Public Comments

MS. CARR: We have one public comment.

DR. TUCKSON: We have one public comment? Terrific. Where? David, come on up.

I got to say this because it's official and I have to sound sonorous when you do it. One of our critical functions is to serve as a public forum for deliberations on the broad range of health and human societal issues raised by the development and use of genetic technologies. And no playing around. We do greatly value the input we receive from the public. It is very important to us. So we do set aside time each day to hear from members of the public, and we welcome and appreciate the views they share with us. So we're happy that David Mongillo -- did I do that right?

MR. MONGILLO: Better than most. Mongillo.

DR. TUCKSON: I haven't gotten one right this whole meeting. He's with ACLA, and actually based on the discussions yesterday, I'm sure that you're going to have some very interesting comments to make today.

MR. MONGILLO: I hope so. Thank you very much.

DR. TUCKSON: Five minutes, but you know, I'm pretty tough.

MR. MONGILLO: Thank you very much. I'm David Mongillo with American Clinical Laboratory Association. ACLA represents local, regional, and national hospital and independent clinical laboratories across the United States. All of our members, to some degree, perform genetic testing. Thus, we have a keen interest in these issues that are addressed by the committee.

ACLA certainly shares the goal to bring the full promise of genetic/molecular medicine to the health care system by incorporating the highest quality of diagnostic testing. We applaud the committee on such an ambitious and strategic approach to the multiple complex issues on yesterday's and today's agenda.

We wish to focus on one particular item that was discussed yesterday and that has to do with the regulatory oversight of genetic testing. ACLA is preparing our formal response to FDA on their recently released guidance document. So these comments should be considered preliminary.

There was a key question raised during yesterday's discussion. It was asked, is there a gap in the regulatory oversight of genetic testing? And the committee reached the conclusion that support for clinical validity and utility may be an area that needs further study.

Let me speak to that question from a CLIA perspective. The laboratory director of a high-complexity laboratory, which is the only laboratory that can perform genetic testing, is responsible to ensure that the test systems provide quality laboratory services for all aspects of test performance. That's subsection 493, dah, dah, dah.

Further and more importantly, in the same subsection, CLIA explicitly requires the laboratory director to ensure that -- and I quote -- "the test methodologies selected have the capability of providing the quality of results required for patient care." We believe that implicit in that statement is the requirement of the responsibility of the lab director to select test methodologies

that have the capability of providing quality laboratory services for effective patient care. We believe this service is in keeping with the ordering physician interest in patient management and is consistent with clinical validity.

CLIA also explicitly requires in subsection 493.1417 that the laboratory must have a clinical consultant who provides consultation regarding the appropriateness of the testing ordered and interpretation of test results. This is also a CLIA requirement component, in our mind, used to ensure clinical validity.

Our intent is not to dismiss the issue, but to raise this as a point of discussion. We heard from the agencies that there are some very colorful players that are performing direct-to-consumer tests that have questionable clinical validity, as was described in the recent GAO report and the congressional hearings. All laboratories that do human clinical testing must be CLIA-certified. They provide tests that advance patient care and are held responsible for false marketing and advertising claims. All ACLA members are CAP-accredited. Most are licensed in New York and, thus, are subject to the highest level of regulation, inspection, test validation, and accreditation. As was stated yesterday, 75 percent of all genetic testing is performed in labs which are licensed by the State of New York. Let's not let the minority drive regulations for the well-meaning majority.

Continuing that theme, the second point I wish to make has to do with the new FDA guidance on IVDMIAs, multivariate indexed assays, in vitro diagnostic MIAs. Essentially this guidance defines a new category of laboratory-developed test that will be subject to FDA approval, and essentially it will make laboratories manufacturers. Again, because our comments are underdeveloped and without taking a stance on the need for such regulation, let me touch upon the impact this guidance may have or will have on laboratory-developed tests and innovation.

CLIA regulates labs, as we heard yesterday. FDA regulates tests. There are fundamental differences and redundancies between these regulatory approaches which will make simultaneous compliance with both sets of regulations difficult, impractical, and burdensome.

What are some of the differences? FDA requires quality system regulations to produce essentially identical products from the first kit to the last. This is because it ensures that each approved product will perform in multiple settings as expected.

CLIA, on the other hand, operates as a QA/QC package, as Judy Yost described, so that each individual laboratory on a daily basis can responsibly perform thousands of different laboratory tests with an assurance of quality.

The new FDA guidance will include package insert requirements consistent with the need to perform the test by multiple laboratories. On the other hand, laboratory-developed tests are developed and their standard operating procedures can be quickly modified and validated in a particular laboratory consistent with CLIA quality assurance. There are also major differences to ensure compliance with test modifications. But most importantly CLIA explicitly allows for the timely ability to modify tests to incorporate the latest medical knowledge and enhancements.

FDA has consistently stressed the importance of smart regulation and following the least burdensome approach. The future of genetic testing will include numerous IVDMIA test applications. ACLA is concerned with the ability of FDA resources to keep pace with not only the initial approvals, but with the ongoing approval of valuable test modifications that contribute to medical innovation and improved patient care.

I probably don't have to tell this committee as an example of how this works, but I'll use one. HIV genotyping was used as a laboratory-developed test. Laboratories had the ability to modify that test to include the latest innovations, the latest thinking, the latest information that was provided. It really revolutionized the care of patients with HIV. It really has done wonders for that dreaded disease. As time went on, as the tests matured, manufacturers now have produced kits for HIV genotyping in therapy. That's a sort of natural evolution. But the point is that laboratories early on can be innovative and move nimbly and quick to make these tests available to patients.

We appreciate this committee's thoughtful deliberations on this and all the issues associated with the need for increased genetic testing, but not at the expense of innovation and timely patient access. We thank you for the opportunity to comment and we look forward to working with the committee and the regulatory agencies on this important issue.

DR. TUCKSON: Terrific. So two things come up. First, that is great.

The last paragraph, page 1. It sounds like what you're saying here is there is a rule that says that any CLIA lab must have a smart person who provides consultation on the appropriateness and interpretation of the test. So do you really believe that that sort of "must have" is reasonable enough to say to the public that the evaluation of clinical validity of a test being done by that laboratory is sufficient? Because Dr. Joe Jones with a license says I'm hired by the lab and I'm here, and CLIA says I'm supposed to certify it. Therefore, I do certify that this is a clinically valid test and that the interpretation of this test by a doctor that then leads to a therapeutic intervention on this kid is absolutely A-OK. You all go back home and don't worry. Is that what you're saying?

MR. MONGILLO: You heard yesterday a couple things. One of the things we heard yesterday was that the College of American Pathologists has actually introduced additional checklist questions into their inspection process that get at these issues of test validation, particularly for genetic and molecular testing. These tests are done in highly sophisticated laboratories, genetic and molecular testing, the highest complexity level of testing. And, yes, there are laboratory directors that have the expertise, the knowledge, and the ability to make sure that these tests that are ordered by physicians and are integrated into patient management have clinical relevance and are effective for patient care. So, yes.

DR. TUCKSON: So the ability to oversight of that process and how well it works -- somebody is going out there and saying, okay, Dr. Consultant Jones, let's review every decision you've made. I was to review the criteria you use for clinical validity for that test and I'm going to make sure that it's squared away because you may be a well-meaning doc, but how do we know, so that somebody is actually on the case reviewing that.

And by the way, somebody in government and CLIA would know whether or not the appropriateness criteria used by Dr. Jones is the same as Drs. Smith, Henry, and Johnson in four different places, and that would all be completely consistent. And we could get that from CLIA.

MR. MONGILLO: I think you're talking about the expertise of the inspection and how --

DR. TUCKSON: And the criteria.

MR. MONGILLO: And the criteria.

The other thing you heard yesterday -- you heard it from Judy Yost at CMS that they are enhancing the individuals who will be inspecting laboratories in this area of molecular and genetic testing. The College of American Pathologists has already moved to have individuals who are highly expert in this area when there are genetic and molecular testing performed as part of the laboratory's routine testing. They bring in experts to do that kind of credible inspection that's necessary.

DR. TUCKSON: The second question for me, and I'll see if others want to ask you some things. I guess I'm a little confused. So you represent folks who must jump through the CAP hoop and the New York State hoop. That's what your people do.

MR. MONGILLO: We have a member pledge that in order to be a member of the American Clinical Laboratory Association, you have to be CAP-certified or equivalent, and New York State, as we heard yesterday, is certainly --

DR. TUCKSON: So why is it if you are taking -- and you sound like you are -- a responsible position on behalf of responsible laboratories who are more than prepared and willing to be subjected to the tough regulations of New York, why would you say it's okay that the other 25 percent not have to go through that? What should be done? What is your remedy for --

MR. MONGILLO: We're not saying it's okay. In fact, what we're saying is let's not regulate for the lower 25. If there need to be changes -- yesterday the recommendation that came out of this group was a multi-agency approach. I think the main message we're sending is that let's make this multi-agency and let's do it in a way that doesn't --

DR. TUCKSON: Well, what do you want us to do about the 25 percent? What should we do about them?

MR. MONGILLO: At a minimum, they all should be CLIA-certified because we heard from the GAO report --

DR. TUCKSON: No, no. You're terrific. Let me just make sure. You're willing to play by super-CLIA because that's New York. Let's just say New York is super-CLIA, CLIA on steroids.

(Laughter.)

DR. TUCKSON: It's probably illegal. But you're willing to play New York-level CLIA. Are you saying that everybody else should play New York-level CLIA?

MR. MONGILLO: Our members abide by the College of American Pathologists accreditation process and New York State licensure.

It's not for us to make decisions about this 25 percent. I really think that's a government responsibility. You suggested they should get together. What is the issue? What's the concern? If there needs to be some enhancements, the agency should look at that.

DR. TUCKSON: You're a responsible organization representing mature corporations and laboratories and others in this field, and you have the opportunity to advise us as to what we should say. What do you want us to say about the 25 percent? If we make the assumption, as you are asking us to make, that the 75 percent that go through CAP plus New York, that combination, you're saying it's pretty damn good and don't pile on any more than that on our

members because it's sufficient for the protection of the health of the public. So you're prepared to say that for you. What do you want us to do about the 25 percent?

MR. MONGILLO: Have them all become members of ACLA.

(Laughter.)

DR. TUCKSON: Others, please help out.

DR. FERREIRA-GONZALEZ: I think that the issue here is that there have been changes in the process of the CLIA inspection through the College of American Pathologists. Most laboratories performing genetic testing today are CLIA-certified through the College of American Pathologists. The CAP checklist has significantly been strengthened to specifically address questions of the clinical validity of this testing. Actually we took the template that the FDA uses for their review and kind of translated it within our capabilities to the checklist. So there are a number of issues. They are still very similar to the FDA review.

Now that there's a multi-agency or the need to add more agencies to this regulatory oversight, currently there is oversight of genetic testing through CLIA. The issue is that also the FDA now has introduced through the multivariate indexed analysis a new category of testing for the laboratory-developed assays that will have to go through FDA clearance. So in here we have the FDA saying we do have statutory authority over laboratory-developed assays, but then CLIA said we have authority over the laboratory-developed tests. So I'm not finding that there's a need to increase oversight.

The idea that I have is maybe we need to strengthen a little bit CLIA in certain specific areas for creation of a specialty, for example, to assure that there is proficiency testing to strengthen the quality of the testing that is being done in this country.

DR. TUCKSON: Does anybody want to ask any other clarifying questions of our guest?

MS. CARR: I just want to ask you about the last sentence in your fourth paragraph. You're talking about the role of the clinical consultant, and you say that "this is a CLIA requirement component used to ensure clinical validity."

Yesterday Judy Yost -- and I think we've always understood that CLIA does not speak to, address clinical validity. She made that, I think, very clear. This sounds a little bit -- it's confusing. Can you clarify that?

MR. MONGILLO: I tried to build the case, using the CLIA language, where we believe that there is specific language in CLIA that addresses the need for effective patient care. The tests have to be effective for patient care. Is that the word "clinical validity"? We think that there's clearly comparable intent associated with effective patient care and clinical validity. So our opinion is that that language leads one to perform in a way that the tests have clinical validity.

MS. CARR: But I just wonder whether CMS would agree that their regs ensure clinical validity that way, through that component.

MR. MONGILLO: I think that's a question for CMS.

DR. TUCKSON: Well, I want to thank you. I do hope, as you heard yesterday, that as we try to write something and refer this to the Secretary to be thinking about -- and I'm just making an observation here. But one of the things that private sector people often do when there is confusion like this is they will often think that it is in their interest to step up to the plate and actually try to form a public/private partnership that actually gets at the solution to these things.

I sincerely hope that you guys will use the time available in the next weeks to try to get with the people in government and try to see if you all can't just decide to get the right people together across government and the private sector and try to work this thing out without somebody having to like beat you in the head to do it.

This is just a little, old small advisory committee working in the woods trying to do the best we can day by day. All we can do is advise and so forth and so on. But I think a lot of people are going to wind up paying attention to the transcript of this kind of discussion that we've been through in the last couple days, and I've got a feeling that it's going to get some people's attention. If I've got anything to do with it, it will.

MR. MONGILLO: I appreciate it.

DR. TUCKSON: So I just hope that you guys will just jump up to the plate and say, hey, you know what? We're going to take care of this. Whatever this loophole is, whatever this little problem is, we'll work with government and then we're just going to solve it. That way everybody can go home and not worry about it. But anyway, that's on you.

Hey, listen. You're terrific. Thank you.

Now, here's the deal. Do we have in the audience yet --

DR. BOURI: I have a question. Thank you.

I'm not going to question the clinical --

DR. TUCKSON: Name.

DR. BOURI: Sorry. My name is Khaled Bouri. I'm from the George Washington University.

I'm not questioning the validity of the test, but in the clinical setting usually, there is a genetic counselor who delivers the test to the patient. In this case there's a test that is directly between the laboratory and the patient. So there's a specific thing about this test that you're not telling him that your cholesterol level is 200. You're telling him that in 5 or 10 years, you're going to have cancer. So how are you going to deal with this issue?

MR. MONGILLO: That sounds like a direct-to-consumer issue.

DR. BOURI: Yes.

MR. MONGILLO: And we actually use that in some ways as the example of what is now being sort of considered that this 25 percent. So we believe that those are the tests that certainly there should be physician involvement at a minimum. They should be CLIA-certified labs that are performing those tests, meaning that there would be medical oversight. There would be some acknowledgement that the tests have to be effective for patient care, and because of the physician

oversight, we think there should be communication as a clinical consultant to communicate the results.

DR. BOURI: Because usually this is done by mail. They send you the results by mail.

MR. MONGILLO: And that was the whole issue of the GAO oversight hearing.

DR. TUCKSON: Thank you for that.

I think one of the things that our questioner reminds us of again is that that's a big part of the complexity here, and always the thing about what's so special about the genetic stuff is that this is the predictive value of these things. It's probabilities. It's prediction. That's what's continuing getting at this underbelly of concern around the clinical validity of these tests. It's not just your hemoglobin was up too low or high. It's something else going on here.

So, Suzanne, I think one of the things that I want to make sure that we at least think about going forward is do we know anything about the behavior of these certified consultants who are supposed to make sure in a CLIA lab that the clinical validity of these tests is actually intended to address. What do they use? Does anybody know anything about inter-rater reliability? Is there any set of standards in that regard?

DR. FERREIRA-GONZALEZ: CLIA has specific standards for who actually is a clinical consultant.

DR. TUCKSON: So the standard is for who is a consultant. I'm questioning does anybody go back and look at the actual behavior of the consultant. Does anybody know what the consultants say, what they use as a yardstick to determine clinical validity? Is there a standard format?

DR. FERREIRA-GONZALEZ: Well, this will be for the --

DR. TUCKSON: So in other words, could you go back and look at performance assessment criteria for a clinical laboratory consultant who made a decision on clinical validity? How do you know if they're any good?

DR. FERREIRA-GONZALEZ: Well, during the process of inspection, if you're using the CAP with a specific checklist, your inspector will come and look at your clinical validity not only of what you have introduced in the last two years, but they can go back to anything that they have done in the past.

DR. TUCKSON: So the answer, just to make sure we heard that -- and this is a very helpful comment for us to think about in the future -- is that what we are hearing is that the College of American Pathologists guidance may be good enough and specific enough that you could use that as a performance assessment tool for the quality of the consultation from this particular person.

DR. FITZGERALD: Just asking a question of some fact, if you have that. At the end of this first page, you mentioned that in the GAO report, certain labs were called very colorful players, and some of those labs are doing direct-to-consumer tests, as we've heard. How many of those labs -- I don't need specific numbers. Let's put it this way. Are some of those labs in ACLA?

MR. MONGILLO: No.

DR. FITZGERALD: Are any of those labs CLIA-certified? Do we know?

MR. MONGILLO: Some are, some aren't.

DR. FITZGERALD: Thank you.

DR. TUCKSON: All right. So here's the deal. We've got people who have to leave at 3:00. We're going to take our lunch break now, and the actual lunch is available early. We're going to be back in this room ready to rock and roll at 1:10. Our guests that were coming at 3:00 are coming at 1:15. So we don't want Sylvia to miss anything. So you're going to come back at 1:10 and we're going to do five minutes of business. At 1:15, the presentations start, and then we're out of here early.

Thank you all. See you at 1:10. Not 1:15, 1:10, because Sylvia has to go.

(Whereupon, at 12:25 p.m., the meeting was recessed for lunch, to reconvene at 1:10 p.m.)