collaboration between families and researchers. We donated blood and skin samples to a researcher. The researcher identified the gene disease causing mutations.

We knew that the research would eventually lead to carrier and prenatal tests. That was really our goal, as well as understanding what the disease was, so as to benefit extended family members, others in the community. There was never any consent, either verbal or written, regarding the use of our genes by the hospital, no mention of patents, licensing for profits, anything else that could hinder the public's benefit from the use of our genes or those of our sick children, either for prevention or eventual therapy or cure.

To give you a feeling for the kinds of relationships, we talked yesterday about whether family members were participants or partners in the research, it was a partnership. One of the researchers involved, Guang Ping Gao--and I don't know if I am pronouncing that right --who is also mentioned on the patent, was at the news conference announcing the finding of the gene and mutations, and there was a family there with a child named Jacob who was affected with Canavan disease.

And Dr. Gao went up to this child and said, and I am quoting from the newspaper, "I cloned his gene. I held his gene in my hand. It's nice to meet him." This is partnership. We are not subjects. This is partnership. So this kind of cooperation is not unique to Canavan disease. All of the disease genes isolated to date have been identified, with the participation of affected family members. That is how it is done.

Unbeknownst to us, in 1993, the same year that the article came out, Miami Children's filed a patent, and the patent was awarded in 1997. I have given people copies of the abstract of the patent, but it says the invention provides, and it goes on to list 10 or 12 different things, including everything from diagnostic methods, polypeptides, genetic screening methods, methods of treating the disease, methods of genetic therapy for the disease. I don't know if they have left anything out, but it certainly is comprehensive.

We in the consortium first learned of the hospital's patent and its intent to enforce it when letters were received by all of the labs carrying out Canavan disease testing. Remember, this is public domain information. No one knew that the patent had been applied for. And the letter stated that the hospital holds the patent for DNA-based technology and that it intends to enforce vigorously the intellectual property rights relating to carrier, pregnancy, and patient DNA tests for Canavan disease.

The letter was sent out in November 1998, one week after the American College of Obstetricians and Gynecologists announced that screening for Canavan disease was now standard of care for Ashkenazi Jewish couples. A coincidence? Maybe. For the past year and a half the hospital has proceeded to enforce its Canavan patent, and has restricted access to carrier, diagnostic and prenatal testing for Canavan disease, and has also impeded research.

I would like now to fairly quickly try to describe how the patenting of genes in general, and then specifically Canavan's, has actually restricted access to genetic testing for families at risk. First, I would claim that gene patents can physically restrict the public's access to genetic testing.

When patents for genetic tests are enforced, the patent holder can limit and/or control where a particular test can be done by controlling what labs receive licenses to perform it. It can choose to license labs in any of a number of ways. It can choose an exclusive license that we have already talked about; it could do open licensing to all preapproved labs; or it could do a semi-exclusive license, which is what Miami Children's tried to do, where they look for a "market leader" in the commercial sector to carry out a large fraction of the testing; and then they were going to license academic labs with these caps on them that Mike mentioned before, limiting the number of tests they could do.

I would claim that any limitation in the number of labs able to carry out a genetic test compromises consumer access to genetic testing. Consumers lose the option of choosing which lab they want to do their testing, be it the cheapest; the one that provides on-site genetic counseling; the one with the shortest turn-around time, if they are already pregnant; the one in which they have the most confidence.

Additionally, consumers may face problems if their health insurer approves testing at only certain labs and they happen not to be licensed, say, for the gene in question. The sample will be sent to that lab and then sent out elsewhere, increasing costs, perhaps, as well as turn-around time in terms of doing this.

And also the situation that Mike described from a consumer perspective, say the Ashkenazi Jewish panels or whatever they are called, there could be five, six, seven tests. If one lab is licensed for one test, another lab is licensed for another test, because all of them are patented, either the sample is going to be split into many different ways, which cannot be done with some of the samples, or it will be sent sequentially from lab to lab. Or what I am also afraid of is that it will drive the small labs out of business and focus on semi-monopolies of large labs carrying all the patents, all the licenses on all the gene patents, and drive competition down. That seems to be another case.

In the case of Miami Children's and the Canavan disease patent, initially they tried to find an exclusive licensee. That apparently failed. They then spent a year looking for a market leader in the commercial sector, while at the same time signing licenses with caps on the academic labs.

We were notified two months ago, a month and a half ago, that the hospital was actually unable to identify a market leader in the commercial sector and is now licensing labs in a slightly more open fashion, since caps no longer make sense for them financially--this is not a moral position--and so licensing is opening up a little bit. But not all labs can obtain a license, and no testing is being allowed without a license.

In the case of cystic fibrosis and Delta F 508, at least, I have been told that labs carrying out fewer

than 750 tests a year need not apply for a license nor pay royalties; they may do that. Labs larger than that must obtain a license. So small, relatively small operations can continue to provide genetic testing. This is not the case, to date at least, with the Canavan story.

Other labs have stopped testing for Canavan disease voluntarily, rather than go through the licensing process or sign what one lab director has called a "wretched contract," and so the number of labs carrying out Canavan disease testing has dropped since the gene patent was enforced.

Another lab which was responsible for virtually all carrier testing for an organization called D'or Yeshorim, stopped all Canavan testing for months due to the licensing flap. People in D'or Yeshorim rely on the results of carrier testing for Tay-Sachs. They are ultra-Orthodox Jews. They rely on the results of carrier testing for Tay-Sachs and Canavan disease to determine the couple's suitability for marriage, and this stoppage had a serious impact on couples contemplating marriage within this small community. And it is particularly ironic that D'or Yeshorim was hurt because it was their 5,000 or 6,000 anonymized samples that were used by Dr. Matalon to determine the carrier frequencies of the various Canavan disease mutations in the Ashkenazi Jewish population.

My take-home lesson is that patents on disease genes may lead to practices that hurt the public's health. Gene patents can also restrict a person's access to testing because of financial considerations. Gene patents certainly restrict access financially when the patent is enforced in such a way that a royalty is charged for every test done.

Some are low, some royalties are high, in the case of Miami Children's, $12.50, and it was a fixed royalty, so that over time as the cost of the test decreased, this would become an increasingly higher percent of the cost of the test. And I think added to this is the fact that the cost of a patented genetic test is more likely to stay high over time, since it is protected from the usual market forces that apply.

Now, the person negotiating licenses on behalf of Miami Children's, Mr. Marc Golden of New York, has said, and I am quoting, "We don't envision the cost of our royalty being passed along. We expect retail pricing to remain unchanged." That is what I would call a small probability outcome. I am married to a physicist.

And even if a single royalty failed to increase the cost of a test for one genetic disease, let's make that an assumption, what will the public do when it becomes routine to test people for 25, 30 or 50 different disease-causing genes or disease-susceptibility genes all at once? If each is patented and each carries a royalty, those with money and/or very generous health insurance policies will be able to be tested, though at great expense. Others, I would claim, will be left out, unable to pay.

Now, although Mr. Golden claims, and again this is a quote, that "charging for a gene is no stranger than charging for a Band-Aid," I would argue that no one dies from want of a Band-Aid, but some families unable to pay for carrier and/or prenatal tests could actually lose a child to Canavan disease or any other genetic disease if testing is restricted by high royalty fees. I see this as different from patenting a Band-Aid.

Some argue that cost is not an issue because insurance picks up the tab. Well, the optimal time to have carrier testing for diseases like Tay-Sachs or Canavan, where reproductive issues are at stake, is actually prior to pregnancy, and many insurance companies will not cover that. They will only cover it if a woman comes in already pregnant, and then there are issues of timing, issues of whether you test both members or just the pregnant woman, and it becomes difficult.

Academic labs often provide testing free of charge for families unable to pay, but licenses and royalties do not generally allow for charity deductions. So the conclusion, to me at least, is that access to testing becomes money limited when genes are patented and the patents are enforced.

I mean, there are two steps there; there is the patent and the enforcement.

Third, gene patents can restrict a person's access to genetic counseling and education. Couples considering genetic testing, either for carrier status or prenatal diagnosis, benefit from and often need genetic counseling as part of their decision-making. Genetic counselors are health professionals uniquely trained to provide information and support regarding options, decision-making, issues about the sensitivity or specificity of a given test.

Academic centers usually provide genetic counseling to couples, either by a counselor or a medical geneticist, often face-to-face, which is the ideal. By contrast, many commercial labs, though not all, provide no direct genetic counseling to patients or clients. And our concern is that the proliferation of gene patents and restrictive licensing will drive more and more testing into the commercial sector, thereby limiting access to genetic counseling and informed decision-making by knowledgeable and experienced counselors.

Education is also important. The fewer labs involved in genetic testing and/or research, the more limited the sources of information. A company holding an exclusive license will no doubt provide educational materials, but I would ask, are they as objective as possible? How much is the message in that educational material affected by self-interest?

The Canavan Consortium received a very telling and ominous lesson regarding the power of patents in response to its suggestion that Miami Children's set aside funds from the royalties to promote education about Canavan disease, as well as support testing for those unable to pay for it. In a letter to the consortium dated April 3rd, the hospital offered to provide the Canavan Foundation, a member of the consortium, with about $20,000 a year from its royalties to be used for education and screening, but the offer came with unacceptable strings attached. On April 7th the Consortium notified Miami Children's Hospital that it could not accept the offer. The money was most welcome, but we could not accept the offer of support for education and testing under the restrictive terms stipulated by the hospital, and the Consortium indicated in its letter that its commitment to freely addressing the issues raised by the patenting of the Canavan gene, such as we have done today, was too important to be abandoned.

DR. McCABE: If you could conclude soon.

DR. TSIPIS: Yes. The final issue is that gene patents can restrict access to important clinical research, and Mike has given you some examples of that as well. And rather than tackle the huge areas of pharmacogenetics or gene therapy, I would like to conclude with the simple story of a young couple. They are both 20. He is Jewish and she is not. They have a beautiful daughter, newly diagnosed at 8 months with Canavan disease. His mutation has been identified; hers has not.

They urgently want to find a lab which will identify her mutation for clinical use so they can have other children. The enforcement of the gene patent restricts their options to a very small number of licensed labs. Is this restricted access to clinical research in the couple's, or more broadly, the public's best interest? I think not.

So, given all of the above, wouldn't it be better ethically, morally and clinically not to patent disease-causing genes? It would ensure that human heritage, our DNA, would be put to work for the public good rather than for either commercial or personal gain. Patents are to protect inventions. Is a naturally occurring gene an invention?

I personally do not feel, and the Consortium does not believe, that hospitals or companies should be able to patent disease-causing genes or enforce the patents in ways that restrict access to testing, increase its cost, or limit research, genetic counseling and education for the consumer.

Thank you.

DR. McCABE: Thank you, Dr. Tsipis.

While Dr. Merz is getting the microphone, I will just comment that Miami Children's Hospital was invited to participate this morning, and upon declining was invited to submit written material to SACGT, but none was received. (Pause.)

DR. MERZ: Good morning. I am going to talk a little bit, and very quickly, I will even cut this up and try to make mine 10 minutes, on the exclusive licensing of disease gene patents and the issues that we have been focusing on about these things. I want to acknowledge the collaboration of Mildred Cho, who I have continued to work with, and Debbie Leonard, Madeline Robertson, Anna Schissel, and Antigone Kriss, in some of the work that was done.

I don't know how many saw this press release. Rome, Italy, in Reuters:

"The Vatican announced today that it has entered into an agreement with Dr. Marc Bogart which grants to the Vatican exclusive rights to U.S. Patent No. such-and-such. The patent, granted to Bogart in 1989, covers the one first part of the human chorionic genotropin maternal serum triple test for Down's syndrome when performed between 18 and 25 weeks of pregnancy. Bogart, who was collecting royalties of several million dollars per quarter from hospitals and testing labs throughout the United States, sold his interest in the patent for an undisclosed sum.

The Vatican's statement made clear that the church intends to enforce its patent and prevent further use of the test in the United States."

This is only partly true, fortunately.
The reason I show this, it is a rhetorical device. Basically, I think that patents are somewhat incompatible with, fundamentally incompatible with medicine and medical practice. Is this coming through?

DR. McCABE: Yes, can you try and move that up a little bit, again, your microphone. And again, your microphone. And the mikes around the speaker, could you make sure they are off?

DR. MERZ: It also shows some other things. One is that patents are not necessarily, just because they are issued on a medical procedure, are not necessarily going to be used in the public's interest, nor by people who are best able to practice those patents in the public's and patients' interests.

My overview was going to discuss what are disease gene patents, talk about the ethical issues, talk about three surveys, and conclude, but with the time constraints, I won't do that.

We have talked about the public's interest and focused on these issues. And here is "Marry me, Virginia. My genes are excellent, and as yet unpatented." At least the cartoonists have a good sense of humor about this stuff.

All right. I do want to step back a little bit. A lot of the discussion this morning was talking about gene patents as kind of like a gross thing, and there are thousands of them and all. And the problem is, and the thing that we have been focusing on here is what we call disease gene patents. It is a small but rapidly growing subset of gene patents. Gene patents are things that claim DNA sequences.

Thomas et al, which was published in 1996 in Nature, showed diagnostics to be the fifth most prevalent class of claiming in U.S. patents issued between 1981 and 1994. A follow-up a year later said that diagnostics was first. Celera, of course, has stated that it intends to patent around 300 SNPs or what they call "gene systems" having diagnostic potential, and more recently Celera, Incyte, and Athersys, have filed tens of thousands of provisional applications on sequences.

So what is the disease gene patent that we are talking about? It is a type of a narrow claim that

shows up in more broad sequence and cDNA patents, claims the observation of an individual's genetic makeup at a disease-associated locus, when done for the purpose of diagnosis. So you have ApoE, for determining whether someone is at risk for developing late onset Alzheimer's disease by looking at the status of ApoE-4, period. That is the end of it.

And we have argued, my colleagues and I have argued that this is not patentable subject matter and it shouldn't be, and I can go into that if anybody has any requests, inquiries. These are based simply on the discovery of a statistical association or causal connection between the genetic variability and disease risk or occurrence. They cover all methods of looking at that locus, and they may be used and have been used to monopolize the provision of a clinical service.

Most of the ethical issues have already been raised, and what I do want to say is one thing. One thing I wanted to add is that patenting, on all of these patents, physicians are always involved in the research and physicians are always on the patents, and since 1847 the AMA Code has basically said that it is unethical for physicians to patent. More revised versions of that now say that it is okay for physicians to patent devices and products that can be sold, but it is still unethical for a physician to patent.

Robert Sprinkel, in his book, "Profession of Conscience," says this is the evidence of a deprofessionalization of medicine. You get physicians who are willing to kind of shut down and stop other physicians from practicing medicine, and that is why this case with the Vatican buying the HCG patent was interesting, because it was kind of a natural, unintended experiment. When this was published in March of 1999, when the abstract hit Pub Med, they actually carried forth this fake press release into the Pub Med summary.

And I had been subscribing to a couple of OB/GYN lists because of some research I am doing, and the OB/GYN lists went nuts. It was like, "What is this?" You know, it was basically all these physicians who would go, "This is the standard of care. Is this true? Is somebody actually going to stop us from delivering standard of care medicine?"

All right. I am going to skip the other ethical concerns and talk a little bit about surveys that we have done, my colleagues. The first was in the summer of 1998. It was an IRB-approved survey of patent holders about their licensing efforts, marketing of the patent and genetic tests, known uses of the tests, and enforcement of these tests.

We identified, in fact I skipped the slide here, the background for this was that we identified 37 U.S. patents issued from about 1989 through 1997, containing these extremely broad claims. And CF wouldn't fall into this category because it wasn't issued at that time. It was a search of Lexus and genetic medicine databases to identify this core set of patents. We read all of the claims, kind of limiting ourselves to these very broad claims.

We also took out, that gave us 36, we took out two patents with non-u.S. inventors and two patents that had lapsed, which left us with 33 patents issued from 1991 through '97. They were assigned to 16 universities, three companies. Most of these had acknowledged federal funding. And they cover, and this is the Nature paper that everybody has been given, cover neurological diseases most prevalent. The cite is Schissel et al in Nature in 1999.

It was IRB-approved, again. We held 17, for this core set of 20, we held interviews covering 27 of these 33 patents, which was 17 of the 19 institutions that held the patents. Nine of the 14 patents had been issued more than two years previous to our interview, and most of these were slightly more likely to be unlicensed. Tests for which respondents reported known clinical uses were also more likely to be licensed, which you would expect.

And I hate to put up something like this, but the interesting thing here was, there was a little miscommunication earlier. We held 27 interviews. There were 14 licenses granted. All 14 licenses were exclusive. There were no non-exclusive licenses.

A couple of other interesting things here is that we asked whether or not people thought that a license should be required to do research, whatever that is, with these patents, and six of the inventors said, "Yes, without exception."

Our study conclusion is that many institutions are granting exclusive licenses on disease gene patents, not all, obviously. We have talked about that. The exclusive licenses are being used by various parties to restrict clinical and clinical research uses of patented tests, and the reason, there is no good, defined line between research and what is research and what is clinical care in this area.

Our opinion is that NIH should not grant exclusive licenses, and universities should limit exclusive licenses to non-exclusive performance of the testing, so that a person who gets the exclusive license can only either perform it and license others to perform it, or just sub-license.

I am going to skip the pilot study that we did. Based on some pilot survey data that suggested that labs are, like we saw a couple of minutes ago when Michael talked, some labs are giving up performance of testing services, we did a study last summer with Antigone Kriss, a survey of labs regarding hemochromatosis testing. Again, it was an IRB-approved study.

We identified 117 labs in the Gene Tests Database and the AMP Test Directory that could be doing this kind of testing. We used snowball sampling. We basically asked people, you know, "Who else do you know that might be doing this testing?" Yielding another 11 labs. Of the 128, Antigone contacted by phone 121 and completed 112 surveys, 9 refusals. The refusals were partly because of secrecy agreements, which is another issue.

Eighty-six respondents were lab directors, 11 were supervisors. Current hemochromatosis testing, more than half were performing HFE testing at all. Of the 104 respondents, 94 stated they were aware of the HFE patent. Fifty-six heard about it from their colleagues at meetings, and 30 reported first learning upon receipt in the summer of 1998 of a letter from SmithKline Beecham. Fifty respondents reported receiving a letter.

Those receiving a letter were more likely to say that the patent had influenced their decision whether or not to continue to offer a test at all. Twenty-one percent or 19 said that they had not developed a test, at least in part because of the patent; they knew about the patent. Five labs said that they had stopped performing the test because of the patent, at least.

Now, one of the things in the Clinical Chemistry paper that we had posited is, one of the problems with doing clinical research is that the flow of clinical research is that you are continually doing discovery and exploration, and at some point you kind of come up with this patentable invention, this little discovery. In this case it may be cloning the gene. And at that point you get a publication and patent application. The patent application kind of goes through the process of, you know, one to three years through the Patent Office until a patent issues, and then you get somebody, you know, who may have to kind of start enforcing it.

In the meantime, publication happens. You get clinical testing, you know, like that. Right? Because, unlike other technologies, as soon as you publish the sequence and the mutations known to be causative of disease, any skilled laboratorian can put that test into clinical use, and that determines fairly quickly the standard of care.

So we asked people, when did you adopt the test? Now here is the patent application. This is actually interesting, because we were wrong on our little model in a couple of ways. Patent applications were filed in early 1995. Paper wasn't submitted until more than a year later. Labs, immediately, right after the papers came out, labs adopted the test, and this is the number of labs adopting the test across time. This is non-cumulative, and between 1997, '98 and '99.

And the patent was issued in 1998. Mercator Genetics, which paid about $10 million doing this research, basically went bankrupt doing it. They sold the patent for $3 million to SmithKline

Beecham. In June of 1998, SmithKline started enforcing the patent, sending out letters to laboratories.

Now, one of the concerns is that if you stop labs from doing this kind of observation, you wind up, I mean, you really do kind of stifle clinical observation which has utility. And there were two cases actually that published in 1999. One on HFE from two Australians came out in, I think, Nature Gen, two Australians and a Canadian researcher who found a mutation in a non-coding portion of the HFE--wait a minute--no, this is HFE, a hemochromatosis gene that yields a certain, I think it yields false positives in a particular number of cases.

This is Australian and I think Canadian, so it is basically in their performance of clinical testing, they realized that the sequences and the probes that were published in the original papers of Mercator were wrong or they had a problem with them. And if no one else could do this testing, you are not going to find that.

There was another case last year as well, involving a Canadian investigator who in the course of doing 2,000 clinical tests, which he totally wouldn't have been able to do if he was in the United States, he found and kind of described in a letter in Clinical Chemistry in September, I believe, his experience with these two 1 in 1,000 type rare mutations and the problems in kind of handling the testing itself, and also in counseling and dealing with the patients in handling it. And our concern, I have a commentary to that letter, that that kind of observation, that kind of clinical management may not be feasible to do in this country anymore.

Really quickly, in conclusion, as of August 1999 at least 20 percent of labs nationwide had refrained from performing hemochromatosis testing because of the patents and exclusive license. The patents create uncertainty for laboratorians regarding expenditure of resources to develop and validate the tests.

This case is still evolving. SmithKline sold its clin labs service to Quest Diagnostics, and I am not sure what Quest is doing right now. While many of the labs reported signing confidentiality agreements to begin negotiations, no one reported having completed the negotiations at the time of our survey, and we are hopeful we are going to get money to actually repeat this survey next year.

In conclusion, numerous questions have been raised here about the relative benefits and burdens of genetic testing patents. Because of the ethical concerns about the risks to patients and public health, to the practice of medicine and to medical science, perhaps we should shift the burden of proof to show that these genetic testing patents are really kind of worth it.
We should consider policies or law that prohibit exclusive licensing or require the licensing of physicians and labs at reasonable royalties who are willing to perform the tests. This can maintain the putative incentives and rewards of the patents, while limiting the potential negative effects.

Thank you.

DR. McCABE: Thank you very much. Because of just the time constraints, I think we are going to defer the questions until the roundtable, and we will have the panel discuss it then. I just wanted to make sure that the committee was aware of a press release that came out yesterday. It is relevant to our discussions yesterday.

"Edward Greg Koske, Ph.D, M.D., will serve as the first director of the Office for Human Research Protections, OHRP, a new office at the Department of Health and Human Services, to lead efforts for protecting human subjects in biomedical and behavioral research, HHS announced yesterday.

"The OHRP will officially come into existence this month. At the same time, HHS will also charter a new National Human Research Protections Advisory Committee, to provide broad-based counsel on patient protection and research needs. OHRP will also work with NIH and the Food and Drug Administration to carry out new patient protection initiatives announced by Secretary

Shalala last month.

"In the longer term, Dr. Satcher has said that HHS will look to the new OHRP to develop new, stronger and clearer patient protection policies, with an expanded focus on performance and prevention as well as enforcement. The overall policies will apply to research funded or regulated by all HHS agencies, and will provide a model for other federally- and privately-sponsored research."

So this is relevant to our discussions yesterday about the family history issue, that we hopefully will have time to take up this afternoon.

We will now take a 10-minute break, and will return here in 10 minutes.

[Recess.]

DR. McCABE: Our third panel of this morning is the Importance of Gene Patenting and Licensing: Industry Perspectives.

We will try and get a few more of our committee in here. Can somebody go out and scream in the hallway, please?

While people are now assembling, let me do the introductions. Tom Frank is medical director and vice president of Medical Services of Myriad Genetics Laboratories, and clinical associate professor of pathology at the University of Utah School of Medicine.

Before joining Myriad Genetics Laboratories in 1996, he was an associate professor of pathology at the University of Michigan School of Medicine, where his responsibilities included molecular diagnostics and gynecological oncology.

Dr. Frank is an active member of several professional societies, including the United States-Canadian Academy of Pathology and the Association for Molecular Pathology. Dr. Frank received his medical degree from Washington University School of Medicine in St. Louis in 1984, and completed residency and fellowship training in pathology at the Hospital of the University of Pennsylvania, and was board certified in anatomic and clinical pathology in 1989.

James H. Davis is senior vice president and general counsel of Human Genome Sciences, Inc. Before joining HGS in 1997, Dr. Davis worked as an intellectual property attorney for the law firm of Finnegan, Henderson, Farabeau [ph], Garrett, and Dunner.

His practice focused on an integrated analysis of legal issues affecting the commercialization of new technologies, including intellectual property rights, regulatory compliance, and licensing. Dr. Davis has also held senior legal management positions at Crop Genetics International Corporation, was a partner in the firm of Weil, Gottschul [ph], and Mangees [ph], and also worked for the U.S. Environmental Protection Agency. He holds a doctorate degree in organic and theoretical chemistry from CalTech, and a law degree from the University of Virginia.

Dr. Bendekgey is the general counsel of Incyte Genomics, Inc., which features the world's largest and growing intellectual property portfolio of genomic information. He directs the company's patent and non-exclusive licensing strategy.

Prior to joining Incyte, Dr. Bendekgey was the director of Strategic Relations at Silicon Graphics, Inc., a company specializing in high-performance computing and advanced graphics solutions. From 1982 to 1983, Dr. Bendekgey held associate and partner positions with Graham & James, a San Francisco law firm specializing in intellectual property protection and licensing. He graduated from Kalamazoo College and earned a law degree from Stanford University.

Chris Palatucci is the director of Business Development at Athena Diagnostics, Inc., a division of

Elon Pharmaceuticals. His responsibilities at Athena include identifying the discoveries that will form the basis of new diagnostic tests to be offered by the company and licensing them from academic institutions.

Dr. Palatucci received his undergraduate degree from the University of Rochester, his Ph.D. from Clark University, where his research focused on behavioral recovery from traumatic brain injury. He conducted pre- and post-doctoral research on basic neurobiology of vertebrate olfactory systems at the Worcester Foundation for Biomedical Research.

Dr. Palatucci is a member of the Bioethics Committee of the Biotechnology Industry Organization, BIO, the task force on genetic privacy and discrimination of the Massachusetts Biotechnology Council, and the Neurogenetic Section of the American Academy of Neurology.

He was recently invited to participate on the Expert Panel on Bioethical Issues of Gene Discovery at the White House -- initiated NIH conference, Curing Epilepsy: A Focus on the Future.

Thank you all. Dr. Frank.

DR. FRANK: Thank you, Dr. McCabe and members of the committee. This is going to be a combination of low tech and high tech. The low tech in my hand, the high tech is a very brief home movie that I will showing.

I am going to present a diagnostic perspective, that is, the perspective of the diagnostic lab.

Actually we're not quite ready for that. If you can just hold it up. Okay, you can -- sorry, no -- as I said, that was the low-tech portion of our show.

DR. FRANK: There will be a new matinee performance.

Two genes called BRCA1 and BRCA2 are responsible for most hereditary breast and ovarian cancer. The complete coding sequences of these genes were discovered by Myriad Genetics in 1994 and 1995, respectively, and a clinical genetic sequence test for abnormalities in these genes associated with hereditary risk of breast and ovarian cancer was introduced by Myriad Genetic Laboratories in late 1996.

Myriad Genetic invested the equivalent of about 150 person-years of effort and tens of millions of dollars into the discoveries of these genes, and into the development of a highly automated and accurate clinical test. This investment would not have been possible in the absence of the potential for patent protection for these discoveries.

In considering whether patent protection for diagnostic genetic testing is beneficial or detrimental to the public interest, I would like to compare diagnostic tests for two analogous hereditary cancer syndromes. The first is the one I just discussed, hereditary breast and ovarian cancer, diagnosed through analysis of the two genes BRCA1 and BRCA2, for which Myriad has been awarded a total of eight U.S. patents. The handout to the committee and the public says seven. I am informed that that is now eight.

The other is hereditary non-polyposis colorectal cancer, commonly abbreviated as HNPCC, which is diagnosed through analysis of two genes called hMLH1 and hMSH2, and there is no exclusive license for clinical testing of these genes. My understanding of the situation on that, is that anybody can do that test if they are willing to pay a royalty. And it's a fairly modest royalty, again, from my understanding.

I believe that the evidence demonstrates that the protections offered by patents actually foster the development of high quality genetic diagnostic tests, broaden access to clinically valuable information, and strongly promote research.

I am not a patent attorney. As you can tell, I am not a computer expert, nor have I personally cloned or patented any genes. So the perspective that I would like to share with the committee is that of a laboratory pathologist whose main responsibilities and concerns are for patient care and clinical research.

The first thing I would like to address is the quality issue. It has been told that without stringent competition, quality suffers. I think that these examples will illustrate that quite the opposite is true. In fact, the financial success of our laboratory, or any laboratory, depends on providing a service that is widely acknowledged as being the best possible.

Because of the protections offered by the patents, our laboratory was able to invest in an advanced and highly automated reference lab performing clinical full-sequence analysis of the BRCA1 and BRCA2 genes. Our own informatic staff developed all the software necessary to analysis over 17,000 nucleotides of code per patient.

In fact, we have been called on on several occasions to provide a definitive answer for discordant or questionable results generated by other laboratories, including some academic laboratories. Even critics of gene patents acknowledge that Myriad Genetic Laboratories provides clinical gene sequence analysis of unprecedented quality.

Now, having a patent does not obviate the need to continually assess and improve our quality. We have an ongoing and rigorous program to evaluate and validate our systems, including the extensive and regular use of blinded proficiency samples. These are samples which our quality assurance director sends out to collaborating genetic counselors around the country; they come in; the laboratory has no idea that it is a sample that has a known answer, and it is run entirely blinded.

Nobody is aware that it is anything other than a clinical sample, and the results are compared to the known answer. We have done over 100 of these, and we do several a month.

In addition, our laboratory continually assesses alternative technologies. For example, we are actively participating in a comprehensive comparison of laboratory methods for detecting mutations in BRCA1 in collaboration with investigators who are members of the NIH Breast Cancer Information Corps. This is a collaboration of four laboratories, academic labs, around the world that have no affiliation to Myriad Genetic Laboratories, and the results will be collated by an unbiased observer at the NIH.

Now, in contrast, none of the laboratories offering clinical testing for HNPCC have made a comparable investment into laboratory quality for the purposes of performing that test. In fact, testing for that syndrome is offered by several labs, but using a variety of techniques, SSCP, CSGE, PTT, and the rest of the alphabet soup, that are known and acknowledged to miss mutations that could otherwise be detected by sequence analysis.

Laboratories offer these methods because they are less expensive to develop and perform than sequence analysis. While high quality sequence of BRCA1 and 2 is widely available, there is no test of comparable quality for the diagnosis of HNPCC.

And now, if this works, I will illustrate what I mean by that. Thank you, Chris. I am sorry to put you on the spot. The tricky part is that I am doing this at an angle.

DR. McCABE: It looks like it's going to come on.
DR. FRANK: Good. Myriad Genetic Laboratories is actually part of Myriad Genetics, which is a gene discovery and characterization company. These are the research labs that identify BRCA1 and 2. The diagnostic lab is entirely separate. It is in an adjoining but separate building. The procedures that we use are diagnostic, not research procedures.

Bar-coding is essential to everything we do. The requisitions, the tubes, are all bar-coded. We

have got a lot of thermocyclers, which are off-the-shelf equipment, but they too are linked through our computer system with bar codes. We have extensive use of robotics, which ensures very accurate and precise measurements of volumes.

The robots are controlled by computers running software that we ourselves developed. The robots also track all the samples through. So even the sample plates are bar-coded, and our robots have bar-code readers on the beds, and they come along and read the bar code on each sample plate. So we have positive tracking for everything that we do.

The sequencing itself is done by off-the-shelf equipment, but the analysis of the data is done by a dedicated, trained staff that go through a rigorous procedure for validation. The analysis of the data is done not by commercial software, which isn't up to the task, but by software that we ourselves developed.

One of the unique things about the software is that it compares a consensus wild-type sequence to the patient. There is no commercial software that does this. We had to do it ourselves. So we have got a full-time staff of 10 programmers who do nothing but support the clinical laboratory, and that is a larger staff than many molecular diagnostic labs in an academic setting.

The ultimate goal is a diagnostic report of quality. As Dr. Watson alluded to earlier, it is not simply the generating of the data, but the interpretation of the data. If you don't generate accurate data, you won't get a good interpretation.

So that is what I am referring to when I am talking about the quality of genetic testing, and nothing like that exists for HNPCC.

Now I would like to address accessibility issues, which have been raised by numerous speakers. In fact, a commercial reference lab has a very strong interest in making its services widely available to health care professionals. In order to ensure that the cost of our test is not a barrier, we have worked diligently to obtain insurance reimbursement for BRCA1 and 2 testing. In fact, we have a dedicated program to assist individuals seeking insurance coverage for our diagnostic services.

In 1998, we collated and presented data that 94 percent of completed claims resulted in insurance reimbursement. Today, all major insurers in the U.S. pay for BRCA1 and 2 analysis for appropriate patients, thanks to our unceasing lobbying efforts that they do so. Again, we have an interest in that.

As part of the group, Myriad also has specific contracts with 50 insurers. These are specific contracts that cover 64 million managed care lives that provide for preauthorization and no co-pay.

Now, in contrast, the labs that offer clinical testing for HNPCC, most of which are in academic centers, don't provide such reimbursement assistance. If you look on the Web page and find those tests, you will see that they require patients to pay for the tests themselves, cash up front and in full before they will perform that test. This is what limits access to testing.

So the absence of mechanisms for insurance coverage for HNPCC testing denies patients access to valuable information. Several studies have demonstrated that patients' access to genetic testing services is also limited by a lack of education among health care providers. As a reference laboratory, we are highly motivated to support educational efforts that relate toward services. Since 1996, we have sponsored hundreds of CME-approved talks by academic physicians on the subject of hereditary breast and ovarian cancer.

Such talks have reached many thousands of health care professionals. We have recently sponsored a CME monograph issued by the AMA and written by the AMA, that was distributed to over 150,000 physicians. This greatly exceeds the scope of educational programs for health care

professionals about HNPCC.

As a result, testing for hereditary breast and ovarian cancer is far more accessible than for HNPCC. An international database of observations of mutations in the two genes responsible for most HNPCC contains fewer than 400 entries.

In contrast, the Breast Cancer Information Corps has tallied over 5,000 observations of mutations in BRCA1 and 2, more than 10 times the number tallied for HNPCC. By far, Myriad Genetic Laboratories is the largest contributor of these observations.

The prevalence in mutations in BRCA1 and 2 is thought to be, at most, twice that of hMLH1 and hMSH2. So we believe that the difference between the databases likely reflects substantially greater accessibility of testing for hereditary breast and ovarian cancer than for HNPCC.

Then finally, a very important point, do patents issued to clinical labs impair research. In fact, knowledge about the clinical significance of a genetic alteration contributes not only to the medical importance of the gene, but to its commercial value as well.

So, for this reason, a commercial diagnostic laboratory that holds a patent on a gene greatly benefits from research, not only its own efforts but those studies performed by other investigators.

Myriad Genetic Laboratories encourages investigators to perform analysis of BRCA1 or BRCA2 without restriction for the purposes of their research. There is no license, there is no application. They never even know that we exist. Document of this policy has been provided to members of the committee.

Not only does our lab encourage research, but we actively contribute to it, as well. Since 1996, Myriad Genetic Laboratories has provided approximately 3,000 sequence analyses of BRCA1 and 2 to investigators at reduced cost or entirely at our own expense. We have also provided start-up funds and ongoing support to a Dana Farber Cancer Institute study, a longitudinal study, of individuals tested for hereditary breast and ovarian cancer.

And through an agreement with the NCI, we have begun to provide analysis of BRCA1 and 2 at less than half the normal price to NIH-funded investigators who have grants to study those genes. No profit is netted to us by such testing, and investigators are free to return results to patients. The benefit to us is the knowledge afforded by the research.

In contrast, laboratories offering HNPCC are in competition with each other, making it impractical for any one laboratory to subsidize research at its expense since its competitors would also profit equally from its contribution. Consequently, none of the clinical laboratories offering testing for HNPCC have provided support for research comparable to what we have provided for BRCA1 and 2.

A search of Medline demonstrates the impact of this difference. Since 1994, there have been 213 published articles citing the two genes most often tested for HNPCC. In contrast, in the same time period, there have been over 800 articles about BRCA1 and BRCA2.

In closing, I would like to make three additional points. First, the only restrictions placed by Myriad Genetic Laboratories on testing of BRCA1 and 2 are on commercial competitors who did not bear the cost of the discovery of the genes, nor in developing the market for testing services.

Now, of note, many laboratories offering commercial genetic testing are in fact based at academic centers, whether they are profitable or not. Labs that do testing for revenue that is not derived directly from a grant are considered to be doing commercial testing. In fact, some academic labs perform both commercial and research testing.

With regard to BRCA1 and 2, our policy has been to restrict only the competitive, commercial aspects of testing offered by such labs but allowed them to continue their research unimpeded. A recent sidebar in a recent issue of the JNCI makes that point, and that has also been provided to the committee.

It should also be emphasized that we have licensed 13 academic laboratories to perform commercial testing for specific mutations in these two genes.

A second final point is that patient care is best served when complex genetic tests are performed in specialized reference laboratories. There is a principle, which has been validated by numerous examples, that patients benefit when demanding medical procedures are centralized in facilities that specialize in them and perform them commonly, rather than in smaller facilities that perform them infrequently.

Clinical gene sequence analysis, as you've seen, requires significant and specialized technical resources provided by the investments made possible by patent protection. In addition, the knowledge and expertise that enabled our scientists to discover the sequences of these genes is frequently drawn on to interpret the results of our clinical tests.

These resources, which allow us to provide a superior diagnostic service, are not found in other laboratories, including those that perform other genetic tests. Consolidation of expertise benefits patients.

Finally, I would suggest to the committee that its draft recommendation calling for new regulatory hurdles will likely increase the importance of patent protection. Expensive regulatory requirements will add to the cost of offering new genetic tests to health care professionals. It would be unfeasible and unfair for a laboratory that has assumed the cost, not only of discovery and development of a genetic test, but also its regulatory approval, to be forced to share those benefits of its efforts with competitors who assume none of the cost.

Without commercial protections for intellectual property, such regulatory burdens will make it even more impractical for labs to develop and introduce new genetic tests. The examples I presented illustrate how commercial rights to a diagnostic test, not only allow the discover to recoup the cost of the discovery, but also result in enhanced medical care, improved access to diagnostic services, and increased research. I believe that such protections do benefit the public good.

DR. McCABE: Thank you, Dr. Frank.

Dr. Davis?

DR. DAVIS: I'm just going to sit up here and talk to you a little bit about how these issues can have a tremendous impact on patients, how the effect of gene patenting and what you recommend, and what other people might do in this area, can really have a significant impact on the availability of new pharmaceutical products.

You spent a considerable amount of time this week, and on the panel before, talking about genetic testing, but our goal in the end isn't to tell a couple not to have children. Our goal is tell that couple to have a child, that that child will have a happy and productive life, that we can deal with the genetic diseases, we can deal with the environmental diseases, and that as that child grows and ages, we have ways and medicines to make that child have a long, happy, and productive life.

So when you think about gene patenting, you can't think about it just in the context of diagnostics. You have got to think about what your facts, what your recommendations could have on the therapeutic area.

Let me give you the perspective of Human Genome Sciences. We are a company with a mission to treat and cure disease by bringing new gene-based products to patients around the world. We

were founded on the principle that human proteins, antibodies, genes, cells, can be used to restore the normal function of those parts of the body damaged by disease, injured by trauma, or worn by time.

Our goal is to discover, manufacture, and sell new gene-based products. Patents are a critical component of our ability to develop and sell new products to treat patients, to deal with their unmet medical needs.

Now, HGS is not involved, and has not been involved, in the sequencing of the human genome. We do not have any interest in patenting genomic DNA or the human genome itself, but we are very concerned about the ability to patent human cDNA, and the proteins that are expressed by those sequences, and the ability to use products based on those products, those genes and those proteins, to develop new pharmaceuticals.

Rather than sequencing the genome and looking at genomic DNA, we are focused on a multi-step program consisting of identification of expressed human genes, identification and production of the proteins produced by those genes, determining the natural function associated with each of those genes and proteins, and using that knowledge and information to identify medical uses of those genes and proteins, and thereby promote the development of new gene-based pharmaceutical products.

Our efforts to discover, develop, and hopefully to sell new products is a time-consuming and expensive process. We began eight years by sequencing millions of expressed sequence tags, or ESTs, using the knowledge of those sequences to discover novel genes and proteins, genes and proteins that had not yet been discovered using conventional techniques.

We then began an extensive biological program to identify their medical function and the utility of those genes and proteins, so that we could use those genes and proteins as a basis for new pharmaceuticals.

We and our partners have in the clinic today three new pharmaceutical products developed using this method, and we hope to enter the clinic shortly with our fourth product. Let me just give you a quick overview of those products so you have a sense of what this technology can lead to.

The first product is Reprifermin [ph], or KGF-2, which just finished its first phase II-a clinical trial for the treatment of chronic wounds. These are wounds that result in massive sores on people's lower extremities, destroy their quality of life, keep them so they can't move, they can't go out in society. If you have seen one of these wounds, they are ugly. They are oozing, they are pustular, they are a very nasty wound that simply won't heal.

This protein that has resulted from our effort has shown positive clinical activity in the treatment of these ulcers. Whether it will ultimately prove successful will require a great deal more testing, but it's a promising treatment.

We also are testing Reprifermin in treatment for oral mucositis in chemotherapy patients. Oral mucositis is sores all through your mouth, into your GI tract, that comes from chemotherapy. Many of you who have friends who have gone through it know how devastating that side effect of chemotherapy can be, and more importantly how it can prevent future rounds of chemotherapy to prevent the actual cancer, to treat the cancer.

Our second product, M-PIF [ph], also in clinical trials, is for the protection of bone marrow stem cells that result from damage during chemotherapy. If these two products together are successful, patients will be able to withstand the rigors of chemotherapy far better than they can today.

Our third product being developed by a licensee is VEGF-2, a new growth factor that holds the promise to create new blood vessels in the heart, and in other tissues having insufficient blood supply.

These three products are just the beginning of what we hope will be a large range of gene-based products to be developed by HGS, but to discover each of these products, to develop each of these products, has required us to sequence thousands of potential new genes, produce hundreds of proteins, identify the medical utility of those, and to analyze in detail the biological characteristics of those proteins.

All of this has been necessary for these products. To accomplish this task, to get to where we are today, we have spent over $450 million, and we have not even begun large-scale efficacy trials. These trials will be extremely expensive and will take years to complete. Just to get one product on the market will cost easily $3-, $4-, $500 million. A typical pharmaceutical product today costs well in excess of $500 million to get to the market.

Without patents, no one could afford to develop these products. Without patents, no one would be able to raise the financing necessary to support the development of these products. The patent applications that HGS and the other leading biotechnology companies are filing are not directed to human genes in your body, or anybody's body. What we are doing is filing and obtaining patents on isolated cDNAs and the proteins expressed by those cDNAs.

There is nothing new in what we are doing today. Recombinant proteins in DNA that encode them have been patented in numerous instances over the past 20 years. As Chuck mentioned this morning, examples include recombinant insulin, recombinant human growth hormone, recombinant erythropoietin.
Without the ability to patent gene-based inventions, these products likely would not be on the market today. More importantly, these patents have been the foundation of a whole new biotechnology industry that holds the promise of numerous products to meet unmet medical needs.

Filing patent applications is not limited to private universities. You have heard today, key patents in the biotechnology area have been filed by universities and research institutions.

Now, in recent months, there has been considerable controversy raised over the patenting of human genes. Some of that controversy, as Chuck mentioned, was caused by President Clinton and Prime Minister Tony Blair's comments, but if you read those comments, it was clear that what they said, and I quote: "Intellectual property protection for gene-based inventions will play an important role in stimulating the development of important new health care products."

The PTO’s new guidelines on written description and utility requirements make it clear that patents on gene-based inventions should be allowed. They are not intended to restrict the patenting of human genes or proteins, but rather to clarify the guidelines and the requirements for obtaining a patent.

The rules that PTO is implementing are the same rules that apply to patents on any invention, whether it be for a synthetic chemical or for a new windshield wiper for an automobile. The guidelines don't represent new rules, but it guides in interpreting the rules that PTO has always used and has been proven to work in the development of new technologies.

To obtain a patent, you must prove that your invention is novel and non-obvious. You must prove it has a utility, a real-world usefulness, but most important, you have to teach the world how to use your invention. What is important to understand is that patents play an important role in the evolution of technology. Patents allow a company to invest the funds to discover a new invention, and then to share that invention with the world, so that other parties can build upon it.

The hundreds of thousands of sequences of full-length genes for which patent applications have been filed on by the biotechnology industry, have, in almost all cases, been published under the international patent system. The disclosure of those gene sequences, and the information contained in those applications, allows the researcher to use that information to discover new

inventions and to advance the knowledge of human genes and proteins, but at the same time, those patents are the foundation for companies to invest funds and to develop new products.

In the same way that strong patent protection stimulated the growth of the U.S. chemical and electronics industries during the century, patents are now helping to stimulate the growth of the biotech industry in the 21st century.

Patents on gene-based products are not a block to development of new treatments for patients. Far to the contrary, they are the very fuel that is necessary for a company to invest the funds and bring to market new pharmaceutical products to meet the unmet needs of the public health.

Without patents, the biotechnology industry of today would not exist, and there would be no progress in the development of new pharmaceutical products.

Thank you.

DR. McCABE: Thank you very much.

Mr. Bendekgey?

MR. BENDEKGEY: I'm glad that I was just introduced as Mr. Bendekgey. As a liberal arts major who went to law school because he didn't know what else to do, I wanted to clarify that I certainly do not deserve the honorific title of Dr. Bendekgey.

The topic that we are talking about today, not only has important professional relevance to me, but important personal relevance, having just received the results of a CVS test on the third child that my wife and I are expecting.

I am both conscious of the improvements in the availability of genetic tests since our first child was born six years ago, and I am very concerned that those who are not fortunate to have the kind of insurance coverage that I have, have access to the kind of testing that we were fortunate enough to have.

Incyte Pharmaceutical is a genomics company. Our mission is to revolutionize health care by providing genomic information through a worldwide network of academic, biotech, and pharmaceutical collaborators.

To summarize my presentation today, in case I run out of time, the discovery and characterization of genes has already had a profound impact on the acceleration of drug development and the availability of new molecular diagnostics. The real-world utility of these discoveries entitles them to patent protection. And as I will illustrate with Incyte's licensing program, the availability of patents, in fact, enables the broad licensing of genomic information for research and development, and diagnostic uses.

As I mentioned, Incyte is a gene-discovery company. We were founded in 1991, with 10 employees. Today, we have over 1,200 employees engaged in a variety of scientific endeavors. I would like to highlight the fact that of our 1,200 employees, nearly 150 have Ph.D.s. We often hear that companies like Incyte that are in the information business, where much of the analysis is in silico, there is this implication that what we are conducting is not real science, and that our value-add amounts to having purchased a bunch of sequencing machines and computers, and having some people who flip on and off switches. I think, as you will see, this intellectual capital helps to illustrate that what we do is real science.

With regard to the patentability of genes, as has been said repeatedly, genes are the product of nature and they have been around, well, at least as long as humans. I guess, given some of the recent scientific publications, it would probably be more current to say that they have been around at least as long as fugu, but until recently, no one has been able to use genes to diagnose, cure

or predict disease, until now, since they have been isolated, purified, characterized, and put into commercially useful formats to develop diagnostics and therapeutics. And it is those activities that entitle them to patent protection.

The genomic revolution is revolutionizing health care, and we think that the computer industry provides a useful example. Like the computer revolution, the genomics revolution will increase efficiency, which will result in lower costs and will enable the development of new products that would not otherwise have been available.

To give you a further illustration, if you think back to the computer industry in the late 70s and early 1980s, it was highly vertically integrated. You had individual companies doing everything from developing the microprocessors, the operating systems, the computers systems themselves, the application software, and selling them themselves.

This was a highly inefficient industry, the result of which was that computers were only available to a small number of people who are either at large and well-funded research institutions or at Fortune 100 companies. We all know what happened in the late 80s and the 90s, which was the emergence of a new horizontal computer industry. By allowing companies to focus on individual components of the total integrated solution, the economies of scale and the specialization resulted in the unprecedented availability of computers, broadly, to everyone in this room at prices that would have been thought impossible in the early 80s.

A similar evolution is going on in the pharmaceutical industry. The pharmaceutical similarly has historically been characterized by a high degree of vertical integration with multiple companies engaging in duplicative activities, starting with target discovery through drug screening, preclinical/clinical development, and patient management.
We all know how inefficient this system is, how much it costs to develop a drug or a new diagnostic, how many of them fail in the clinic. That, clearly, is not having a beneficial impact on the availability of drugs or diagnostics for patients.

This industry, like the computer industry, is evolving with the genomics industry increasingly taking over target discovery, high through-put screening, preclinical development being replaced by pharmacogenomics, clinical development being managed by CROs, and HMOs handling patient management.

The result of this will similarly put diagnostics and therapies in the hands of a broad number of patients by making the world efficient. We think that in a matter of two to three years, the concept of target discovery and validation will become obsolete. We will have virtually all of the key drug targets, and that activity will have been eliminated.

What will this enable? We think that this year every gene will be sequenced. By next year, we will have microarrays with every gene on a chip. By the Year 2002, all frequent coding SNPs identified and a full-length cDNA for every gene. By the Year 2005, a minimum marker set for every pathway. By the Year 2007, a chemical compound that modulates every key signaling pathway, and by the Year 2010, we hope to see the understanding of the molecular basis for most human diseases. That is what the genomics industry is helping to enable.

One of the things, again, that we have heard a lot, including from Mr. Bent, this morning is this concept that in silico analysis of information is somehow suspect and is not real science. We think that as increasing quantities of information become available, that the world will transition to electronic R&D, where new discoveries will be based largely on mining known data, and that the wet lab biochemistry will largely take place either in a confirmatory setting or in the clinic.

The structure and function relationships are the basis for all pharmaceutical research. With all due respect to the representative of the Patent and Trademark Office, the concept that to be entitled to a patent a utility has to be unique, has no basis in the patent law. Knowing that a new gene is a GPCR makes it useful. Otherwise, one would have to conclude that if I were to discover

a novel pain reliever, that I would not be entitled to a patent because the utility applicable to that compound, which is to relieve pain, applies to a whole class of compounds, and that is clearly false.

Let me give you an example, both of the transition to what we call ER&D and the importance of this information. This involves the hunt for the Tangiers Disease gene, which was conducted by one of our collaborators, CV Therapeutics. The low HDL, which is what some of you may know as good cholesterol, is associated with a six-fold increase in a risk of coronary heart disease.

Tangiers Disease happens to be a rare disorder which manifests itself as extreme HDL deficiency. As a consequence of this deficiency, people with this particular gene have a five- to six-fold increase in coronary heart disease. They typically die in their 30s.

What our collaborator decided to do was to do the closest we could come to a whole genome scan, analyzing and comparing Tangiers Disease patients with those with normal genetic systems. So what you have here is a slide that shows those genes that are up-regulated or down-regulated in a statistically significant way when comparing normal patients to those with Tangiers Disease. That reduced the 58,000 genes to about 800 or so.

What they were then able to do was a little bit of data mining. It was known that this gene is located somewhere on Chromosome 19. So when they looked, they found that only one gene out of these up-regulated or down-regulated genes was on Chromosome 19. When they checked the structure of that gene, they discovered that it was a transporter gene.

So this discovery was given the American Heart Association Award of one of the top 10 discoveries in 1999. One of the things I want to emphasize is that this discovery was made over a course of about four weeks, and that, we think, is one of the benefits of genomic research. So this idea that somehow the fact that you can discover things by mining data devalues the invention somehow, we think is patently false. Obviously, the benefit is that it accelerates these discoveries.

We have a lot more examples, increasingly. And one of the things that is great is we often know what our collaborators are doing, but we often can't talk about it. But in the last few weeks, we have seen a number of announcements. We have a number of our pharmaceutical partners begin to publicly state that, using our information, they have been able to shorten the target validation step from 36 months to 18 months. As I indicated, we hope to shorten to zero within the next two to three years.

A number of pharmaceutical companies have reported that they are getting over 50 percent of their drug targets from our database. So by extension, it is resulting in roughly 50 percent more drugs under development, perhaps more. Last week, Johnson & Johnson announced a breakthrough in their research with regard to central nervous system diseases such as Alzheimer's and Attention Deficit Disorder, as a result of the use of our database.

So, frankly, with this kind of information, we find it sort of perplexing, and perhaps an only-in-Washington sort of experience that people can talk about whether these discoveries have real-world utility or are benefitting health care. Clearly, they are and will result in more drugs and diagnostics at lower costs.

Gene patents enable the discovery and broad dissemination of new genetic tests. This has been discussed at some length, so I won't belabor the point, but I will point out a couple of things. One is that, if we were not able to get gene patents, we would not be able to have the licensing program which I will describe in a moment, which actually broadens freedom to operate in research.

We think that gene patent licensing policies to benefit the public and to be efficient should meet the following criteria. They should encourage their ubiquity of diagnostic tests. The transaction cost should be low, meaning that it should be easy to get access to the intellectual property, and

the cost in terms of royalties should be reasonable.

We refer to our patent portfolio at Incyte as the IP Trust, and by that we mean that we are licensing our patents in a way that we think benefits both our shareholders, the research community, and the public. All of our gene-based inventions, whether they are know-how or patented, are licensed only non-exclusively for both research and diagnostic uses. We charge very low royalties, in the low single digits, to encourage the use.

One of the important points is that we have a provision in all of our agreements in which we ask that if any of our customers use our information to identify new genes and to patent those genes, they grant back freedom to operate to Incyte and any other Incyte customer who agrees to the same provision. This is very much like the open-source movement that some of you are aware of in the computer business.

The important point to note is that if we didn't have our own gene patent portfolio, we would not be in a position to make this request of everyone who is licensing our patents and our information from us. The result is that 18 of the world's 20 top pharmaceutical companies have licensed our database and they are already covered, not only under our own patents, but under the patents of everyone else who has agreed to this provision.
The next page illustrates this.

One of the things I have to point out is that this has not been a difficult sell in the private sector. In our experience to date, we have now over 30 private sector companies that have agreed to this provision, including many of the leading biotechnology companies. The only entities that have refused to agree to the grant-back freedom to operate and research have been a couple of universities, and as of last week, the NIH, in commenting on a draft agreement that would have given all of its researchers to our human gene database, indicated that they would not agree to this provision.

So to the extent that there is some assumption that the private sector in interested in using gene patents to inhibit research and the academic sector is devoted to the free sharing of this intellectual property, I would respectfully submit that that has not been our experience.

I will just quickly go through. This slide gives you an idea of some of the companies that have agreed to these provisions. They represent roughly 75 to 80 percent of the pharma-research spend. So what we have is a private sector system that actually makes it very efficient and easy to have access to this intellectual property, and as a result, we have a network which is increasingly including nonprofit and research organizations, The Huntsman [ph] Cancer Institute, Cambridge University in the United Kingdom, Stanford, and actually this week I believe we announced -- I hope I am not letting the cat out of the bag -- collaborations with Baylor and the Roy Castle Institute in London, which focuses on lung disease.

In conclusion, private sector genomics companies are making substantial contributions to a revolution in the ability to detect, prevent, and treat disease. Patents provide the critical incentives to the private investment necessary to enable this revolution. We agree that patent owners have a responsibility to exploit their patents in a way that benefits both their investors, who are enabling the research and development, and the public. We believe that we have come up with a licensing program that does that.

We understand and sympathize with concerns about the consequences of costs, and the fact that there may be segments of the population that may not be able to afford royalties on patents. We think that that should be addressed, not through the patent system.

The role of the patent system is not to make health care policy any more than it is to make industrial policy in any other sector. We think that addressing funding issues, in the way that Vice President Gore suggested last week in a speech at Emory where he talked about increased funding for genetic testing and for clinical trials, we think that those are appropriate ways to make

sure that these tests are available to those who need them in a way that does not do violence to the incentives to do the research and development that make these tests possible.

Thanks for your attention.

DR. McCABE: Thank you very much.

Dr. Palatucci?

DR. PALATUCCI: Thank you, Mr. Chairman. I apologize to the committee for not having distributed the materials earlier. I learned only when I got here, by speaking with Susanne, that we apparently had an e-mail melt-down at our office last week. So while I thought I had sent everything ahead of time, apparently I didn't.

So I apologize. I will get that to you as soon as possible. But thank you again, Mr. Chairman, and other members of the committee, for allowing me to present these comments.

Just a couple of words of background. Athena Diagnostics, Incorporated, as was mentioned, is a division of Elon Pharmaceuticals. We are clinical reference laboratory that provides testing services to physicians utilizing a wide range of analytic technologies.

Much of our business is derived from DNA-based testing services, so we welcome the opportunity to participate in this important debate. I would like to emphasize that while we respectfully disagree with some of the comments that have been made this morning, we recognize that these issues are emerging and they are generating important questions that require discussion. So we welcome the opportunity to work with this and other groups to address these questions and identify solutions as colleagues.

So, as we heard earlier today from a number of sources, the Patent Office and others, patents encourage risk and innovation. It is notable that virtually every significant technological advance that has had a fundamental impact on society has required substantial risk and innovation. At the core of the patent system is the desire to provide incentives for people to take those risks in order that society will benefit from those innovations.

From its beginnings, Athena has worked closely with universities and medical schools across the country to transform discoveries into widely available clinical diagnostic testing services that have provided benefit to thousands of physicians and patients.

In order for organizations like ours to continue to work with academic partners to identify, develop, and provide these services, it is critical to support the protections provided for by the United States patent laws. The ability to exclusively license these discoveries from these partners through the mechanisms provided for in the Bayh-Dole Act.

Without these protections, many of these discoveries would remain just that, discoveries with unrealized potential. They would have limited availability, physicians and patients would not be able to benefit from the latest advances in scientific and medical discoveries useful in the diagnosis of disease, particularly rare diseases, and patients would be left without a diagnosis, even more so than now.

We know, for example, in the field of neurology, that a third of the patients that are referred to neurologists never receive a diagnosis.

Now, why do I say that many of these tests would not be offered without the existence of patents and exclusive licensings, well, at the core of Athena's mission is a dedication to seeking out opportunities to advance the state of diagnostic service available to physicians, and to provide them, the physicians, with the widest possible array of testing services. We are very proud of our record, and currently offer some 80 tests for neurological diseases.

This array of testing services represents widely known neurogenetic diseases, Huntington's Disease, for example, but it also includes those that are very obscure and extremely rare conditions, such as oculopharyngial muscular dystrophy and Unvarich-Lindborg [ph] myoclonus epilepsy, which has an estimated incidence of one in 20,000 in the Finnish population.

Of course, for affected patients, the fact that one's condition is extremely rare is of little comfort if the technology exists to provide an accurate molecular diagnosis, but few practitioners are aware of its availability. There is an economic reality here. In order to provide this wide array of testing services, we need to ensure that there is a mix of tests, of services, that are requested by physicians in sufficient volumes that will help support those tests that are ordered infrequently.

Our physician clients repeatedly tell us that both types of tests are virtually equally important in their clinical practice and in the relevance to the practicing physician. Were we to devote resources to commercialize a non-patented discovery and then expend the considerable effort required to inform the physician community as to the availability of the testing service and establish its role in routine practice, it may well become of sufficient volume that large risk-averse laboratories would capitalize on our efforts and begin offering the tests.

We all know that it is much easier and cheaper to follow than it is to innovate. Therefore, with lower commercialization costs, we would yield market to these large laboratories that would pick off the most accessible, higher-volume tests, despite our having years and significant resources in developing the market.

In fact, the model is working quite well. Our many university licensors tell us that they are not in the business of, not equipped to, and not interested in commercializing discoveries made by their faculty. Our research collaborators, the people who make these discoveries, tell us that they are not in the business of, not interested, and not equipped to perform clinical testing. They are more interested in performing research.

The university licensing officials are quite pleased that we are interested in licensing these types of discoveries. As we heard this morning, MIT, who licenses a number of their technologies out, is happy when companies like Athena are interested in licensing these discoveries because the licenses directly contribute to the Bayh-Dole requirement to move government-funded discoveries as rapidly as possible into widespread use, and they provide a royalty stream back to the university.

Further, we contribute in a significant way to the missions of these institutions through licensing fees and royalty payments, to date, amounting to millions of dollars that support further research. We also contribute, by cooperating with academic researchers so that they can access our accumulated data set by exchanging unusual or interesting samples, of course, under appropriate patient confidentiality and other patient protection requirements, and by assisting academic researchers in their efforts to identify additional molecular correlates of disease.

So rather than increasing patient access to genetic testing of services, outlawing patents covering gene discoveries would have the opposite effect. The diagnostic test component of health care in the United States, the premiere system in the world would deteriorate into the kind of system that exists elsewhere. There would be a patchwork quilt of quality assurance and quality control. Only those in the know would have access to molecular testing. There would be no incentive to provide educational support, and fewer tests would move out of academia and into clinical practice.

In short, physicians and patients would be denied access to the benefits of the latest scientific and medical advances. Indeed, in combination with this committee's proposal that the FDA regulate the clinical reference industry and the significant economic resources and devotion of time required to obtain FDA clearance, very few diagnostic discoveries would ever be made available.

I would like to thank the committee for this opportunity to present our views on why patenting and

exclusive licensing on gene discoveries allows physicians and patients to have access to diagnostic technologies that they wouldn't otherwise have. Thank you.

DR. McCABE: Thank you very much.

We have about 10 minutes for questions before we break for lunch. So, are there questions, comments from the panel, or from the committee members? Pat Charache.

DR. CHARACHE: I am wondering how this group would suggest we address the issue that was raised about the array approach to diagnosis when some of the components of that array would be exclusively patented, and therefore have to have separate samples sent to various other locations.

DR. FRANK: I am not aware of a lot of examples of that. I think that clearly it is easier for one sample to be sent to one lab. It certainly does not prohibit doing a panel of tests. If part of that sample goes to another lab, the results can still be interpreted together, but I do think that labs are highly incentivized to pull all those things together. The labs that each have a component of that array would each benefit if they could share the ability to do the entire array.

So I am not sure if we are talking hypothetically at this point, or if this is a real problem with a specific panel.

DR. McCABE: Well, I think that one of the examples that has come to the fore has been the Canavan Disease gene, with, first of all, attempts at exclusive licensing, the fact that a number of labs have put together panels for a high-risk population, that this was considered by some to have been a problem.

DR. FRANK: Well, the original attempt at exclusive licensing certainly would have interfered with that, but of course that failed. I think it is another example of how things that don't make sense medically don't make sense commercially. My understanding is that there are labs that are offering this panel. Please correct me if I am wrong.

DR. BURKE: Tom, I just want to comment that I think those of us who send genetic tests related to cancer to various laboratories are well aware of the quality that Myriad Laboratories provides, and are very appreciate of that, but I would like to register a caveat about your comparison between BRCA1-2 testing and HNPCC testing.

I suggest, or would presume, based on my clinical experience, that the reason for the difference in utilization of tests has much more to do with a tremendous awareness and concern about breast cancer. I think a lot of data suggesting that that particular disease is much more in the public concern than colorectal cancer.

Certainly, I can say in our genetic counseling clinics, we see at least a four-fold excess of people seeking genetic testing for BRCA1-2 versus colorectal cancer.

DR. FRANK: I certainly appreciate that breast cancer is a highly visible cancer, but with Katie Couric's colon going on display, I think that is starting to change.

But I do think that there is a little bit of the chicken and the egg, namely that a lot of the public awareness of hereditary breast cancer has been driven by the widespread availability of a test for that condition.

Now, that doesn't mean that everybody should be tested who is aware of this, but the availability does drive the public's questions about that, and appropriately so.

DR. BURKE: We could have a long conversation about that. I think some of the public awareness has a downside to it. We certainly spend a fair amount of time in our counseling clinics explaining

to women why they are not candidates for BRCA1-2 testing.

Also, as I am sure you are aware, we get a substantial proportion of results back that are of indeterminate significance, I would say 20 to 25 percent of our results. Again, we appreciate tremendously Myriad's willingness to follow through on families and try and sort out what those tests mean, but I think we are dealing, perhaps, with a test where we may sometimes be doing more testing than we should.

DR. COLLINS: I would like to address this question of patenting of genes for therapeutic purposes, which I think there the argument is certainly a lot stronger in many people's minds that this sort of fits the standard model of what patents in other circumstances have been applied for, not to say that that argument is not also quite credible in many diagnostic situations.

The examples, Dr. Davis, you gave from Human Genome Sciences were focused specifically on those where you have a direct connection between that gene and using that, then, as a protein therapeutic.

I guess I would like to hear some discussion, maybe from you, and perhaps others as well, about other circumstances where the patent was filed based upon an in silico analysis suggesting that this might be a protein of a particular function, and then ultimately information came to light indicating that was the case, but not necessarily from your own endeavors, and, how does that play out. The obvious example is CCR-5.

So I guess I would like to hear from, perhaps, both you and Mr. Bendekgey about whether the issuance to Human Genome Sciences of a patent on CCR-5 is going to turn out, in the long run, to have been a good thing for the public. I suspect I know what your answer will be, but I would like to hear the logic behind it.

DR. DAVIS: Sure. I mean, I would be glad to address it.

First of all, let's clarify one thing about CCR-5, and this applies to any patent. If I discover a new chemical that has a use, I can get a patent on that chemical, and I can get a patent on that use. That use, in the long run may not turn out to be the most important use of that compound.

That doesn't make my patent invalid. It doesn't mean I shouldn't have gotten the patent in the first place. It does mean that somebody subsequently who discovers how to use that compound for that new use can get a patent on that use, but it doesn't call into question my original patent.

So the fact that you look at a gene, you find a medical function, you talk about how it can be used for
T-cell mediation, how it can be used in rheumatoid arthritis, and there are papers out there on CCR-5 showing the role it plays in that, it doesn't mean that a patent on a given gene is not valid. The fact that somebody, later on, discovers that same gene has a key role in AIDS isn't important.

What makes the access, what makes the ability to get that subsequent invention? One of them is that the sequence is out there.
Now, I am not saying that is the case in CCR-5, but it is clearly the case in other cases.

CCR-5 was filed on by numerous parties for a whole range of uses. All the initial parties thought it had important roles, none were involved in HIV. That was discovered later on. Having sequences out there, understanding how that plays a role in the body, whether it is done in silico, whether it is done in a laboratory, is a valuable public information.

And if we can't file patents, we are not going to tell the world until we have a product. We are going to keep it secret. We don't have a choice. I can't justify $450 million of private money to put all this in the public with no hope of recouping an economic reward for that.

MR. BENDEKGEY: I am not going to comment specifically about CCR-5, but I will make a couple of comments. One is that, it has never been necessary to know everything about an invention and all of its possible uses to be entitled to a patent. And as Dr. Davis said, someone who discovers a new use later, may be able to get a patent themselves on the new use.

Particularly for a company like Incyte, the characterization of a gene as belonging to a particular class has real-world value to our customers. More than 50 percent of the blockbuster drugs, the top drugs right now, target GPCRs. If I, as a pharmaceutical company, become aware of a new GPCR, then I am going to immediately want to test the drugs that I am developing, not only against the specific GPCR that I was working on, but against all known GPCRs, and that has real value.

If, you know, there were not patents available for that kind of a discovery, we would have two courses of action. One would be, we would have to turn ourselves into a drug company ourselves and would not be in a position to put our information in the hands of the people who are spending 80 percent of the pharmaceutical research dollars.

The alternative would be to rely on trade secret protection which would seriously inhibit the availability of that information and certainly would not put us in a position to put all of our information online and make it broadly available, as we are during the course of this year.

So we think that those categories of invention are very appropriate for the patent system and enable us to engage in the kind of business that we engage in, which puts our inventions in the hands of those who are most productively able to use them.

DR. McCABE: One brief follow-up, Francis, and then Reed will have the last word.

DR. COLLINS: I appreciate your response. I would just like to say for the record that I don't think either of you addressed the issue of the anticommons effect of all this, that, sure, one can see the potential benefits of having patent protection granted rather broadly for utilities that are perhaps lower on the scale than what the Patent Office is currently proposing to do, but the consequences of that, as outlined, I think, as has already been mentioned in the Heller and Eisenberg article, weren't really addressed in your response, in terms of what this might inhibit as far as other investigators from other places trying to follow up on those particular gene sequences to learn what their utilities might be in a different way.

DR. McCABE: Reed, I will let you have the last question. I would ask that the question and the responses be brief, please.

DR. TUCKSON: Lee sort of, maybe, got at it a little bit. I am trying to understand, in what way is your industry, from a business point of view, different from the pharmacologic manufacturers and device industries, such that, as we look at the concerns regarding patents, in what way, if any, are you different, or should be viewed different, from the way we would view the pharmaceutical industry in these same regards.

Lee, you started to get at some kind of a distinction, but I don't know if I quite understood it. Are you the same? Is your argument basically, we are no different than those other people, everything goes? Just like, if you have got all this history about it, you wouldn't do anything to Merck and the rest of these people that don't do it to us.

Is that your argument?

MR. BENDEKGEY: I guess our argument is that we are different in the nature of our business. We are an information business, and what we do is we invent things and we share that information, broadly, with as many people as can make productive use of it.

If we were to adopt a system in which the only people who could get patents were the people who ultimately developed drugs using the information, then what we would be doing is encouraging the vertical integration of the pharmaceutical industry in the way that I indicated, which we consider to be terribly inefficient. We think that a patent system that allows and values early-stage enabling technologies that stimulate further innovation is appropriate.

I guess my hesitation is that when you say we are no different, I think what we are saying is that the role of the patent system is not to make health care policy. So an approach in which we say certain kinds of inventions should not be patentable, or should be given different kinds of protection because we have a particular health care concern, or we have a particular concern about competitiveness in the computer industry, or whatever, that is not what the patent system should be doing. There are other regulatory and governmental ways of approaching those kinds of problems, is really what I am saying.

So in that respect, I would say the patent system should apply in a similar way to everyone.

DR. McCABE: Which is why I point out that we have asked all of the panelists to be here today. There was a concern expressed about us making policy regarding commerce. That has never been our intent, but to the extent that PTO policies do impact on health care, and we are advisory to the Secretary of Health and Human Services, I think it is very appropriate that we have these discussions.

Any other brief comments before we break?

MS. BEARDSLEY: I was just going to say exactly what you just said. I think that to say that the patent system is not for the purpose of affecting health care is, sort of, to avoid the issue, because the patent system is affecting health care.

MR. BENDEKGEY: I don't disagree with that. In fact, we think the patent system is having a beneficial impact on health care. What I am trying to say is, if there are some negative consequences of that, I would suggest that the way to approach them is not by changing the patent system. It is through other mechanisms, like funding mechanisms. And I am sorry if I wasn't clear on that point.

DR. McCABE: Thank you to all of the panelists this morning. We will take a one-hour break. We will resume at 1:00. All of the presenters, as well as the committee members, are invited to the Alcove Room for lunch.

And please, all of the panelists from this morning, I hope that you will come back between 1:00 and 2:00 for the roundtable discussion this afternoon. Thank you.

[Luncheon recess taken at 12:00 p.m.]

A F T E R N O O N S E S S I O N

[1:05 p.m.]

DR. McCABE: I want to thank you all for being here this morning and helping us to get the broad picture of this issue, but also for staying so that you could be part of the roundtable this afternoon. I know all of you have very busy lives and I appreciate the time that you've taken.

First of all, I'll ask if there are any questions from the committee, especially for the second panel who did not have a chance to answer questions before.

DR. BURKE: I would appreciate the panel commenting on the feasibility of developing some guidelines or standards around licensing. It seems to me a fairly strong argument has been made by many of you for keeping the patent system in place and for benefits of the patent system. But it seems to me that there is a sort of much less standardized approach toward licensing and we certainly have some story of harms from licensing.

It seems to me we've also heard some very enlightened views about the ways in which licensing might be used, including some of you from industry using what seemed to be enlightened licensing policies to promote further research, for example. So I would appreciate comment on the need for more standard setting in that area?

DR. WRIGHT CLAYTON: This is Ellen Wright Clayton. I will pick up this particular glove, knowing that others will do it as well, and say that we have certainly heard some arguments here that there need to be exclusive licensing provisions, and in fact that's the only way things will work. And I guess I would just counter that and say that there are in fact other sorts of intellectual property that exist in this country that are not subject to exclusive licensing. And so I think that we can actually appropriately think of other models.

For instance, copyright does not exist on exclusive licensing. Once you've got a copyright, anybody can use it, you just have to pay a licensing fee. And so I would suggest that you really can consider the possibility of making licensing relatively broadly available.

Particularly because part of your mandate is to ensure that whatever use is made of this information, whether in the delivery of genetic tests or in the delivery of products down the road, necessarily will have to meet certain quality requirements.

So I think that I certainly was impressed by Dr. Frank's argument about the high quality of service that's achieved by Myriad Genetics, which is certainly a very good thing, but I would say that exclusive licensing is not necessarily the only way to achieve that.

So I think that that is very much on the table, and I think it needs to be on the table, particularly as a way of ensuring access, which I think is not ensured in a monopolistic system.

DR. McCABE: Other comments from the panel?

DR. FRANK: As I am proud of repeating, I don't know anything about law. But I am certainly not free to take Stephen King's latest novel and go and reprint it and publish it and distribute it, regardless of what fee I would pay. So I am not sure that the copyright is an example of a non-exclusive license.

I think that the concerns of the committee are legitimate concerns in that patients want access to good quality tests. I think that the concern should focus on the goal and not on the process. So guidelines would be one way of establishing what it is that the committee would like to see, widespread access, unimpeded research, high quality. And we were talking about not having panels broken up rather then going right to the patent issues.

DR. McCABE: Thank you. Go ahead.

DR. PALATUCCI: Yes, I also thought that the question was more directed to establishing standardized guidelines. The only comment I would make is that, from experience and, I think, in working with quite a number of university technology transfer offices, after Bayh-Dole, there was developed a standard set of guidelines for lots of things like material transfer agreements and licensing agreements, and so forth.

And over time, I would say certainly in our experience, virtually no one adheres to those originally proposed guidelines anymore. And because there are many situations where it does require some creative and insightful approaches to how you are going to deal with the peculiarities of a certain disease gene and a certain license, and so forth, and those cannot possibly be anticipated in a standardized set of guidelines.

MR. LUDLAM: I think there is quite a difference between recommendations as part of the market, meaning people say, "We think this is a good idea, we think that's a good idea," whatever

commentary or standards. We have AHCPR that puts out practice guidelines for medical best practices in medicine, all of kinds of people that put out, you know, various proposals regarding the way the world ought to be.

I think that's quite different than a government's statement that it would intervene to change the market in a mandatory sort of way. That, I think, is no different than any other price controls or expropriation, or regulation of private property. I mean we could make arguments, I suppose, that we ought to have regulation of university tuition fees.

We could make arguments that we ought to have regulation of doctor's fees in the private sector, not the Medicare but in the private pay. We can propose price controls in any context. We could talk about tenure as to whether that's a restriction on competition.

I think in every context we can propose those kinds of restrictions and regulations that are mandatory where the government can say "This is the way it's going to be, irrespective of what the market otherwise would go to." I think you have significant costs that can be imposed, and I think that's the question. We have a surplus of good science right. And we're going to have a fantastic surplus of good science, as we have more of this genomics information come forward.

And in order to find enough companies with enough industrial capacity to take those products into real things at the bedside for patients, you are going to have to give them tremendous incentives, tremendous ability to form capital. And that's where you get into exclusive licenses.

51percent in the autumn survey of the university licenses were exclusive. 10 percent of the NIH licenses were exclusive. I think in those cases it was for the reason that Tom said that is the way to really get that company or that institution to throw everything they have at it as their principal lead product, as their principal basis for their company, to develop it in every possible elaboration. And you give them that incentive with exclusive licenses.

DR. McCABE: Other comments from the panel?

DR. MERZ: I am not sure it's exactly responsive to the question originally, but it's responsive to the last comment. One thing about the breast cancer standard and Myriad's kind of imposing a standard of care on the practice of medicine, you have basically said that sequencing is the way that medicine shall be practiced, thank you very much.

And it's not because of your medical competence, it's not because of your technical competence, good as it is, it is because you have a patent. I don't believe that I am buying medicine by patent.

DR.WRIGHT CLAYTON: My final comment about this, again in response to Chuck's comment in response to Chuck's comment, is that I think it is important to recognize that patent rights exist because the government confers them. And it is not as if we are taking away or modifying something that came down from God, but because we as a government decide that there is something that is a different policy from what ought to exist otherwise.

So, you know, when I say, you know, all these property rights exist only because we as a polity say they exist, that is the Alpha and the Omega of the answer. So it is not as if we are taking away, that we have somehow disturbed the natural order by talking about licensing.

DR. McCABE: Mike Watson, you have a comment?

DR. WATSON: Yes. I think one of the problems we run into is the genomics field is enormous, and we're actually probably talking about at least three different kinds of industries within genomics. The ownership of information, I think, is a relatively new concept that's come with both the Internet and with biotechnology and it brings issues in just the ownership of information.

I think everybody in laboratories across the country would welcome the development of kits, and

devices, and products that we can buy that would make our testing, our services, better, cheaper, more accurate, whatever.

And then we also very much value the protection that a patent affords and incents the development of therapeutics. So, you know, I think to some extent it's separating those three things so that we don't compromise the current service industry in order to protect.

And that's really the difference between the copyright and the patent, I think, is that the patent allows one to exclude and the copyright doesn't. And I think that's really where the issue comes in, excluding one's ability to provide services and compete at that level.

DR. McCABE: Any other comments from the panel?

DR. TSIPIS: This is Judith Tsipis. I personally have a moral dilemma about the concept of patenting human genes. But as a consumer, as a biologist, I also understand that in order to discover new genes and in order to carry out a lot of research, patents may be necessary.

It's really not the patent, per se, that has done damage in our particular case for Canavan disease, it's the way the patent was enforced. And from a consumer perspective, I believe that exclusive licensing is not in the consumer's best interest.

There are ways of regulating, perhaps, how patents are enforced that would allow the industry to proceed, or allow more research to occur, and still provide the public with adequate access, both physically, financially, educationally, as well as to research.

MR. LUDLAM: Can I just make a comment on --

DR. McCABE: Yes. I am sorry, I am just getting your names so that we can have it for the transcript and so that Pat knows who is speaking. So this is Chuck Ludlam.

MR. LUDLAM: I think what we have, and we don't represent Miami Children's Hospital, so I know some of the facts in the case but certainly not all, it strikes me that what happened here was a market situation and you were part of the market. And the market situation was that the patent holder had certain ideas about how they would develop this patent, and how they would license it, and everything else. And you had other ideas. And it was quite a market.

And they had an idea that the best way to get the most tests done was through an exclusive license with a market leader. And they decided you didn't like it. They decided it didn't work. It didn't happen. There are now no caps and a non-exclusive license.

Now, that may not have happened quite as fast as anybody would like it to happen. There may have been a good deal of friction, and unpleasantness, and everything else, all the way around until that result occurred. That was the market. Markets do not know in advance, necessarily, what is the right price. They do not know what is the right license term.

Markets work on those problems and they nosh on those problems, and you are a vital force in the development of that product. Now it turns out that, I would think, because of the publicity about this market situation regarding this particular test, that other companies developing other tests will have learned something from this situation. And you would hope that would be the case.

I can only say that I represent a lot of companies with a lot of diverse viewpoints, I would think they are listening. We're here listening. And I would think that that is the way in which these kinds of conflicts are resolved without heavy-handed, counterproductive, government intervention.

DR. McCABE: Dr. Tsipis?

DR. TSIPIS: Thank you. I agree that the situation is not as bad today with regard to Canavan

testing as it was initially. And part of is because a small group of us were very outspoken.

Now, I don't think that public interest should require that necessarily everyone should have an advocate out there fighting each individual thing. I would hope that forcing a gene patent does not require that kind of advocacy, time, energy. And it has taken a long period of time.
So, yes, people may have learned.

People's memory tends to be quite short so I do not see that what we have, or what has happened with the Canavan disease patent is going to change things in general. I think it was fortuitous. We played a small role, I think the clinical lab directors played another role. And I don't see that, because it's ending up less bad than it was originally, is reason to say, "let the market be in charge."

DR. McCABE: Actually, we're going to move on.

DR. WRIGHT CLAYTON: Can I just make one follow-up comment to this? This is Ellen Clayton. The one thing that I wanted to say about this is that I don't think that we should say that the Canavan thing is a success either.
And, in fact, I would say that a good society would say that there ought to be a mechanism by which people like Dr. Tsipis are routinely heard, rather than have to fight the hand of the free market. A good society allows for public input, and allows something else to go other than just the free action of the market.

DR. McCABE: Dr. Davis, you are the only member of the panel who hasn't spoken, so I'll give you the last comment on this issue. And then we'll address a question from Pat Barr.

DR. DAVIS: Great, thank you. I think we have to be careful when we look at the Canavan situation. There is an adage in law that hard cases make bad law. We shouldn't take a single incident and use that as a basis for some sort of broad licensing policy or compulsory licensing program.

What you look at is you've got to look at how the market has operated over the last few years, the last 100 years, the last 200 years. And when there is a market that makes sense for a non-exclusive license, people have given it. When the market's made sense for exclusive licenses, they've given it. I think you have to take a broader policy look and not focus on an individual case.

DR. McCABE: I remind you that some of us come from a medical background which has been accused of not policing itself and, therefore, others coming in to police. And frequently in the medicine, the examples were these hard examples. So while that may be an adage in law, society tends to look at these things differently. And, unfortunately, hard examples like this do tend to generalize policy.

DR. BURKE: Just a quick follow up to your comment and some comments of the panel. I think it's also a reality of medical practice that in fact free market does not dictate what is charged for services or issues that influence access of services. The government has been very involved via Medicare, and that's a reality of health care.

MS. BARR: I want to say that I have an instinctive reaction as a consumer about the notion of patenting gene sequences. But I want to play devil's advocate in two ways, specifically, with Ellen Wright Clayton.

You mentioned the therapeutic model, or someone recently mentioned the therapeutic model, as being appropriate where there should be a patent. And, yet, in that model people participate in clinical trials in which they are giving of themselves, it's not their DNA but it is sometimes their lives, in order for the public benefit. And there has been no claim that they or their families should have some right to profits from the sale of the medicine.

And, on the other hand, it would seem to me that if as a society we do not address the needs of the consumers in some way with some logical argument, you are going to get groups like the National Tay-Sachs and Lyme Diseases Association getting together, getting themselves patent lawyers and making agreements with researchers before the research can get done.

But there are going to be a whole spectrum of diseases where organizing such groups is going to be very difficult or where researchers are going to have access to other partners, unknowing partners, who will not make those deals. But how do we distinguish? We have government subsidy of research all the time. That research does go, does develop into medicine, often, and somebody makes a profit.

DR. WRIGHT CLAYTON: Well, Pat, I think that's a great question. And I think one can certainly make a colorable claim that because we devote so much of our money and so much of ourselves as subjects to research that in some senses that we really do expect at some level to reap the benefits of that. So I think your question is a really telling one.

And it maybe goes to some of the questions that some of the other commentators have made, that that in fact would underlie a broader social responsibility to provide fuller access to the armamentarium of medicine that is currently available.

I was struck by a comment earlier today about how all insurance companies pay for BRCA-1 testing. I am a pediatrician and I am used to working in a system where all of the patients I am taking care of have their health care paid for by Tennessee's equivalent of Medicaid. And I know full well that whatever it is that I get is not what I can get from my patients.

So I would say that at some level there has to be a recognition of the public trust and of the public investment in this. And I think for that reason it's utterly appropriate for a society to step in and say, "This isn't a free market. We know it isn't a free market. It's completely different from the free market." And we ought to be able to step in and say it.

So I guess what I would do is I would take your analogy as an opening wedge to say, you know, this is yet another argument, why some kind of social involvement is actually entirely appropriate, rather than less appropriate.

DR. LEWIS: One of things that I learned in my economics course was when it is appropriate for there to be government intervention in our capitalist society, and one of them is in the area of market imperfections. And I would argue that our health care has a lot of market imperfections, and the major one of which is the fact that there is not perfect information out there.

And that there is a real inequity and imbalance of power in who has the information and who is making the decisions. So I would say that perhaps this is an appropriate time for some government intervention, simply because it's not a level playing field.

And what I really worry about is access. And in terms of what Ellen was saying previously about the fact that somebody alluded to the fact that most insurance companies will pay for genetic testing, I also notice over 40 million people in this country who either have no insurance or are under insured.

And I believe that we have a responsibility to make sure that this doesn't become a two-class system, that those who can afford to pay get the highest level of testing from the highest quality labs. And that those who can't afford to pay are either denied testing or they are not necessarily having the same level of access.

So I really believe that we're looking at a system where there are significant market imperfections. And I am wondering, for example, if those of you who are patenting, or doing that kind of work, are saying that those who can't afford to pay will get care regardless of their ability.

And I don't have any problems with people recouping their R and D money, because I think that's important. But I also think there needs to be some safeguards in place to ensure that we level the playing field just a little bit.

MR. LUDLAM: In terms of access, I think there are two entirely different access issues. There is access to currently available products. Absolutely an important issue. Lots of uninsured, lots of inadequate insurance. The TennCare system, I think is one of the most restrictive in terms of quality of care in terms of Medicaid. So I think that there are huge issues on access to what's on the shelf.

Most diseases have no effective treatment. I mean, saying that we have insulin for diabetes is not like saying we have something that works for diabetes. Twenty or thirty of my companies have profits and products. But they have thousands of products that might eventually face the question of how will people get access to them, if they are developed.

We have the entire genomics possibilities now. A total revolution in medicine. Everything we know now will look like, you know, dentistry with pliers. And the question is whether or not anybody will ever have access to it, or how many extras tens of years they will have to wait. So I think we need to focus on both issues. And if we focus just on distribution of current products at the expense of research, we have made a tragically misguided mistake.

DR. FRANK: I do want to make the point that we, as do many other diagnostic labs, have an indigent assistance program, so testing is available for patients who do not have insurance and don't have the funds for testing. Having said that, it's hard for me to see the difference between an argument saying that we should use law to redistribute diagnostic services versus using the law to redistribute pharmaceutical services and pharmaceutical drugs.

Clearly, there is a problem with over all, in this society, access to health care. But I am not sure that addressing exclusive licenses, for diagnostic genetic tests, as a component is going to address the overall concerns that were raised.

DR. LEWIS: I couldn't agree with you more. And I mean I think that this is just one area. The issue is that this is the area of the problem where we're dealing with it right now and we have a chance to make a difference. And I am not saying that you are wrong.

I mean, if I had my druthers, I would call it "health" care rather than "medical" care. And I am not sure we've got a health care system right now. But this is the area in which we're having the opportunity to make an impact and you've got to start somewhere.

DR. COLLINS: I should start my remarks by a disclosure, and that is that I am a co-inventor on a gene patent for cystic fibrosis, it's been talked about already today, and two or three other similar patents.

I think I would like to come back to the licensing issue, which I agree is perhaps the crux of the problem that seems most troublesome right now in the genetics arena.

I don't mean to speak for the rest of the committee, but I think the general sense from today's discussion, for myself, has been that in terms of patent applications for genes that are directly tied to a therapeutic product, the model fits reasonably well with the long tradition of using the patent system for small molecule pharmaceuticals but becomes somewhat more problematic when the amount of the information you have about that gene drops below a certain level and makes you wonder, am I really on the pathway to a therapeutic here, or am I hoping to be?

That, of course, is something which the Patent Office has been wrestling with over the last few months in terms of their revised utility guidelines. And I think they deserve a lot of credit for having taken that on.

But when it comes to the diagnostic arena, which is clearly the one that we've spent a fair amount of time on, I have to say the problem really does not seem solvable at the patent level. It seems pretty clear that a gene which is directly connected with a disease and, therefore, directly offers the opportunity of turning into a diagnostic test is going to meet the current standards of utility, by any definition I know of.

To sort of blame the Patent Office for allowing the patent in the first place isn't probably going to fly, unless there is sort of a major overhaul of the system. And I think the consequences of that would have to be really carefully thought about because they might actually be quite negative.

The problem often then comes down to, as Wylie points out and as some of you have addressed already, the licensing issue, particularly in circumstances were we're talking about diagnostics. And, I have to say, oftentimes the problem arises not in the private sector, it's in the university tech transfer offices, who are faced with what may be a fairly unfamiliar situation for many of them, of an investigator who has happened across a disease gene that sounds pretty cool, and that's being written about in the press that day, sets about to try to recoup some of the investment in this, oftentimes, I think, with only a limited evaluation of the downstream consequences.

It's almost as if we need more of an environmental impact assessment when that decision is being made about exclusive versus non-exclusive licensing. And yet the investigator who has made the discovery often is in a very limited position in terms of understanding the consequences of all this and oftentimes are basically hands off, like, "I don't want to know about this." That was my attitude certainly in those circumstances. And there is nobody sort of looking at this circumstance.

So I guess my question is, to come down to specifics, do we have remedies in this situation, either in the university situation or in the private sector situation that are within the existing law? I think the answer is probably not.

But, if not, are there other kinds of remedies that could be applied to the licensing decision making that would make it more responsive to the public good than what we currently have and perhaps avoid the Canavan kind of situation, which is not just one of a kind?

It happens to be a particularly dramatic one but one which I fear, without some change in the system, we will repeat over and over.

DR. MERZ: Just on that note, ever since the federal government started funding research in the 1930s, the '20s and '30s, it was a tension there about, you know, a) should we be patenting federally funded research inventions? And then, if we do patent, how do we make those things useful to the community? How do we make sure that the public, who has paid for the research, gets the benefit of those inventions?

And there was, I think it was the Attorney General Commission, in the late '30s, and maybe the AG did it in the '40s. There was a panel in the '30s that addressed tissue, there was a panel in the '40s that addressed the issue, there was a panel during Kennedy's administration that addressed the issue. And then there was a panel during Nixon's administration that addressed the issue.

And all of them concluded the same exact thing, that was on the MIT Technology Transfer Principles, Principle 3, on the bullet on there. It was that if something is ready for commercial use, if it is basically an invention that can be taken out and given to the public and anybody can exercise it, then it should not be exclusively licensed.

The exclusive licensing should be not the default. The exclusive licensing should be reserved for situations where you need to get someone to dedicate further development money to bring something to market. All right.

And the problem with the diagnostics is that these things are essentially -- and we can argue

about this -- but I believe that the diagnostics and my evidence on HFE shows that as soon as the papers are published, the clinicians can adopt the tests and implement them, and start using them clinically. Other researchers skilled in the art can actually start using those, from the day go. That doesn't necessarily mean that they know how to go the therapeutic route, so the therapeutics should maybe be treated differently. But these disease genes, for diagnostic purposes, are ready for prime time and there is no reason that they can't be made available broadly.

DR. COLLINS: But there is no way to enforce it.

DR. MERZ: Well, you could do it through NIH. NIH, I understand, has a licensing policy that looks like that. I am not sure that they enforce it. I know that they didn't enforce it in some cases.

DR. COLLINS: So Bayh-Dole would prevent NIH taking that kind of action. Obviously, the decision making about patent application and licensing is ceded to the grantee institution, unless you declare exceptional circumstances.

DR. MERZ: If I may? I mean, just working through autumn, and working through the tech transfer offices, and all, I mean, they I think understand this. NIH could come out with a very strong policy on why they should kind of follow this licensing paradigm and kind of impose it. And I do think that because Bayh-Dole didn't do this, I think it was a shortcoming of that law. That it could have said, you know, "government is funding this research" and kind of impose that model on it, but didn't.

MR. LUDLAM: Just three comments. We think basically that the Bayh-Dole Act is as close to the tablet from the mountain as you can get, is one of the most brilliantly conceived statutes ever enacted. And we defend it all the time against people who would want to modify it.

Now, NIH has come out both for the intramural program and the extramural program with research tool guidelines which include genes. They include everything except compositions of matter, basically. And they are, I would say, definitely not pro-patent, definitely not pro-exclusive license, and definitely not in favor of resale agreements.

Not unalterably and not in every case, but the leaning is very, very strong against patents, exclusive licensing, and resale agreements. And they will just go into effect and we'll see what they mean in this context and any other context. And whether or not that facilitates collaboration with the private sector, and utilization, and commercialization of research, or it doesn't, some people are skeptical and some people think it will work great.

In terms of royalties, there is no doubt in the world that the industry expects to pay royalties to any federally-funded institution in a technology transfer context. We expect to pay it if it's company to company, we expect to pay to a university. Now, if the university or the government set up commercially unreasonable terms that are not comparable to the terms if it was a license between companies, then likely in that market, the technology market, the company would go somewhere else.
There is plenty of other science to work on, and they would say, if those are your terms and if they are too complicated, or too bureaucratic, or too expensive, or whatever they are, they don't have to do these deals. They can go to someone else.

So I think that you have to make sure that whatever the terms are, that the government sets for access to the technology that it funds, be such that they will promote development, which is what the Bayh-Dole Act is all about.

DR. FRANK: Jon made a comment that genetic tests are doable right out of the box as soon as the paper is published, that the only thing that keeps the labs from introducing them is exclusive licensing. That's actually not true for a substantial proportion of the genetic tests that we're going to be seeing in the future.

I would like to make the distinction between tests for specific mutations that are basically yes-no

tests versus tests that require a much more complex kind of analysis, of the kind I illustrated, that requires you to do a complete sequence of the gene.

In our experience, academic labs do not do as good a job of that as we do, frankly, because they have to do so many other things.

And the investment required to do that sort of a test very accurately is prohibitive for most academic labs.

So to require licensing of a lab -- and I'll pick on my friend Chris here. Let's just take a straw man and say that Athena wants to do BRCA-1 and 2 sequencing. And they are not going to use sequence analysis, they are going to use SSCP -- this is obviously a farcical example -- and we are required by law to give them a license to do this, I don't think that that does benefit the public.

Now you can respond to me, Chris.

DR. PALATUCCI: Actually, I will make several comments. But I would also echo yours with respect to Jon to your comments. As a specific example, I would also add that there are many tests currently available, many which we currently carry out, that are far from ready, sort of once the paper is published.

A specific example is when we launched the first test for Charcot-Marie tooth disease. That was a test that required the use of pulse field, which we were told at that time no one in their right mind would do that, no one would set it up commercially, it can't be done. We are now some six years later and we are quite a substantial provider of Charcot-Marie tooth disease testing.

And it's only now, that other people are interested in providing that testing, that we have demonstrated that it has utility in medical practice.

And, in fact, when we were setting that test up, the institution and the inventors were clear that they wanted a single laboratory to handle the testing precisely for that reason, because there is an extremely complex test, technologically, and they wanted to have access to monitor quality assurance and quality control issues. And to date, we work very closely with that group to monitor those kinds of issues.

We've supported a world congress on Charcot-Marie tooth disease. We do a lot of work towards that end, towards ensuring that the tests are carried out accurately, and that improvements in the technology are incorporated into providing that test.

I would also like to come back to, Francis, to your original question which was, and I agree with you, the issue is not the patents and I think we've heard that over and over again today. The issue is not patent law, per se. The issue is how do you license these things and what's appropriate.

And I think there are ways to address those issues. As I said, I mentioned in the intro, we've got something like 80 different tests. Quite a large number of them are licensed from universities. And we have a very wide range of different licensing strategies, depending on the peculiarities of a given disease, a given technology, and so forth. And I think those things can be addressed.

And I agree with you that that is where those issues should be discussed, but not at the level of recommending that gene patents should be somehow barred or outlawed.

DR. McCABE: Mike Watson. And then we're going to -- do you have a quick follow-up, Francis?

DR. COLLINS: Yes.

DR. McCABE: Okay.

DR. WATSON: It's a follow-up to a comment that Tom Frank made. I take your point that you shouldn't be obligated to license another laboratory to do a test in an inferior way to the way you are doing it. But you've got to turn it the other way around.

If another laboratory comes along that has a better way and -- actually maybe, you know, direct sequencing isn't going to be the answer for the next 15 years, something better will come along which might be a heck of a lot cheaper -- and if another laboratory has that technology up and going, it might be good for the public if they had a chance to do this kind of test. So one has to consider all the various outcomes here, when asking the question whether an exclusive license in this instance is good for the public or not.

DR. McCABE: Mike Watson, I am going to give you the last comment on this question. And then we're going to move on to a new question.

DR. WATSON: Francis actually just said a good half to three quarters of what I would have said, which is really, though, that in this area we don't have the standards yet by which the medical practice is established. And that's the part that most frightens me in an exclusive, monopolistic approach to the delivery of service, is that with that monopoly, one is essentially the repository of how this country is going to practice medicine for that gene for whatever period of time because there is no competition and because they can exclude others from participation.

DR. TUCKSON: Two quick questions. One, to Judith. As a result of your conversation and debate with Chuck, our charge here continues to be as a committee to explore what is it about genetics and testing that either does or does not require some new way of looking at these issues.

When Chuck described this free market sense of your scenario and how it came out, I wonder, based on your earlier comments, if what they had was a molecule that was then turned into a product to which all this mish mash occurred? That's one thing. This was your biology, this was your humanity. Is that in any way part of the frustration of your community or were those not part of this issue here? Because that's what I am trying to understand, the difference between cold-blooded, inert, molecule versus you.

DR. TSIPIS: An excellent question. It is hard to separate. Part of it is certainly the emotional sense that this was my DNA, my son's DNA, other affected children's DNA, there is no question about it. And that's probably why at a more moral kind of level I personally do not accept the concept of patenting human disease-causing genes.

On the other hand, that was not what this issue was really about. I mean the issue was really about here was a test that had been developed. We wanted it only for the public good, we did not piece of the money coming out. This was for the public good, to help other families so that they might prevent the birth of children with Canavan, or deal with the information, however they chose.

And the patent and the enforcement of the patent, which is really what we responded to because we didn't know about the patent, was that it shut down the opportunities for widespread carrier testing, for widespread use of this information to help other families. And that was the real thing.

DR. TUCKSON: Thank you so much. The second question, maybe you can handle quickly and I think you just sort of alluded to it a little bit. Chuck, again, you make the point brilliantly that where we are now is with the genomic revolution will make dentistry, it's analogous to where we are now in terms of practicing dentistry with pliers.

And that scares the hell out of me.

Because what I need to be assured of, or can you assure me, that as a physician that what it seems is as if it's analogous to the land rush, when this country was first born into the West. Those that can rush and get there immediately stake out their territory. They then control, or to

a significant degree, can control all the other subdivisions of discovery, of "This is my creek. No, no, this ain't your creek because this is on Mr. Gilmore's property."

And so what I am trying to get at here is that there is a potential here for a few who get there quick to have their stakes, not only stake out enormous amounts of territory, but territory that will theoretically expand the more that smart researchers discover more things related to their stake.

So at the end of the day, a few people are going to control all the new anesthesia, all the new pliers, all the new techniques. Why do I not need to be worried about that?

MR. LUDLAM: We need hundreds and hundreds and hundreds of billions of dollars invested in genomics research. That is because the potential is so phenomenal. We need something like happened to the Internet market, in terms of the flood of capital. That is what we need to bring this technology as quickly as possible into real things, tests, you know, therapeutics and everything else.

We cannot wait for the government to do all that research. We have got to mobilize the private sector. And in order to get there, we need a land rush. We need people who can go out there and say, "You can make a buck. You should not invest in the Internet, you should invest in biotech.

"Yes, it's 10 to 14 years, yes, it's the FDA. But don't do dot com because there is a limited amount of capital and we have to divert it in this area."

That is the kind of climate that we have to have. People will say, "This is really, really, really exciting and worth it." Because investors have a wallet, they do not have a heart.

MS. BARR: Can I ask a naive question, Ed?

DR. McCABE: Yes, please, Pat.

MS. BARR: What I am trying to distinguish here is that it seems to me that there is a difference between identifying a disease-related gene and processing a test. And it would seem to me that the gene sequence ought not to be patentable, even though it's related to a gene and someone figured that out, but the application of a particular kind of test for that gene ought to be.

So that if another group of researchers discover another way to test for that sequence that is more effective, they can do it in and apply for their own patent. And it would seem to me that the system where we're patenting the sequence really stifles that kind of competition. And it would not stifle biotech development, if the sequences were out and folks were really looking at the best technology to get the best test.

DR. McCABE: Chris Palatucci, do you want to respond?

DR. PALATUCCI: Yes. Pat, if I understand your comment, I would say that that is precisely the point. That one thing that a patent does, if you have a patented technology, it encourages people to find a way around your patent so that they can practice that same -- so they can get the same result using a different methodology. And you are right, it may in fact be patentable, the new method. And that can only encourage research.

DR. MERZ: Can I respond to that?

DR. McCABE: Yes, Jon.

DR. MERZ: Jon Merz. The problem with these inventions and the diagnostic claims to these particular types of things are that they are extremely broad. They claim all methods of diagnosis of Charcot-Marie tooth 1, type 1-A, by any method that you choose, whether known or unknown. So if somebody were to later develop something, the next thing to PCR, that you could also use

to diagnose TMT 1-A, you couldn't exercise that new method without a license.

DR. McCABE: Chris Palatucci, do you want to respond?

DR. PALATUCCI: Yes. Patents, and I think we heard from the Patent Office, the claims in a patent have to be supported by what's in the specification. You have to have shown that you have the method and the tools required to perform that type of testing. They don't cover all possible embodiments that might be discovered in the future, they patent and claim what is currently known. And if somebody finds a new method that is clearly patentable, there is no question.

DR. McCABE: Mary Davidson? Or was there another comment on that, Chuck?

MR. LUDLAM: A subject matter that Judith brought up in her presentation earlier and was alluded to here, on the whole question of altruistic voluntary donation of tissue samples and the question of exploitation, and the whole series of questions around that subject matter.

I've heard a lot about this in the Third World context, because we hear about it in terms of agriculture, commodities, and whatever else. And I was a Peace Corps volunteer who lived with an aboriginal tribal group that had no written language and was heavily exploited. I have a lot of personal interest in this subject matter.

Obviously, any group, let's say a small disease group of 20 people, or a small group, that band together and say, "We're going to organize ourself. We're going to give you all tissue samples, get all the medical histories together. We're going to make it easier for academia, we're going to provide some funding, you know, everything you want."

And they can say, "Here are terms for the deal. You want to go into this, you are in academic research or a company, here's the deal, no patents, or non-exclusive," or whatever you want to say, they can obviously do that. They might not find a buyer, but they can obviously do that.

And I think that tradition in our country is that people believe that the ultimate benefit is to get a therapeutic that will help everybody in that category, and that that is the pay off. That there isn't any intermediate pay off. That that is the pay off. So people, I think, in our society don't say, "I have a property right in my tissues, I want royalties," or anything else.

And I think it would be destructive, not illegal but destructive, if a trend developed where groups tried to set terms like that for access to tissue samples. They could do it. I think it would be destructive.

DR. McCABE: What about, you've touched on a topic that we've been discussing and will be discussing more in the future, probably, and that's the orphan diseases or the orphan tests? And in terms of a profit-driven society, an entrepreneurial society, how do we assure that those with orphan diseases who require orphan tests will not be relegated to a different category within our society? How will they have access?

MR. LUDLAM: Well, access in terms of research. Let's me start about the research side not the access in terms of end product. We are very much involved in the orphan tax credit and the orphan drug exclusivity as incentives for research on orphan diseases. In fact, we were the ones that got the orphan drug tax credit made permanent.

And we have many, many times defended the orphan drug exclusivity, which is not patents per se, but an exclusivity of the FDA. We're now working on the question of incentives for research on Third World diseases in terms of vaccine research. We work on these questions all the time, and they are very, very important questions.

And we're happy to work with you both on the research side but also, obviously, on the delivery side I think is the more continuous with the other delivery questions in terms of access. But on the

research side, it's a huge problem.

DR. WATSON: I think there is an additional issue beyond just the rare diseases. It's one we mentioned yesterday which is the common disease with the rare mutation. And as we saw in cystic fibrosis, over 850 mutations now. I have no doubt that there is many ways of asking those "yes-no" questions technologically about mutations of which we have current knowledge of pathology.

But I am very much concerned as we move to that next level of genome scanning, for instance, that those things become restricted. That there is no assurances in the patent system that anybody who has the exclusive right to provide a test will actually be taking those additional steps and to look for those unknown mutations.

The much more expensive, much more complex types of testing done, which are really the medical genetics procedures of now, and I think are there forever. I mean, there are rare and private changes in genomes that have to be interpreted in a medical way, and I think that's very different than the yes-no question that one might ask.

DR. PALATUCCI: Yes. I would just respond, Dr. McCabe, both to your question and, Dr. Watson, to yours. First of all, let me address yours. I think you can argue very easily that virtually all of the tests offered by Athena are what would be in the drug realm well below the bar 4 orphan drug status, in terms of incidence and prevalence.

I think what encourages -- and this is precisely at the core of the debate and what I've argued and what I've tried to present this morning was, without the assurance of some kind of protection, there would be no test for most of those diseases.

I pointed out Odveg-Quinborg Disease [ph] is one in 20,000 incidents. Some colleagues of mine have questioned what was in my mind when I thought of recommending that we offer that test. And I am sure my colleagues over here might be thinking the same thing. But we consider that as an important part of the array of tests that we offer.

And without the incentive that's offered by an exclusive licensing arrangement under a patented technology, there is no chance that anyone, any company would take the risk and invest the resources to develop that test. And, I am sorry, I've forgotten what I was going to say.

MR. LUDLAM: Could I add three sentences to that?

DR. McCABE: Sure.

MR. LUDLAM: The first research to go will be orphan diseases, if these incentives are cut back. The first to go. We already have a terrible problem, especially with the large companies devoting themselves to these mammoth markets and nothing else.

The biotech industry is the industry that has done all the research on orphan diseases. We are the industry that has done the collaborations with NIH. It is not large pharmaceutical industry in either case, with rare exceptions. The first research to go.

And then the last point is, we're now going to get to the point where we have diseases by the interaction of four or five genes. And talk about the complexity of the research, and the amount of investment that has to go in, and the complexity of actually running the tests, it is absolutely staggering.

The simple, you know, single disease genes, I mean I am sure there are plenty more to discover but there are thousands and thousands of diseases that will be more than one gene, maybe 40 genes, or whatever. Think about the incentives we need to provide, the capital to work that through.

MS. DAVIDSON: Yes. First of all, I would like to make the observation that this has really been tremendously important and wonderful open discussion, and it really needs to be the first step in bringing all of the interests of the community together. And I think these are issues that hit all of us, because ultimately when we go home, and we are all consumers and we all have families, we all know people with rare diseases and with common diseases.

And what I wanted to do was to, this is really more of a comment, is to try to link this conversation to the one yesterday about human protections and research. And I've been called certainly overly naive and optimistic many times in my life, but I think this is really an opportunity for us to begin to think differently about the whole research process, and about research partners, and about, really, the opportunity to think about collaboration in the research process from start to finish.

I want to commend the Canavan Foundation. I think what you did was really ground-breaking work that probably no other group is going to have to do because they've all learned from it. You know, particularly because you have publicized what you've gone through.

And we're already seeing a sea change, really, in the consumer community because groups have gotten very crafty and very wise. And, Chuck, just as a segueway to your remarks, we've seen definitely, and you heard yesterday from two groups, that research is being processed in a very different way. And I think that is working within the current patent and licensing system.

But it does give us an opportunity to think about research from start to finish in a different way, to think about human protections, to think about really ensuring the participant pool, because we're talking about only the first mini-stuff in terms of research. There is lots of research that has to happen.

One of our concerns, sitting at the alliance, is that we not wear out populations. And this is exactly the kind of conflict intention that will wear out disease-specific communities. So this is, as I said, really just a comment and an observation.

And I hope that this kind of dialogue can continue to happen, and that we can think about this, not only in terms of patenting and licensing and the legal structure, but really about bringing the interests of the research community together in the most productive way possible from the start, and there is never any finish, but along the whole process.

DR. McCABE: Before the responses to Mary's comment, I am going to ask Dr. Haga to circulate in the audience and see if there is anyone who wishes to make a public comment, and we can develop a list on that. Is there anyone on the panel who would like to respond to Mary Davidson's comment?

MR. LUDLAM: I would say BIO is absolutely committed to that kind of dialogue. We've had that kind of dialogue in many other contexts. We've already reached out to the groups that we thought were the most concerned on this subject. And invited them to a meeting and, basically, all of them are coming. We interact with the Agency and with the PTO, and with the Congress.

I mean, we can't hide in the biotech industry from anything and we don't want to. We have a full-time Bioethics Counsel, we have a full-time Patent Counsel. We work on these issues. And we're happy to meet with anybody do discuss the legitimate conflicts, and values, and everything else, policies and laws, and almost any time, any place. You know we're dealing with so many issues at this point so --

DR. TSIPIS: I want to thank you for your comments. And I just want to add that I do hope that others have learned. But it would really be nice, and I also share and I tend to be called naive and overly optimistic and all of these nice attributes, but if the consumer groups could be reassured that there were some policies in place whereby our participation in research for a common good, be it a mix of commercial good, personal, medical, that it would be able to be used by the public

in the way that was accessible to all not just to the rich.

And I think that would go a long way, if there were some policies in place. Not necessarily changes in the patent law, that's a very different situation.

And I think that's certainly a direction that I think would help everyone down the road, rather than each individual group having to donate enormous resources, mainly at the personal level in terms of time, to fight. Whereas, that's not what we're about but we end up being backed into it. So I think it would be very productive if the dialogue moved in that direction.

DR. McCABE: Other comments from the panel?

[No response.]

DR. McCABE: If not, I want to thank you very much again for your informative discussions, presentations, and discussions on the roundtable this afternoon. Thank you very much.

We have one speaker from the public who has asked to address us, and that's Wendy Uhlmann, who is president of the NSGC, National Society of Genetic Counselors. Wendy, please keep your comments to about three minutes or less, please.

MS. UHLMANN: Actually, I am responding more as a genetic counselor working in a cancer genetics clinic. And I wanted to challenge several of the points that were made in Dr. Frank's presentation this morning.

And, first off, as Dr. Wylie Burke has already pointed out, HNPCC is a much rarer heredity cancer syndrome than hereditary breast ovarian cancer syndrome. So, actually, the number of mutations listed in the respective data bases, and the articles in the literature, is a reflection of this and the evolving nature of our knowledge still of HNPCC.

In fact, at least five genes have been identified that cause HNPCC. Clinical testing is only available for two of them. And testing is just a lot more complicated than testing right now for BRCA-1 and 2.

But more importantly, and this is what I wanted in the record, is that patients do not pay cash up front in full for genetic testing. If testing cannot be billed to the patient's insurance, and this is the case that several laboratories will not bill insurance from out of state, what will happen is that the institution will be billed. And the institution will then turn around and bill the patient's insurance.

And so I thought that this was very important to point out that the genetic testing, whether it be for HNPCC, BRCA-1 and 2, or any other conditions, it is done by either billing the patient's insurance directly or having the institution turn around and bill the patient's insurance.

And also I just wanted to point out that in fact for HNPCC there is an inexpensive screening test that we do where you are able to analyze tumor blocks for microsatellite instability. And that's a hallmark feature of HNPCC. And so actually testing for HNPCC is actually more accessible than testing for BRCA-1 and 2, not just because of the low cost of the screening test but also because of the effective surveillance for this condition.

DR. McCABE: Thank you, Wendy. Are there any other comments from the public before we move on to complete our agenda?

[No response.]

DR. McCABE: Okay, thank you very much.

Let me tell you what our agenda is, then, for the next, roughly, hour and 25 minutes, because we

will be finished here at 3:30 because of a plane reservation that I have.

If we get out earlier, it will be even better.

The five things that Sarah has kept track of for our agenda are, we need to discuss what, if anything, we wish to do with the discussions about patent and licensure, beyond what we spent today on so far; how do we wish to proceed on the informed consent family and family history question; clarify the decision about the education study, and where we go with that work, or if we wish to proceed with that. Though, as I recall "we wish to proceed," it's just how we will proceed.

The thing we must do on this five-point agenda is review and finalize changes on oversight, so that then Sarah and her staff can work on that document, get it back to you for a quick grammatical look, and "quick" meaning a 24- to 48-hour turnaround because this will be going to Dr. Satcher by July 1st, prior to July 1st. No changes in substance will be made after this meeting.

So if there are changes in substance, they need to be discussed here because we do all of this in a public forum and we will not do those after this meeting, and then discuss next agenda items. One of the topics, there had been a panel presentation on high through-put technology. It has come up a couple of times during this meeting already, and it has implications in a number of the areas that we have been addressing.

So I would suggest that we review, finalize the changes in the oversight document, since I feel that's our highest priority, and if we don't get to the others until the next meeting, so be it. Though I think we can deal with them pretty quickly.

MR. HILLBACK: I think we need to make sure we reserve a few minutes, because the others are somewhat agenda setting, I think, for the next meeting.

DR. McCABE: Well, they are.

MR. HILLBACK: So I think we all need to work pretty hard to make sure we at least get 10 minutes or something to --

DR. McCABE: My experience is, though, if we start talking about them now, they'll take 45 minutes. If we talk about them with 10 minutes left, they'll get done in 10 minutes. So that's the logic here.

Above the asterisk –. Points 1 through 3 are Reed's outline that he presented to us yesterday. Sarah will take this and turn it into appropriate background non-bolded type, above that bullet that we spent so much time discussing about. Exactly where it falls, I trust her, and exactly how this is reworded, I would also trust her.

MR. HILLBACK: One of the things that several of us had brought up, Mike Watson, from the audience, myself, others, were some of the characteristics of genetic testing. We didn't want to say "unique" because we don't want to single everything out, that we wanted to put as a precursor, even to Reed's piece that had to do with the interactive nature, had to do with the large number of potential tests that were coming our way, that had to do with the fact that we might have orphan tests for diseases that weren't orphan diseases.

We wanted some of those concepts there because we thought that they led into Reed's piece which then leads into Joann's piece. So I have a draft that I've given to Sarah, that no one has seen yet, of some of those points. I think they were the factual points on volumes and everything else. Whatever you wanted to do. I hope you can read it.

DR. McCABE: I'll assume I can read it:

"The characteristics of genetic diseases and related tests require government oversight through

different methods than those historically used for most diagnostics. These methods must be sensitive to a number of issues."

First, is that there will be a very large pool of analytes greater than 50,000 genes. But the real question is, how many pathological variance in the 2-plus billion base pair? So this addresses the SNP issue, as well as individual variation, and gene/gene and gene/environment interaction increases the number of relevant tests.

Any discussion of that?
The very loaded part of this, that I picked up was the first sentence, "The characteristics of genetic diseases and related tests require government oversight through different methods than those historically used for most diagnostics."

I think that is what we have agreed upon, is that you can't do three a year when you have got this many tests in the pipeline, as well as those. We have expressed different ways of approaching it, but I just wanted to point that out for people.

DR. CHARACHE: I am not sure that there will always be different methods. I think there are really a very broad range of methods that are available, including asking outside groups to do the primary assessment. So I like the concept but I wonder if it should be different methods or --

DR. BOUGHMAN: I propose use of different strategies.

DR. CHARACHE: I think that would be great.

DR. McCABE: Okay, fine. Changed on the hard copy. Next major bullet. Many analytes will effectively be, quote, "orphan analytes," end of quote, even if the diseases they are related to are not orphan diseases. This is the concept of the orphan tests, i.e., there may be many, quote, unquote, "causes" or markers for genetic diseases which may occur in only a very small subset of individuals. Any objection to that?

[No response.]

DR. McCABE: Everybody is agreeing with you. The next bullet. "An analyte may have a number of different uses." That's straightforward. The next bullet. "Knowledge about the clinical validity and clinical utility of an analyte will change in rapid iterative ways." Elliott got his iterative into the document, if we accept this.

DR. CHARACHE: I think I would say "may change."

DR. McCABE: Do you want to leave the "interative" in there?

DR. CHARACHE: Oh, sure. I wouldn't dare take that out.

DR. McCABE: May change.

DR. BURKE: And I would add that I don't know that we need the word "rapidly." I think we just need to, you know, I would even go with "are likely to change over time."

DR. CHARACHE: Yes, that's good.

DR. BURKE: So it's the "over time" is the issue.

DR. McCABE: I'll read it back. "Knowledge about the clinical validity and clinical utility of an analyte is likely to change in iterative ways over time." Is that okay?

MR. HILLBACK: There is one on the back.

DR. McCABE: The next bullet. "The iterative knowledge generation process is not driven by laboratories alone, since they do not interact directly with patients, but from the whole health care system." Let me read that again. "The iterative knowledge generation process is not driven by laboratories alone, since they do not interact directly with patients, but from the whole health care system."

I would take that middle out because I don't think it's necessary. And, in fact, one of our concerns has been direct laboratory-to-patient advertising. And we even have a bullet about that. So to say that they don't interact when some of them may or do --

MR. HILLBACK: The reason this was in there was as part of the lead in to the issue of data collection. And maybe we've covered that well enough in other places, but we had that discussion about the need for unique ways to collect data system wide.

DR. McCABE: I am not taking the whole thing out, just take out -- I would read it that "The iterative knowledge generation process is not driven by laboratories alone but from the whole health care system."

DR. LEWIS: I think "iterative" could come out of there, too, Ed, because knowledge generation may be interative and it may not be.

DR. McCABE: When was it not?

DR. LEWIS: And the other thing is, I do think that patients interact with labs and that labs may have changes based on their interaction with patients. I would hope there would be some interactivity there.

DR. McCABE: So, let me read it again:

"The knowledge generation process is not driven by laboratories alone, but by the whole health care system." Okay?

I mean, that accepts that you need the clinical side as well, which I think was your point there, your primary point. Is that right?

"If the old style system is still used, the risks that many tests will not be developed at all, the risks that most small labs would face difficult, if not impossible, cost burdens reducing broad availability and competition, the risks that tests in the market will be significantly out of date, unable to keep up with the real state of knowledge about the disease."

DR. BURKE: I agree with what I think is the intent of that, and would like to propose that instead of "old style" methods, we say, "if existing FDA procedures are used without modification." I think that goes to what you are trying to say.

MR. HILLBACK: I am not even sure I want to pin it on the FDA. As I said yesterday, I think there is a whole lot of issues about --

DR. BURKE: You could say, "if existing procedures are used without modification," because I think we want to make a strong statement that we know modifications are going to be necessary.

MR. HILLBACK: Right. I am happy with that.

DR. McCABE: A friendly amendment.

Any other comments about this last point?

[No response.]

DR. McCABE: So this would go along with Reed's outline, which you have before you, and would be included in that unbolded material as a prologue to the big bullet.

MR. HILLBACK: I think it almost follows, although I am sure that our writers will do a better job of saying "therefore," and then Reed's first point is a system of -- so it sort of leads to the points in Reed's with a "therefore," but probably more sophisticated.

DR. McCABE: Yes. Joann got some of Reed's stuff into -- the bullets have changed a little bit from when you saw them yesterday. First of all, they are organized a little bit better, since this is the real core of the entire document. As we discussed the letter of transmittal yesterday, we really need to be sure that this is understandable.

I know that Joann spent a lot of time, including tolerating a computer crash last evening, in getting this work through. A little bit more of this background information has been included in the bolded bullets now.

So, yes, I think that is a good way of organizing, Elliott, your stuff, "therefore," Reed, and followed by the big bullet.

DR. BURKE: In fact, it's worth noting that Reed's first No. 1 one just says "a system of classification." Elliott's point is, this is the justification for a system of classification. So I think he is right.

DR. McCABE: Right. Now let's spend some time going over what has been written because this was one major bullet. Joann suggested that she break it down into several bullets because some of the meat was getting lost in the middle. So it now says, "To ensure adequate oversight of genetic tests, multiple agencies, in collaboration with the private sector, will be required to implement a new multi-step process of evaluation for genetic tests."

Again, we'll change the English a little bit. Let's not get hung up on the English right now, unless you feel the English needs to be changed for meaning rather than just for clarity. So, basically, that's the introduction to the bullet and lays out the whole thing.

"A working group of SACGT members, representatives of relevant agencies, professional organizations, and the public and private sectors should propose an algorithm for categorization of genetic tests to be proposed" -- again, we'll need to work on the grammar -- "to be proposed by September 2000. The initial step of the process of test evaluation is the categorization of tests according to the level of scrutiny required."

DR. BURKE: Two comments. One is just for consistency. I propose that we use "classification" every place that we have used "categorization," or go the other way, but be consistent and use one word or the other. I kind of like "classification." That is a minor point.

The major comment is, do we have to put a timeline on this? I would prefer leaving out the "by September 2000."

DR. McCABE: We put the timeline in -- as I recall the discussion yesterday, the concern was that if you don't put a timeline, then what we are saying is it is business as usual until the new system kicks in. The concern was that this could mean business as usual forever, if there wasn't some time limit on kicking in the new system.

This was an arbitrary date that was established. If you think it's too short, if that is the concern, and it may be too short, but I think that to not put a finite point on when the new system will be constructed, there is the possibility that it might never be constructed.

MS. BARR: I think it's important that we at least attempt to get it constructed before so it can be

acted upon before November. So I would say leave it September. If the group can't make it, they will let everybody know and we will give them more time, just as we press Satcher for more time. But that would be a reasonable goal.

DR. BOUGHMAN: An option might be to use "Fall 2000," so that we don't have an actual date. The other question I want to raise is whether -- as you go through this, one of the questions that came up in my mind was should this be a sub-bullet here under Issue 4, or should this bullet go at the end of Issue 2?

DR. McCABE: Well, I am wondering, this is so core to the whole document, whether it actually goes to the very beginning and we put the logic that we just discussed in front of it? Lay this out before any of the issues, and then the issues really address this.

Because as we went through yesterday, it ends up getting buried in the middle. Whether we put it in Issue 2, or Issue 4, or Issue 5, it ends up being buried in the middle when it really is the core of the entire document, is within this piece.

Does that seem reasonable to people?

As we get into the recommendations, it would be the first, and it would precede Issue 1, and then it would be a prominent part of the executive summary.

DR. CHARACHE: I have two points. The first is very simple. The second sentence, I would like to suggest that rather than say "the initial step is the classification of the test according to the level of scrutiny required," I would suggest the thought that it might be "an initial step," because I think we will be able to move on classification recommendations, for simple things, before the entire structure is in place.

DR. McCABE: So "an initial step," so that we have some parallel process there.

DR. CHARACHE: I would suggest that that be the beginning of that bullet because that is the important concept. Secondly, I don't want to preclude recognition of the fact that the laboratory forum group, which actually does have representative relevant agencies, professional organizations, public and private sector, has as its goal reporting back to this committee by September with this type of recommendation.

So I don't want to exclude the fact that that group is going to be working on it, many of them. And I don't know if we want two groups, or you want to see their product, or whatever you want to do?

DR. McCABE: I would speak to the September. If it slides a little bit, that's good. If we make it November 15th, or whenever, that Tuesday in November, you know we won't make it.

MR. HILLBACK: I thought her point was different, Ed. I thought her point was --

DR. CHARACHE: It is.

MR. HILLBACK: -- the lab forum have already committed --

DR. McCABE: Right. So that we can see what model they come up with.

DR. CHARACHE: Sure. But you might say "such as."

MR. HILLBACK: The question is do we want to co-opt that?

DR. CHARACHE: The lab forum.

MR. BAKER: Actually, to that end, the recommendation I would make is instead of "should

propose" you could language it, "should review proposed algorithms." And the second, "to be proposed by September" could be modified to be "and provide recommendations."

So the first "proposed" would be "review proposed." The second would be "and provide recommendations," and it would enable the input of the lab forum but would still give the purview to the committee as was discussed earlier this week.

DR. McCABE: What was the last phrase there?

MR. BAKER: "And provide recommendations by September."

DR. McCABE: Okay. Let me go onto the next bullet then.

Oh, I am sorry, Barbara.

DR. KOENIG: Wylie helped me with this, too. We talked about this a little bit last night. I still have some concerns as to when we create this classification system or categorization system using the consortium model, will this simply be turned over? I am worried about the initial screening of tests, and where that will be done, and by whom that will be done.

To put them into categories, will this be purely within the FDA or, at that initial point, will there be involvement from other organizations? That's still not clear to me as to how it will happen or if we are making a specific recommendation.

DR. McCABE: There is another bullet to that effect in there. I would have to take some time to find it but I think we were suggesting a creative process to that.

MR. HILLBACK: Well, my assumption was that the next bullet that says we're going to create, you know, ask the FDA and others to create this process, part of the process, I think, has to say who will do what. And I think that's where we'll get to that.

I think what we're trying to do is a little parallel processing here by saying there is two requirements we're setting out right now. One is to start on a classification system. Secondly, to start on the design of quote, unquote, "a new review process," whatever that is. They are both required in order to get to the end point that we want to get to.

DR. BURKE: I would just add that, you know, in agreement with Elliott, I think we are specifying an algorithm for classification. Let it be in our record here that that includes both a who and a what. I think that makes it particularly important that we are proposing that members of SACGT be part of that activity.

DR. KOENIG: Precisely. What I am addressing is some of the concerns of the public comments, and from industry, and others about how to set up a new system that doesn't just do business as usual and lead to excessive delays, et cetera.

DR. McCABE: Well, we had made some changes, and we'll get to those shortly, about some language that basically says that we will be responsible ultimately for review of this.

DR. BURKE: Again, just to emphasize, I think the issue is no matter how good a classification system you have, if the body that's putting tests into different categories is not a disinterested body or viewed as a disinterested body, there will not be confidence in the classification scheme.

DR. McCABE: Let's go on to the next bullet, and I've already made one change here at the end of the first line: "Because of its regulatory authority, the FDA should be the federal agency responsible for" -- I think we had discussed this concept of lead and made it "federal agency responsible for the review, approval, and labeling of all new genetic tests."

"That have moved beyond the phase of pure research." This was a phrase that Francis inserted and discussed with me this morning. The concept being, again, what we had discussed yesterday. That there is this research, there is the clinical, there is a grey area.

This would be, once it's moved beyond the pure research into that other phase, which we may not want to call "investigational" but where additional data need to be acquired, "the level of review applied by the FDA should correlate with the level of scrutiny required by the test as well as the complexity of the testing technology, as defined through the system developed by SACGT outlined in the preceding bullet, "using criteria and standards informed by practice standards in place in professional organizations and regulations of other agencies, including CLIA, the FDA must delineate review processes for premarket evaluation.

"These processes should focus on the claims of analytical and clinical validity made by the developer of the test, and must minimize both the time and cost of review without compromising the quality of the assessment of test validity."

Let me just finish this one: "To facilitate test availability, requirements for postmark at data collection may be imposed in the approval process before actual implementation of the review process, and in a timely fashion, detailed modeling of the proposed plan for a variety of tests at current scrutiny-level should be undertaken, including the analysis of cost and potential delay in test availability."

Wylie, you had an insertion in the middle there?
DR. BURKE: Yes. "Clinical utility" got lost again.

DR. BOUGHMAN: We moved "clinical utility" down to the next step, as we included both pre- and postmarket evaluation, because of the discussion around the table that indicated that outcomes data would, in fact, be the exception rather than the rule in premarket test evaluation.

DR. BURKE: Nevertheless, the phrase says, "claims made by the developer of the test." It is not saying you have to have a claim, it's just saying the process you should focus on, the claims of analytic and clinical validity. I would propose that we should not lose "clinical utility" there, for completeness.

DR. McCABE: Okay, so this is not a requirement of FDA, but it's rather claims made. Okay.

DR. BURKE: I had one other concern. And that is, I actually think the second sentence of this bullet can be made simpler, by virtue of our efforts preceding this to be clear about what we're going to do in classification.

I think it's going to be possible for us to say "the level of review applied by the FDA should correlate with the level of scrutiny required by the test," and lose the next several sentences and say, "as defined through the system developed by SACGT outlined in the preceding bullet."

In other words, we did add here an issue of complexity of testing technology, but there are many issues that go into classification. We don't want to list them all here, we simply want to refer to our process.

DR. McCABE: Okay. Sarah's gotten that. Pat Charache, you have a comment?

DR. CHARACHE: I have one concern about the addition of clinical utility to that strength. And that is that I don't think it's going to be available. But I think the first two must be available. So I don't want to confuse anyone who wants to look at this by thinking that they don't have to have clinical validity, simply because they don't have to have clinical utility data.

DR. BURKE: I think if you want to do that, we have to change the sentence altogether. And it would need to say something like "these processes should focus on" -- or it should even say,

"drugs cannot be brought to review without claims of analytic and clinical validity," or something of that sort. The way the sentence reads, it's not stating a requirement.

DR. McCABE: So you want to say, "These processes should focus on the data regarding analytical and clinical validity and the claims made on clinical utility by the developer of the test"?

DR. BURKE: That's good.

DR. CHARACHE: That's excellent.

DR. McCABE: I mean it's basically data on the first two and claims of, which is probably where you will be at on the utility.

DR. CHARACHE: And that makes it very clear they have to have claims for clinical validity and can't simply say, "I can detect this gene."

DR. BURKE: Right. But it is also stating the different level that's expected, yeah.

DR. McCABE: So it's data on analytical and clinical validity and claims regarding clinical utility, is that agreeable to everyone? Any more on that bullet? Barbara?

DR. KOENIG: On the next sentence, actually. My concern is the issue of duplicative and potentially conflicting oversight because of CLIA and FDA now becoming involved. I just want to make it clear that people are sure that it's clear that we are suggesting to the FDA that, with exception of adding the premarket approval phase, that we're happy with the level of CLIA review for many aspects of genetic testing.

No?

DR. LEWIS: No, I didn't hear that.

DR. McCABE: I don't think --

DR. CHARACHE: I am not satisfied with it.

DR. KOENIG: Well, I mean, for many things.

DR. McCABE: It is the augmented CLIA.

DR. CHARACHE: It is the augmented, and we still have to get that process through and so on. So I wouldn't modify that.

DR. KOENIG: Okay.

DR. McCABE: Yes. That's under process right now, and I don't think we even know whether we're going to agree with the outcome of that process since it hasn't come out yet. Can we move on to the next bullet?

"Data format for pre- and postmarket evaluations should be developed in conjunction with the CDC. Postmarket collection, aggregation, and analysis of non-identifiable data will be performed under the auspices of the CDC and may be required of the test developer, as well as other uses of the approved tests."

Now, before I entertain questions or comments on this, there had been discussion of some other agencies being involved here. Do we want to add that as well? Again, arguing that perhaps CDC might be the agency responsible but might draw upon expertise elsewhere within HHS.

I think it was Pat. Someone before Elliott? I thought I saw a hand here. Judy, okay, and then Elliott. Pat Charache.

DR. CHARACHE: Three thoughts. I think CDC, it should take advantage of other input, as opposed to CDC alone. I think it should be with the leadership by CDC, if we wish, as we said FDA should coordinate it. I think there should be a time element expressed here in some way. I think that it could go on for a very long time. I am not sure how to put that in, if it should be in there.

But I am concerned because we have to probably also triage at this level, as well as we've suggested there be triaging in terms of classifications for the FDA. I think we're not going to demand the same level of filling up boxes for some entities or tests as we will for others. And I think that concept may best be expressed.

DR. LEWIS: My concern is with just the wording, not the concept of non-identifiable data. It sounds a little bit vague. I think it needs to be worded in a way that it's data, you know, that it's either aggregated or it's stated that it's not able to be, you know, associated with an individual.

DR. McCABE: It's not the data that is not identifiable, it's the individuals who are making up those data.

DR. LEWIS: It sort of doesn't sound terribly scientific the way it's worded right now.

DR. McCABE: We'll work on the grammar, but the point is well taken. It's just a movement of the adjective around so that it's clear that it's the person that can't be identified, not that the data could not be identified.

MR. HILLBACK: I think one of the things we want to be careful of is we don't get too specific. And I think both on the "will be performed under the auspices of CDC" sounds a little too specific, unless "auspices" is thought of as kind of encompassing everything that ever has anything to do with data, and then it's okay.

But the same with the unidentifiable term. I mean there may be real needs to do something other than that. It has to be done in a different way, but I would like to create something that someone then can fall back on and say, "Well, you told us we didn't have to do anything with that, we just have to do things that are unidentifiable data."

DR. McCABE: Let me take a crack at the first sentence. And I think we can deal with that one and then worry about the second one. "Data formats for pre- and postmarket evaluation should be developed in conjunction with the CDC, comma, utilizing the expertise of other federal agencies and private sector organizations, as appropriate."

Is that acceptable to everyone? Is that a problem?

MR. BAKER: One question. It says "should be developed" and who is that directed toward? Because it would seem to be worded better to direct CDC to do it in conjunction with.

DR. McCABE: Well, it says, "developed in conjunction with." I think it meant the FDA but we could say "developed by." But we want to be cautious that these don't end up as siloed processes.

MR. BAKER: Agreed. But a question --

DR. LEWIS: How about "developed under the leadership of"?

DR. CHARACHE: Do you have Muin's written comments?

DR. McCABE: Well, we can use the same construct. We can say "should be the responsibility

of the CDC in conjunction with."

DR. LEWIS: I was going to say, "should be developed under the leadership of CDC in conjunction with other agencies and private sector, as appropriate." And that way we've got a responsibility loop so that the accountability piece is there.

DR. McCABE: Yes. I think that we had talked about, we had took the concept of lead agency out of the FDA yesterday. I mean, being responsible for is essentially being the lead. But the concept that it's a little bit of a flatter organization than one individual way out in the front of the others.

DR. PENCHASZADEH: I think we have to be careful on what we want to say. If we want to say that the responsibility will be of the FDA in conjunction with CDC and other agencies, we should simply say that, because of the other comment that we should say it should be developed by whom and in conjunction with whom.

DR. McCABE: Well, if we say "should be the responsibility of the CDC," I mean that's what we're really saying here. The issue is, how do we keep this from being two independent activities. Is there a way to get that in.

DR. CHARACHE: Just to make it a little more complex. There are two reasons for the postmarket work. One is what is now the legitimate postmarket activity of FDA which has to do with the validation of the test. And the other is the postmarket need to gain more clinical utility information.

So there are really two reasons for postmarket, one is commercial and the other is medical and scientific, so we can't lose that understanding.

DR. BURKE: I don't see why we can't say "CDC in collaboration with FDA and other agencies and private sector, as appropriate, would be responsible for data formats." In other word, just CDC responsible. Add in whatever partnership concepts we want to add in, but say either "in collaboration with FDA" or "in conjunction with the development of the FDA review process." I mean, a phrase of that kind can capture it so that we're saying this is a coordinate process.

DR. McCABE: So, "data formats for pre- and postmarket evaluation should be the responsibility of the CDC, in collaboration with the FDA and other federal agencies and private sector organizations, as appropriate."
Is that correct?

DR. GUTMAN: I am really quite uncomfortable with this. The deal here is that FDA doesn't do well when it plays by rules that are established by another agency. We actually are having a fairly significant problem moving forward with the waiver process, based on rules that were developed by CDC.

It's actually going to result in a public meeting in August to decide whether we'll play by those rules, and how we'll understand those rules, and whether we'll maintain those rules.

So I obviously think there has to be tremendous synergy between the premarket and the postmarket studies that are being requested. And I frankly think that what you could expect in postmarket studies would be, as I get the sense of this committee, perhaps higher levels of standards than what you might expect in the premarket, because you really are looking for us to make sure there is utility but not complete characterization.

But I really think if you are going to assign a supreme market review, then you need to give us the lead in determining the questions we're going to ask. If you don't want us to take the lead and want CDC to, we might talk about having CDC take the lead in the premarket review.

DR. BURKE: I appreciate your comment and I appreciate that we're talking about something that

will be difficult, but I think we knew going into this that this would be difficult. I think we've stated very strongly that this has to be a process that includes collaboration.

I think we've already heard a lot of information about the importance of pilot efforts already under way that CDC had taken the lead in developing and identifying the kind of data that would be needed in postmarket surveillance, so I think we could try and make the language general.

But I think it's very important that we keep, in a sense, mandated in this the concept of collaboration and not say that because it's hard FDA should be the lead in all steps of this process.

DR. McCABE: I think we made the decision yesterday that we would more define a process, recognizing that it might be a new process, rather than try and fit it into the current process, that that was a lot of the discomfort with our original draft document.

MR. HILLBACK: It seems to me, and I am not sure why we're so worried about the premarket data format, CDC. I mean I guess I, a little bit, agree with Steve -- that may get him fired -- but that the premarket format, if we're asking FDA to do the premarket review, and we're suggesting to them that they, with our guidance and input, need to develop some process to do that, they are going to have to come up with a format. We're going to get our two cents worth in and, in the collaborative spirit, so are CDC and others but we've given them that responsibility.

On the postmarket side the problem has been, that most of us have recognized, is getting access to information on the genotypes, and that's where CDC can really come in. So I would just as soon take out the phrase "pre- and" and just leave "post" on the second --

DR. McCABE: Is anybody wetted to –. Because I think that's your issue, is that right, Steve, that it's really the postmarket, and I think that, really, the bullet above was to be premarket. This was to be more postmarket.

Joann, you are the author. Are you satisfied with this?

DR. BOUGHMAN: I think that my thought process could have, being a pragmatist, could have gone in reality like this. That CDC would inform the premarket data format but, in fact, when the FDA brings forward, after the working group gets together, they will determine what actually has to be there or does not have to be there.

That not only the data format but that the collection and analysis of postmarket data under the auspices -- and when I use the word "auspices" of the CDC, it could be the test developer that is challenged to collect and aggregate all of that data. But, in fact, "under the auspices of" ensures that link with the sharing piece that we had talked about before.

I think that we will, in the premarket process, not be blind to the CDC. And I think the FDA knows enough about what they are doing, and this committee can double check that when they come back with their proposed review process, that, in fact some sort of data format review that could link eventually in a useful way to the postmarket process can be ensured at that point.

MS. BARR: My concern, in terms of being clear about CDC authority, is that when we are asking for more resources, that while FDA will need more resources, CDC will also. And so I think we have to consistently, throughout this document, try and identify those places for which CDC will need more resources, and this is one of them.

DR. McCABE: But, in fact, it might be cleaner for resources if we separate these, because it may difficult to interpret, and the Secretary's Office, also, if we jumble them up, within these items.

DR. LEWIS: I think there are pieces of the premarket and the postmarket that are very different and very unique. And I think one of the reasons I think the CDC needs to be primarily responsible

in the postmarket is this seems to me to be really epidemiological.

That we are not looking necessarily at results of any specific tests that we do before it becomes premarket, but that what we are able to do is look at population-based data and differences among tests and among populations within the same test.

So we are really looking at a whole model of epidemiological research, and data collection, and analysis that is somewhat different than the premarket piece which is looking at the clinical validity and utility of a test.

MR. HILLBACK: Can I respond directly to that, though?

DR. McCABE: Go ahead.

MR. HILLBACK: I think we have to remember, though, that based on the principles we have, every lab that does the same test is being reviewed separately. And so it's not just the epidemiological data that's valuable, it's the performance of that individual lab's test in a postmarket sense, not only the performance of the combined group of all tests, because they may test different mutations, they may have different capabilities.

So we have to be careful we don't think that all we are going to look at postmarket is the entire world anonymous and not caring which lab did the test. I don't think that's right, because then each lab can't update its own validity data as it goes along. It's still got to be lab-specific.

MR. BAKER: Joann hit some of the points. The key thing being we are talking about formats, and there is going to be experience we are going to gain as we look at the analysis of the various data that comes in that needs to be incorporated into any one of these. That's the role that we see serving, however it's characterized.

DR. CHARACHE: FDA has to be permitted to design formats that are specific for the follow-up understanding of the test itself. And this often requires clinical information, requires expanding the population in which the testing has been done to get a more complete and accurate understanding.

So I think that we've got these two purposes for postmarket and we're concentrating on one, but the FDA has to be able to have their own format on a test-by-test basis for that purpose.

DR. McCABE: Well, we're really talking about clinical utility in this bullet.

DR. CHARACHE: That's right, but we have to make that clear.

DR. McCABE: In the last sentence it says, "The focus of this effort is to attain full understanding of the clinical utility of the test."
DR. CHARACHE: So that does not preclude other postmarkets that don't apply here?

DR. McCABE: Right. We aren't describing the entire universe, we're more talking about changes in the current universe, is the way I see this.

DR. CHARACHE: That's fine.

DR. McCABE: Are there any other problems with the rest of that bullet, then? Let me just read it to you. I'll read it with the changes as I have:

"Data formats for postmarket evaluation would be the responsibility of the CDC, in collaboration with FDA, and other federal agencies, and private sector organizations, as appropriate.

"Postmarket market collection, aggregation and analysis of non-identified" -- well, we'll change

that -- "will be performed under the auspices of the CDC and may be required of the test developer, as well as other users of the approved test. The focus of this effort is to obtain full understanding of the clinical utility of the test."

Okay? We will rewrite parts of that to make it clearer.

The last bullet:

"To ensure continued collaboration among agencies, professional organizations, the private sector, and consumer representation in this critical transition, the SACGT proposes to serve as a resource for the Secretary in facilitating the development and implementation of these review processes."

Okay. Let's go now to the other sheet that was handed out and we will add, under Issue 2, some additional bullets. This has to do with the criteria that are necessary but not necessarily sufficient for all tests: "Is the test used to detect sematic or germline variations? Is the test used to detect a rare disease or a rare mutation?" And a third one, "Does the complexity of the test make interpretation difficult?"

DR. BURKE: Just a minor consistency of language. It may be that we want to substitute "analyte" for "mutation," because that is the word we use somewhere else in the document.

DR. McCABE: That is appropriate because we talk about proteins as well, and there may be other ways of doing that.

DR. CHARACHE: On that last new bullet, "Does the complexity of the test make interpretation difficult," it should be, "make performance or interpretation difficult."

DR. McCABE: Okay.

MR. HILLBACK: Don't you want to say "complexity of the test procedures"? It's not complexity of the test, because now we're going to get back into -- it's lab complexity versus medical complexity.

DR. McCABE: Right. So, "test procedures." Now I'll go to the next, and this is where Sarah was being clairvoyant at times, because we weren't very prescriptive in our language. This was: Add to the end of the bullet on page 21.

So if you want to find page 21, just so that you can see it in context. Some people said they wanted to see these in context. So this is: Add to Issue 3, Recommendation 3.

We will also work on consistency, but let's look at this one. It has been a moving target. So this goes at the end of Bullet 3. "The DHHS agency should involve relevant experts, organizations, and public representatives in the data collection efforts.

"The data collection can lead to a variety of assessments such as, (1) Preparing short assessments based on information gathered together from existing literature sources; (2) Carrying out pilot projects that assemble data from published and unpublished sources and formal technology assessments."
Any questions about that?

[No response.]

DR. McCABE: It gives a variety of mechanisms, doesn't prescribe any specific one, and they are examples. It is "such as," so there could be other examples as well.

Now I'll go to page 25. These are things that we really discussed in detail yesterday, or Monday.

I just want to be sure we capture something close to the language that's appropriate. This is recommendations regarding IRB review, on page 25. So this goes into this bullet, at the end of the bullet.

"When test results are reported to individuals, families, and health care providers, the testing must be performed in a CLIA-approved laboratory." Actually, there was a slightly different wording of this: "Since we recognize that tests reported to individuals, families, and health care providers require the testing be performed in a CLIA-approved laboratory, therefore, HCFA and the parent institution should provide technical assistance to laboratories performing testing for orphan diseases to help them meet these requirements."

PARTICIPANT: [Off mike.]

DR. McCABE: Well, it was a clause, it was a logic. We understand that this is the rule, but we put it in as a logic to the second part, really.

PARTICIPANT: [Off mike.]

DR. McCABE: Yes. "Recognizing that when test results are reported, testing must be performed in a CLIA-approved laboratory, therefore HCFA" -- and I think that's what we discussed on Monday.

MR. HILLBACK: Is "and" there appropriate? "And health care providers," or is it "or"?

DR. McCABE: Well, it is "and/or." It depends on the state. It is an "and/or."

MR. HILLBACK: Can we at least go "and/or"?

DR. McCABE: It's "and/or."

DR. BURKE: Just for completeness, "orphan diseases or analytes."

DR. LEWIS: Editorially, "and/or" is inappropriate. "Or" would deal with both. "Either or" is "or."

DR. McCABE: Okay.

DR. CHARACHE: I am just going to suggest it shouldn't only be HCFA, it should be federal agencies.

DR. McCABE: Well, HCFA is the one that volunteered. It's CLIA. Well, it's CLIA. So, "HCFA and other federal agencies," I guess, because it does involve CDC potentially.

PARTICIPANT: [Off mike.]

DR. McCABE: Well, but in terms of education, it might involve both. I don't understand these notes.

Okay, page 26. Will you just walk us through this?

MS. CARR: There is a change in the text. We're on page 26, in the section called "Review of tests already on the market." We have just taken out the reference to the U.S. Preventive Services Task Force in the initial paragraph, and that's what we've outlined there.

It should just begin, "a multi-disciplinary group could develop." And then the actual recommendation would read as is shown there, and modified by a suggestion from Pat Charache, that we use the principles employed for new tests that are reviewed, I think.

DR. McCABE: We had discussed that, and I think we had agreed to that amendment. And then regarding genetic education and counseling, which is, where? Okay, 26 and 27. "Genetic education and counseling is required for any test of high scrutiny.

There is an insufficient supply of health professionals trained in genetics and greater efforts are needed to train health professionals in genetics. Because genetic education counseling is an essential feature of genetic tests, organizations that pay for genetic tests should also pay for the education and counseling services." Make that plural.

On page 27, the last change: "Written informed consent must be obtained for tests requiring high scrutiny." This is a revision of the first sentence under that bullet.

DR. LEWIS: Can I speak to that?

DR. McCABE: Yes.

DR. LEWIS: I think we get a little bit confused sometimes as to the difference between signing the form and doing the informed consent process. So I think that written documentation of informed consent, or something. But I think the issue of written informed consent, having somebody sign a form doesn't necessarily guarantee informed consent, so I would like to see the informed consent, however you write it, be stronger. I think informed consent is different than signing a piece of paper.

DR. McCABE: Why don't we say "documentation of informed consent," because pretty soon none of us are going to be writing anything, with any luck. So "documentation of informed consent must be obtained for tests requiring high scrutiny." Is that okay? That could be written documentation, there may be other forms of acceptable documentation.

Actually, that probably deals with the informed dissent issue, too, that we had struggled with, because there it's argued that there is documentation of dissent in the informed dissent for newborn screening, which Michelle Puryear had talked about.

MR. HILLBACK: I want to come back to one thing, actually, on Reed's comments. I didn't know whether we are going to get into those in detail or you are just going to wordsmith a little bit?

DR. McCABE: We are going to wordsmith --

PARTICIPANT: [Off mike.]

DR. McCABE: Yes, but we're going to put them into up-front documentation.

MR. HILLBACK: Yes. The one that concerns me a lot, and I think we want to get away from this concept, is this idea of temporary conditional approval, because what we're saying is that the test, that any test changes regularly over time.

DR. McCABE: Again, it's been a moving target. We understand the discussion and we will make them consistent with --

MR. HILLBACK: As long as we can say "approval." And I think the other phrase that maybe we can help avoid is "premarket approval." That phrase is an existing term. I think we've been using "premarket review" to get away from an existing term at FDA. Just so that we don't have any confusion in people's minds. Thank you.

DR. McCABE: Okay. Thank you.

Any other issues about this stuff because --?

MS. DAVIDSON: I just want to come back to the bullet. Let's see, it was the one on 25 about orphan diseases and just kind of raise, as I understand the wording -- Tim and I were just talking -- what we have said, then, is that HCFA and parent institutions should provide technical assistance. I just want to raise whether that is strongly worded enough.

DR. McCABE: Well, it's one of those. If we say "must" it means that every institution must have technical assistance. Shall we say, "must make available to," or something like that?

MS. DAVIDSON: I think, in just looking at this from the perspective of the orphan disease community, it needs to be worded in stronger language.

DR. McCABE: Okay. What if we say "must make available to"? But it's one of those things like saying everybody has to go through this process, not all may need to go through the process.

MS. DAVIDSON: Right, exactly.

DR. McCABE: Okay.

PARTICIPANT: [Off mike.]

DR. McCABE: if it is wordsmithing to change its meaning, we need to talk about it today.

DR. KOENIG: Have we, anywhere in the document, addressed the issue of direct submission of samples to labs?

DR. McCABE: Yes. We say that there is a bullet where we say that FDA and FTC should enforce --

DR. KOENIG: No, not direct to consumer marketing. I mean actual direct submission of samples by individuals to labs without being ordered by a professional.

DR. McCABE: We have not addressed that here.

DR. KOENIG: Is that something we're purposefully deleting, or do we want to --

DR. McCABE: We were told that that actually does not fall under HHS. At either the last meeting or the one before, we were told that that was FTC and that it really is a commerce issue. And that's what I remember of the discussion. And why we got away from that, we were told that HHS had no control over this. We might ask to become more informed about this again in the future.

Kate, do you understand this better?

MS. BEARDSLEY: Okay.

DR. McCABE: Can you get close to the mike, please?

MS. BEARDSLEY: Yes. FDA currently prohibits for home brew tests the direct submission of samples to labs. So, for existing tests, it will be prohibited. I think, for future tests, we could probably rely on FDA in its approvals to do that. I think you are right, I think this is not an FTC issue. In some cases it's a state issue because states have laws as well but I think FDA's current regulation trumps those, at the moment.

DR. KOENIG: Well, there were public comments on this issue, and so, if I am the only one who has a concern about this. The AMA statement also had a concern about this.

DR. BURKE: I think there are a number of issues that we probably need to identify as loose ends,

and stuff that probably isn't developed enough, or thought through enough, or necessarily immediately relevant to this document that should be a part of this document, but that should be part of ongoing consideration by this committee.
I would propose that direct-to-consumer marketing, or not just marketing but making available of genetic testing opportunities is on that list.

DR. McCABE: That's fine, but we do have under here, on page 9, continuing on to page 10, we have documented that, in addition, the regulation prohibits direct marketing of home-brew tests to consumers.

DR. KOENIG: These are two very separate but related issues. Even with prescription drugs, in which you require a prescription from a physician, you can still have direct-to-consumer marketing of the product, so that they are separate. So I don't think that they are the same thing.

I am talking about the situation, apparently in some states people are simply able to order their own diagnostic procedures that don't require a prescription under state law.

It's more the second. I am concerned about both issues. I do think we need to say a bit more about direct-to-consumer marketing than we've said so far and give more explicit directions to FDA but --

MS. BEARDSLEY: Steve is pointing out to me that there is a small subset of home brews that's not covered by their regulation. So there is a subset that maybe we need to reach as an issue to discuss.

DR. McCABE: Well, we're going to have to go on. We can capture it as an ongoing issue. This is not the final document to end all documents. It is a work in progress. It is the best we could do in this period of time. The important thing is that we do capture it, that there are other issues that we need to deal with.

This gets into international issues as well because, as you recall, one of the things that people are doing is sending tests to Canada, because in Canada you can directly submit without going through a physician. So we are developing offshore laboratories for these things as well.

For us to tackle international issues, and everything, at this time, I think it is an important issue, but we will put it on the list to consider in the future.

Other things that we need to deal with in this document?

Wylie, you had an insert on page 20?

DR. BURKE: This probably needs some additional wordsmithing to be consistent with the language that we had. But we have at the end of our Issue 2 statement currently, on page 20, a summary of an example of what might represent a high scrutiny test. And I think there was some concern to flesh out, also, what might represent lower scrutiny tests, so I added in additional description of complexity.

But I think we should use the language that Elliott and Pat have given us for describing the more complex tests, and then attempted to list those circumstances where a test was likely to be lower scrutiny. So that was just intended to create more consistency, under Issue 2, with what we do later. And it isn't intended to add any new concepts.

DR. McCABE: Okay.

DR. PENCHASZADEH: Just a very simple comment on overarching principles in the first bullet, reading through the first sentence.

DR. McCABE: Which page, Victor?

DR. PENCHASZADEH: The first page, I guess. The first sentence, it says, "One of the main goals of genetic testing is to improve the health and well being of individuals and families."

And talking yesterday with Mary, I really tried to think if there is any other main goal, and why shouldn't we state simply "The main goal of genetic testing is"? I would propose to change it to say "The main goal of genetic testing is to improve the health and well being of."

DR. McCABE: Yes. I think Sarah is reminding me that there are other types of genetic testing which we've excluded from this document. There is forensic genetic testing, so there are other categories, other types of genetic testing.

So the reason why it was specified -- for us it's the main goal, but among genetic testing, there can be other goals. So that was the logic behind that, it's not that we're saying that health and well being aren't primary for us.

Is that acceptable logic?

MS. BARR: I don't know. When we say "individuals and families," are we integrating the public health factors? I mean I know it's a circle, but we've spent an awful lot of time trying to be very clear that we're looking at genetic tests both for the individual, their families, and understanding them in a public health context.

DR. KOENIG: Pat, this is Barbara. I think the only problem is you get into very complicated issues in terms of the history of eugenics, if you start talking about the goal of genetic testing being social well being, even though at some level it is as well. So I think we're probably better off keeping it individuals and families in this context.

MS. BARR: Okay.

DR. McCABE: Okay. Other discussions? I would like to have some time to move on to other issues. So that takes care of the most important activity of this meeting in the past year, or 11 months, has been to craft this document, which we will get to Dr. Satcher by July 1st.

You will get it. If you are traveling between now and July 1, and you want to see it, you better let Sarah know, because it is going to come to you by e-mail, and you will be given somewhere between a 24- and a 48-hour response time. So please be attentive to your e-mail.

The other issue that we need to do is, is there any additional direction that we want to take on the discussion on patents and licensure, beyond that which we heard today?

I think that it was beneficial. I don't attend those meetings. So others of you who may, may know that all of these people have been in the same room together, but, at least for me, it was nice to have them all in this room and hear the discussion. There is definitely a tension between different issues that are brought to bear here.

DR. TUCKSON: I guess the question is, what are we going to do with it all? I think that clearly there is a need for us -- I mean, having opened the door, I guess, at this point, after we've done this report to the Secretary, to Dr. Satcher, what is the format for the next thing we send?

DR. McCABE: Well, we had said the other day that we -- but we've now had several days of additional material -- we had said the other day, yesterday morning, I guess it was, education was paramount. That testing could not be carried out without an educated professional community and public. We were going to focus on the professional first.

DR. TUCKSON: I am sorry, I guess what I was getting at is, are we going to create another document that we send forward that we will use? We will have public comment again, shape, and that sort of thing. If we are, I think what you are getting is -- because I think we are. I mean, I would imagine we are going to give another report or two forward.

I think the agenda that we have carved out in terms of education and patenting and licensure, and those, I think we have to speak to them. So what I would call for is, I think we have to refine what we have heard, and have a chance to challenge. But we are not there yet. That is for sure, and we are not there on education yet.

DR. McCABE: Let me tell you where we are on education because I think it has taken us a year to get this document out. I am hoping that the next document won't take us quite as long. We were given a very difficult charge. I think we have come to some consensus. Someone had asked, I think it was you, Reed, had asked it on the very first day, would this be an consensus document or a majority document.

From all the body language, it is probably good that we basically have a vote on this point right now. The document that we just approved, is this a consensus document? Can we say that the committee is in 100 percent agreement with these positions that we have reached?

I would like the voting members, I would like to see if those of us who are present -- and Pat, you can vote by voice -- we will all put our heads down on the table so that we can't -- but I would like to take a vote so that, again, in my letter to Dr. Satcher, I can say that this was a consensus document or was not a consensus document.

DR. TUCKSON: I would have just one clarifying question. I think we should do the vote and I hope it will go the way that you ask. In voting as a consensus document, that doesn't mean that we all are saying that we agree to every single point, but that we agree with the document as a product, you know, as a whole, and we can embrace the document.

If that be the case, I would like to make the motion that we approve the document unanimously, in terms of the spirit of document itself, although, with the proviso that each of us may have individual points. But on whole, it represents how we believe.

DR. McCABE: Do I have a second to the motion?

[Seconded.]

DR. McCABE: Okay, the motion is seconded. Further discussion of this motion? Remember the federal representatives are not voting members of the committee.

MR. HILLBACK: I think we all have -- this is an iterative process too. My favorite word. And I do think we've come a long way. I think that each individual, as Reed says, has individual words, individual phrases that are not their favorite words or phrases.

I think to say that you are not in support of this document means that you have a major problem with it's major conclusion, rather than niggling questions with one phrase or another. That also means that as it goes forward and as we try to work the document into a living set of regulations, that all these discussions aren't over.

DR. McCABE: Right.

MR. HILLBACK: And so on that basis, and I think that's the spirit that we have come over this year to get to, I think that we're in the right place.

DR. LEWIS: Well, consensus would mean that we don't have to vote on it. Consensus would mean that we would just sit here and say that there is no one who has serious reservations.

DR. McCABE: Well, but I think if we can vote --

DR. LEWIS: I am not opposed to voting, but just the whole consensus process is one where you don't vote.

DR. McCABE: Yes. I think, though, the motion has been made that if the motion is carried unanimously, then I can state to the Secretary that the feeling of this committee is that, as a document in toto, the members of the committee are in full support of it. That's the way I read this motion.

All in favor of the motion, please raise your hands.

[Show of hands.]

DR. McCABE: Any opposed to this motion?
[No response.]

MS. BARR: You can note that Pat said "Yes."

DR. McCABE: Pat Barr is also in agreement. Any opposed to this motion?

[No response.]

DR. McCABE: Any abstaining from this motion?

[No response.]

DR. McCABE: The motion to unanimously endorse this document carried unanimously. Thank you very much.

[Motion carried.]

MR. HILLBACK: I think that what we need to do now is be careful we don't over-extend ourselves. I think, Ed, you were talking about education as being a crucial piece. We have also committed ourselves in a relatively short time frame to work with various parts of DHHS to move this process along.

So I would hate to put four things on the next meeting's agenda, each of which had a huge tail, and find that we weren't putting any time into finishing. Just because we send this letter, we have a lot to do to implement it, and I would like to make sure we reserve enough time of all of us to do that.

DR. McCABE: Well, I see some hands up, but let me tell you where we are on the education piece. During the course of this meeting, Joann has actually drafted the skeleton at least, if not more than that, of an education piece, and it was based on the discussion the other morning.

I would propose that we have a draft of that at our next meeting. We can decide what we do with it at that time, but decide whether or not we want to proceed with that.

DR. KOENIG: I just have some concerns that we haven't had an opportunity -- there has been an assumption that there has been a consensus about education being a priority.

DR. McCABE: No, no.

DR. KOENIG: I would just sort of like to, at some point, have a discussion about that, because what the presentations at this meeting actually said to me was that there are so many educational activities already ongoing, that in order to make a real contribution to that, we really need to think

very strategically.

There may be other areas that are even more important for us to work on than education, since there is so many things going on already by other groups. So it's not clear to me that it's -- at the risk of angering the chairman, I am, you know, sort of speaking against education which is like being against apple pie.

DR. CHARACHE: Personally, I would like very much to have a discussion at the next meeting about the patent issue. I think it would be very helpful for this group to put together and synthesize what we think of the issues that were raised, and whether this is something that we should or shouldn't get into.

It certainly is key to the laboratory testing part to have thought through how some of these applications fit together, including the quality of the testing that's being done in the monopolistic setting.

DR. LEWIS: I wasn't privileged to hear the education discussion the other day, but I can certainly tell you that in my experience one of the key things is educating both clinicians and educators so that the next generation of students can be educated. And while I don't know what was talked about in terms of current efforts, I certainly think it's a major issue in the professional community and I would like to see us continue with it.

DR. BURKE: I would argue strongly -- and I know we all need to go, and I apologize that I need to go very shortly -- that I don't think we can resolve the prioritizing process that we're trying to accomplish in the time we have left today, because I think it's a tough one.

I think we've heard interesting, substantive issues about education put forward, about IRBs, about patenting, and I think we have a number of loose threads still left, direct-to-consumer advertising, direct availability of genetic tests, and other issues.

I would make a strong pitch for a discussion, an open discussion of the committee, starting our next meeting that is a priority-setting.

MS. BARR: I am just wondering if some of that, since they are on the table, the public knows what they are because we have listed them, would it be all right for us to do some e-mailing so that Sarah could create an agenda for us that has the appropriate panels coming in to move us forward?

DR. McCABE: I would propose that what we will do is Sarah and I will work on an agenda. We will pass that agenda around by e-mail to everyone. People can amend -- that will not have the details of the panels but we can discuss this in the interim.

DR. BOUGHMAN: At this point it seems to me that our thought process should be that we might move to a different plan of attack, if you will, and move from over arching and integrated reports and/or assessments to more like a white paper type of approach. And we may come to the point where we have an opinion or a one paragraph conclusion on any one of these, after a single discussion, with much more data collection, or whatever it might be.

But it seems to me that now that we have opened some of these issues that we should, at least, in letter format make some comment to the Secretary about whether we are or are not going to comment further. But it could be after the next meeting that we say what it is our action plan is, after the next meeting.

MR. HILLBACK: I think I am sort of going to try and say what you said in a different way. It seems to me that today, and yesterday, and the day before, we had a lot of discussion, heard a lot of panels on a number of these topics. We really haven't had any time to debate those topics among ourselves.

And rather than set off on our next quest, although I do have a personal priority that I believe education ought to be the right one, I can understand how we ought to take at least the three issues that we've talked about, IRBs, education and this patenting issue, and have our own debate with, I won't say no panels, but with enough time that we can really have at it.

I think sometimes we spend a lot of time listening to others, and we don't have enough time going back and forth with each other and understanding and learning from each other and working opinions out. So I would push that way. And then I think we also ought to spend some time on the implementation part of the report we're sending to Dr. Satcher.

DR. McCABE: Yes. That came through very clear that we have loose ends there. We will pursue that. I want to thank the committee, I want to thank the public for your input.

But especially, I want to thank all the members of the committee for working very diligently over the past year so that we could get this document to Dr. Satcher.

Thank you very much. Have a safe trip home.

[Whereupon, at 3:30 p.m., the meeting was adjourned.]