UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION

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PUBLIC MEETING:

IN VITRO DIAGNOSTIC MULTIVARIATE

INDEX ASSAYS (IVDMIA)

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Thursday, February 8, 2007

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This transcript has not been edited and FDA makes no representation regarding its accuracy

The public meeting was held in Salon B of the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland, at 8:00 a.m., Dr. Larry Kessler, moderator, presiding.

FDA PANEL PRESENT:

LARRY KESSLER, Sc.D. Moderator

ALBERTO GUTIERREZ, Ph.D.

STEVE GUTMAN, M.D.

LINDA KAHAN

DANIEL SCHULTZ, M.D.

JAMES WOODS

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1 P R O C E E D I N G S

2 (8:02 a.m.)

3 DR. KESSLER: Good morning. It's 8:00
4 a.m., and we're going to start.
5 My name is Larry Kessler. I'm the
6 Director of the Office of Science and Engineering
7 Laboratories, and I'm moderating today's meeting.
8 I'm going to turn the podium over to Dr.
9 Steven Gutman, Director of the Office of in Vitro
10 Diagnostics, followed by Dr. Courtney Harper to make
11 a presentation. then I'll provide the rules of the
12 road for the day after those presentations.
13 Dr. Gutman.
14 DR. GUTMAN: Good morning. I would like
15 to welcome you to the open meeting on the in vitro
16 diagnostic multivariate index assay guidance.
17 FDA has a dual mission to protect public
18 health through its regulatory programs while promoting
19 public health by assuring timely access to cutting
20 edge, new products. There's an inherent tension in
21 this dual mission, which I think comes clearly into
22 play as we consider issues related to today's topic.
23 Because of the complexity of the issues
24 involved, FDA has extended the public comment period
25 for the IVDMIA guidance for 90 days, until March 5th,

1 and has arranged this opportunity for public
2 discussion. FDA is clearly here to listen and to try
3 to understand the concerns, issues, and ideas of all
4 of our key stakeholders.
5 I want to thank the members of the FDA
6 panel who will include throughout the course of the
7 day Dan Schultz, our Center Director; Linda Kahan, our
8 Center Deputy Director; Alberto Gutierrez, Deputy
9 Office Director; and James Woods, Deputy Office
10 Director, as well sa me.
11 I want to thank Dr. Altaie for
12 coordinating this event, and Dr. Kessler for
13 moderating, and of course, I want to thank you for
14 coming to Washington and participating and being here.
15 Last and most important, I want to set a
16 good example by concluding my remarks within the
17 requisite five minutes so that you will all do the
18 same.
19 Thanks.
20 DR. HARPER: Good morning. My name is
21 Courtney Harper, and I am going to give a brief
22 summary today on our guidance document entitled "In
23 Vitro Diagnostic Multivariate Index Assays."
24 I'd like to give a little bit of
25 background information to start off this day in which

1 we're going to receive public comment on this
2 document. We believe that there is a lot of confusion
3 about the regulation of diagnostic tests that are
4 developed by and used in a single laboratory. We
5 believe that this confusion actually is derived in
6 part from our approach to the regulation of laboratory
7 develop tests that use analyte specific reagents and
8 other commercially available FDA regulated components
9 in these tests.
10 FDA actually stated in the preamble of the
11 final ASR rule that clinical laboratories that develop
12 in-house tests are acting as manufacturers of medical
13 devices and are subject to FDA jurisdiction under the
14 act.
15 When these laboratories who develop in-
16 house tests actually use ASRs, there's often some
17 confusion in that the ASR regulations themselves do
18 not actually extend to the tests that are made from
19 them. That is that laboratory developed diagnostic
20 tests that use, for example, Class 1 exempt ASRs,
21 another sort of Class 1 exempt FDA regulated products,
22 such as general purpose reagents, the test themselves
23 are not by extension necessarily Class 1 exempt tests,
24 but as you all know, historically, FDA has generally
25 exercised enforcement discretion in the regulation of

1 laboratory developed tests.

2 However, we have noticed a growing
3 category of tests that include elements that are not
4 standard primary ingredients of laboratory developed
5 tests, and we believe that these differences, such as
6 complex, statistically driven data derived algorithms
7 actually raise new safety and efficacy concerns.

8 Therefore, these types of tests, which we
9 call IVDMIAs, we are basically stating that these do
10 not fall within the scope of laboratory developed
11 tests over which we have generally exercised
12 enforcement discretion.

13 To communicate this policy and to actually
14 define this class of tests, we created a new guidance
15 document that was released in draft form in September
16 of 2006 called "In Vitro Diagnostic Multivariate Index
17 Assays." This document was intended to define a very
18 narrow niche of devices, and these devices may be
19 commercially distributed for use in laboratories
20 across the United States or they may be developed in
21 a single laboratory for use within that laboratory,
22 and we believe that this narrow niche of laboratory
23 developed and commercially distributed tests should be
24 subject to active FDA regulation rather than
25 enforcement discretion.

1 The guidance document contains three
2 criteria that define IVDMIAs, and here I have
3 abbreviated them. Basically an IVDMIA is a test that
4 is developed using clinical data. Often these types
5 of tests are developed from what's called a test set,
6 a training set and a test set.
7 Basically they use a clinical data set and
8 they use that data to derive an algorithm that
9 basically can be used to discriminate between, for
10 instance, two clinical parameters.
11 Then in unknown patient data, the test
12 will employ the algorithm to integrate data from tests
13 and/or demographic data to calculate a patient's
14 specific result. This result is often called a
15 classification, a score, a pattern, an index or
16 something similar to that.
17 And this result cannot be interpreted by
18 clinicians using their prior knowledge of medicine
19 without information from the test developer about the
20 performance of the assay.
21 Some potential examples of tests that
22 might be IVDMIAs might be a microarray that predicts
23 colon cancer recurrence based on an RNA expression
24 pattern or perhaps an assay that integrates
25 quantitative results from immunoassays to obtain a

1 score that predicts a person's risk of developing
2 Alzheimer's disease, or even a test that integrates
3 demographic data, such as age, gender, et cetera, and
4 the genotype of several genes to diagnose
5 cardiovascular disease.
6 But we realize that after the publication
7 of the guidance a lot of the questions that we have
8 been hearing have been related to the clarification of
9 this definition. So we'd like to point out that a
10 device may actually use an algorithm and not be an
11 IVDMIA. That's one common misconception.
12 Devices may also use software and not be
13 IVDMIAs, and devices may be multivariate, measure
14 multiple parameters at one time and not be an IVDMIA.
15 For instance, some devices that are common laboratory
16 developed tests that are not IVDMIAs would be things
17 such as standard creatinine clearance determination or
18 perhaps using the measurements of total cholesterol,
19 HGL cholesterol, triglycerides, and a calculation to
20 determine LDL concentration, or even assays that
21 measure, for example, 25 snips in the CFTR gene to
22 determine a patient's genotype. These things would all
23 not be IVDMIAs.
24 But since there is a lot of confusion out
25 there and the guidance comment period is still open,

1 we would really love to see a comment from the public
2 to help us clarify this definition. Give us concrete
3 suggestions on how to make the definition of IVDMIAs
4 clearer so that industry has clear guidance going
5 forward.
6 The regulation of an IVDMIA will be just
7 like the regulation of all other medical devices in
8 that it will be regulated by the risk of its intended
9 use. Therefore, there's actually opportunity for an
10 IVDMIA to be any of the three classes, Class 1, Class
11 2 or Class 3.
12 And we believe that for good IVDMIAs, FDA
13 regulation will not be a significant barrier to
14 innovation in this area. FDA regulation will provide
15 an independent assessment of the data and the labeling
16 claims, but we're also grounded by a least burdensome
17 mandate and that we ask questions about the science
18 that are the least burdensome way to answer safety and
19 effectiveness questions.
20 But all in all, we believe that good
21 science is good science, and if tests such as IVDMIAs
22 are being used on patients, we believe that the data
23 probably already exists to show that they're safe and
24 effective, and so we encourage companies to come and
25 talk to us about that.

1 In fact, this week we actually cleared the
2 first IVDMIA by de novo. This is the Agendia
3 MammaPrint Test, and it is intended to predict the
4 likelihood of breast cancer recurrence. This
5 particular test is a laboratory developed test
6 intended to be used at a single laboratory site.
7 This was very efficiently reviewed by FDA
8 in that the total time of FDA's portion of the review
9 actually took a total of less than 30 days, including
10 classification.
11 This particular test was classified de
12 novo and a Class 2, and it as such can actually now be
13 used as a predicate device for IVDMIAs who had a
14 similar intended use.
15 We intend to publish the special control
16 guidance document for this new regulations fairly
17 soon, and this guidance document will contain valuable
18 information describing the type of information that
19 should be submitted for these types of assays.
20 With that I'm going to close this
21 introduction, and I'm going to remind everyone that
22 this draft guidance document is open for comment until
23 March 5th, and now we welcome your comments today.
24 Thank you.
25 DR. KESSLER: Thank you, Dr. Harper.

1 There is no truth to the rumor that Dr.
2 Gutman personally cleared the IVDMIA this week just so
3 he could be on TV.
4 I'm going to provide just a few logistics
5 comments, and then we are going to being with the
6 first speaker. I'll moderate today, and I'll be ably
7 assisted by Dr. Susan Altaie, who is standing over
8 there at the podium right now.
9 We have 31 speakers today, and we want to
10 hear all of them in their entirety. We're going to
11 insist that they take no longer than ten minutes, and
12 to do so there's a little timer up there by the
13 podium. It will start off green. At seven minutes it
14 goes yellow. At nine minutes Dr. Altaie will hand the
15 speaker a one-minute warning. At ten minutes it will
16 go red, and at about ten and a half minutes I'll stand
17 up, and at ten minutes and 45 seconds I'll walk over
18 to the podium and push the button so that the speaker
19 is turned off.
20 (Laughter.)
21 DR. KESSLER: Actually I'll do that.
22 (Laughter.)
23 DR. KESSLER: There are two reasons for
24 that, and the biggest reason is to be fair and
25 courteous to the other speakers. Thirty-one people

1 have asked to speak and they have a right to be heard
2 today, but just as important, if we stay on time,
3 there will be a few minutes for open discussion by the
4 rest of the audience who is here, and we would like to
5 preserve some of that time for the open discussion.
6 So that's very important.
7 If I leave the podium for a little while,
8 Dr. Altaie will take over the moderating duties.
9 Okay. We're going to conclude promptly at
10 5:00 p.m. I'm hoping we'll have some closing remarks
11 at the time. If we go over, we won't. We'll just
12 walk out at five o'clock. Dr. Gutman unfortunately
13 has to leave a little bit before then. So if we are
14 a little bit earlier, that would be great as well.
15 I ask that you either turn off your cell
16 phones or put them on vibrate so that they're not
17 ringing while we are having -- ah, if you want, the
18 agenda is outside at the desk where Anne Maria and
19 Shirley Meeks are sitting.
20 Finally, just a comment from me, why we're
21 here. As you heard from Dr. Gutman, we're here to
22 listen. We're here not to have an active interchange
23 today. That's not what the purpose of this meeting is.
24 We're here to hear and listen to your comments.
25 And so I'll start off in a slightly

1 unusual fashion with a brief passage from the Bible.
2 It's from Isaiah 1:18. "Come now and let us reason
3 together." And the whole phrase is, "'Come now and
4 let us reason together,' sayeth the Lord. 'Though
5 your sins be as scarlet, they shall be as white as
6 snow. Though they be red like crimson, they shall be
7 as wool.'"
8 There's a metaphor in there somewhere.
9 I'm just not exactly sure where it is. Maybe you'll
10 help me today.
11 We're a few minutes ahead of schedule,
12 which is terrific, and I'm going to ask our first
13 speaker, Paul Redensky of McDermott, Will & Emery to
14 stand up and talk, and I will not od any fanfare with
15 the introductions. Just a name and where they're
16 coming from.
17 Thank you, Paul.
18 DR. REDENSKY: Good morning. My name is
19 Paul Redensky. I'm an internist by training and a
20 health law attorney with McDermott, Will & Emery,
21 residing in their Miami office where it's much warmer.
22 and McDermott, Will & Emery represents a
23 number of clinical laboratories who may be affected by
24 the policies announced in the draft guidance if
25 implemented, but this presentation is not intended to

1 represent the policies or opinions of either our
2 clients or the firm.
3 The draft guidance on in vitro diagnostic
4 multivariate index assays raises a large number of
5 issues. Included among them are questions about FDA's
6 legal authority to regulate in this area, what is the
7 most appropriate regulatory framework for laboratory
8 developed tests, and what is the least burdensome
9 pathway to approach that.
10 But those are not the topics that I'm
11 going to discuss during the presentation today. What
12 I'm going to focus on are what are the questions that
13 laboratories really need to have answered if they are
14 going to be required to comply with the policies
15 announced in the draft guidance, and those include
16 concerns about the definition of an IVDMIA. As
17 Courtney outlined, there is a lot of confusion.
18 Second, identifying what elements are a
19 medical device within the laboratory service.
20 Three, what are the pathways for premarket
21 review and how we would understand what are likely
22 pathways.
23 Four, the compliance with FDA quality
24 system requirements and how that dovetails with CLEA.
25 In particular, there are certain conflicts existing in

1 the regulations between the two regulatory frameworks.

2 And then lastly, with respect to whenever

3 a policy is finalized, what the time lines will be for

4 coming into compliance.

5 First, with respect to the definition of

6 an IVDMIA, laboratories considering the development of

7 a novel assay have to have a clear and predictable set

8 of rules to know whether or not a particular test

9 will or will not be subject to FDA regulation. It is

10 not a question of good science. Good science is

11 there, as was in Courtney's slide, whether you go

12 through a CLEA pathway or an FDA pathway.

13 But those who fund research on new tests

14 will not find it acceptable to find out midway that

15 FDA has issued a new guidance document or an expanded

16 guidance document that will bring new tests under

17 regulation.

18 So what is subject to FDA regulation and

19 what is not subject to FDA regulation must be clear,

20 and any changes in that have to have a fair amount of

21 explanation as to why and timeliness in any change.

22 Second, and a key point is identifying

23 what is the medical device within the laboratory

24 service. If you're going to prepare a premarket

25 application, if you're going to put down policies and

1 procedures to comply with quality systems
2 requirements, you have to be able to start by saying
3 what is the device.
4 That is clear with an IVD that's a kit.
5 You have something that's going out in interstate
6 commerce. It is not at all clear with a laboratory
7 developed test.
8 The proposed guidance mentions test system
9 and says in a footnote that that term does not mean
10 the same thing that those same two words mean in the
11 CLEA regulations. That's very good to understand, but
12 what does it mean and how does it differ from what
13 CLEA is saying? It begs the question to simply say
14 it's different.
15 Three, what are the pathways for premarket
16 review? FDA regulation of medical devices is risk
17 based, as everyone knows. The draft guidance
18 indicates that IVDMIAs are likely to be classified as
19 Class 2 or Class 3 and talks about prognostic claims
20 most likely being Class 2 and predictive claims being
21 Class 3.
22 One of the difficulties is that it's not
23 clear what is the difference between a prognostic
24 claim and a predictive claim. Generally, you will
25 have a claim that is talking about the likelihood of

1 some outcome, survival, disease free survival, cancer
2 recurrence, a cardiac event. That's going to be on
3 some therapy.
4 Is that a prognostic claim or is that a
5 predictive claim with respect to the particular
6 therapy? These things are key because if something is
7 going to require a PMA versus a 510(k), those are
8 important decisions that are there in developing the
9 initial thoughts about the service and also for the
10 funders to know what the time line is likely to be and
11 what the amount of capital is likely to be required.
12 Four, compliance with the QSRs. CLEA has
13 substantial quality system requirements that the
14 laboratories already must comply with. In addition,
15 there are state law requirements that are imposed as
16 well, and for laboratories that accept specimens
17 throughout the United States, New York State requires
18 that laboratories be regulated by New York State and
19 has proof up requirements prior to using tests in
20 clinical practice.
21 How those dovetail to requirements under
22 the quality system requirements is something that
23 needs to be explained with particularity. It is not
24 something where it is sufficient to say we're not
25 going to go after folks the day that we begin enforcement.

1 Laboratories need to understand what they
2 have to do, and again, this dovetails to what the
3 definition is of what is the product, what is the
4 device that the quality system requirements were
5 looking at having processes in place so that you can
6 be assured that the device is as it was intended to be
7 and how that differs from laboratory quality control,
8 which is really focused on accuracy, reliability of a
9 process, not a widget.
10 The fifth is conflicts between FDA and
11 CLEA requirements. FDA limits what manufacturers can
12 say promotionally to those things that are four square
13 within labeling. The new publication comes out that
14 is not four square within labeling, and you can only
15 send that out in response to an unsolicited request.
16 CLEA, by contrast, puts an affirmative
17 obligation on laboratories to update information so
18 that the treating physicians can interpret the
19 laboratory test. So if a new publication comes out,
20 CLEA would require that you include that information
21 proactively to help doctors understand your test
22 report.
23 These two systems are in conflict, or at
24 least I wouldn't know how to tell someone how to
25 comply with the two systems without further policy

1 instruction on that.

2 Sixth, a transition. These are new
3 requirements for the laboratories. Make no mistake
4 about that. This is a substantial new regulatory
5 burden with laboratories. They have to propose
6 policies go forward as drafted. A laboratory is going
7 to have to look through its portfolio and determine
8 what is an IVDMIA, what are the elements within the
9 IVDMIA that are a medical device, what premarket
10 pathway they're going to have to go through, how they
11 can set up quality system requirements to meet FDA.
12 All of these things need to be addressed.

13 It will take time. There's a lot of
14 questions inherent in the draft guidance. Those
15 questions need to be answered so that everyone knows
16 what the rules will be, and folks need to have time
17 after a final policy document comes out in order to be
18 able to come into compliance. It cannot happen the
19 day that the final policy comes out because no one
20 knows what FDA is thinking.

21 I'm not saying that in a negative way.
22 Everyone is learning and trying to understand this
23 space. We would recommend a period of at least two
24 years for coming into compliance for those products
25 that would be Class 2 and four years for those that

1 would require a PMA.

2 That's not to say that there's no

3 enforcement mechanisms that are out there. If FDA is

4 concerned today about any laboratory test, CLEA can

5 shut a laboratory down tomorrow or tell them that they

6 have to cease and desist performing a particular test,

7 and the Federal Trade Commission can challenge

8 promotional claims that are deceptive.

9 So there are tools today that can be in

10 place if there are concerns from a public health

11 perspective until a final regulatory policy is set

12 forth and time to come into compliance is completed.

13 Lastly, FDA has not really articulated

14 what are the public health concerns it has about

15 IVDMIAs, why putting something together in an equation

16 is something that concerns the agency other than

17 suggesting that it's new.

18 There has been some discussion about these

19 are black boxes, but many of these are things that

20 have been published. The algorithms have been

21 published. They've been independently validated, and

22 we don't see that that is sufficient.

23 We would urge the FDA to explain the

24 findings that have led it to lead to regulation here,

25 that the agency provide formal notice and comment

1 rulemaking, not on every detail, but on the
2 fundamental issues of why it's extending regulation,
3 what the types of services that it plans to regulate,
4 and at least top line on the key issues that I raised
5 in the presentation.
6 Thank you very much, and we definitely
7 appreciate the opportunity to speak here this morning.
8 DR. KESSLER: Thank you, Dr. Redensky. We
9 appreciate it.
10 Dr. Thomas Grogan from Ventana Medical
11 Systems. He has some slides for us as well.
12 DR. GROGAN: My presentation emphasizes
13 the medical practitioner's perspective. My objectives
14 are to demonstrate the medical utility of multivariate
15 analyses and multiplexing and to suggest the kind of
16 draft guidance would impede medical practice.
17 My career has been in patient care and in
18 cancer biomarker development, as shown.
19 Next.
20 I will use two medical examples to make my
21 points.
22 Next.
23 EGFR and HOA.
24 Next.
25 EGFR is a trans-membrane molecule often

1 associated with cancer and, importantly, the object of
2 targeted anti-EGFR therapy. There exists today a PMA
3 approved single analyte diagnostic. The use of this
4 assay is limited by the observation that EGFR negative
5 tumors may respond to anti-EGFR therapy.
6 This leads to the NCCN to discount EGFR
7 testing. This lack of single analyte EGFR testing
8 effectiveness is not surprising, given our deeper
9 knowledge of EGFR molecular biology shown here.
10 To decipher this complexity, we have used
11 multiplexing with QDots directed at EGFR related
12 molecules. These non-bleaching fluorescent QDots
13 allow ready quantitation and give us ratiometric
14 mathematical findings. The draft guidance suggests
15 this type of mathematical result may not be
16 decipherable by a medical practitioner, but I contend
17 that if ratiometric results are put in the context of
18 systems biology as shown here, then the medical
19 meaning is readily interpretable. It is medically
20 relevant to discern that an anti-EGFR therapy has
21 decreased downstream signaling and affected
22 proliferation and apoptosis.
23 The second example is HLA expression in
24 lymphoma. Here I cite my ongoing six-year experience
25 as an investigator on the NCI DNA array project where

1 13,000 ESTs were reduced to five prognostic
2 signatures. One of these signatures shown here calls
3 out the medical relevance or high risk of low tumor
4 HLA expression. As shown in the left, there is a
5 surprising mathematical relationship between HLA and
6 the risk of death. As the HLA level drops,
7 arithmetically the risk rises logarithmically.
8 This emphasizes the importance of analyte
9 quantitation. To extend our knowledge of the HLA risk
10 equation, we again went to QDots to multiplex the HLA
11 associated molecules. This illustrates the complexity
12 of HLA transcription which necessitates multiplexing.
13 Utilizing multiplexing, we discovered as
14 shown that the change of the HLA family members is
15 coordinate. Hence, the description as a signature.
16 Again, I contend that the multiplex signature is
17 medically more useful than the single analyte.
18 To further illustrate my point that
19 signatures trump single analytes, in the next slide
20 I'll show you text in which every word is misspelled,
21 but you will discern the meaning by context and by
22 signature.
23 Could you go back to that one? Just make
24 sure you can read every word.
25 Notice the word "total mess."

1 Okay. Lastly, the patient's perspective.
2 This patient report indicates the current state of
3 anatomic pathology. Our reports now go well beyond
4 the diagnosis found on the top line to include items
5 found in the middle on prognosis and targets of
6 therapy.
7 In 2007, the patients asked for much more
8 than a diagnosis. On the left are the dozen questions
9 they want the answer to.
10 Next.
11 By demand, we are going beyond diagnosis
12 to treatment questions and beyond single analytes to
13 multiplexing.
14 To conclude, from the lab director's
15 perspective, we need as soon as possible the next
16 generation of tests, and we need to get there probably
17 by successive approximation.
18 From the patient's perspective, we need
19 now to have their questions answered as soon as
20 possible. So my recommendations are that we not apply
21 single analyte logic to multiplexing. We allow new
22 assays informed by research. We let the practitioners
23 sort it out. We don't impede the practice of
24 medicine. We keep the current status for IVDMIAs and
25 ASRs until we find a flexible regulatory alternative.

1 Thank you.

2 DR. KESSLER: Thank you, Dr. Grogan.

3 The next speaker is Steven McPhail from

4 Expression Analysis.

5 MR. McPHAIL: Thank you.

6 My name is Steve McPhail from Expression

7 Analysis, a genomic service provider in Durham, North

8 Carolina.

9 What I'd like to cover this morning are

10 the current state of genetic testing, draft guidance

11 issues as I see them, and potential unintended

12 consequences, a possible alternative approach, and I'd

13 like to close with what I consider to be some of the

14 challenges to widespread genetic testing.

15 The application of genetic testing to date

16 has typically been associated with rare genetic

17 disorders, but is currently moving into certain

18 therapeutic areas where disease etiology is not well

19 understood, and these are all complex diseases.

20 So the majority of diagnostics coming out

21 of this disease I contend will use multiple analytes.

22 There are over 1,000 genetic tests today offered by

23 reference laboratories. There are a few FDA cleared

24 and approved tests, and many, many laboratory

25 developed tests.

1 Issues with genetic testing today are
2 perceived lack of oversight. Now, it depends on who
3 you talk to. If you talk to a CLEA laboratory,
4 they'll tell you that there's plenty of oversight.
5 There's oversight from a federal level. There's
6 oversight from a state level, and from voluntary
7 organizations, such as the College of American
8 Pathologists.
9 However, there is a lack of transparency
10 associated with this testing. Does a patient and a
11 physician really know what they're getting?
12 There's also a lack of consistency
13 associated with this testing. If I were to order a
14 cystic fibrosis test in California and order the same
15 test in Texas, would I necessarily be getting the same
16 results? Not necessarily, depending upon the number
17 of variants that are actually tested.
18 There is also an issue with validation
19 standards. As we're aware, CLEA laboratories are
20 required to form analytic validation of assays that
21 they provide, which include performance measures of
22 sensitivity, specificity, accuracy, and
23 reproducibility versus clinical validation that may be
24 required in a PMA format by the Food and Drug
25 Administration.

1 There's also potential problems with data
2 interpretation and, therefore, I do believe that some
3 level of enhanced regulation is necessary to insure
4 high quality genetic testing.
5 But I would make suggestions for
6 improvements in future guidance. These suggestions
7 include an increase in the specificity of the
8 guidance, and I think we've heard that already this
9 morning. The way that I read the guidance, I believe
10 that many, many genetic tests could fall under IVDMIA
11 regulations.
12 Also, it's very important to reconcile, I
13 believe, the laboratory quality systems versus the FDA
14 quality system. If we force laboratories to move into
15 the FDA quality system requirements, that is a
16 significant cost and regulatory burden for
17 laboratories and cannot be implemented overnight.
18 I think we also need to address a path for
19 test improvements. Genomic information is coming at
20 us very quickly. If new variants are found, for
21 instance, for cystic fibrosis, we should be able to
22 implement those quickly without having to go through
23 potentially another PMA submission again.
24 We also need to define a mechanism to
25 assess risk versus technology, and when I look at the

1 IVDMIA guidance, what I see is a technology driven
2 guidance more so than a risk driven guidance.
3 So some potential unintended consequences
4 of the guidance, I believe, are reduced patient access
5 potentially, potential interference in physician
6 practice of medicine, a potential barrier to
7 innovation.
8 When we look at many of the companies that
9 are developing these tests, they are small companies,
10 small laboratories. They need access to capital to be
11 able to innovate, and this may have potential negative
12 unintended consequences on their access to capital.
13 So here's a potential alternative to the
14 guidance, and that is a laboratory developed test
15 registry. I believe that the laboratory developed
16 test registry could include analytical performance
17 characteristics, clinical performance characteristics,
18 both in terms of papers that have been published, as
19 well as laboratory experience. It could include
20 information on adverse events, volume, controls, et
21 cetera.
22 I believe that this type of a registry
23 would provide a path to additional regulation where
24 necessary. It would allow for regulation based on
25 risk versus technology, and it would provide

1 transparency for regulatory agencies, patients and
2 physicians.
3 I think I'd like to close with this. I
4 know that the FDA is certainly very excited about
5 personalized medicine and the use of pharmacogenomics
6 in personalized medicine. There are a lot of
7 challenges associated with bringing this technology to
8 use, to widespread market use. I've listed just some
9 of them here, and I think that it's prudent for the
10 agency and for the legislature to focus on how do we
11 reward innovation associated with these types of
12 companies that are struggling to bring this testing to
13 market.
14 Thank you very much.
15 DR. KESSLER: Thank you, Mr. McPhail.
16 Mary Steele Williams from the Association
17 for Molecular Pathology is next.
18 MS. WILLIAMS: Good morning. My name is
19 Mary Williams. Thank you for the opportunity to speak
20 with you today.
21 AMP is an international, not for profit,
22 educational society representing over 1,400
23 physicians, doctoral scientists and medical
24 technologists who perform molecular diagnostic
25 testing. For the last several years, AMP has provided

1 national leadership to advance safe and effective
2 practice and education for molecular diagnostic
3 testing in the health care industry.
4 AMP is dedicated to the advancement,
5 practice and science of clinical molecular laboratory
6 medicine and translational research based on the
7 applications of genomics and proteomics. Our goal is
8 to represent all members, regardless of the setting in
9 which they practice, because they are united in the
10 end intent to provide high quality, relevant
11 information for the purpose of directing individual
12 and patient community health management.
13 We acknowledge, however, that different
14 perspectives may emerge from those widely diverse
15 settings. In those instances our primarily
16 responsibility is to comment from the standpoint of
17 molecular testing laboratories and the patients they
18 serve.
19 Next.
20 AMP supports the development of tests and
21 test systems for in vitro diagnostic use and
22 encourages industry to pursue FDA clearance and
23 approval where current regulations require. We would
24 like to comment on the recently issued draft guidance,
25 "In Vitro Diagnostic Multivariate Index Assays," or

1 IVDMIA.

2 The FDA defines IVDMIAs as test systems
3 that employ data derived in part from one or more in
4 vitro assays and an algorithm that usually, but not
5 necessarily, runs on software to generate a result
6 that diagnoses a disease or condition or is used in
7 the cure, mitigation, treatment, or prevention of
8 disease.

9 In this guidance, FDA asserts that IVDMIAs
10 are not within the ordinary expertise and ability of
11 laboratories and, therefore, raise safety and
12 effectiveness concerns. The FDA then advises that
13 these test systems meet pre and post market review
14 requirements for Class 2 and 3 devices.

15 AMP questions the agency's interest in
16 regulating medical algorithms, particularly those that
17 are disclosed by the manufacturer and are transparent
18 to both the laboratory and the clinician.

19 The use of an interpretive algorithm is
20 routine in medical practice and should not in and of
21 itself raise specific concerns with FDA. Algorithms
22 using patient information, such as tumor size, extent
23 of malignancy and node involvement, have long been
24 used to determine the recurrence risk and to
25 classified certain cancer. Many laboratory tests

1 cannot be properly interpreted unless patient data is
2 collected.
3 One example is interpreting a glucose
4 reading without knowing when the patient last ate.
5 Many algorithms are published with peer review and are
6 available for professional scrutiny.
7 Next.
8 As our members routinely design and
9 perform many molecular tests in oncology, hematology,
10 human genetics and infectious disease, we are
11 particularly concerned about the broad language in the
12 document. We feel it could severely reduce the
13 availability of certain laboratory developed testing
14 services and compromise the quality of molecular test
15 development by laboratories under CLEA, many of which
16 have become the diagnostic or prognostic standard of
17 care.
18 Reduced availability of testing services
19 would limit a health care provider's ability to manage
20 patient care and ultimately limit patient access to
21 new or improved molecular tests.
22 For example, broad interpretation could
23 classify maternal serum screening or Bayesian analysis
24 for cystic fibrosis carrier screening, both of which
25 use well defined risk calculations as IVDMIAs.

1 Laboratories offering these tests would not likely be
2 in a position to meet FDA requirements as
3 manufacturers.
4 The FDA identifies IVDMIAs not as
5 laboratory developed tests, but as test systems that
6 combine data derived from the laboratory assay with an
7 algorithm or calculation to reach a patient specific
8 result.
9 This definition is not found in the
10 federal Food, Drug, and Cosmetic Act, nor in any
11 regulation from the FDA, and was not developed through
12 notice and comment rulemaking. With this proposed
13 definition, the laboratory is the manufacturer of a
14 test system and is subject to FDA regulation as a
15 medical device. We are unaware of such a definition
16 in any FDA regulation.
17 This area of laboratory operation
18 currently is regulated by the Centers for Medicare and
19 Medicaid services under the clinical laboratory
20 improvement amendments of 1988.
21 AMP respectfully requests that FDA provide
22 the scientific rationale for their new concerns over
23 the safety and effectiveness of laboratory developed
24 tests, as well as the justification for their
25 jurisdiction over medical testing algorithms.

1 Next.

2 FDA convene a classification panel, for
3 example, as was done in the reclassification of
4 immunohistochemistry tests, so that criteria for
5 determining which tests will be subject to FDA
6 regulation will be transparent to laboratories
7 developing such tests.

8 Next.

9 FDA clearly and specifically defined the
10 scope of IVDMIAs that it intends to regulate.

11 Next.

12 FDA insure that any new guidance does not
13 insert FDA into the purview of CMS regulation of
14 laboratories under CLEA.

15 FDA apply restrictions requiring PMA or
16 510(k) clearance of an IVDMIA only when the
17 interpretive algorithm remains undisclosed by the
18 manufacturer.

19 FDA clarify the scope of its regulations
20 that renders laboratories responsible for meeting
21 criteria as medical device manufacturers, that is,
22 premarket review only or all general controls,
23 registration and listing, quality systems, labeling,
24 medical device reporting.

25 Thank you for the opportunity to comment

1 on this important document. AMP will provide a
2 formal, written comment to the docket and remains
3 available to work with FDA to develop clear,
4 reasonable guidelines consistent with FDA's mission to
5 promote and protect public health in the development
6 of molecular pathology tests, balancing safety
7 concerns with access and availability of exciting new
8 medical breakthroughs.
9 DR. KESSLER: Thank you very much.
10 We will now hear from Richard Samp from
11 the Washington Legal Foundation.
12 MR. SAMP: Good morning. My name is
13 Richard Samp. I am Chief Counsel of the Washington
14 Legal Foundation, a public interest law firm and
15 policy center located here in Washington.
16 WLF devotes a substantial portion of its
17 resources to improving health care delivery in this
18 country. We believe that that goal can be best
19 achieved if government regulators devote their energy
20 to addressing proven hazards to public health while at
21 the same time allowing medical professionals the
22 freedom and flexibility to arrive at innovative
23 solutions to our ever changing health care needs.
24 WLF has no direct financial stake in the
25 issues being addressed at today's public meeting. We

1 have no connection with any of the laboratories whose
2 tests FDA is proposing to regulate. If FDA has
3 received financial support from any laboratory, it is
4 negligible.
5 I am testifying today because I am
6 convinced that any FDA effort to impose significant
7 regulation on laboratory developed test will be a
8 setback for public health. My background is as a
9 lawyer, not a medical professional. So I can speak
10 with somewhat more confidence when I tell you my other
11 reason for testifying today.
12 I am convinced that FDA's proposed
13 regulatory effort is contrary to law.
14 For those reasons, WLF filed the citizen
15 petition with FDA on September 28th, 2006. The
16 citizen petition requests that FDA determine that it
17 will not attempt to regulate as medical devices any
18 assays developed by clinical laboratory strictly for
19 their in-house use.
20 The petition was prepared independently of
21 FDA's September 7th, 2006 draft guidance and raises
22 several legal issues not addressed in the draft
23 guidance. The citizen petition docket is open, and we
24 encourage those with any interest in the issues
25 addressed today to file comments in that docket.

1 Because I do not claim expertise as a
2 medical professional, I've only briefly described why
3 I view laboratory developed test, or LDTs, as so
4 important, and why FDA's proposed regulation could
5 significantly hinder effective development and use of
6 LDTs.
7 Well, over 1,000 different tests are being
8 used every day by clinicians to better inform
9 diagnostic and therapeutic decisions. When new
10 infectious agents first appear and a new diagnostic
11 test is urgently needed for patient care, it is
12 generally an LDT, not an FDA approved or cleared
13 device that first meets that medical need.
14 For patients with cancer, LDTs have
15 entered wide clinical use in helping to manage their
16 care. Moreover, while inaccurate tests have the
17 potential to cause health care problems, there is no
18 evidence to suggest that currently available LDTs are
19 inaccurate and clinical labs are already subject to
20 regulation by CMS under CLEA.
21 If the system is not broken, it is
22 difficult to understand why FDA feels such a
23 compelling need to try to fix it.
24 Moreover, it is plain to anyone with an
25 understanding of clinical labs that requiring them to

1 go through FDA's premarket review process and comply
2 with FDA's device regulatory rules would have a
3 crippling effect on their ability to continue to
4 provide access to LDTs. Laboratories are not operated
5 as medical device manufacturers. Although they must
6 comply with CLEA, they do not maintain the procedures
7 and documents for compliance with FDA's quality system
8 regulation, its QSR.
9 Nonetheless, FDA is now asserting that
10 labs are subject both to the QSR and to the adverse
11 event reporting regulation. Labs are being told that
12 they will have to figure out for themselves how
13 procedures developed for device manufacturers would
14 apply to them. Yet I don't know anyone who knows how
15 one would go about retrospectively developing design
16 history files as required by the QSR.
17 Food and drug law attorneys are unanimous
18 in concluding that these and other medical device
19 regulations will preclude at least some tests from
20 being offered at all. Labs constantly innovate and
21 improve their tests. The need to comply with FDA
22 regs. would prevent many of these changes from being
23 made and severely inhibit the flexibility of
24 laboratories and their ability to meet clinicians'
25 needs, e.g., identifying rapidly changing pathogens,

1 such as SARS or HIV.

2 Moreover, if, as is likely, FDA regulation
3 requires many existing tests to be labeled
4 investigational, patients' ability to obtain
5 reimbursement for these often expensive tests will be
6 thrown into doubt. Many insurers balk at paying for
7 procedures deemed investigational.

8 I recognize that FDA may be reluctant to
9 heed medical advice from the Washington Legal
10 Foundation, but I ask you to heed our legal advice.
11 The regulation of LDTs proposed by the draft guidance
12 is contrary to law. I have three grounds for that
13 conclusion, all spelled out in more detail in our
14 citizen petition.

15 First, Congress has spoken, and it has
16 allocated the requisite regulatory authority to CMS
17 under CLEA, not to the FDA under the Medical Device
18 Amendments of 1976.

19 Second, the Secretary of HHS confirmed in
20 1992-93 that the regulatory authority lies with CMS.

21 Third, even if FDA does possess authority
22 to begin to regulate LDTs as medical devices, it is
23 going about doing so in a manner that violates the
24 Administrative Procedure Act, the APA. The only
25 congressional legislation directed specifically at

1 laboratories is CLEA, a 1988 statute whose enforcement
2 responsibilities have been assigned to CMS.
3 CLEA establishes quality standards for
4 virtually all clinical laboratory testing. Clinical
5 labs that offer LDTs fit to a tee the type of facility
6 that Congress said would be regulated under CLEA, and
7 I quote: "a facility for the biological,
8 microbiological, pathological or other examination of
9 materials derived from the human body for the purpose
10 of providing information for the diagnosis,
11 prevention, or treatment of any disease or impairment
12 of or the assessment of the health of human beings."
13 In contrast, the 1976 medical device
14 amendments under which FDA claims regulatory authority
15 does not have anything at all to say about
16 laboratories or lab testing, nor is there anything in
17 the MDA's legislative history to suggest that Congress
18 intended to grant FDA authority to regulate labs, nor
19 is there any evidence that in the years immediately
20 following adoption of the MDA, FDA understood the law
21 as granting such authority.
22 It was not until the 1990s that FDA first
23 began to suggest that it might possess regulatory
24 authorities over labs offering LDTs, and it is only in
25 the past year that FDA has sought to exercise that

1 alleged authority.

2 Under these circumstances, it is simply

3 not credible to suggest that Congress did, indeed,

4 intend in 1976 to grant FDA its newly discovered

5 regulatory authority. It is theoretically possible,

6 of course, that Congress in adopting the MDA and CLEA

7 intended to create parallel regulatory schemes each

8 with independent authority over lab testing.

9 But such an intent is highly improbable

10 when one considers that the MDA said nothing about lab

11 tests, while 12 years later CLEA specifically mandated

12 regulation of lab tests without once suggesting that

13 a preexisting statute provided for a more elaborate

14 set of regulations.

15 In the absence of authority from Congress,

16 FDA's recent attempts to regulate lab tests are

17 improper and should cease.

18 Second, even if the regulatory language

19 were deemed ambiguous, subsequent action by the

20 Secretary of HHS removes any doubt that FDA lacks

21 authority to act. It is the Secretary, not any of his

22 subordinate agencies, that possesses the authority

23 through lawful rule making to decide where the

24 authority to regulate clinical labs should lie.

25 The Secretary made that decision in 1992-

1 93 when he approved comprehensive CLEA regulations
2 that assigned regulatory authority to CMS. In
3 February 1992, final regulations took effect that set
4 forth, and I quote, all requirements applicable to
5 clinical laboratories engaged in testing and
6 interstate commerce.
7 The final regulation adopted in January
8 1993 established, and again I quote, uniform
9 requirements to insure the quality of lab services.
10 CLEA regulations underwent extensive revision in 2003,
11 and again there was no acknowledgement of any FDA rule
12 in regulating LDTs.
13 The Secretary's approval of those
14 regulations is wholly inconsistent with FDA's argument
15 that it possesses the authority to impose a regulatory
16 regime that would void huge parts of the existing CLEA
17 rules.
18 Third, even if FDA really did possess the
19 regulatory authority it now asserts, it is attempting
20 to assert that authority in a manner that violates the
21 APA. Although FDA has quietly said for about a decade
22 that it possesses regulatory authority, it never
23 attempted to exercise that authority until the past
24 year. It is not the character of LDTs that has
25 changed. It is FDA policy that has changed.

1 Before a federal agency may change
2 policies in a manner that materially changes
3 established benefits and burdens, it must comply with
4 formal APA notice and comment procedures.
5 Let me skip ahead and finally say a few
6 brief words about First Amendment concerns that I have
7 with FDA's assertion of regulatory authority. When a
8 lab professional provides a physician with test
9 results, he or she is communicating medical
10 information that FDA has no reason to believe is
11 untruthful.
12 Even if FDA asserts that such
13 communication should be deemed commercial speech, it
14 is still entitled to a substantial degree of First
15 Amendment protection. Before FDA gets into the
16 business of regulating such speech, it ought to think
17 long and hard about whether its regulatory objectives
18 are sufficiently compelling to justify government
19 impairment of free speech rights in this manner.
20 Thank you for the opportunity to share my
21 views with you today.
22 DR. KESSLER: Thank you.
23 Next we'll hear from Thomas Tsakeris,
24 Coalition for 21st Century Medicine.
25 MR. TSAKERIS: Good morning. My name is

1 Tom Tsakeris, and I'm speaking today on behalf of the
2 Coalition for 21st Century Medicine.
3 I am not being compensated by the
4 coalition or by any of its member companies.
5 Many of my comments this morning are in
6 parallel to many of the earlier speakers. However, I
7 think given the impact that the IVDMIA guidance
8 document has on the practice of laboratory medicine,
9 I think whatever points have been made previously
10 about any adverse unintended consequences are
11 certainly worth repeating.
12 The coalition represents innovative
13 diagnostic companies, clinical laboratories,
14 researchers, physicians, venture capitalists, and
15 patient advocacy groups who believe in a common
16 mission to develop and offer specialized diagnostic
17 testing to improve the quality of health care for
18 patients. Innovation in quality patient care are the
19 key objectives for the 21st century medicine.
20 The timely development and availability of
21 high quality, innovative diagnostic tests and services
22 meet today's needs for personalized medicine and,
23 therefore, public health.
24 The Coalition is concerned that in its
25 current form, the draft guidance document will have

1 adverse unintended consequences. In my discussion
2 today, I will identify some of these unintended
3 consequences and stress the need to obtain better
4 clarity from FDA on the scope of its intent to
5 regulate these types of tests and also to present
6 alternatives to the draft guidance.
7 The coalition has identifies several
8 serious adverse consequences.
9 Number one, active FDA regulation of
10 IVDMIAs will impede the innovation of new tests and
11 services, while precluding improvements from being
12 made to existing tests and service.
13 Two, implementation of the guidance will
14 impose undue regulatory burden on clinical labs by
15 adding new regulatory requirements that conflict with
16 existing CLEA requirements.
17 And, three, implementing the guidance will
18 preclude tests and services from being reimbursed by
19 health plans, thereby creating disincentives for
20 future research investment in new diagnostic
21 technologies.
22 I will elaborate on these points.
23 In its current form, the draft guidance
24 will significantly affect ability and incentives for
25 clinical labs to develop new diagnostic tests and

1 services that build on current medical knowledge.
2 Innovation and diagnostic testing traditionally has
3 been a key attribute of clinical labs.
4 The draft guidance extends the scope of
5 FDA regulation to certain clinical laboratory tests
6 referred to by FDA as IVDMIAs on the premise that
7 IVDMIA test results -- and I'm quoting directly from
8 the guidance -- cannot be interpreted by well trained
9 health care practitioner using prior knowledge of
10 medicine without information from the test developer
11 regarding its clinical performance and effectiveness.
12 On the contrary, the coalition believes
13 FDA should be clear that the primary incentive for
14 clinical labs to develop technologically new
15 diagnostic testing capability derives from the demand
16 from physicians and other health care providers to
17 obtain new innovative testing services commensurate
18 with their advancing knowledge of the potential
19 usefulness of such testing to laboratory medicine and
20 not vice versa.
21 In short, the coalition believes that the
22 clinical labs which offer new tests, IVDMIAs or
23 otherwise, are typically serving informed physicians
24 who are sufficient knowledgeable about a given test
25 technology and its potential clinical utility to seek

1 its availability.

2 The coalition believes that subjecting
3 clinical labs to added burden of complying with FDA
4 regulatory requirements will result in physicians and
5 patients experiencing either unnecessary delay or
6 doing without access to important tests in rapidly
7 advancing fields, such as genetics, oncology, and
8 infectious disease.

9 As written, the draft guidance introduces
10 additional unnecessary regulatory burdens on an
11 already highly regulated clinical laboratories.
12 Clinical labs are currently regulated by CMS under
13 CLEA. This has been mentioned before. I won't go
14 through all of the requirements that laboratories are
15 subject to. You're well familiar with all of them.

16 However, under the draft guidance,
17 laboratory tests and services that are already subject
18 to CLEA's quality standards would now also be subject
19 to FDA's QSR requirements which are tailored for
20 traditional medical device manufacturing operations.

21 For laboratories to develop systems that
22 comply with FDA's QSR requirements while continuing to
23 comply with CLEA could take years, would be
24 prohibitively costly, and will likely drive up health
25 care costs.

1 In short, what would result for both
2 existing and prospective clinical labs is, at best an
3 untenable business model.
4 If the draft guidance is implemented
5 immediately, existing products regulated as IVDMIAs
6 will become illegal unless they obtain FDA clearance
7 or approval. Labs will not be able to complete the
8 review process for a long period of time.
9 Offering tests that are deemed illegal
10 raises serious risks to labor licensure and
11 accreditation and exposes labs to unnecessary
12 liability risks.
13 Of even greater concern, labs may also be
14 prevented from being reimbursed by federal, state, and
15 private insurance coverage. The lack of coverage,
16 along with other increased regulatory obligations will
17 hinder the ability of labs to maintain current
18 operations, as well as attract adequate financial
19 capital to support research and development of new
20 tests and technologies.
21 The coalition is also concerned by the
22 ambiguities that exist under the current draft
23 guidance. As has been mentioned previously, the
24 definition of the IVDMIA itself is ambiguous and
25 introduces new terms that are not included in FDA's

1 existing regulations. We heard from Dr. Harper.
2 You're asking yourselves for clarification on what the
3 definition should be. Interesting.
4 This ambiguity creates uncertainty as to
5 which tests are IVDMIAs subject to regulation by FDA.
6 As written, the definition could be interpreted to
7 include a broad array of testing, including standard
8 medical treatment algorithms.
9 The coalition has identified scores of
10 algorithms that are not in use and many more are being
11 published each month. FDA could be faced with
12 regulating hundreds of IVDMIAs. This will require a
13 tremendous amount of agency resources, diverting
14 personnel from reviewing new marketing applications
15 for manufacturers of assays.
16 The draft guidance sets forth a major
17 change in laboratory regulation and establishes a new
18 regulatory regime. Yet remarkably the document is
19 only five pages long. In those five pages, there is
20 very little detail about the proposed new regulatory
21 path or any mention of FDA enforcement policy.
22 In short, labs need far more clarity than
23 has been provided by the draft guidance.
24 We believe FDA should adopt alternative
25 paths. The coalition has developed several possible

1 alternatives to the IVDMIA guidance. For purpose of
2 this meeting, we'll focus on four important
3 alternatives.
4 First, FDA should not pursue regulation of
5 IVDMIAs by way of the draft guidance route. Rather,
6 the agency should propose new regulations that are
7 detailed, clear, predictable and establish the least
8 burdensome regulatory controls in light of the actual
9 risks and benefits of IVDMIA testing.
10 FDA's exercise of authority over
11 laboratory developed tests represents a substantial
12 change in the regulation of labs and needs to be
13 implemented through new regulations, not a guidance
14 document. This will insure the maximum public
15 participation and scrutiny.
16 Given the precedent that is being set,
17 rulemaking is imperative.
18 Second, FDA should base any level of
19 regulation of IVDMIAs on risk. The level of risk is
20 higher for IVDMIAs that are predictive and that result
21 in a binary therapy recommendation to treat or not to
22 treat based solely on the IVDMIA outcome. Other
23 IVDMIAs, whether predictive or prognostic, advisory or
24 adjunctive, that do not give binary therapy
25 recommendations are lower risk. These types of

1 IVDMIAs should not be held to the same regulatory
2 standards.
3 A risk based approach would lead to a more
4 appropriate allocation of regulatory effort by both
5 labs and FDA.
6 Third, there needs to be a transition
7 period to assure labs with IVDMIAs to adjust from the
8 current CLEA regulatory path to a CLEA plus FDA
9 regulatory path. The lack of a transition period
10 could severely disrupt the availability of tests. If
11 FDA imposed the device requirements on labs without
12 any transition period, it could halt the use of
13 development of tests, as well as improvements to
14 existing tests.
15 If based on risk an IVDMIA is subject to
16 FDA regulation, a lab should have between two and four
17 years to submit an application to FDA. During the
18 transition period, FDA should not require labs labeled
19 with IVDMIAs as investigational and IDE should not be
20 required.
21 Note that in 1998 FDA released its draft
22 compliance policy guidance titled "Commercialization
23 of IBDs labeled for research use only and
24 investigational use only," which permitted a
25 transition period for subject IBD companies to come

1 into compliance with the agency's premarket submission
2 requirements. A similar transition period should also
3 be applicable to IVDMIAs.
4 Fourth, FDA could institute a disclosure
5 program. This registry could provide reliable
6 information about the strengths and particular
7 limitations of IVDMIAs and allow FDA to understand the
8 scope of these tests. The information available
9 through the registry could help FDA create a more
10 specific definition of IVDMIA and could help show how
11 these tests should be regulated. This would
12 facilitate FDA's regulatory approach.
13 In conclusion, we believe that the draft
14 guidance, if implemented in its current form,
15 important medical tests may become unavailable, be
16 frozen at their current technological state, become
17 more expensive, or potentially lose insurance
18 coverage. None of these outcomes benefit patients.
19 Labs have been a significant source of
20 innovation for decades. Laboratory developed tests,
21 including tests and services that would be considered
22 IVDMIAs under the guidance, are an essential part of
23 public health and are the future of personalized
24 medicine.
25 To preserve the future, FDA should go

1 through formal rulemaking procedures and carefully
2 consider the alternatives we have presented.
3 Again, on behalf of the Coalition for 21st
4 Century Medicine, I thank you.
5 DR. KESSLER: Thank you.
6 Before we hear from our next speaker, a
7 brief logistics comment. I want to thank all of the
8 speakers for not only their thoughtful and articulate
9 comments this morning, but for staying on time. After
10 the next two speakers, we'll have approximately a half
11 an hour to open up the mics to the floor. So I'm
12 giving you a chance to think about the comments and
13 questions you have.
14 We will concentrate on your comments on
15 the previous speakers or other comments we want to
16 make. We're not going to be handling questions from
17 the front of the room here, but the mics will be open
18 for quite a little while. If we get a chance, we may
19 even advance a couple of the speakers from after the
20 break into the morning session so that we can advance
21 the whole day.
22 Next we're going to hear from Dr. William
23 Clark from the American Association of Clinical
24 Chemistry.
25 Dr. Clark.

1 DR. CLARK: Good morning. My name is Bill
2 Clark, and I'm a clinical laboratory director at Johns
3 Hopkins Hospital in Baltimore.
4 Today I'm speaking on behalf of the
5 American Association for Clinical Chemistry.
6 AACC is the principal association of
7 professional laboratory scientists whose membership
8 includes M.D.s, Ph.D.s, and medical technologists.
9 Our members develop and use chemical concepts,
10 procedures, techniques, and instrumentation in health
11 related investigations and work in hospitals,
12 independent laboratories, and the diagnostics industry
13 worldwide.
14 AACC would like to thank the agency for
15 holding this public forum. We believe this meeting
16 gives the agency an opportunity to clear up much of
17 the confusion surrounding the IVDMIA draft guidance
18 while also giving the public and other stakeholders an
19 opportunity to express their views on this important
20 document.
21 Although AACC is still finalizing its
22 comments on the draft guidance, we generally supported
23 the agency's goal, which is to insure that IVDMIAs
24 provide accurate, verifiable test results.
25 Further, we agree with the FDA's decision

1 to leave primary oversight of traditional laboratory
2 methods, develop tests with CMS utilizing the CLEA ADA
3 standards.
4 AACC is concerned, however, that the
5 agency may be moving forward too quickly in this area
6 without fully examining the unintended consequences
7 that could arise from this policy. AACC suggests that
8 the FDA consider and address the following questions
9 before fully implementing its IVDMIA policies, such
10 as:
11 What impact will this policy have on
12 incremental advances to existing technologies as well
13 as the development of first of a kind assays?
14 Also, will tests no longer be offered as
15 a result of this policy? If so, which of these tests?
16 And will the loss of these tests hinder
17 the delivery of patient care?
18 Will the agency allow laboratories to
19 continue utilizing existing unapproved algorithms
20 until it or similarly approved algorithms are approved
21 by the FDA?
22 How will the FDA inspect laboratories
23 under the promised QSR guidance?
24 Also, we are requesting that the agency
25 clarify whether IVDMIAs can serve as a predicate

1 device, particularly if the IVDMIA is not available
2 for clinical comparison or precision comparison
3 studies. Typically devices approved or cleared under
4 the PMA or 510(k) processes serve as predicate for
5 future submissions to the FDA.
6 In this instance, however, a manufacturer
7 laboratory would not have access to the reagents since
8 they are not in commercial distribution, although I
9 think this was partially addressed through the
10 comments in the introduction.
11 Finally, AACC recommends that the agency
12 include examples of tests which employ algorithms but
13 would not be subject to this guidance. For example,
14 we expect that a test employing simple calculations to
15 result, such as creatinine clearance addressed in the
16 introduction, would not be considered an IVDMIA, nor
17 would an assay utilizing publicly available algorithms
18 or clinical guidelines, such as prenatal screening for
19 open neural tube defects.
20 AACC believes these and other examples
21 would more clearly demarcate the limits of the
22 document. AACC welcomes the opportunity to comment
23 here today and will provide more detailed comments to
24 the agency by the March 5th deadline.
25 Thank you.

1 DR. KESSLER: Thank you, Dr. Clark.

2 We're next to hear from Dr. Carolyn
3 Compton of the National Cancer Institute.

4 DR. COMPTON: Thank you.

5 I appreciate the chance to speak to you
6 today because I'm bringing a new focus to the table,
7 one that is not directed toward the test itself but
8 toward the thing being tested.

9 I'm here from the National Cancer
10 Institute, which as you know represents a vast
11 scientific enterprise that's dedicated to the
12 development, validation, and application of new
13 methods of diagnosing, treating, and preventing cancer
14 for the American public and cancer patients, and it
15 has been the perspective of this agency that the new
16 methods, the new technological platforms that are
17 being developed to focus on analysis of human
18 specimens that raise the bar for specificity,
19 sensitivity, and complexity, especially multiplexing
20 tests, raise the bar for the quality of the thing
21 being tested, the human specimen.

22 And, in fact, the institute has focused on
23 this problem in such a critical way that a year and a
24 half ago it created the office which I now direct, the
25 Office of Biorepositories and Biospecimen Research,

1 which is focused on optimizing and standardizing the
2 quality of human specimens for the research that will
3 drive personalized cancer medicine, and certainly
4 IVDMIAs fall into the category of personalized
5 medicine very centrally and to remove the current and
6 future barriers to cancer research represented by the
7 limitation in quality of human specimens; that human
8 specimens are not regulated in any way right now, and
9 in fact, very little guidance exists as to how to
10 standardize or optimize the quality of human specimens
11 as they are used in analytic testing across the
12 medical enterprise.
13 Our office, the OBBR, has in the last year
14 and a half taken direct steps toward providing
15 guidance for our research enterprise, and hopefully
16 this will translate into clinical medicine very
17 shortly, by providing the first of its kind, first
18 generation guidelines for NCI supported
19 biorepositories that represent the state of the
20 science, best practices for the handling of human
21 specimens for molecular analysis.
22 And we have many other initiatives in
23 place that are focused toward developing second
24 generation guidelines that will be largely, if not
25 entirely data driven because the state of the art at

1 it exists today is mostly empirical and based on
2 expertise and experience, but not objective scientific
3 data as to the effects of handling, processing and
4 storing variables of human specimens on molecular
5 profiles, and therefore, guidance on how to optimize
6 the handling of these specimens for consistency in
7 testing results does not exist.
8 Next slide.
9 Our view of biospecimens is a dynamic one.
10 We view the biospecimen as a viable entity that, in
11 fact, has two phases as it enters clinical analysis.
12 One is the preacquisition phase, before it becomes a
13 specimen and comes out of or off of the patient. It
14 is subjected to iatrogenic variables that can
15 dramatically change its biomolecular profiles, and
16 after it is removed and sent to the pathologist or
17 into the testing process, additional variables can
18 also change these specimens biomolecular profiles
19 because it is, in fact, still viable until it is
20 suspended in biologic animation by fixation or
21 freezing.
22 Next slide.
23 These are only a few of the pre and post
24 acquisition variables that we know can dramatically
25 change singular molecular profiles and certainly

1 complexes or fingerprints of molecular profiles in
2 specimens of a different type, and each one of these
3 variables can have differing effects on different
4 types of specimens and even from the same specimen
5 type, such as a cancer specimen, from different sites
6 in the body.
7 So we expect this to be a very complex
8 issue and one in which we have undertaken a serious
9 scientific effort to sort out.
10 Next slide.
11 One of the most critical issues has just
12 come forward recently when it was pointed out that a
13 diagnostic test, which in fact I am a pathologist so
14 I can speak for this very strong. This is the first
15 diagnostic test in pathology that determines whether
16 or not a patient will be treated with a specific
17 therapy irrespective of any clinical input.
18 HER2 new testing, as you know, is
19 performed on breast cancer tissue, and it is performed
20 by an immunohistochemical test that if it is shown to
21 be positive and the cut points for that were
22 determined, of course, by validation tests, that the
23 patient will receive herceptin therapy, and positive
24 results trigger a therapeutic burden for the medical
25 system of $60,000 per patient per year, and false

1 positive results can carry a risk of cardiotoxicity.
2 So this is a very critical test which it
3 was learned several years after this therapy had been
4 on the market and had been actively being used in the
5 clinic for patients, was discovered that there was, in
6 fact, no strictly standardized testing method for the
7 biospecimen.
8 ASPA went to the College of American
9 Pathologists, and just recently a standardized
10 guidance was published. However, even in the process
11 of writing this guidance it became clear to the
12 College of American Pathologists that there were
13 unanswered questions about handling of the specimen,
14 and this brings up a general issue about the way the
15 FDA approaches its diagnostic testing guidances and
16 its regulations.
17 There's very specific guidance typically
18 about how to do the test. Yet even if your test is
19 validated, standardized, and perfect in its execution,
20 you can build in the variation up front in the
21 biospecimen if the handling processing of the specimen
22 itself is not standardized.
23 So standardization of the analyte is at
24 least as important as the standardization of the
25 analysis, again, as pointed out by HER2 testing, and

1 it was documented by Asbill and Capp that as much as
2 20 percent of the diagnostic tests performed on breast
3 biopsies were, in fact, inaccurate based on handling
4 variables, such as type of fixation, length of
5 fixation, temperatures in imbedding machines, and
6 other types of variables.
7 Next slide.
8 So with the emergence on the horizon of
9 other diagnostic multiplex tests, this problem becomes
10 even more significant, and on the horizon we certainly
11 have, as was mentioned by previous speakers, EGFR
12 testing, Oncotype Dx testing, which is now in clinical
13 trials, Lymphochip tests, and in fact, some of these
14 multiplex tests, such as Oncotype Dx, are performed on
15 specimens that are handled for clinical purposes and
16 borrowed from the clinical enterprise with no specific
17 guidance up front as to how to handle the specimen
18 specifically to acquire reproducible results from the
19 tests.
20 So, in fact, on matter how clever, how
21 standardized, how perfected your test, or even how
22 highly diagnostic or prognostic, under the correct
23 conditions these tests are still subject to the rules
24 of all good science, which is garbage in, garbage out.
25 Next slide.

1 So I don't come here to suggest that
2 biospecimens are something that the FDA can or should
3 regulate. I'm only bringing this issue to your
4 attention as a problem that affects multiple
5 stakeholders, may, in fact, affect multiple government
6 agencies, but for which there is no answer at the
7 moment as to where and how to develop standards for
8 specimen handling, how to draw the development and
9 implementation of biospecimen quality standards, or
10 how to provide the reimbursement that will be
11 necessary to make certain that the pathologists who
12 are the people that handle these specimens for the
13 most part or if the handling of the specimen for a
14 given test happens up stream are reimbursed for the
15 extra time and expert input that they will have to
16 provide in order to standardize this critical variable
17 for testing.
18 Thank you.
19 DR. KESSLER: Thank you, Dr. Compton.
20 We're glad to have our NCI colleagues here and have
21 your program presented. We appreciate it.
22 We're doing great on time. I want to
23 thank all of the speakers of the morning so far, and
24 leave the microphones open. We'll try to recognize
25 you in some order if you stand up, and please feel

1 free to comment, particularly about the morning's
2 presentations.
3 And, please, for the record, state your
4 name and your affiliation. And you can use the mics
5 in the center if you prefer.
6 MS. CHARACHE: My name is Patricia
7 Charache, and I'm representing the American Society
8 for Microbiology.
9 And I'd like to first agree with my
10 colleagues, including my co-member of Johns Hopkins
11 University from AACC, that there's a need, and all
12 other speakers, there's a need to clarify the
13 definitions so that we know more clearly exactly
14 what's meant by the different categories.
15 We are concerned about the needs to
16 address patient safety with these tests, and I would
17 point out that although CLEA is responsible for
18 laboratory processes, thus far CLEA and its deemed
19 agents that review laboratories through CMS have
20 emphasized analytical validation of tests rather than
21 clinical validation as they review development of new
22 tests.
23 The FDA, and I'm familiar from advisory
24 panels particularly in microbiology, does address the
25 clinical validation area.

1 The point that Dr. Tsakeris pointed out
2 that there is a major increase by clinicians for the
3 use of these molecular tests is certainly supported
4 and our own experience at Johns Hopkins, and this
5 pressure comes primarily from two sources. One is the
6 literature, but the other is a new tendency that we've
7 seen very heavily in our home institution, which is
8 direct to clinician marketing by laboratories that
9 offer this type of complex test.
10 This direct to clinician marketing in our
11 institution has covered diverse diseases, such as the
12 ability to diagnose inflammatory bowel disease, some
13 endocrinopathies, to cancer management and to the
14 diagnosis of genetic disorders.
15 And all of this has bypassed the expertise
16 of anyone who can objectively look at the quality of
17 the information being provided. We've had to
18 interrupt when we've learned about these processes
19 direct sending of specimens to at least four such
20 laboratories that had not done clinical validation.
21 So that we do feel that there's a need to
22 look closely at this type of test, which has very
23 major impact upon patient management, particularly if
24 the quality of the test or, as the NCI just pointed
25 out, the way in which the test was validated, have not

1 been addressed.

2 So we think that the underpinnings of the

3 desire to improve quality of these complex tests and

4 our knowledge that the clinicians despite their skill

5 and their excellent knowledge of clinical diseases are

6 not equipped to know whether the test is one in which

7 they should be managing their patients presents a need

8 to look further into how to achieve those goals.

9 Thank you.

10 DR. KESSLER: Thank you very much.

11 Are there other comments from the floor,

12 questions, clarifications, funny jokes?

13 (Laughter.)

14 DR. KESSLER: Well, we're not yet ready

15 for a break. So I'm hoping that a couple of the

16 speakers for the next session of the morning are

17 prepared and we'll begin with a few of those

18 presentations. We'll break a little bit early and

19 that will advance the schedule today.

20 So I'd like to call up Carolyn Popper if

21 she's here from Exagen Diagnostics.

22 Well, it's not true that if you snooze you

23 lose. We'll come back to Carolyn. Perhaps Alan Mertz

24 is here from the American Clinical Laboratory

25 Association -- oh, wait, wait. Carolyn, is that you?

1 No, no, no. Come on. Thank you.

2 So we are going to begin with Dr. Carolyn

3 Popper from Exagen Diagnostics, correct?

4 DR. POPPER: Correct.

5 DR. KESSLER: Okay.

6 DR. POPPER: And I'm not going to tell a

7 joke.

8 DR. KESSLER: You just did.

9 DR. POPPER: Good morning. I'm Carolyn

10 Popper, and I'm a physician and a senior regulatory

11 advisor to Exagen Diagnostics.

12 I very much appreciate the opportunity on

13 behalf of Exagen to comment on the draft guidance. In

14 sum, we at Exagen appreciate the FDA's efforts to

15 protect public health by a reasonable regulatory

16 oversight, and we particularly are glad to have this

17 opportunity to offer our thoughts and perspective on

18 many of the issues raised both in the document and in

19 the comments here today.

20 Exagen was founded in 2002 in Albuquerque,

21 New Mexico, and it discovers, designs, validates,

22 manufactures, and commercializes small sets of genomic

23 markers to provide prognostic and diagnostic kits for

24 commercial laboratory testing and for use in clinical

25 trials by drug developers.

1 Exagen is currently developing a number of
2 products that fall under the food drug and cosmetic
3 act and FDA regulations. During the past year, we
4 have been working closely with the Office of in Vitro
5 Diagnostics as we are pursuing regulatory review for
6 the first of several products in the coming months.
7 We understand that new technologies giving rise to
8 new, more complex marker sets challenges conventional
9 diagnostic regulatory paradigms and believe that
10 reasonable oversight to protect public health is
11 entirely appropriate.
12 Like the FDA, we feel that an IVDMIA that
13 utilizes data from an IVD assay which is then
14 manipulated by an algorithm to produce a final result
15 in tended to help diagnose, mitigate, treat, or
16 prevent disease is, indeed, a medical device and
17 should, therefore, be regulated by the FDA.
18 We hope though that as the FDA seeks a
19 regulatory framework for IVDMIAs that the agency takes
20 what it describes as the least burdensome approach,
21 thereby facilitating regulatory oversight while not
22 impeding commercialization of new technologies.
23 In that regard we congratulate Agendia at
24 having achieved FDA clearance.
25 It is also important to note, in our

1 opinion, as have others here this morning, that not
2 all IVDMIAs are equal. The agency should take into
3 consideration the intended use of new IVDMIA products
4 and recognize that they vary quite considerably. As
5 such, a whole variety of new regulatory approaches may
6 be warranted based upon the risk to the patient and
7 the benefit of the test.
8 We agree with the statement in the draft
9 guidance that most IVDMIAs will be either Class 2 or
10 Class 3. As for example, any device intended as an
11 indicator of the patient's risk of cancer recurrence
12 would be a Class 2. The IVDMIA which provides another
13 data point to the physician without specifically
14 dictating treatment is not relied upon by the
15 physician as the sole decision point in the diagnosis
16 or selection of therapeutic options.
17 Exagen does request clarification of an
18 item on page 3 of the guidance. On page 3 in the
19 guidance document under the section about definition
20 and regulation of status of IVDMIAs, there's a
21 sentence which reads, "Even if a laboratory or other
22 IVDMIA manufacturer. . . . " This sentence we find to
23 be ambiguous, and we recommend that the FDA clarifies
24 its position.
25 I believe other speakers before me have

1 raised this position, too. It is clear that the
2 IVDMIA applies to laboratories. However, Exagen does
3 not believe that manufacturers seeking premarket
4 review under the act for interstate commerce fall
5 under this guidance.
6 Clearly, this is a very exciting time for
7 science and medicine and for patients, with a promise
8 of many new discoveries and IVDMIA products on the
9 horizon from many companies and innovators. Given
10 that laboratories and IVDMIA manufacturers are in the
11 early stages of discovery and development and
12 validation of these IVDMIA products, it is important
13 that the FDA guidance and regulations support the
14 degree of innovation that we have seen in the industry
15 in recent years.
16 We look forward to continued discussion
17 here this morning and in the weeks ahead, and look
18 forward further to the opportunity to offer our
19 thoughts as the FDA refines its position in the coming
20 months.
21 Thank you.
22 DR. KESSLER: Thank you very much.
23 We'll turn now to Alan Mertz from the
24 American Clinical Laboratory Association.
25 MR. MERTZ: Good morning. I'm Alan Mertz,

1 president of the American Clinical Laboratory
2 Association, and we're an association that represents
3 local, regional, national, hospital and independent
4 clinical laboratories, and we thank the FDA for this
5 public meeting this morning.
6 This is important because many of ACLA
7 members perform laboratory developed tests that could
8 be very much affected by the FDA's draft guidance on
9 IVDMIAs.
10 Next slide.
11 ACLA strongly supports the goal of the
12 draft guidance, namely, to dispel the existing
13 confusion and lack of clarity regarding FDA's
14 regulatory approach towards certain laboratory
15 developed tests.
16 Although the concerns identified by FDA in
17 its draft guidance are clear, the guidance falls short
18 of achieving the goal. We would like to work with FDA
19 toward resolving these concerns in a manner that
20 promotes the promise of personalized medicine and
21 encourages the continued investment in these rapidly
22 advancing areas of laboratory medicine.
23 Next slide, please.
24 We focus on three key recommendations this
25 morning. First, ACLA recommends that FDA issue a

1 proposed rule to address this important subject matter
2 through the formal notice and comment rulemaking
3 process rather than through subregulatory guidance.
4 Second, we recommend that FDA consider
5 proposals to narrow and clarify its definition of
6 IVDMIAs to avoid confusion and unintended
7 consequences.
8 Third, we recommend that FDA work with CMS
9 through HHS to address its concerns through
10 enforcement and better enforcement of the regulations
11 promulgated under the Clinical Laboratory Improvement
12 Amendments, CLEA.
13 Next slide.
14 The procedural recommendation in favor of
15 notice and comment rulemaking is important. Since the
16 draft guidance announces the laboratory developed
17 tests deemed IVDMIA are Class 2 or Class 3 devices
18 requiring FDA premarket clearance or approval, it
19 represents a significant change from the agency's
20 historical practice regarding laboratory developed
21 tests and has a present binding effect.
22 Rather than merely stating the agency's
23 current thinking on the topic without creating or
24 conferring any rights or binding FDA or the public,
25 the draft guidance operates as a substantive rule. As

1 such, its subject matter should be vetted through the
2 formal, on-the-record notice and comment rulemaking
3 procedures of the APA.
4 Similarly, while FDA declined to classify
5 laboratory developed tests as Class 2 or Class 3
6 medical devices in the ASR rule, on the policy
7 grounds, laboratory developed tests have contributed
8 to enhanced standards of medical care in many
9 circumstances, and the significant regulatory changes
10 in this area could have negative effects on the public
11 health.
12 The draft guidance seeks to regulate
13 certain laboratory developed tests on the ground that
14 the public health requires it. Since the FDA's
15 advisory opinion in the ASR rule was published in the
16 Federal Register as part of a formal notice and
17 comment rulemaking, the modification of that policy
18 which the draft guidance represents must be treated in
19 the same manner procedurally.
20 The best substantive result for all
21 stakeholders is most likely to be achieved only when
22 all stakeholders are afforded the full procedural
23 protections of notice and comment rulemaking.
24 Next slide, please.
25 While FDA has noted that IVDMIAs are

1 intended to describe a narrow niche of devices, the
2 draft guidance defines IVDMIAs so broadly and so
3 vaguely that the scope of the draft guidance's
4 application could easily be interpreted to extend far
5 beyond its intended reach.
6 Specifically, the draft guidance defines
7 IVDMIAs as, quote, test systems that employ data
8 derived in part from one or more in vitro assays and
9 an algorithm that usually, but not necessarily, runs
10 on software to generate a result that diagnoses a
11 disease or condition or is used in the cure,
12 mitigation, treatment, or provision of disease, end
13 quote.
14 It further describes three interlocking
15 criteria of IVDMIAs, use of clinical data, an
16 algorithm, and a result that cannot be interpreted by
17 a health care provider without the help of the test
18 developer.
19 As written, the draft guidance could be
20 interpreted to apply to many well established tests
21 that are already the part of the standard of care.
22 Upon citing examples of such tests to FDA, ACLA was
23 informed by FDA that it was not their intent to
24 include such well established tests within the scope
25 of the draft guidance, and FDA requested our

1 assistance in clarifying and narrowing the definition
2 to conform to its intended application.
3 Next slide, please.
4 While the following recommendations for
5 clarifying and narrowing the definition of IVDMIA
6 should not be construed as an endorsement by ACLA of
7 FDA regulation of any lab developed test nor an
8 acknowledgement that FDA has the authority to regulate
9 these tests, and while ACLA and its members reserve
10 the right to offer modifications at a future date, we
11 offer the following recommendations in a good faith
12 effort to make progress toward achieving our shared
13 goals.
14 FDA should consider the following link
15 factors in formulating a definition.
16 One, a new single source test system.
17 Two, use as patient and/or clinical data
18 derived from one or more in vitro diagnostic assays
19 together with a proprietary non-published algorithm.
20 Three, generate a patient specific binary
21 result that is intended definitively to diagnose a
22 condition or to direct behavior for the cure,
23 mitigation, treatment or prevention of disease.
24 And, four, present significant safety and
25 effectiveness risk not present in test systems which

1 have become part of the standard of care.

2 Next slide.

3 Moreover, certain factors, if present,
4 would indicate the FDA regulation is not warranted.
5 Specifically, test systems which meet one or more of
6 the following criteria should not be deemed IVDMIAs:
7 low risk consequences of invalid or inaccurate test
8 results; independent verification by one or more
9 laboratories; support of clinical relevance in peer
10 reviewed literature, transparent algorithms,
11 interpretation support for clinicians, support in
12 clinical guidelines, established use, CPT code
13 assignment, and payer recognition.

14 We'll provide further elaboration of these
15 points in our formal written comments on the draft
16 guidance.

17 next slide.

18 Nevertheless, ACLA firmly believes that
19 FDA should also consider working with CMS and through
20 HHS to enhance this CLEA regulations and provide means
21 for the systematic and rigorous enforcement. This
22 approach has the potential to address the concerns
23 that prompted FDA ot issue the draft uigdance in the
24 contest of the regulatory framework specifically
25 designed for clinical laboratories and the services

1 they provide, CLEA, and could avoid the difficulties
2 associated with regulating services under a regulatory
3 framework designed for commercially manufactured and
4 distributed products.
5 Next slide.
6 CLEA regulations explicitly require the
7 laboratory director to insure that selected test
8 methodologies are capable of providing the quality of
9 results required for effective patient care, which
10 implicitly requires the selection of medically
11 relevant tests that have an effective clinical
12 purpose.
13 Likewise, CLEA regulations require the
14 laboratory to have a clinical consultant who is
15 responsible for providing information about the
16 appropriateness of a test in a clinical context.
17 Systematic and rigorous enforcement of these
18 requirements by CMS could approximate the independent
19 validation of clinical relevance that FDA seeks to
20 achieve for IVDMIAs through the IVDMIA draft guidance.
21 CLEA regulations also require the
22 laboratory to validate the performance characteristics
23 of laboratory developed tests, including any algorithm
24 or formula that the laboratory relies upon to issue a
25 result, and further require the laboratory director to

1 insure that an ordering clinician can properly
2 interpret results by including pertinent interpretive
3 information in the reports and making consultation
4 available.
5 Thus, the foundations for algorithm
6 transparency and interpretive guidance for clinicians
7 already exist within the CLEA regulations. Amendments
8 to the CLEA interpretive guidelines or to the CLEA
9 regulations themselves, if deemed necessary, coupled
10 with systematic and rigorous enforcement by CMS, would
11 be consistent with the FDA's emphasis on smart
12 regulation and following the least burdensome approach
13 to address the issues which prompted FDA to issue the
14 draft guidance.
15 Thus, we encourage FDA to consider working
16 with CMS in this matter.
17 Last slide.
18 In conclusion, we look forward to working
19 with the FDA in an ongoing dialogue to achieve our
20 shared goals of providing continued access to safe,
21 effective, and innovative clinical laboratory services
22 for patient care.
23 Thank you.
24 DR. KESSLER: Thank you.
25 We'll continue with Michael Goldberg from

1 the Mohr Davidow Ventures Group.

2 MR. GOLDBERG: Good morning. Thank you

3 very much.

4 I'm here first as a patient, second as a

5 parent, and third as a child. My parents are

6 fortunately still alive.

7 I spend a lot of time professionally as a

8 venture capitalist. I'll get to that in a moment, but

9 principally I'm a patient advocate, and I've been on

10 the board of the National Childhood Cancer Foundation

11 as a trustee for the last 12 years. I was also a

12 founder of that organization. I was instrumental in

13 the passage of Prop 71, the Stem Cell Act in

14 California two years ago where seven million

15 Californians stood up and voted on behalf of patient

16 advocacy to liberate funds for embryonic stem cell

17 research, which our federal government at the moment

18 is severely limiting.

19 I have since been appointed to the

20 oversight committee of the California Institute of

21 Regenerative medicine, where I spend many days sitting

22 as you do listening to the public, and I have

23 extraordinary respect and regard for the time you give

24 to your service.

25 Professionally, I've been involved in the

1 biotechnology industry for the last 25 years. I've
2 watched recombinant DNA go from being a gleam in
3 scientists' and clinicians' eyes to treating hundreds
4 of millions of patients daily around the globe. It
5 has taken billions of dollars of capital to get there.
6 I think we're all better served as a result of it.
7 The FDA has been a magnificent partner
8 with industry in causing that to occur.
9 My concern today has to do with not your
10 intent, but simply the tactical implementation of what
11 you're proposing to do, and with that if you'll permit
12 me to make two comments before I begin my remarks.
13 Do any of you know how to get a one armed
14 venture capitalist out of a tree? You know that joke.
15 You wave at him.
16 Secondly, for the first time in
17 California, which is where I arrived from last
18 evening, I saw a personalized license plate. Actually
19 it said IVDMIA. You should be pleased to know it was
20 on a Prius.
21 (Laughter.)
22 MR. GOLDBERG: Next slide, please.
23 My background isn't relevant.
24 DR. KESSLER: You can have more than ten
25 minutes.

1 (Laughter.)

2 MR. GOLDBERG: So at the risk of stating
3 the obvious, the diagnostic and laboratory industries
4 really are in the cusp of dramatically innovating in
5 the field of medicine and in health care. We're
6 excited in the venture capital community and in the
7 entrepreneurial community, where I spent most of my
8 career before I became a venture capitalist, because
9 new, innovative diagnostics, we believe, can expand
10 the scope of personalized medicine, improve outcomes,
11 reduce costs in many cases, and hopefully reduce
12 adverse events.

13 Next slide, please.

14 Many of the companies and laboratories, as
15 you know, developing these innovative diagnostics are
16 small and entrepreneurial. They aren't the large
17 corporations that frequently pay homage to Rockville.

18 And in order ot make the benefits of their
19 products a reality, these small companies and
20 laboratories really need access to capital.

21 Funding for diagnostics for research has
22 historically been much lower than funding for drug
23 research or other devices. Furthermore, funding for
24 diagnostics continues to lag behind that of drug and
25 other devices.

1 My concern personally is if implemented in
2 its current form, the draft guidance may leave even
3 less funding for diagnostics. You have to understand
4 in the context of a broad technology based Silicon
5 Valley venture capital firm, my projects compete for
6 capital with projects to invest in Clean Tech,
7 projects to invest in the next generation of high
8 technology infrastructure, and regulatory uncertainty
9 creates a disincentive around our partnership table as
10 we make these decisions.
11 The ambiguity and regulatory uncertainty
12 can be, I think, captured from our standpoint, and not
13 having clarity as what type of lab services will be
14 subject to regulation by you, if laboratory service is
15 subject to regulation, it's not clear what the level
16 of regulation will be.
17 I know that's your goal to clarify all of
18 this for us and we appreciate that.
19 Next slide, please.
20 It's not clear how labs will deal with the
21 competing requirements of both the FDA and CLEA
22 requirements, how products or services determined as
23 IVDMIAs will actually be labeled, if labeled, and
24 what, of course, the costs of compliance are as young
25 companies are trying to forecast what their capital

1 requirements are to actually bring products to market.

2 So to attract investors, young companies

3 and laboratories need to know whether their product or

4 service is going to be regulated by the FDA, what the

5 nature of that regulation is, and what the cost of

6 complying with those regulations are.

7 Under the draft guidance, we simply don't

8 know this.

9 From an investor perspective, we need to

10 understand and evaluate the risk and benefits of

11 competing investments in different fields and an

12 ambiguous regulatory scheme and regulatory uncertainty

13 makes this evaluation very, very difficult.

14 The ambiguities and uncertainty under the

15 draft guidance we believe have the risk of deterring

16 investment in innovative diagnostics. If the draft

17 guidance is implemented, investors looking for

18 opportunity in technology or health care will look to

19 alternative opportunities, I fear personally, and

20 without these investments in innovative diagnostics,

21 we won't be able to experience the benefits of

22 personalized medicine, better health outcomes, lower

23 health care costs, and reduced adverse events as we're

24 all seeking to achieve.

25 Thank you very much, and I'm a big fan of

1 the critical path, and I hope wherever you end up on
2 this issue it enhances that regulatory scheme.
3 Thank you.
4 DR. KESSLER: Thank you. We do as well.
5 I want to thank the morning speakers, and
6 before we take a break, here's what we're going to do.
7 I'm going to take a 20 minute break now. The line
8 down the hall at Starbucks will get quite long. I'm
9 aware of that. So we may take a couple extra minutes,
10 but we'll try to convene promptly at ten after ten,
11 and because we are fairly far ahead, some of the
12 speakers who would normally be speaking right after
13 lunch we'll take in the morning.
14 So I'd like the panel, who should be here
15 for the afternoon, to check in with Susan to make sure
16 you're here and so that we can get moving. So I'd
17 like to make sure that David Levison, Stuart Hogarth,
18 Jonathan Cohen, Sherry Black, Robert Erwin-Marty, Elda
19 Railey, Carol Berry, and Elissa Passiment, please
20 check in with Susan.
21 Let's take a 20-some odd minute break.
22 We'll see you at ten after ten.
23 (Whereupon, the foregoing matter went off
24 the record at 9:49 a.m. and went back on
25 the record at 10:12 a.m.)

1 DR. KESSLER: Thank you all.

2 We're going to begin. Dr. Arthur Beaudet

3 from Baylor College of Medicine.

4 DR. BEAUDET: Thank you.

5 I appreciate the opportunity to be here

6 today. I'm going to focus more specifically on one

7 particular test.

8 I think you can go to the next slide.

9 One of the more comment tests done in

10 genetics is chromosome analysis, and this is sort of

11 the traditional appearance of the result that's been

12 available for decades now, and most of the chromosomes

13 there are two copies, and many of the diagnoses you

14 want to make involve the gain or loss of a copy so

15 that a region that should have two copies now has only

16 one or has three.

17 Next.

18 The chromosome analysis has gotten

19 extended by a method called fluorescence in situ

20 hybridization, or FISH, so that you can detect

21 particular spots in the DNA here, a normal chromosome

22 with a green and a red spot, and here a deleted

23 chromosome with a green spot but not red spot present.

24 And the next slide shows another example

25 of this kind of FISH at a different stage in the cell

1 cycle where there's a normal chromosome with a red and
2 a green dot, and a chromosome that has one green dot
3 and two red dots, the extra red dot indicating
4 additional copies.
5 So we can have a gain of copy or loss of
6 copy.
7 The method that is replacing this is
8 called array comparative genomic hybridization, or
9 array CGH or sometimes called chromosomal microarray
10 analysis or CMA, and they're equivalent in the
11 meaning.
12 Next.
13 In this test, DNA from a test sample like
14 a patient is labeled with a fluorescent dye and DNA
15 from a control is labeled with a second fluorescent
16 dye, and this red and green combination will, if the
17 mixes are equal representations of the genome, give a
18 balanced yellow color.
19 Go to the next slide.
20 If you then hybridize these onto bits of
21 DNA on a glass, and these could be large pieces of
22 DNA, kilo bases size like BACs or it could be small
23 bits of DNA like allogonucleotides of 50 or 60 base
24 pairs.
25 If there's a region in the test genome

1 that has a duplication here, it would give a greener
2 color or a deletion would give a redder color.
3 Next.
4 This is a demonstration of what a result
5 looks like in our laboratory. The red data are from
6 one hybridization and then the dyes have been reversed
7 to give a second hybridization shown in blue, and
8 Chromosomes 1 through 22 are here, and you see that
9 the data fall on a single line, but here we've
10 hybridized a normal male to a normal female, and you
11 see the difference in the X and the Y chromosome down
12 here, and you can very easily see gains and losses in
13 the genome.
14 Next slide.
15 This is one of the most common genetic
16 diagnoses, Trisomy 21, where the old test shows three
17 copies of Chromosome 21, and here on the new test you
18 see that all of the clones on Chromosome 21 are
19 showing a gain being shifted to the right.
20 This is just an example of now many
21 diagnoses which the old tests have not made, but the
22 new tests can make. So this is a child with various
23 abnormalities in the neonatal period with cleft lip
24 and palate, congenital heart disease, and a normal
25 chromosome analysis.

1 And the next slide shows the test detects
2 that many of the clones on the short one of Chromosome
3 21 are shifted to the left, meaning a deletion.
4 This is usually missed. This is what the
5 chromosomes can look like in their most stretched out
6 form, and maybe in retrospect you can suspect a
7 difference here, but in general these kinds of
8 chromosomes are usually interpreted as normal.
9 And this test can be confirmed with the
10 FISH method. Again, so we always have the old and the
11 new tests side by side to work with.
12 Now, there's a lot of potential here for
13 platform equivalency where many different platforms
14 can detect gains or losses in the genome, and we
15 currently use a back chromosome array in the clinic,
16 but we're in the process of switching to an
17 oligonucleotide array and dead arrays are also
18 possible.
19 So the results can be specified for
20 particular parts of the DNA, the genomic segments with
21 precise locations in the genome now that the genome is
22 sequenced and available in various browsers.
23 Next slide.
24 This is an attempt to show the same
25 patient I showed you a minute ago with the back array,

1 but now with a oligonucleotide array from adjulent
2 (phonetic). You see here each black dot is an
3 oligonucleotide, and you can see that there are lots
4 of black dots here at the tip that are normal. Then
5 you have a whole bunch that are involved in a
6 deletion, and if you do a dye reversal and smooth the
7 curve, you get this very precise detection of this
8 deletion, and this is a lesion which by chromosome
9 analysis is not detectable in any kind of consistent
10 way.
11 So array CGH detects many abnormalities
12 missed by chromosome analysis. They're missed for two
13 reasons actually. Some are just absolutely not
14 detectable by the karyotype method, and another
15 problem is that there's great variability in the
16 quality of chromosome analysis that's performed out
17 there. We see many abnormalities that should have
18 been detected by karyotype, but they were not. They
19 were missed by the group that did the karyotype.
20 So this test allows you to do hundreds or
21 even thousands of FISH test equivalence on a single
22 slide at a low cost. It's also particularly good for
23 detecting extra copies, which most of the FISH methods
24 are more difficult to use to detect extra copies.
25 So our approach is to suggest that what we

1 are proposing is a test that detects copy number
2 changes in the genome, and we think there's a lot of
3 analogy to say that an MRI of the brain or a
4 mammogram, many different machines can detect and give
5 an image that's useful, even, say, a CAT scan versus
6 an MRI.
7 There's multiple components to this
8 process. There's a raw image of the data. Then
9 there's an algorithm to process the data. In fact, in
10 this case there's not that really that much of an
11 algorithm. It's more a statistical analysis to
12 determine is there a gain or a loss at a particular
13 site.
14 Then there's some need for interpretation
15 that's typically provided by some Board certified
16 laboratorian that says gains or losses in this region
17 usually are associated with a particular syndrome or
18 NOD or benign or whatever, and I think this, I think,
19 is parallel to what the radiologist does.
20 The radiologist says there's something on
21 this brain MRI that means one or another possible
22 clinical implication, but then the clinician has to
23 integrate this result further. The neurosurgeon or
24 neurologist needs to take the radiologist's
25 interpretation and integrate that back into the

1 family, and that's what's going on in our situation.
2 Many times you'll have a parent and a
3 child with the same gain or loss in the genome, but
4 maybe the child has a severe phenotype and the parent
5 may have a much milder phenotype. So there's not a
6 perfect correlation of the genotype with the clinical
7 findings in the patient.
8 So we believe that array CGH is the
9 biggest advance in genetic diagnosis in decades. We
10 believe that it is rapidly replacing the standard
11 chromosome analysis or karyotype.
12 Delay in this transition is actually
13 depriving many families of valuable diagnostic and
14 counseling information. People are having the old
15 test and coming up with no abnormal result and not
16 knowing the cause of their child's problem, would know
17 the cause of their child's problem if they had the
18 newer test.
19 This ultimately is a test that will be
20 less costly than a karyotype. You don't need to do
21 tissue culture. You don't need technologists doing
22 lots of work, and you don't need a qualified
23 cytogeneticist to scrutinize the chromosomes and try
24 to interpret them.
25 And so ultimately we are going to have the

1 good fortune of having a test that is cheaper than the
2 old test and better than the old test.
3 Array CGH is applicable to prenatal
4 diagnosis, but 99 percent of the work is now being
5 done on pediatric patients with blood samples.
6 thank you.
7 DR. KESSLER: Thank you very much.
8 Our next speaker is Michael Ostrolenk from
9 the Association of American Physicians and Surgeons.
10 MR. OSTROLENK: Good morning, and thank
11 you.
12 The Association of American Physicians and
13 Surgeons is a national organization of physicians in
14 all specialties. Founded in 1943 to preserve and
15 promote the practice of private medicine, the sanctity
16 of the patient-physician relationship and ethical
17 medical practices according to the oath of
18 Hippocrates, physicians are obliged to prescribe for
19 the good of their patients according to the best of
20 their ability and judgment.
21 We are very concerned about the
22 destructive impact of the proposed guidance for
23 several reasons.
24 One, professional discretion is essential
25 if the medical profession is to serve individual

1 client needs. The guidance constitutes
2 (unintelligible) of regulations of the practice of
3 medicine.
4 Physicians undergo a lengthy period of
5 rigorous education, including scientific reasoning and
6 standards, to prepare them to function as independent
7 professionals. Independent professionals' judgment is
8 essential, as has long been recognized in law, if
9 physicians are to serve the needs of the patients
10 competently.
11 There is tremendous individual variations
12 in clinical problems as they present and in the
13 individual responses of patients to various diseases
14 and other insults. Increasingly, we are recognizing
15 a wide range of biochemical individuality, which
16 results in great variations in response of patients
17 due to therapeutic regimens, particularly drugs based
18 on the genetic endowment.
19 This guidance would not only deprive
20 physicians of their clinical tools that they need to
21 meet their patients' needs, but new regulations
22 encroach upon the practice of medicine itself. The
23 FDA is supposed to be regulating products to assure
24 their safety, not services.
25 But with this guidance, it appears they're

1 trying to expand its scope even as far as to declare
2 which methods of mathematical analysis may or may not
3 be used by professionals.
4 Number two, innovation is needed to meet
5 new threats. Human health is endangered by an
6 increasing array of new threats, as microorganisms
7 adapt to antibiotics and as mutant organisms,
8 including influenza viruses and vector borne diseases,
9 such as the West Nile virus, gain the ability to
10 proliferate rapidly throughout the world, as a
11 consequence of modern transportation.
12 Genetic engineering also raises the
13 sinister threat of bioengineered organisms being used
14 as a terrorist weapon.
15 Then there is the continuing AIDS
16 epidemic, which is changing manifestations demanding
17 constant advances in therapeutic strategy. As
18 diseases change, physicians must have the ability to
19 respond rapidly. The physicians' ability to serve
20 their patients would be crippled by blocking
21 innovation and laboratory testing and data analysis.
22 This innovation can only be achieved if
23 laboratories are able to use their personnel,
24 facilities, and other resources in creative, efficient
25 ways determined by the needs of the clinical situation

1 rather than by rigid, ambiguous, bureaucratic dictate.
2 Number three, the FDA lacks the authority
3 to expand its power as contemplated in the guidance.
4 We are strenuously to the FDA efforts to overreach its
5 statutory limits in its attempts to regulate
6 laboratory developed tests that have previously been
7 explicitly exempt. It lacks both constitutional and
8 statutory authority to do this.
9 Number four, the proposed guidance will
10 stifle innovation. Neither scientists nor investors
11 will have any interest in using their talents and
12 resources in ways that could be instantly stifled at
13 bureaucratic whim. It's not rational to take the risk
14 that efforts will simply be thrown away because of an
15 arbitrary or capricious change of government policy.
16 It appears that the FDA proposed
17 regulations can only make it more difficult and
18 expensive for laboratories to comply, but may make it
19 altogether impossible to comply with conflicting
20 demands from the FDA, the Center for Medicare and
21 Medicaid Services under the clinical laboratory
22 Improvement Act.
23 The effect of contradictory demands goes
24 beyond freezing medical progress, but will likely also
25 cause regression as techniques are withdrawn because

1 of regulatory fiat or ambiguity.

2 Our member physicians and the millions of
3 patients that they serve need access to innovation,
4 including laboratory developed tests, and also the
5 freedom to practice their profession without constant
6 fear of violating bureaucratic guidelines concerning
7 allowable methods for diagnosing or analyzing a
8 problem.

9 Number five, the proposed guidelines will
10 increase the cost of innovation already extremely
11 burdensome, possibly to reportable levels. We know
12 that life style drugs have been delayed by years or
13 decades because of FDA requirements and that the cost
14 of bringing a new drug to market has rapidly
15 escalated.

16 Everyone is concerned about the high and
17 rising costs of medical care, regulations making a
18 tremendous and unusually acknowledged contribution to
19 these costs. A large portion of the regulatory burden
20 is counterproductive. We believe that the FDA should
21 not be allowed to impose new regulations without
22 employing the equivalent of evidence based medicine to
23 show that the regulations do not do more harm than
24 good, with the waste of resources being included in
25 the calculation of harm.

1 No such methodology has been applied to
2 the proposed guidance.
3 Number six, the net effect of the guidance
4 is likely to imperil patient safety rather than
5 improving it. The FDA attempts to justify delays in
6 regulatory barriers as necessary to protect patient
7 safety. Its record of protecting safety is not
8 impressive, as recent drug recalls have shown, but it
9 has never ever attempted to calculate the lives that
10 are lost because better products are prevented from
11 entering the marketplace, some of them permanently
12 because the cost barriers cannot be overcome
13 The cost of regulatory delay needs to be
14 measured in lost lives as well as dollars. We agree
15 with the concerns expressed by the Coalition for the
16 21st Century Medicine that the new FDA guidance
17 documents are impermissibly vague and are also in
18 violation of statutes such as the Administrative
19 Procedures Act. Their effect will be to increase
20 costs enormously while crippling physicians' ability
21 to serve clinical needs.
22 Proposed changes would impose an unlawful
23 straightjacket upon clinical practice. They would
24 force laboratories, if they continue to function at
25 all, to develop wholly new, expensive and

1 nonproductive infrastructure in an attempt to do what
2 is impossible, to begin with, namely, comply with
3 conflicting obligations.
4 The FDA has not stated a problem that this
5 guidance is supposed to solve. In fact, it apparently
6 cannot even define such terms as service product or
7 device in a clear and rational manner. This guidance
8 should simply be rejected in its entirety. If the FDA
9 is able to define the problem, then new guidance to
10 address the need should be the least costly and
11 intrusive manner in compliance with existing law.
12 It is not acceptable for the FDA to
13 transgress the boundaries that forbid it to engage in
14 or interfere with the practice of medicine.
15 Thank you.
16 DR. KESSLER: Thank you.
17 And our next speaker is Mara Aspinall from
18 Genzyme Genetics.
19 MS. ASPINALL: Thank you.
20 Good morning. I am Mara Aspinall,
21 president of Genzyme Genetics, and I very much
22 appreciate the opportunity to be here today and to
23 focus on one aspect of the draft IVDMIA guidance.
24 But first I'd like to say that Genzyme
25 greatly appreciates that the FDA in response to

1 concern with the guidance took two important steps:

2 First, to extend the deadline for the

3 comment period; and

4 Secondly, to convene this session today.

5 These two steps are necessary, we believe,

6 to insure that we begin the dialogue to look at what

7 is essential in having new regulations and the

8 potential of those, to make sure that they're

9 necessary and appropriate and, most importantly, that

10 any changes to the regulatory environment improve

11 physician access to and confidence in diagnostics that

12 help health care today.

13 Thank you for taking these steps.

14 However, because of the legal,

15 administrative, and time and other constraints,

16 neither a public docket or a public meeting such as

17 this can truly provide the optimal opportunity for an

18 active exchange. That active exchange of information

19 or scientific information between FDA experts and

20 those outside, we believe that we would like the

21 agency to convene an additional meeting before

22 proceeding further with an independent third party, if

23 appropriate, a session that's a workshop or a similar

24 format where true interactive dialogue can occur.

25 Such a format would give us the

1 opportunity to listen and hear, to engage in an open
2 dialogue with the agency, with you about the details
3 that are so important in producing this guidance.
4 This kind of truly interactive format will
5 allow us to hear your response issue by issue,
6 question by question. So we look forward and would
7 like you to consider a potential future opportunity to
8 do that.
9 Today, however, I want to focus my
10 comments on a concern amongst the many that have been
11 discussed today, and this issue is the impact of the
12 draft guidance on innovation, directly and indirectly
13 through the reimbursement system and, therefore, on
14 the timely physician and patient access to the most up
15 to date and newest science and technology.
16 Health care today is moving from
17 traditional medicine to personalized medicine, and
18 personalized medicine involves getting more specific
19 information on the detailed health status of a patient
20 and will require more and more targeted tests to
21 smaller and smaller patient populations.
22 To fulfill this promise of personalized
23 medicine, we will need to insure that innovation is
24 possible and is fostered in the laboratory developed
25 part of the industry. If we fail to do that, we will