

Public Comments and Q&A

DR. TUCKSON: All right. Now, ahead of schedule. I'm warning our public comment people that if you know anybody that thought they were on at 9:15, they are on now. So if somebody ran out of the room, come back.

One of our critical functions is to serve as a public forum for the deliberations on the broad range of human health and societal issues raised by the development and use of genetic technologies, so we greatly value the input we receive from the public. We set aside time each day of our meeting to hear from members of the public, and we welcome and appreciate the views they share with us.

In the interest, of course, of our full schedule, we ask the commenters to, as always, please keep remarks to five minutes. We have copies of your full statements, which will be made a part of the meeting record.

In a few moments, as I indicated, we will be addressing the oversight recommendations in depth. Prior to this meeting, we requested that those who have comments on oversight speak to the Committee today so that we can keep these comments in mind during our discussion.

Some of our commentators, unfortunately, were unavailable today and they will be speaking to us tomorrow, but we are really pleased that we have several folk who have made it their business to travel here today to give us their input. So we are very pleased.

Let me invite to the microphone Paul Radensky from the Coalition for 21st Century Medicine. As Paul comes up, just so we don't have a loss in terms of travel time, if Jeff Kant from the College of American Pathologists is here, Jeff, why don't you come on up as well. Then we will just start to shuttle people in. Thank you very much.

Paul, we appreciate your being here. Please give us your comments.

DR. RADENSKY: Good morning. Thank you all. Can you all hear me okay? My name is Paul Radensky. I am with McDermott, Will & Emory, and McDermott, Will & Emory serves as counsel to the Coalition for 21st Century Medicine as well as counsel to a number of the laboratories that are members of the Coalition for 21st Century Medicine.

The Coalition was formed a little over a year ago in response to two draft guidances issued by the FDA, one related to the in vitro diagnostic multivariate index assay and the other for analyte-specific reagents as an FAQ document.

The Coalition formed including both laboratories that develop laboratory-developed tests in that area as well as manufacturers of analyte-specific reagents to address concerns that both groups had with the content of those two draft guidances.

But the purpose of the Coalition was not to say "This doesn't work" or "Nothing works. You have to stop these." The purpose was to develop workable solutions that would support public health concerns about appropriate oversight for these technologies as well as provide incentives to continue developing in this area.

We submitted fairly substantial, detailed comments to the record in response to the draft oversight report that came out in November, and those comments were submitted in late December. I'm not going to repeat the 15 pages. We tried to be constructive and to respond specifically to every

recommendation, particularly in the chapters dealing with clinical validity, clinical utility, and decision support systems.

What I want to focus on today is something that we appended to our comments, which was a proposal in response to the IVDMA draft guidance that we submitted to the docket that the FDA has on that draft guidance. I want to explain a little bit about that proposal, how it came about, and very high level, what our objectives were in putting that together and why we believe that it is useful for the Committee to consider that in the recommendations for the final report to the Secretary.

We identified in the draft guidances, both the September 2006 and the July 2007, a number of concerns that stakeholders had, both that we had and submitted to the record as well as those that were submitted by others in the March deadline and then the August through October deadline for the second draft. We also were very aware and had a number of discussions with folks at FDA about their concerns.

The concerns that we identified were, one, transparency, a concern about advanced diagnostics having inherent in them algorithms, equations, and interpretation functions that were different from past diagnostics that folks wanted to understand better and viewed at some level as a black box. So we wanted to address that transparency concern.

There was also the concern of the fox guarding the henhouse. If you have the laboratories saying this is what our tests do, is there some independent reviewer. Is CLIA sufficient; is FDA the right way to address that.

Third was a risk-based regulation looking at a framework that is not technology-based but more risk-based.

Also, looking for clear definitions. There were lots of concerns about the definition in both the first and second draft guidances and a concern that essentially the definitions of IVDMA in both draft guidances were inherently subjective, looking at what physicians could interpret, what are standard functions, things that would lead to a lot of confusion by the regulated community.

Looking for clear and predictable pathways. What will be required. What does the science need to look like in order to get various types of claims for these assays.

A transition timeline, because we are talking about laboratories that have been regulated by CLIA, not medical device manufacturers. If they assume those new roles, it will take time for them to adapt to those new roles.

Lastly, needing to have continued incentives toward innovation. The diagnostic life cycle is a short life cycle. If you require substantial amounts of data and substantial timelines for follow-up, by the time you finish the studies you will have new diagnostics already in place and the ones you study will no longer be relevant.

So with those principles in mind, we came up with a proposal. We were encouraged to start with first principles by representatives from PCAST and representatives from the Department, saying rather than simply respond to what you saw, come up with a proposal about what you think would be the right approach.

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So we came up with a two-phased approach, saying at the beginning we don't know the number of tests we are talking about. We have heard some say that it is just a few. We have seen others where we have been able to identify a couple of hundred. We don't know. We don't know what the intended use claims are of these types of tests. We don't know the risks related to those. We don't know what the current state of the art is in terms of the science to look at these.

So our view is that in phase one, very much as the draft report proposed, as others like the Genetic and Public Policy Center, Senator Kennedy's bill, ACLA, have all proposed, a registry to try and get information about what are we talking about, how many tasks, what do they look like, what type of data do we have.

Based on that, our proposal is that that registry would be publicly available to provide transparency and would have a role for FDA to review and comment on those claims. So we would have the truthfulness and we would have an independent review of the validity of the data to support the claims.

DR. TUCKSON: Great.

DR. RADENSKY: We propose three to five years because it takes at least a three-year period to get a year's worth of data. If you want three years' worth of data, it is going to take about five years. From that, an experience-based and an evidence-based framework for regulation could evolve.

DR. TUCKSON: Thank you.

DR. RADENSKY: That would be one that over time would have an appropriate risk-based framework. We would encourage the Advisory Committee to look carefully at the proposal and to consider that in your final recommendation. We believe it is the best way to gain evidence for what appropriate oversight should be rather than simply to guess about what appropriate oversight should be.

DR. TUCKSON: Thank you, Paul. You have made that point very well, and we appreciate it.

DR. RADENSKY: Thank you.

DR. TUCKSON: Message heard. Just to make sure, is there any need for clarification? He has been pretty articulate about it.

[No response.]

DR. TUCKSON: We have a very good sense of what your recommendation is. Thank you very much.

As Jeff Kant from the American College of Pathologists comes up, can I ask David Mongillo from the American Clinical Lab Association to come forward as well?

Jeffrey, thank you for joining us.

DR. KANT: Good morning. My name is Dr. Jeffrey Kant. I am professor of pathology and human genetics and director of the Division of Molecular Diagnostics at the University of Pittsburgh Medical Center. I am here today on behalf of the College of American Pathologists,

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also known as CAP, where I chair a resource committee that oversees proficiency testing programs in genetics. We are following up on written testimony the College has provided to SACGHS on its report, U.S. System of Oversight of Genetic Testing, A Response to the Charge of the Secretary of HHS.

I have modified my remarks slightly and omitted the summary statement in your written to keep to the time limits.

CAP is a national medical specialty society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation accredits more than 6,000 laboratories here and abroad. Our members have extensive expertise providing and directing laboratory services and participate as peer inspectors in the laboratory accreditation program.

The College has been a leader in developing quality improvement programs for laboratories, including programs in genetic testing.

Laboratorians have some of the strongest measures of quality in medical practice. The College's experience from its proficiency testing and laboratory accreditation program is that the overwhelming majority of mainstream genetic tests performed in the U.S. are safe and effective.

As noted in the report, performance on multiple CAP molecular genetic surveys for analytic and interpretive accuracy has been excellent over a wide range of methodologies.

Of note, the performance of laboratory tests on our proficiency services is equivalent to assays that are FDA-approved for the same analyte. This is due in part to the robust nature of the analytes, along with rigorous attention to CLIA quality standards and practices, as well as medical oversight of every clinical laboratory by a physician.

The College's laboratory accreditation program stresses both analytic and clinical validation prior to introducing any test into practice, recognizing that tests will continue to be periodically improved after introduction, with each improvement revalidated by the laboratory before you send patient samples.

As medical specialists in the diagnosis of disease, the development and oversight of genetic tests constitutes an important and expanding aspect of medical practice to pathologists. We therefore have a keen interest in ensuring that our ability to provide high quality diagnostic services to patients and other physicians is not comprised by overly burdensome regulation. We recommend that changes to federal oversight of laboratory tests be made within the context of CLIA.

CAP supports further enhancement of laboratory testing through educational efforts, improvement in the quality of CLIA inspections, and additional federal resources for access to controls and standards.

The College agrees that appropriate resources be directed to CMS for required oversight of CLIA and supports SACGHS recommendations for expansion of proficiency testing.

Please consider that CLIA already requires assessment of analytic validity for all assays offered by a laboratory regardless of whether these tests are regulated analyte. We are aware of no evidence that alternative assessment leads to poor quality testing.

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Moreover, CLIA requires knowledge of the clinical utility of tests for use in routine clinical practice and stipulates qualifications and responsibilities of the laboratory to patients.

CAP believes that requiring FDA approval for every laboratory-developed test would result in numerous unintended consequences that would not benefit patients, to include delayed implementation of new tests, reduced innovation, increased cost, and greater limitations of access to beneficial assays. Given that high quality genetic testing is already in place, different regulatory requirements for this group of assays do not seem necessary and, since not all laboratory-developed tests are not genetic tests, difficult to implement.

Finally, the College supports the emphasis in the draft report on public-private partnerships for assessment of laboratory-developed genetic tests. We feel that registration of genetic tests through such partnerships could have positive impacts, but that such a system should be voluntary and devised with broad stakeholder input.

CLIA already requires submission of test lists by laboratories as a condition of inspection. Thus, additional information submitted should remain within the context of CLIA and CMS. New mechanisms for the collection of information should be tested before implementation to assure that the most useful information has been captured and that submission is not overly burdensome for laboratories.

This information could then be made publicly available, assuring clinicians and patients of the analytic and clinical validity of tests they are ordering while not impeding the medical practice of the College. Thank you.

DR. TUCKSON: Thank you very much, Jeffrey. Any inquiry of Jeffrey's comments? Yes, Muin.

DR. KHOURY: Did I hear you say that CLIA requires evidence of clinical utility? Or maybe I wasn't paying too much attention.

DR. KANT: We interpret the requirement for the medical director oversight of the laboratory in well-run laboratories to incorporate that. Certainly that is part of our accreditation inspection process.

DR. TUCKSON: Thank you very much, Jeffrey. Yes, one more question.

DR. FERREIRA-GONZALEZ: Yes, Jeff. Thank you so much for that comment. You have mentioned in your letter that FDA review of all the laboratories tests in CAP have a significant impact. I was wondering if you could further elaborate, as the director of a laboratory, what is, for example, the impact of having to follow quality regulation systems or additional inspections by the FDA on top of what currently you have to go through.

DR. KANT: I think it would be primarily in the additional time required to generate the supporting documentation and to host the inspections. Many laboratories, as you well know, a great deal of that work is done by the laboratory director him- or herself, and that is clearly less time you have to focus on developing tests and interpreting tests.

DR. TUCKSON: Great. Thank you again. As David Mongillo comes forward from the American Clinical Laboratory Association, Suzanne Feetham from the American Academy of Nursing, you can come forward. Thanks. David.

MR. MONGILLO: Thank you, Dr. Tuckson. I have had the pleasure of presenting comments to the Committee more than once, and I have always felt welcome. I know that the ACLA members have always felt that the comments have been well received and given full consideration. We recognize to a large degree that is because of the leadership of Dr. Tuckson. So we really thank you for your tenure and appreciate the fact that you have made us feel welcome and the full consideration.

Now the comments. As the Committee discusses the final report recommendations to the Secretary, we want you to focus your attention on one particularly important recommendation that, if not carefully communicated to the Secretary, could have unintended consequences. Namely, the recommendation in Chapter 4, Recommendation No. 4, which references the debate about the FDA's role in regulating laboratory-developed tests.

That recommendation as currently written states that SACGHS supports FDA regulation of LDTs and the flexible, risk-based approach the Agency is taking to prioritize laboratory-developed tests, an approach that should be robust enough to accommodate new genetic testing technologies and methodology.

ACLA applauds SACGHS in recognizing the need for a flexible, risk-based approach to genetic test oversight and the important role of laboratory-developed tests to keep pace with the rapid developments in this area. However, if the above recommendation is interpreted to mean that FDA's Food, Drug, and Cosmetic Act requirement should be applied to laboratory-developed tests without interagency coordination, needless redundancies and duplications will result.

Let me be more specific. Although there are many similarities between FDA's and CLIA's quality validation procedures, there are clear redundancies and duplications that, if not coordinated, harmonized, and streamlined, will stifle innovation in this area. These include separate inspections, separate quality system requirements, separate reporting and labeling requirements, and additional requirements for design control, corrective action, and prevention.

That is not to say that FDA does not have an extremely important role in this oversight or that any of these requirements are not important, but it is premature for SACGHS to definitively support FDA regulation of LDTs without recognizing the important first step of interagency coordination and requirement harmonization.

Further, the recommendation as written is inconsistent with the rest of the report's clear and overarching guidance to HHS to, and quoting from the draft report, "to enhance interagency coordination so that the agencies with regulatory roles, CMS and FDA, are working synergistically with one another, with other regulatory agencies, and with knowledge generation agencies."

ACLA firmly agrees that interagency coordination is fundamental to ensure that oversight is least burdensome and does not place unnecessary or duplicative regulation on clinical laboratories providing genetic test services.

ACLA and others have proposed regulatory models that build on this interagency coordination, are consistent with principles of least burdensome regulation, fill the regulatory gaps, avoid overlapping and potentially conflicting regulatory oversight, and allow for a participatory approach that draws on the expertise of industry stakeholders, CMS, and FDA. By invoking public-private partnerships, these models avoid significant new costs for the agencies.

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I have provided in the copy of my comments a graphic representation of ACLA's models. We do believe it fills the gaps, it does it in the least burdensome way, it is mindful of limited agency resources, it allows for full public transparency, and really does build on its interagency coordination.

What we are asking is that you take another look at that recommendation and revise it. We have given specifics, and I will read the change that we would like you to consider. The recommendation would read, "SACGHS supports," adding the words, "an interagency role for FDA," and adding the words, "CMS's regulation of LDTs." The rest of the recommendation would stand.

Very much appreciate the opportunity. Thank you.

DR. TUCKSON: Thank you very much. Let me just take any questions there. I really like the specificity of the comment. He is not playing around.

[Laughter.]

[No response.]

DR. TUCKSON: That's fine. Thank you so much, David. As Suzanne comes forward, let me ask Peter Lurie from the Public Citizens Health Research Group if he might come forward. And, Suzanne from the American Academy of Nursing.

DR. FEETHAM: Thank you.

DR. TUCKSON: Thank you, and welcome back.

DR. FEETHAM: Thank you. Delighted to be here. Thank you for the opportunity to speak with you. You have a written statement that will provide more information than I will present at this time.

The American Academy of Nursing and the Genetic Healthcare Expert Panel of the Academy appreciate this opportunity to comment on the SACGHS draft report. We commend your comprehensive work and recognize that this is still a work in progress.

The American Academy of Nursing comprises more than 1,500 top nursing leaders and is constituted to anticipate national and international trends in health care and address resulting issues of health care knowledge and policy.

The genetics and genomics is obviously one of the most significant trends impacting health care, the public, and all health professionals. The integration of genetic and genomic technologies in the clinical arenas is unprecedented in its implications for health care.

The Academy commends the Committee on its efforts to assess the systems of oversight and regulation of genetic tests and for recognizing that the benefit of this burgeoning technology is dependent on establishing the analytical and clinical validity of every test. We provide the following considerations.

The Academy is concerned about the decision of CMS not to create a genetic testing specialty and associated proficiency testing, a reversal in the previous position. We strongly support

establishing a genetic testing specialty and associated proficiency testing for all laboratories performing genetic tests.

We encourage that you strongly recommend that CMS take action to establish a minimum degree of quality required of any laboratory performing genetic tests and that further study on the issue of performance assessment should be executed while instituting genetic-specific proficiency testing.

The Academy commends the Committee for recognizing the need for interagency coordination in the oversight and regulation of laboratory-developed tests and strongly supports the need to convene the relevant agencies to make recommendations on further regulation of genetic tests, an effort that should not delay instituting the genetic-specific proficiency testing.

We concur with your recognition that there are deficiencies in the genetic and genomic knowledge of all healthcare professionals. We are concerned that the Committee has not recommended that the HHS allocate resources to address these knowledge deficiencies. In today's fiscal climate, education efforts will be extremely hampered by the lack of funding to develop and implement innovative education strategies. We will propose a different strategy.

The Academy recommends an adjustment in the education strategies for all healthcare providers to one that focuses on system and practice change. There needs to be a shift from the traditional education approaches in schools and CE to one supporting the embedding of genetic and genomic knowledge into practice. Evidence of this knowledge being embedded into practice should be a component of every patient record for hospital and institution accreditation.

For example, education could include that the family history and patient family education materials address genetics. A successful model of this recommendation is the interdisciplinary program for integration of genomics into practice at the Mayo Clinic in Rochester.

When there is evidence of the application of genetics and genomics in practice, regulators will be influenced to include the expectation of this knowledge for all healthcare providers in licensing and accreditation.

To facilitate the shift of the education focus to practice, SACGHS may want to invite the representatives of accrediting bodies such as the Joint Commission and Health Facilities Accreditation Program to a meeting of the Committee to demonstrate the significance of the application of this knowledge to practice.

The Committee's recommendations on communication and clinical support will not be realized without the key foundation of an adequate healthcare practitioner knowledge base. We know that the Committee has noted that the number of healthcare providers with genetic expertise is not sufficient or adequately prepared to support best genetic test practices in the absence of clinically competent practitioners.

Many clinically available tests are supported by practitioners other than genetic experts, and an example is Oncotype DX, a multiple-gene assay performed on early stage breast cancer tumors where standards of practice for utilization support lie in the domain of the oncology specialist. This genetics test is just one of a number of tests that illustrate these implications and applications of practice beyond the genetic expert. This further supports the need for the education of all health professionals.

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In summary, to reach the potential benefits to the public health, all genetic tests must be adequately regulated to assure minimum quality, and healthcare providers must be prepared to incorporate these tests into their practice.

The Academy is poised to engage our fellows and other key stakeholders to develop an interdisciplinary initiative to increase the competency of healthcare professionals in genetics and genomics as well as develop the standards and practices that assure the highest levels of health care to all.

I will be happy to respond to any questions.

DR. TUCKSON: Good. Thank you so much. By the way, I just want to make note [of] not only the relevance of your comments for this report we are about to chat about but also on the Taskforce for Training and Education.

Barbara is not here with us today because of a pressing emergency, but I think, Joe, you are on that committee as well. If you will make sure, also, that those comments are delivered into that other process, I would much appreciate it. [They have] another mechanism for dealing with it and you have been pretty explicit, so we will make sure that this gets in to that committee.

Marc.

DR. WILLIAMS: I just wanted to speak specifically to that point, also being on that Education Taskforce. I will certainly take your comments to heart there.

Recognizing that we are focusing on the Oversight Report here, I just wanted to get your sign-off, if you will, that if your sense is that our devoting an entire taskforce to this educational issue is sufficient that we could leave the education recommendation alone here. Otherwise I think we are just trying to make this report all things to all people, and I just don't see that that ultimately will serve our best interests.

So I would just like to get your perspective if that is an appropriate way to proceed rather than trying to modify the recommendation as it currently stands.

DR. FEETHAM: We recognize that, and part of it is, obviously, the interdependence of all of these recommendations and that the knowledge is inherent in the issues on genetic testing and the validity and reliability of those tests.

DR. WILLIAMS: In our revised recommendation for the report, we specifically articulate the fact that there is a taskforce of SACGHS that is devoted to education. So we are attempting to do that.

DR. TUCKSON: Great. Thank you so much. Very well done.

As Peter Lurie comes forward from Public Citizens Health Research Group, let me invite Mark Sobel from the Association of Pathology Chairs to also come forward. Peter, thanks.

DR. LURIE: Good morning. I'm Peter Lurie, a physician with the Health Research Group of Public Citizens. We are an advocacy group here in Washington. My conflict of interest statement is that we take no money from either government or industry.

I want to talk from the patient perspective and make clear that from the patient perspective there is no distinction whatsoever between a genetic test or any other kind of laboratory test that they might undergo. They don't understand the regulatory framework behind a genetic test or a laboratory-developed test. They just get a blood test or a cheek swab. They assume that the amount of regulatory oversight that is associated with both of those tests is equal.

The fact is that we have a form, to use your phrase, of genetic exceptionalism taking place whereby the vast majority of genetic tests are indeed barely regulated, whereas the vast majority of other tests fall under the FDA. So indeed there is genetic exceptionalism, and I think very few patients, if any, will understand that. I think that we owe patients that amount of equality and of comprehensiveness in oversight.

Indeed the report itself seems to reach a similar conclusion. "Genetic tests and the laboratories performing them should be expected to meet the same high standards of accuracy, validity, and utility to which other medical information is subject, and that is decidedly not the case here. I don't think that the taskforce's current recommendations will do much to rectify the situation.

Part of the problem is that the voices of consumers have not really come before this Committee or the taskforce to a significant degree, despite what Dr. Tuckson describes as assiduous efforts to reach them, except for a consultant pathologist whom I don't know much about. All 33 members of the taskforce come from government, academia, or industry, and the vast majority of comments that have been submitted to the record, of the 64, only two of those are coming from consumer or advocacy groups.

Despite that, however, it is notable that these primarily professional groups and even groups with a financial interest in the outcome of this report primarily disagreed with the thrust of the taskforce's recommendations. Let me go through three of those recommendations in turn.

The first of those is with respect to CLIA. As throughout this report, the taskforce does an excellent job of diagnosing what ails the system. It concludes that assuring the analytical validity of genetic testing is paramount, and it goes on to identify a litany of problems with the current situation. However, despite the rigorous documentation of the centrality of PT and the limits of current CMS oversight, the draft report provides no rationale whatsoever for failing to endorse a genetic testing specialty. Moreover, as the report itself acknowledges, this is contrary to congressional intent, which is to generally require PT for all laboratories for all clinical tests, no exceptions for genetics.

So we would like to see a much stronger endorsement of PT. If it takes a genetic specialty in order to make that happen, this taskforce should be endorsing just that.

With respect to FDA regulation, the problem is similar. Again, a ringing endorsement of the importance of clinical validity of genetic testing, described again as paramount, but yet despite the well-documented reasons for expanding FDA regulations and again the problems with current FDA oversight, the draft report simply endorses status quo. It seems to endorse the FDA's efforts with regard to the IVDMA, and as important an effort as that is, it really is a baby step in terms of reaching the literally 1,200 or more genetic tests that are currently available.

As in its justification for its failure to endorse a genetic testing specialty, the draft report provides only the most meager of explanations for its failure to recommend vigorous FDA oversight.

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It talks about the backlog, which you do come to have after ignoring two prior reports from committees rather similar to this one dating back a decade. If you don't implement those recommendations, which recommended more FDA oversight as well as more CMS oversight, you do develop a backlog over time.

In fact, even at FDA there is a good example of the ability to clear a backlog. It is called the DESI process, in which drugs on the market prior to 1962 but after 1938 were reviewed. Thousands of drugs. Those that were ineffective were taken off the market. So FDA has an ability to do such a thing.

If there is a problem of lack of resources, well, then this Committee is better placed than anybody to be able to recommend an increase in resources rather than to just sort of surrender to that problem. You should be advocating for that if you think it is important enough.

Finally, a concern that new technologies would be delayed. We often hear those kinds of concerns, but no one really provides any data to back that up exactly. What about the dangers, though, of allowing unregulated products in the market? What about people who have abortions that they shouldn't be having? What about people who don't undergo a particular course of therapy that they should, or do when they shouldn't? That must be considered as part of the calculus as well.

The third main element I think in the report has to do with the registry. As the report acknowledges clearly, no one knows the number and identity of currently available genetic tests. This is an unacceptable situation in this country after these tests have been available as long as they have.

But, what is recommended? The creation of a voluntary registry for a trial five-year period. We already have a voluntary system. We have had it for 14 years. It is called gene tests, and the very deficiencies that we currently have in understanding what tests are available are deficiencies in the voluntary system. So, how can it be logical that the recommendation be more of the same?

Indeed that is the overall problem with the taskforce's report. It does an excellent job of identifying the problems. It lays them out clearly. But when it comes to following its own recommendations to their logical conclusion, it falls short and simply endorses the status quo. Thank you.

DR. TUCKSON: All right. Thank you very much. I appreciate your comments, and you can be sure that we will be wrestling with each of those as we go forward in a very meticulous way.

Does anybody have any questions to ask at this point? Yes.

DR. TELFAIR: Yes. Thank you very much for your comments. I just have a question in regard to something that is always a challenge, particularly with this type of effort. One of the clear challenges that you had, and I will make it as a challenge, was the point about the actual diversity of the comments themselves and where they actually came from.

The challenge is always getting consumer input and consumer involvement with this. I know that every effort is made to do that. Maybe as a parting comment from you, what would you have suggested have been done to get more of the type of consumer that you think should have had comment into this? Knowing that a lot of effort was put into that.

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DR. LURIE: Let me just briefly point out, of course our comments are part of the record. Whereas you point out that there is a diversity of comments, there is some, but as I think Dr. Fomous will agree in her summary of these, the majority of people take a position certainly in favor of a genetic testing specialty, and most as well take a position in favor of some FDA regulation.

I did hear about this report and that it was available for comment via somebody else who sat on the taskforce. Nobody approached me or suggested to me that we might testify before this Committee despite the fact that we had filed the petition with CMS asking for the creation of a genetic testing specialty. I mean, if any consumer group was in play to be invited, it was us, and I only heard about it indirectly.

There are a number of consumer groups in this town who may be interested enough to testify. I can't be certain. I could have led you to them. Somebody might be able to contradict me, but whatever efforts were made to reach consumer groups, they didn't reach me.

DR. TELFAIR: Actually, sir, that was not my question.

DR. LURIE: Oh, I'm sorry.

DR. TELFAIR: My question about the diversity was as to a recommendation to the Committee. This is only one of many reports that we are going to be working on. If this continues to be a challenge, because I have heard it from a lot of people, what is your recommendation how the Committee in its future efforts can begin to engage a broad base of consumer groups and organizations that, you point out, were not engaged, including yourself. That is what my question was.

DR. LURIE: I see. In a way I feel I have answered it in the sense that I have pointed to the deficiencies, or what I see as them, with regard to this. But it is difficult, and I do appreciate that.

I think the best way to do it is to identify key informants, perhaps a group like ours or other groups like the Genetic Alliance, which has members in a large number of different organizations, and to ask them to put the word out further. Certainly there are Federal Register notices and the like, but nobody reads that. So I think you start with a key informant and you hope that you can get the word out that way.

DR. TUCKSON: Thank you. I want to move us forward, but let me be very clear. First of all, I really appreciate the specificity of your comments. They are very helpful to our process.

I will say that the Genetic Alliance and every other major consumer organization in genetics is well aware and has been here testifying for years. It would, I think, be a matter of debate. I really don't have time to go through it all, but there is an extraordinary legacy of involvement by this Committee, and it is extremely well known throughout the genetic consumer and professional community. This Committee is no secret. Its work is well known.

We have solicited extraordinary efforts to make sure that we got [that.] You were told about it. You are here. So I would say to you that I think that what we want to take from your comment, and I really think that Joe did a terrific job in making sure, we can always do it better. I think that we will endeavor to make sure with this spur that we continue to try to do better.

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But I must suggest for the record that this Committee's involvement with the genetic consumer community is extensive, long, and broad, and that I would not want to have the record not have that comment written into it.

However, I think that your comments are very helpful and we benefit from them and your presence here. We thank you.

DR. LURIE: Thank you.

DR. TUCKSON: Next comment, please, from Mark Sobel. Then I'm hoping Linda is on the phone, Linda Avey from 23 and Me. Do we have the ability to know if Linda is on the phone?

MS. AVEY: Can you hear me?

DR. TUCKSON: Oh, you are there.

MS. AVEY: Hi.

DR. TUCKSON: You are next.

MS. AVEY: Great.

DR. TUCKSON: Well, you are sometime soon.

MS. AVEY: Good. Thank you.

DR. TUCKSON: I have a wonderful list. I'm the chairman, and I'm saying you are next.

MS. AVEY: Cool. Great.

DR. TUCKSON: So, just be right there. With that, Mark Sobel is now here from the Association of Pathology Chairs.

DR. SOBEL: Good morning. I'm Dr. Mark Sobel. I'm the managing officer of the Association of Pathology Chairs. APC represents the Departments of Pathology and Laboratory Medicine in all of the accredited medical schools in the United States and Canada. We submitted a comprehensive statement in December, and we appreciate the opportunity to highlight the three most significant points in public testimony today.

Those three points are the definition of genetic testing, determining under whose authority quality assurance is best managed, and identifying the best system for test registries.

As to the definition of a genetic test, we see that SACGHS is using a very broad definition of a genetic test, going beyond heritable changes to include somatic variations, and going beyond DNA and RNA to include proteins and other analytes. Under this definition, the tests would more accurately be called molecular tests rather than genetic tests.

We believe that the document needs to define which intended uses are included in the intended oversight of genetic testing and the Committee also needs to define the difference between genetic and genomic applications.

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SACGHS seems to conclude that genetic tests, given the anticipated breadth of their use in the future, should not be considered as significantly different from other clinical tests, and the APC agrees with this perspective, which is also consistent with the approach recently taken by CMS to not establish the genetic subspecialty.

But if this is so and the Committee is opting against genetic exceptionalism, then it is unclear why genetic tests are proposed to require greater oversight than non-genetic tests that are similarly molecular, laboratory-developed, complex, and potentially high risk.

We recognize, of course, that tests for heritable diseases are unique in several respects, including the risk for misinterpretation by practitioners who are unfamiliar with the limitations of genetic risk assessment.

Nonetheless, at the technical level the diagnosis of genetic disease by molecular methods does not differ significantly from the same techniques that are used to diagnose infectious diseases and neoplastic diseases. Therefore, it is not logical to establish more stringent technical and personnel standards for molecular genetic testing that already exists, including molecular oncology and molecular microbiology testing.

While, unfortunately, harms may occur in genetic testing, these risks are also, unfortunately, present in all areas of health care. We of course must work to minimize all of those, but we are not aware of data that demonstrates that harms from genetic testing are greater or less than from the other medical procedures that are performed or tests.

As to quality assurance and CLIA versus FDA regulations, I think, in the interest of time, my colleague Jeffrey Kant of the College of American Pathologists very adequately expressed the opinion of the APC that further regulation by the FDA in this matter would be inappropriate given the oversight that CLIA has, could be duplicative, and could indirectly have unforeseen consequences such as delaying innovation and the appropriate amount of time used to develop new tests.

Finally, on the system for test registration, the APC heartily endorses the Committee's recommendation to develop a public-private partnership of voluntary registration of tests. CLIA already requires registration of the name and methodology of each test that is performed, but it cannot necessarily retrieve that information and the public does not necessarily have access to it. By making the information that laboratories voluntarily register with CLIA more publicly available, we feel that the public will benefit and there will be no need to establish a new registry system. Thank you.

DR. TUCKSON: Thank you very much. Boy, this is going to be fun, isn't it?

[Laughter.]

DR. TUCKSON: No matter what we do, everybody is going to be upset with us. We will not have a friend in the world when this is over.

That was extremely clear, though, and you were very clear, just as the people before you have been very clear. I just wish you all could all find someplace where everybody could agree so we wouldn't have such a hard time. Boy, we are going to get yelled at everywhere.

Questions?

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DR. KHOURY: I have a question. Do you think consumers and providers today have information on their fingertips that is available as to the analytic validity, clinical validity, and clinical utility of existing genetic tests on the market, and where would they get that from?

DR. SOBEL: No, I do not believe they have that readily available. There are various public sources of that information. There are two websites that come to mind first to me. One, in the relationship to heritable diseases and tests for those, would be the website called Gene Tests, which is run out of the University of Washington which provides information not only about the tests and its background but also has links to which laboratories provide those tests. But I think understanding the unique areas of analytic utility and clinical utility are difficult to access for most people.

The other website that I would tell you about is the Association for Molecular Pathology's Molecular Test Directory, which is called AMPTestDirectory.org, which is a listing of tests but does not provide background information on those tests.

I think herein lies the distinction because the AMP website of tests is not heritable disease tests. They are what I would call the somatic tests. They are infectious disease tests. They are tests for disorders of the hematologic system such as leukemia and lymphomas. They are tests related to neoplasia.

So those have listings of tests and do not provide the information. Here again, it is really the purview of the practice of the laboratorician. These are practicing physicians.

I think there is a lack of understanding of the testing. There is certification of the laboratory directors for all laboratory tests that require an understanding and an expertise, and that is what we are trained in, to actually understand quality control, quality assurance, as well as the test validity, the analytical validity, and the clinical utility of the tests that are ordered.

DR. TUCKSON: So, how do you respond to Peter Lurie's comments? He basically is saying that we are being exceptional by [being] inattentive to being more rigorous in our oversight. You are saying we are being exceptional by being overly oversightful.

DR. SOBEL: I guess my major point would be that, in my opinion, every single test that is performed, whether it is a glucose test, whether it is my protide for whether I am getting the right level of Coumadine on a daily basis, or whether it is for a cancer test such as is done by the onco system that was previously mentioned, or for a test for an inheritable disease condition, all require absolute, 100 percent accuracy in order for the public to be safe.

My colleagues in pathology once noted, in the days of the multi-million dollar contracts that started for baseball players, that you get a batting average of 0.333 and you get \$15 million. If a pathologist misses one out of 1 million tests right, they are sued and their careers are over. People are hurt.

DR. TUCKSON: You are doing wonderful. But other than the legal system for suing them or professionals yelling at them, I think what the question comes down to is how does the public know that that is happening? Other than the tort system, doesn't the public deserve greater? That is the point that I think people have.

DR. SOBEL: I think the public does deserve better knowledge. They need to be better educated. They need to have access to more information such as in the registry that is suggested by the SACGHS report. I think that is all part of consumerism and better knowledge.

But this really does require expertise. Somebody finally needs to have the expertise to say this is clinically valid, and that is what peer review systems are about, that is what test validation is about. This is the daily practice of the pathologist. So it is just like your internist examining you. It is exactly the same level.

DR. TUCKSON: I've got it. You are really helpful here, and I know we have to get on to the next one. I think you have made your point. Because of everything you just said, and this is a criticism that the Committee has to deal with because --

[Interruption.]

DR. TUCKSON: The dilemma you just presented us with is you just gave a compelling reason why people want us to take greater action. You have said this is complicated, the whole thing is complicated, it is a real problem. People can't possibly in their daily lives figure out or want to figure out before they do a test, let me go research 18 things. People are just trying to live their lives and assume that the tests are fine. You have just given a compelling reason why, other than this phenomenal trust. That is all you are saying we should do, is trust.

DR. SOBEL: That's true. I think systems really are in place to justify that trust. We have proficiency tests. We have quality control tests. We have inspections. The inspections very often go beyond what the regulations require.

For example, there was the question about whether CLIA required clinical utility, but actually, the CAP inspections, for example, that inspect all the laboratories, or most of the laboratories at least in the United States, require that as their criteria for passing that inspection.

You think you are in trouble. You should hear the complaints that we on the inspection committees get for how rigid we are and how unreasonable we are about what qualifications we are requiring. We are all getting that. That is why I have trust in the system.

DR. TUCKSON: Mark, thank you so much. By the way, one reason why I have been querying you is because you are very articulate. It is a sign of respect for you.

DR. SOBEL: I appreciate it.

DR. TUCKSON: I wasn't being personally confrontational with you.

DR. SOBEL: I didn't feel that way at all.

DR. TUCKSON: Thank you. You are terrific. Thank you very much.

Linda? Did they allow you to stay?

[No response.]

DR. TUCKSON: Linda?

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MS. AVEY: Hello?

DR. TUCKSON: Oh, good. Linda, you are there.

MS. AVEY: I'm sorry. I thought I just got cut off the call.

DR. TUCKSON: No, we won't let them. We are beating them up. Linda, if you didn't know it, you are with 23 and Me.

MS. AVEY: That is correct, yes.

DR. TUCKSON: You have five minutes, and we are eager to hear you.

MS. AVEY: Great. Thank you so much for the opportunity to address the Counsel. I will just go through our notes that hopefully people also have a copy of.

23 and Me was founded on the premise that individuals have the right to access their genetic information and learn about themselves in a new way. We believe that individuals have the right to know what their bodies are made of and that they should not have to pay for those services of a healthcare professional to find out those facts about themselves.

Consumers understand and cope with risk-based information every day, and history shows that fears about how consumers will respond to information are usually overblown and inaccurate. People were able to handle being told that they had cancer in the '60s, that they were pregnant in the '70s, that they had HIV in the '80s, and that they may have had an increased probability of Alzheimer's in this decade, as the REVEAL studies have shown.

We think that federal and state governments as well as physicians should not impede information development and dissemination based on an old-fashioned and, frankly, paternalistic view of what ordinary people can and cannot understand or handle.

We don't plan to stop at providing information to individuals just about themselves. We are developing a way for them to engage actively with a new research effort, something we call consumer-enabled research.

We think that progress in genetic research will be greatly enhanced by the development of a large database of genetic and phenotypic information contributed voluntarily by individuals interested in getting directly involved.

I'm sorry. Can you hear me? I'm cutting out.

DR. TUCKSON: We hear you very well. Be confident. Just continue.

MS. AVEY: Great. I think instead of reading through this what I would rather do, because hopefully everybody has a copy of this?

DR. TUCKSON: Yes, we do.

MS. AVEY: What I think I would rather do is just comment on the conversation that was going on prior to this because I only have five minutes. What 23 and Me is about is really giving people access to information that will hopefully enable us to understand more about the human

genome. So rather than talking about diagnostic tests, which we really don't believe we are, we are more about bringing information together about a lot of people so that we can learn more about our genomes and then transfer that information back to people.

This really isn't about genetic testing, and maybe it is not the appropriate time for us to be debating whether or not people should have access to this information because it really is not about performing a test. It is more about having this information flow back and forth. Then, as people are able to give more information about themselves, we really hope to gather that together, share that back to the research community, and hopefully make it a benefit for everyone.

We are really not talking here about whether CLIA is applicable or FDA is applicable. We are here to say that we don't know enough information yet. This is really more about a research effort. That is really what 23 and Me is going to be focusing on.

I would be happy to take any questions that anyone might have.

DR. TUCKSON: Great. By the way, would you remind me of what 23 and Me is? I should know it, but I don't.

MS. AVEY: 23 and Me is a private-based company here in California, and we are enabling people to get access to their genetic information through the use of the research tools that are being used by laboratories across the country, and actually across the world. We use large-scale genotyping microarrays to give people this information, and then we wrap context around it to give people an idea of what is coming out of the research community so that they have a better understanding of what these large-scale studies are turning up.

A lot of times you will see publications or stories written in the New York Times and the Wall Street Journal of these reports. Our mission is really to give people the opportunity to learn more about what this means in context of their own genomes.

We don't put it to people that this is a diagnostic test. It is more of a way to give them information that is reflective of what is coming out of the research community.

DR. TUCKSON: We have a couple real, real quick hands, and we will have to have real quick questions and answers. Paul Billings.

DR. BILLINGS: Linda, this is Paul Billings.

MS. AVEY: Hey, Paul.

DR. BILLINGS: We have been hearing this morning about how consumers can judge the quality of the testing that they are provided. Does 23 and Me have a position on that issue?

MS. AVEY: It is a really good question. What we are grappling with right now is finding the right way to provide that QC of the data back to the consumer community because we really don't feel like CLIA is the appropriate vehicle to do that. In fact, if anything, we feel like putting a wrapper of CLIA testing around what we are doing might be disingenuous to our customers, giving them some impression that the information is clinically validated, which we really don't feel it is.

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Because it is coming out of the research community, we are providing this as an educational effort, and therefore to say that this has CLIA wrapping on it really, I think, sends the wrong message.

That said, we are doing everything we can to comply with CMS and we feel like this is an opportunity to have a discussion with them beyond CLIA. Again, we don't argue with CLIA, but it is just that it sends the wrong message, we think.

DR. TUCKSON: Good. Real quick, we have Joe, Jim, and Muin, and then we will stop there. Joe, Jim, and Muin.

DR. TELFAIR: I will pass on my question because it is a little bit longer to answer. I will get it another time.

DR. TUCKSON: We are coming back to that. Good. Jim.

DR. EVANS: This is Jim Evans. For those individuals in the room who are not familiar with the offering and haven't, for example, toured the website, I was wondering if you could just give any kind of general position on what types of SNP associations that you are providing.

For example, there is going to be an offering soon of a company that is specifically designed to look at medically oriented SNP associations. A) Do you have a particular overarching philosophy, and B) do you want to give any specific examples of the types of SNP associations that you report to the audience here?

MS. AVEY: Yes, absolutely. One of the components of our website is something called Gene Journal. We have a white paper on our website that explains the process our scientists go through before we are willing to report on any particular finding. They are mostly focusing on the common diseases that are multigenic. We are not really focusing on Mendelian disorders because those are well documented and a lot of those have already been identified and studied and there are genetic tests that exist for those.

For example, with type II diabetes, currently there are about seven genes that have been solidly established as being associated with that disorder. So we report on those and explain to people what the different versions of the genes are and give them references back to those papers if they are interested to read. But we also break it down into everyday terms of what does this mean for an individual who doesn't have a genetic background.

DR. TUCKSON: This is fascinating. Muin, you have a quick question here?

DR. KHOURY: Yes. Linda, this is Muin Khoury. I'm from the Centers for Disease Control and Prevention. I have co-authored a piece in the New England Journal of Medicine in January about the premature readiness of these kinds of research tools being offered to the general public, but I do appreciate your comments and the fact that you are trying to educate consumers rather than selling them "a genetic test."

But, if these were genetic tests to be offered for prevention of disease or health promotion, they would not pass the test of either analytic validity, clinical validity, and clinical utility. So as long as you appreciate that point, but it seems like you are making a distinction between an educational tool versus a tool that could be offered for health purposes. So I wanted to hear a little bit more of your perspective on this given that these are research tools and they are research

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in progress. What do you expect consumers to do with the information that is probably incomplete and changing as we speak?

MS. AVEY: That is a really good point. When we read the article in January, we were actually very much in agreement with it. We do feel like a lot of this information is so premature. What our mission is, really, as a company is to continue to collect information back from our customers. So we explained to them that this is only research. We point out very clearly that it has only been done in certain populations.

So if, for instance, someone is of South Asian ancestry, there might be a publication that came out but it only applies to Caucasians and maybe Asians. So the research is very limited. What we hope to do is empower people to come back to us and tell us about themselves.

So if someone sees the markers for type II diabetes but it is only applicable to Caucasians and Africans, we can say, well, if you are South Asian, you report back to us whether or not you have type II diabetes and we will continue this research together in a very prospective way.

So we really look at the Framingham Study as a great model. What we want to do is move that concept of prospective long-term study to the Internet and into a social networking capability where people can share that information very directly and very dynamically.

DR. TUCKSON: Thank you so much. Let me, by the way, remind everybody again, if your cell phone or if your Blackberry is on, it is receiving messages and that is what that noise is.

By the way, folks, in July we have the benefit of having a special session where we will learn about companies like this. So we will have a chance to revisit it.

I am very cognizant of being the moderator and the time, but I want to make sure that all the issues are really clearly in front of us. So let me just ask you one thing to make sure I'm hearing what you are saying.

Are you only providing information, not feedback on any aspect of a person's genetic profile? Is it just articles or information? What I think I'm hearing you say is that because you make no pretense about whether something has received any scrutiny of analytical validity, et cetera, et cetera, et cetera, that you are just providing it with information, therefore it, by definition, does not require any oversight.

So it is like a sense that, well, listen, I make no pretense as to what this information is. Here, have at it. How you choose to deal with it is up to your own intelligence as an individual, thereby avoiding any oversight whatsoever. Is that what I'm hearing you say?

MS. AVEY: No. I would say that we welcome oversight and that we are very eager to hear back from both the medical and research communities about what it is we are doing because we do want to educate people about how their genetics are impacted by the studies that are coming out. With the caveat that it is all subject to change.

We don't even know if cholesterol now are as valid as we thought. I think the lay public is pretty used to getting information and understanding it at a certain level. As long as we present it to them properly that this is a work in progress, that this information is going to be changing in dynamics, but it is more about them feeling like they are part of the research process. Right now

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when you talk to most people, they don't feel like they get to have a voice in where the research is headed. I think the autism community is a good example of that.

We want people to feel like they are more a part of the process. I was in Framingham when NHLBI was there celebrating the anniversary earlier this year. It was so clear that the people that are in Framingham have a lot of sense of ownership of that process. We want to move that to the Web in a social networking way so that people have that same feeling.

But we welcome opportunities to talk to committees like you guys.

DR. TUCKSON: Let me just say there are a couple other hands here. I think that you have actually opened up an incredibly important issue here. I'm going to take a little liberty as the moderator and get two more questions in because I think that you have put something on the table that, quite frankly, has gotten my full attention.

DR. FERREIRA-GONZALEZ: Linda, I was just curious. You say that the main goal of the testing is for research purposes. I was wondering, when you provide the report back to the individual that requested the test on themselves, are you stating that these results are for research use only, clearly?

MS. AVEY: We do couch it in a way to say that this is initial information. We cite the publications. We have a vetting process where we explain how our scientists have read these papers that come out. If they don't meet the criteria that we have established, and again, those are up on our website, we explain that there are other studies that are out there.

Because our initial response back from our customers is that they actually want more information and that they are just hungry to know more, we are going to have a way to stack up the research that is coming out and report things to people that we say, look, you have to take this with many grains of salt. We will have more of a gradation of the information.

But people just seem really eager in wanting to get this data in front of them.

DR. TUCKSON: As a last point, Joe, and we will have to close off on this and move to the next commentary. Joe.

DR. TELFAIR: Ms. Avey, it is Joseph Telfair. Thank you for your comments. I think that Dr. Tuckson indicated that groups like yourself have a chance to speak again. To me, it would be very helpful and very instructive if, when you get a chance to present again, you actually map out a case to show how you actually carry out what you do with the information.

Right now, I'm not sure. I just think for myself -- I can't speak for the rest of the group -- there is a number of integrations. You talk about the case. You talk about the process. You talk about also how you think it should go. All of that is integrated in the responses that you are giving. It is hard to follow since we are not as familiar with your program.

So if I can make a recommendation that the next time you do have a chance that you present a case and just walk us through how you use it, what kind of questions you get, how the information itself you pull together, how you then disseminate that information, and then what was the intent of that session.

I think that that would be really helpful to us because what it sounds like you do is a good thing.

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It is just that it is hard to decipher because there is a lot there that you are speaking about.

MS. AVEY: Absolutely. We would be happy to come and give a demo. I think that is the most powerful thing we can do, is show you exactly what it is our customers see and the information that they are receiving.

DR. TUCKSON: Thank you, Linda. Any information you have, send it to the Committee about what you all are doing and examples. I think we would benefit from that. Thank you for taking the time to be by phone and answering our questions. Take care.

MS. AVEY: Thank you so much. I appreciate it.

DR. TUCKSON: Great. Mike Watson, who is well known to this Committee from the American College of Medical Genetics, will come up, and then Emma Kurnat-Thoma? Come on up. Michael will take the floor.

DR. WATSON: Thank you very much for allowing me to make some brief comments here today. I represent the American College of Medical Genetics, an organization, unlike many of the laboratory organizations, that bridges both laboratory testing and clinicians who deliver genetic tests to the population. For the most part, I'm going to focus on the heritable disease side of genetic testing today.

I co-chaired the Taskforce on Genetic Testing back in 1995. I'm not certain we have made tremendous amounts of progress since then. Realizing that this is Reed's last meeting, I'm hoping he doesn't get that same funny feeling in 10 years.

DR. TUCKSON: Well, it was the firm foundation you established, sir, that got us here.

DR. WATSON: Well, I didn't do it to spawn advisory committees. I was hoping we would make a lot more progress over the years than we have. But there are some concrete things I think we can do, and I think we need to look very carefully at why the progress that we have hoped for hasn't been made. I think there are some fundamental aspects of genetic testing that get at why we really haven't been able to make some of the progress we had hoped to have made.

Genetic testing is actually highly complex. It is enormously diverse, so not any one group is really well placed to deal with all of genetic testing. And, there are a huge number of tests. We have recently had the entire gene test library transferred to us in the interest of a project we are working on to develop an analysis to see what it would take to lay down the clinical validity of every genetic test currently in gene tests.

People often talk about there being 1,000 or so genetic tests available. That is so far off the mark it is stunning. There are maybe 1,000 genes that we do tests in, and that is very much the way gene tests are designed, is around the genes on which we focus. From an analytical perspective, I think you can say maybe that we do 1,000 genes' worth of testing.

But from a clinical validity perspective, the problem is one of why we do tests, the intended use of the test. Every single one of our tests can be broken down into a much larger number. When we do diagnostics, we may do directed mutation testing. We may do sequencing that gives us a very much different kind of information and has very different calculations around how one demonstrates clinical validity.

I think that is one of the fundamental problems. The other is that, of the 4- to 5,000 tests that we, roughly, have calculated being present among those in gene tests, the vast majority are for rare diseases. That is another problem that has been very difficult for us to get a handle on.

Manufacturers have not come into the marketplace and done the kinds of studies that are often done when devices are developed because there is no financial incentive in the marketplace to invest in the development of those rare disease tests. It left it to the laboratories to develop them themselves if they wanted them to be accessible to their patient population.

That has made it very difficult because laboratories in general aren't in a strong position nor well enough resourced to lay out the guidelines and the clinical validity at a general level for the population. They do it specific to the test they offer in their laboratory, and there is tremendous diversity around those tests that are offered, both analytically and clinically.

There is also a lot of variation between different populations -- we have heard it alluded to already -- that makes it much more complex than many areas of genetic testing, like infectious disease. It doesn't suffer from huge variations among one population of Asians versus Caucasians. That does lead to us being very often in a clinical practice of medicine position of interpreting what these sequence variations actually mean.

That is very, very difficult from a regulatory perspective. Lots and lots of rare and private variation that is unique to a family or an individual in the world that is not easy to regulate. Therefore, we have become convinced that probably the best way to get at this is the public-private partnership.

The registry is a nice idea, but I think it needs to be a bit more deep than a listing of what people are selling in their laboratories around the country.

As we look at the three primary parameters, the first one, analytical validity, CLIA should be able to manage that. It is very difficult to get at otherwise because most of the variation in the analytical performance of a genetic test is at the local level, in the laboratory.

Inspection is the thing that gets it. Proficiency testing is the thing that gets it. I don't think an FDA rule on the analytical side of laboratory-developed tests will help much. It has a very powerful benefit on the manufacturer test side, but I don't think it translates directly to the clinical laboratory environment.

When you think about what people want, the public wants accessible tests that are accurate and have value to them for whatever clinical situation they are applying that test in. To think about the value side of this, there is certainly lots more information available to the public than there was 10 years ago when we did the Taskforce on Genetic Testing work.

I think people don't really understand what they get with different regulatory models. I think one of the things that is clear from an FDA evaluation of a genetic test is they do clinical plausibility. They are not in the position really to say that a payer should pay for this test. They say yes, that test can detect this analyte and that analyte has a relationship to a disease. But they don't always say that it is X percentage of the time that this will be informative in this particular clinical situation.

So I don't know that FDA is the answer to the question. It certainly needs to be a part of the process of working through the issues of clinical validity, but I think the fact that they focus on

plausibility is not what the public is really looking for. They are looking for better discriminants of what is accurate and useful for their own clinical situations.

Clinical utility is certainly valuable, but genetic tests often don't come with the same level of statistical power that one wants in a clinical utility analysis. Clinical utility is something we all want for things that are done in large populations, significant volumes of testing. But in the rare disease world, it is difficult to get beyond the utility of an etiological diagnosis in the test itself. If you don't accept that utility, it is going to be very hard to accept that any of the tests we do for rare diseases are useful at all.

What we have been doing at the American College of Medical Genetics, as I said earlier, we requested the gene tests send us their entire library. We have built it in now to a complete Access file of every test and gene that is available in gene tests, with the first goal being to see what it takes to lay down the clinical validity for the various intended uses of those tests.

It is hard to do it at a regulatory level because even in a diagnostic setting in heritable disease genetics, you end up in a situation where the variability in a genetic disease is such that you may have a 90 percent chance when somebody has all the features of a disease that you will detect that analyte and it has clinical value to the patient. But as you move down through what may be a very long differential diagnosis in a particular clinical situation, you arrive at less and less likely scenarios that may still be important for that particular patient.

That is what we talk about in clinical validity, and it is not something easily constrained by a regulatory perspective because certainly the regulatory perspective has lots and lots of exemptions for the practice of medicine, which is how we deal with those decreasing sort of values that might be available as one needs to go down that differential diagnostic list.

So our interest really is in forming that public-private partnership. Unlike the people at this table here, I do get to advise legislators, and I'm going to spend the rest of the day doing that. The fundamental problem, I think, in moving towards developing a registry that is not just a listing of all the tests but also information about why they are clinically valid in particular clinical situations, is [it is] going to be an expensive venture. It is going to require the participation of all interest groups to be able to accomplish this.

So we want to figure out how to resource it. We are going to spend a fair amount of our time today trying to do that. Then, who are the participants and how do we organize it. We would be happy to work with this Committee in trying to flesh that out and bring some sensibility to it.

DR. TUCKSON: Mike, thank you very much. You have been very, very clear. I'm not going to take any questions because I think you have been so specific I think everybody on this Committee understands exactly what you are saying. Thank you. Don't leave, though, to go away from us today. You should stay around for a while.

Emma Kurnat-Thoma, who is from the International Society of Nurses in Genetics, and the last person is Michelle Schoonmaker from the Association of Molecular Pathology. I want to respect these last ones. I know we are well on the break, and so hopefully you guys will be able to hold off for just a second as we bring this to closure. But we are very pleased to give our full attention to you, Emma.

MS. KURNAT-THOMA: Thank you very much. My name is Emma Kurnat-Thoma, and I'm a registered nurse here to represent ISONG, which is the International Society of Nurses in

Genetics. It is a global organization dedicated to fostering scientific and professional growth of nurses in genetics and genomics.

We congratulate the Committee's systematic efforts to examine oversight and regulation of genetic tests and test results. In that the Committee found significant gaps in oversight, we share overarching concern that system gaps could lead to public harm.

Furthermore, ISONG is hopeful that the HHS Personalized Healthcare Initiative will advance integration of genomic technologies capable of tailoring treatment and prevention strategies to individuals' genetic characteristics and needs.

Overall, ISONG supports and offers to help implement the Committee's recommendation to enhance interagency coordination of genetic testing oversight. In particular, ISONG supports development of steps to foster resources, education, and knowledge.

In examining analytic validity, proficiency testing on clinical validity, we highlight four considerations today. Number one, we take exception with the Committee's conclusion that gaps can be identified and addressed without creation of a genetic testing oversight specialty. The absolute value on comprehensive reactions of consumers and patients to genetic tests are still largely unknown, secondary to the highly complex and unique nature of genetic tests.

Number two, ISONG is aware of gaps in the extent to which clinical validity can be generated and evaluated for genetic tests. We support the recommendation to create public resources and recognize that the American public will be best served if diverse ethnic, racial, and geographic subgroups are represented.

Number three, in reducing system gaps and improving oversight, ISONG takes exception with recommendations to establish voluntary genetic testing registration. It will not be sufficient given gaps in enforcement of existing regulations, and we support strengthened federal monitoring and enforcement.

Number four, ISONG applauds the Committee's concern regarding certain types of health-related genetic tests marketed directly to consumers and agree there is insufficient oversight of laboratories currently developing them. Given potential for misinformation and exploitation which may taint public perception of genetic testing value, ISONG supports expansion of CLIA's statutory authority.

With respect to communication decision support, nurses in genetics are acutely aware of deficiencies in stakeholder groups' genetic knowledge and agree that current strategies are inadequate to address them. We have further recommendations in the testimony for today.

We fully support HHS collaboration with relevant agencies and private parties. We support genetic expertise as essential when providing and interpreting appropriate genetic tests. As the largest body of healthcare provider, nurses have continual and close contact with patients and can intercede to prevent and/or reduce public harm that may come from direct-to-consumer genetic tests.

ISONG repeats the need for greater visible nursing organization representation during the proposal and development of outreach, oversight, and educational efforts.

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In summary, ISONG congratulates the Committee for the considerable work done to safeguard the public, and we deeply appreciate the opportunities to comment on this important document. Thank you.

DR. TUCKSON: Thank you. I think that is pretty straightforward. Thank you, and well done. Thank you.

Michelle, who is with the Association of Molecular Pathology.

I do need to let you know that, again, I am well aware of the break time, but the principle of trying to get as much public testimony in before we start grappling I think has been well served by the comments that we have been hearing just now and all of the other ones. So Sharon Terry from the Genetic Alliance it turns out is here. We are going to ask Sharon to come forward and present after Michelle, and then I think that will be our last one. But I do not want to miss the opportunity for Sharon to get her comments in.

DR. SCHOONMAKER: Good morning. Dr. Tuckson, Dr. Teutsch, and members of the Committee, I'm Michelle Schoonmaker, and I'm speaking to you as a member of the Association for Molecular Pathology. I will forego the explanation of the mission and membership of AMP since we have provided comments to the Committee on numerous occasions in the past.

Our purpose today is to summarize our previously submitted written comments on eight key points.

One, the definition of genetic tests. Under SACGHS's definition, the test would more accurately be called "molecular tests" rather than "genetic tests." We would encourage the Committee to define which intended uses are included in the intended oversight of genetic testing.

Second, are genetic tests different from other clinical laboratory tests. We recognize that tests for heritable diseases are unique in several respects. We are concerned that certain types of genetic testing marketed directly to consumers fall outside of the current regulatory oversight of CLIA. We encourage the Committee to further explore this issue of potential harm of health-related direct-to-consumer marketed genetic testing on the public health and to state the distinction between clinical genetic testing and health-related direct-to-consumer marketed genetic testing.

Third, requirements for laboratory personnel. CLIA regulations already stipulate the responsibilities of the laboratory director and the clinical consultant. We recommend that these roles be reemphasized with regard to genetic testing. We would like to encourage the Committee to modify Recommendation No. 1B to include the recommendation that CMS work with professional organizations such as AMP to develop interpretive guidelines for their inspectors regarding the levels of expertise that are required for different kinds of genetic testing.

Fourth, the role of CMS, CLIA, and the FDA for quality assurance. AMP offers our expertise to define the molecular targets that would be regulated analytes to promote expansion of proficiency testing programs for better oversight of direct-to-consumer marketing of clinically dubious genetic tests and to assist in the reassurance of the public and members of Congress of the quality of genetic tests.

Voluntary consensus organizations such as the CLSI created detailed practice guidelines which effectively fill many holes that some individuals believe exist in the FDA and CLIA regulatory framework. The team approach in which government, industry, and practicing clinicians work

together is a viable and desirable alternative to regulation for many genetic tests and genomic tests.

Five, voluntary registration. AMP is concerned that registration of genetic tests would duplicate the information already submitted to CMS as required under CLIA. AMP strongly supports that CMS enhance the mandatory CLIA registration of non-waived laboratories by enhancing CMS's infrastructure to achieve this goal.

Six, proficiency testing. AMP supports the proficiency survey programs currently available with additional analytes as necessary. We intend to begin publishing best practices, laboratory and clinical practice guidelines, and look forward to working with other organizations such as the CAP and ACMG to develop these guidelines.

Seven, clinical validity. We strongly favor reliance on the peer-reviewed literature, consensus statements by professional practice organizations, as well as collaborative studies by the CDC, other agencies, private investigators, and manufacturers. We also support integrated efforts to collect post-market data to meet the clinical, regulatory, and reimbursement goals.

AMP is concerned that the current Recommendation 1.4 could develop a duplicative system of oversight for laboratory-developed tests and laboratories performing these tests.

Finally, effective communication and decision support. We reiterate our commitment to participate not only in pursuing the success of this project but in translating the results of this effort for the betterment of the public's health and well being. AMP remains available to the Committee to assist with or provide additional information for your thoughtful deliberations and important work.

On behalf of AMP, I thank the Committee for your time and for listening to our concerns.

DR. TUCKSON: Thanks, Michelle. That was very, very good. Eight succinct, clearly articulated points. The key to your presentation to me is essentially with your Point No. 4, which you say again is ultimately that you will work with others to assure the Congress and others that in fact everything is okay.

I'm trying to make sure; out of all those recommendations, and I'm trying to go back and remember them all, are there any of those recommendations where you are calling for a material strengthening of existing recommendations? Or, the essential aftertaste of your presentation is things are basically okay. You guys are going to work hard in good faith to keep making sure that everybody is doing right?

DR. SCHOONMAKER: Right. We do support enhancements of CLIA where there are clearly gaps in the regulatory oversight structure, particularly for the direct-to-consumer marketed genetic tests, and agree that there may be some analytes that perhaps FDA may be able to provide additional oversight for. We do support continuing public dialogue to identify those analytes and to identify which intended uses may also require additional oversight.

DR. TUCKSON: I think I have it pretty clearly. Thank you very much. Lastly is Sharon Terry from the Genetic Alliance.

MS. TERRY: Thank you for the opportunity to publicly comment on your report for the oversight of genetic tests. Thank you, too, to the Taskforce for your work. It has been enormous.

I speak on behalf of the board of directors of Genetic Alliance, and I know you received our 18 pages of comments so I will not belabor them here. Almost as long as Mark's chapter.

I will call out several important concerns for us and, more importantly, move to a global view of your task and product. The first step to improving oversight of genetic testing is through enforcement of existing regulatory authority under the CLIA program and applying the available funding resources to provide for additional personnel, consultants, training, and to provide the mandated level of transparency of CLIA labs under the current statute.

In addition, it is important to take action on the identified interim steps within the agencies' discretion and to immediately implement the necessary steps for proficiency testing enhancements for genetic testing. For example, proficiency testing expansion incentives for PT reference controls, training of inspectors, and additions to the list of regulated analytes.

Two, it is clear that the mandatory genetic test registration, including all tests across the risk continuum, is necessary to provide stakeholders with information that would greatly improve the oversight of genetic tests. Making test performance characteristics and reference information, including analytical and clinical validity, publicly available should increase confidence and improve the appropriate utilization of genetic tests.

We also believe that the registry should be housed at and managed by a federal agency such as the FDA or NIH to offer the needed capacity and independence. It would also allow the first assessment of harms through adverse event reporting.

Three, we agree that more public resources should be committed to fill in the gaps. We support the establishment of a laboratory-oriented consortium for sharing information regarding method validation, quality control, and performance issues. We believe that any such undertaking must prioritize based on clinical need, availability of information, and appropriate resource allocation.

Four, in order to maximize benefits and minimize harms, a public-private consortium of stakeholders should be created to assess the clinical utility of genetic tests, including the establishment of evidentiary standards and increasing the number of systematic reviews.

Five, we agree with the SACGHS report's concern over FDA exerting regulatory authority over clinical decision aids.

Six, direct-to-consumer access to testing must be carefully regulated to ensure the public safety.

Seven, HHS must convene the relevant HHS agencies as well as interested stakeholders to provide further input into the development of a risk-based framework for the regulation of laboratory-developed tests. In addition, HHS must take the leadership role in coordinating the activities of the federal agencies under its auspices for the benefit of public health.

More important than these concrete recommendations, however, is the overall place of tests and testing in the integration of genetics into medicine and, further, into prevention and wellness. We recommend that HHS take a broad and enlightened view of the landscape. We are at the dawn of a new age, and innovation, development, oversight, and delivery of genetic services in a coordinated manner is critical to advancing human health.

Genetic testing is a disruptive innovation, and this is a critical time for the development of new paradigms. We must avoid applying old models and methods to new technologies. HHS can and

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must require that federal agencies work together with one another to achieve the best possible solutions. Human health is no place for politics and turf battles. Excuses such as "The burden is too great" or "It is too difficult" are unacceptable in the realm of health.

We, the entire genetic testing community, have dialogued a great deal over the past year. I believe we have also achieved a great deal in understanding each other's issues. It is time now to engage each other in meaningful and landmark solutions, novel partnerships, and collaborative models.

As you deliberate over the next two days, you are representatives of the millions of individuals who are suffering, sick, and dying. Not an easy task. You must keep them before you. They are your loved ones, your neighbors, your friends. You cannot offer answers or opinions from your silos or your own self interests today or tomorrow. You must push the boundaries regardless of your company, your profession, your university or constituencies and represent what is best for the public both in this country and beyond.

Before you speak, don't think of your position but instead the greater good to be gained. Focus on the intended consequences rather than the unintended consequences. This is not a zero-sum gain. While the status quo will be destabilized in the short term, we will all win in the long term.

Finally, it is a decade since your previous committee made important recommendations that have been left to history unimplemented. Regardless of the Secretary's response, we as a community are now further enlightened by your work and have a responsibility to one another and to the world community to strive for solutions that will release the incredible potential of biomedical research. We must all remain engaged in dialogue with one another, seeking to tell the truth and discover new pathways together.

We have a historic opportunity before us. Let us commit to measuring our responses, products, and actions against the greater good. On behalf of those who wait for treatments and therapies, thank you.

DR. TUCKSON: Thank you so much. Two quick questions, Sharon. First, remind us who the Genetic Alliance is, please?

MS. TERRY: So the Genetic Alliance is a network of many, many organizations, companies, universities, et cetera. Primarily, our greatest group of individuals and organizations under our auspices are about 650 disease-specific organizations.

DR. TUCKSON: So these are consumers.

MS. TERRY: Yes.

DR. TUCKSON: Secondly, let's just take your seven points real quick. You have provided a terrific bridge to the break and the discussion.

As we go through your seven, in terms of the recommendations that the Committee has made so far, if we go through those seven -- I'm trying to just do the math on what you said -- are there overwhelming, profound differences with the draft, where we are now, as we go into this discussion that you all are concerned about? It sounded like a lot of them you were agreeing with where we are today, and I want to just make sure that we don't lose in the seven points some things that you are really taking the draft report to task for.

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MS. TERRY: I haven't seen your current draft. I believe it is different than the draft I saw. I would say we differ in our understanding of the strength with which I believe this Committee must recommend that CLIA be enhanced, that we really look at proficiency testing. That is really, really important, and it is not strong enough in the draft that I saw.

The second thing would be the mandatory genetic test registry across all laboratory-developed tests, that it be housed at a federal agency. I'm also very clear about that in my mind. That has become very clear. One of the first commentators here from the 21st Century Medicine Coalition talked about that. We have worked together a lot with industry, a lot with universities and thought leaders, and the mandatory registry seems to be the way to get the light on the data.

As I said last time I was here, again, if we tell our kids something is voluntary, it doesn't get done. It is really time to be responsible for that.

DR. TUCKSON: Lastly, one of the things that we keep hearing from some people who comment on over-regulation is the chilling effect on innovation, thereby decreasing access to new knowledge and new tests. As the consumer community, are you chilled by those cautions around, again, especially greater attention to CLIA and so forth? Are you concerned that in fact there could be an unintended [impact]? You told us don't focus on the unintended, focus on the intended. Are you concerned about this potential chilling effect on innovation?

MS. TERRY: If innovation is chilled, I am concerned. I come from the rare disease community, where it is even harder to get people to innovate. I think this has to be done carefully, and that is why our work with especially the companies in the genetic testing space has been very important to open our eyes to what is needed.

I still believe that enhancing CLIA and a mandatory registry doesn't chill innovation. In fact, it begins to bring a lot of stability to the field that venture capitalists, et cetera, are looking for.

DR. TUCKSON: Thank you so much. You are terrific. What a morning.

I think that we are going to, obviously, take our break. It is 20-of. You all know I have a reputation for starting on time. Every minute being precious, we will start at five minutes to the hour.