

1 be unable to carry out the promise or personalized  
2 medicine and our unwaiving commitment to excellent  
3 patient care and to patient safety.

4 To highlight that point, I want to take a  
5 moment to talk about what laboratory developed tests  
6 are, how they come into use, and the benefit that they  
7 bring to physicians who order them and the patients  
8 who need them.

9 These tests often have their beginning in  
10 academic centers in research that results in  
11 scientific publications about the usefulness of  
12 particular biomarkers or assays. Academic centers  
13 then typically look to independent laboratories to  
14 make these tests available to the relevant patients.  
15 In some cases the laboratories themselves develop the  
16 test based on scientific and medical information in  
17 the literature as presented at scientific meetings and  
18 conferences, indicating both the utility and the  
19 importance of these tests.

20 Laboratories then validate the test,  
21 insure the scientific underpinnings are robust, and  
22 develop processes that guarantee the test will be  
23 produced accurately and reproducibly, and that they  
24 are offered and appropriate to the physicians.

25 Tests are developed and validated under

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1 the direction of Board certified pathologists and  
2 clinical scientists. In every case it is the treating  
3 physician that makes the choice about which validated  
4 test is appropriate for a particular patient and to  
5 insure that each test is medically necessary.

6 Treating physicians make the decision  
7 regarding specific tests based on patient need, their  
8 own clinical knowledge, and information from the  
9 medical and scientific literature.

10 So today what typically happens is unless  
11 and until a new diagnostic test reaches a critical and  
12 relatively large volume, no commercial test kit can be  
13 developed.

14 Lacking that critical volume, there is no  
15 market incentive to develop a kit and to spend the  
16 resources required to take this kit through a full FDA  
17 process.

18 The bottom line is that as a result, for  
19 conditions that affect a relatively small number of  
20 patients or, importantly in oncology and infectious  
21 disease, subpopulations of patients. The only access  
22 to valuable and necessary testing is through  
23 laboratory developed tests.

24 And just as balancing expenditures with  
25 potential returns on investment may dissuade a company

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1 from developing a test kit for a small market,  
2 financial realities will apply to laboratories as they  
3 develop cutting edge and innovative tests.

4 Extensive and costly regulatory  
5 requirements would serve as an extremely strong  
6 disincentive to the development of tests such as those  
7 for genetic disorders or from diseases, and very  
8 importantly and increasingly so, cancers that affect  
9 targeted subpopulations.

10 Why is this the case? It simply is that  
11 while diagnostics comprise less than five percent of  
12 hospital costs and 1.6 percent of Medicare costs,  
13 their findings influence as much as 70 percent of  
14 health care decision making.

15 That said, the current reimbursement  
16 system does not compensate laboratories adequately  
17 even now. The added cost associated with an FDA  
18 clearance or approval would be impossible to recoup.  
19 The end result would be that laboratories could not  
20 afford to develop new tests. Diagnostic testing, a  
21 key piece of personalized medicine today, in the  
22 future would suffer enormously. Treating physicians  
23 would be seriously limited to access to the important  
24 cutting edge tests that would help them determine the  
25 best course of treatment for their patients and, above

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1 all, patients would lose.

2 As we look to the future, we envision many  
3 new complex tasks that Genzyme Genetics would like to  
4 develop that would focus on specific and relatively  
5 small populations of patients. Many of these tests  
6 are expected to be in the area of oncology patient  
7 management and will provide critical diagnostic  
8 information essential to selecting the most  
9 appropriate therapies for each and every patient

10 We believe that most of those potential  
11 future tests will meet the definition as currently  
12 defined in the draft guidance of an IVDMIA that would  
13 potentially require additional regulation and/or  
14 costly premarket approval.

15 Because these tests are truly in the realm  
16 of personalized medicine, the market for them would be  
17 small, and even currently the reimbursement system is  
18 a challenge for laboratories making decision, such as  
19 us and others to invest in these new tests.

20 An additional level of regulation would  
21 make such an investment virtually impossible. Because  
22 we believe every patient and every treating physician  
23 deserves access to important information provided by  
24 these tests, we believe that the regulatory system  
25 should not be one that only focuses and only promotes

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1 the development of high volume testing.

2 Our message is this. If you determine  
3 that additional regulation in this area is absolutely  
4 essential, please insure that all the information and  
5 facts are thoroughly vetted and fully considered  
6 before proceeding

7 And please, as you determine your way  
8 forward, look at the costs. Look at the reimbursement  
9 system. And finally and most importantly, the  
10 implications that derive from this guidance for  
11 information for patients and for physicians.

12 Thank you for the opportunity to speak.

13 DR. KESSLER: Thank you.

14 And our next speaker is Gail Javitt from  
15 Genetics and Public Policy Center.

16 MS. JAVITT: Good morning. My name is  
17 Gail Javitt, and I appreciate the opportunity to speak  
18 today on behalf of the Genetics and Public Policy  
19 Center of Johns Hopkins University.

20 We'd like to commend FDA for holding this  
21 public meeting today.

22 The Genetics and Public Policy Center was  
23 founded in 2002 with a mission to help policy leaders,  
24 decision makers, and the public better understand and  
25 respond to the challenges and opportunities that arise

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1 from advances in human genetics. In 2005, with  
2 funding from the Pew Charitable Trusts, we launched a  
3 genetic testing quality initiative with the goal of  
4 improving overall effectiveness, safety and  
5 availability of genetic testing.

6 Today there are more than 1,000 genetic  
7 tests clinically available, and several hundred more  
8 that are available in a research setting. These tests  
9 are used to diagnose disease, to predict the risk of  
10 future disease and, most recently, to guide decisions  
11 about whether to undergo a procedure or take a drug or  
12 a particular dose of a drug.

13 Yet the regulatory framework to insure the  
14 safety and effectiveness of these tests is both  
15 incoherent and inadequate. Most genetic tests are not  
16 reviewed by any entity within the federal government  
17 before they're offered clinically. To date FDA has  
18 cleared or approved only a handful of genetic tests.  
19 Most genetic tests are sold as in-house developed  
20 tests or home brew assays, as others have said, and  
21 each laboratory director makes an independent decision  
22 regarding whether and when to make a test available.

23 So in the absence of FDA review, there is  
24 no independent review of either a test's analytic  
25 validity, meaning whether the right answer can be

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1 obtained with the test, or its clinical validity,  
2 meaning how the particular genetic variation relates  
3 to an individual's current disease or risk of future  
4 disease.

5 While CLEA, as has been mentioned several  
6 times, clearly requires laboratories to independently  
7 establish analytic validity of tests, there's  
8 insufficient oversight to insure that laboratories do  
9 so. And as the Genetics and Public Policy Center has  
10 said on other occasions, there is no genetic testing  
11 specialty today under CLEA, and although we, along  
12 with Genetic Alliance and Public Citizen, have filed  
13 the citizen petition with CMS asking for a genetic  
14 testing specialty to be created, we have not received  
15 a response, nearly six months later.

16 Moreover, CLEA has not been interpreted to  
17 require that laboratories demonstrate clinical  
18 validity, but clinical validity is profoundly  
19 important when considering whether and under what  
20 circumstances a genetic test should be made  
21 commercially available. Offering tests without  
22 adequate evidence of clinical validity endangers the  
23 public pocketbook and, moreover, the public's health.

24 Based on the survey of 190 laboratory  
25 directors that we conducted at the center in 2006, a

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1 significant number of directors lack a clear  
2 understanding of what clinical validity means.  
3 Thirty-six percent of those we surveyed did not select  
4 the correct answer to the question.

5 Additionally, director face considerable  
6 challenges in establishing clinical validity. While  
7 84 percent of those that we surveyed agreed that  
8 standards should be developed regarding the amount of  
9 data needed to establish clinical validity of tests,  
10 76 percent cited lack of clinical data as a  
11 significant challenge in establishing clinical  
12 validity.

13 In addition, because FDA has regulated  
14 test kits and not home brews, there is an uneven  
15 playing field, which creates a disincentive to perform  
16 research to establish clinical validity and deters  
17 innovation of new tests that are able to demonstrate  
18 their clinical validity.

19 A company that invests the time and effort  
20 necessary to develop the test kit for cystic fibrosis,  
21 for example, will encounter competition in the  
22 marketplace from laboratories that offer home-per  
23 (phonetic) tests for the same purpose which have not  
24 undergone FDA review.

25 So this current two pass system has

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1 resulted in very few FDA approved test kits being  
2 available. According to our survey, almost 40 percent  
3 of laboratories do not use FDA approved test kits at  
4 all, and another 26 percent use them for less than a  
5 quarter of the tests that they offer, and the main  
6 reason cited for not using FDA approved test kits was  
7 that no test kits were available for the disorders for  
8 which they were offering testing.

9 So the status quo leave the public health  
10 insufficiently protected and fails to reward genetic  
11 test manufacturers who do perform the research  
12 necessary to demonstrate their test analytic and  
13 clinical validity. FDA has a critical role to play in  
14 insuring the safety, effectiveness, and availability  
15 of genetic tests. Effective stewardship by FDA is  
16 needed to develop and implement a coherent and  
17 equitable system of oversight.

18 So the draft guidance that we are here  
19 today to discuss is an important first step in  
20 articulating what FDA's role will be, and we  
21 appreciate that FDA has begun this public  
22 conversation today.

23 However, based on our review of the draft  
24 guidance and our consultation with stakeholders, we  
25 have identified the following key concerns

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1 First, FDA needs to consider genetic tests  
2 holistically rather than engaging in a piecemeal  
3 regulatory strategy.

4 Second, FDA needs to engage all  
5 stakeholders, including device manufacturers, clinical  
6 laboratories, patients and providers, in discussion  
7 before making binding regulatory changes and to  
8 clarify at the outset what the overarching goals if a  
9 regulatory change will be.

10 Third, FDA needs to provide sufficient  
11 clarity so that the regulated industry knows what it  
12 needs to do to comply at the outset and not through a  
13 warning or untitled letter from the agency.

14 So, first, turning to the need for a  
15 holistic approach, we note that FDA has yet to  
16 convincingly lay out its rationale for starting with  
17 and singling out IVDMIA's. The approach seems to be  
18 purely technology based. FDA seems to be operating  
19 under the assumption that IVDMIA's as a class are  
20 inherently more risky than other laboratory tests.

21 This is certainly true in some cases, but  
22 we are concerned that FDA's piecemeal approach  
23 overlooks other high risk tests that do not fall  
24 within the IVDMIA framework, while at the same time  
25 putting all IVDMIA's in the same high risk class when

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1 compared to other diagnostic tests.

2           Additionally, FDA's rationale for focusing  
3 on IVDMIA's appears to be based on the physician's  
4 competence or lack of competence to independently  
5 interpret the results, but numerous studies have  
6 documented that health care providers lack education  
7 generally to interpret the results of genetic tests.  
8 So clinician competence would appear to be an  
9 insufficient basis for distinguishing between IVDMIA's  
10 and other laboratory tests.

11           Turning to the concern about clarity,  
12 there is scant detail provided in this draft guidance  
13 making compliance difficult. Uncertainty in the  
14 regulatory arena is a significant potential deterrent  
15 to innovation, and FDA should provide clear,  
16 transparent direction regarding its expectations.

17           The definition of IVDMIA's lacks clarity  
18 and leaves some to wonder whether their tests are or  
19 are not IVDMIA's. Clear articulation of what tests do  
20 and do not fall within the category will alleviate  
21 this confusion.

22           FDA has also not yet provided concrete  
23 direction regarding the interaction between its QSR  
24 requirements and the requirements of CLEA, and more  
25 clarity here is needed as well to avoid potentially

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1 duplicative or conflicting requirements.

2 Finally, turning to process, while this  
3 IVDMIA document is cast as a draft guidance, it does  
4 represent a major shift in FDA's thinking about  
5 laboratory developed diagnostics, and for the first  
6 time defines a new subset of laboratory tests that are  
7 subject to regulation.

8 While FDA has publicly declared that the  
9 guidance document is not yet being enforced, the  
10 letters that have been sent to certain in the industry  
11 suggest otherwise and at the very least, FDA is  
12 sending confusing signals at a time when it needs to  
13 be more clear.

14 These signals create uncertainty in the  
15 marketplace and are counterproductive to the goal of  
16 insuring the availability of safe and effective tests.  
17 We hope that today's meeting and FDA's subsequent  
18 interactions will be characterized by greater notice  
19 and explanation regarding FDA's regulatory intentions.

20 In conclusion, we believe that an adequate  
21 regulatory system for genetic tests should insure that  
22 all genetic tests provide accurate information for  
23 diagnosis, treatment or prevention of disease; should  
24 insure that laboratories performing genetic tests are  
25 using validated technologies to perform testing;

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1 should insure that both providers and patients have  
2 adequate information about a test's benefits and  
3 limitations so that they can make an informed  
4 decision; should establish a level playing field for  
5 all companies seeking to market genetic tests by  
6 establishing rational requirements that apply to all  
7 players; should employ a risk based approach that  
8 tailors requirements to the degree of risk posed by a  
9 test; should require post market reporting of problems  
10 with testing that led or could potentially lead to an  
11 adverse clinical event and should promote the  
12 development of new genetic tests, particularly those  
13 for rare conditions and those that can improve  
14 treatment decision making for life threatening  
15 disease.

16 We look forward to working with FDA as it  
17 continues to refine its regulatory approach.

18 Thank you.

19 DR. KESSLER: Thank you.

20 We're looking for Sharon Terry, and if  
21 she's here in the house, please approach Susan, and  
22 while we're doing that, we're going to welcome Craig  
23 Shimasaki. Dr. Shimasaki is from InterGenetics,  
24 Incorporated, and he's going to need a minute or two  
25 to change computers.

1 DR. SHIMASAKI: Thank you.

2 I don't have a joke, but I can tell you  
3 what Henry VIII told his fourth wife. "I won't keep  
4 you very long."

5 (Laughter.)

6 DR. SHIMASAKI: Do I get extra time?

7 (Laughter.)

8 DR. KESSLER: Actually, you're done.

9 (Laughter.)

10 DR. KESSLER: No soup for you.

11 DR. SHIMASAKI: Thank you.

12 I do appreciate the time to share with  
13 you. I've had the good pleasure of working with Dr.  
14 Gutman and his staff over the past 15 years on five  
15 other applications. What I want to do is share with  
16 you though what's with InterGenetics the story about  
17 a real life example about how this guidance does  
18 affect the industry today.

19 And we are a small biotech company, a  
20 predictive medicine company. I need to tell you a  
21 little bit about the background of the company so that  
22 you get an appreciation for that.

23 We started in 1993 doing this research in  
24 breast cancer susceptibility and founded a company out  
25 of the medical research foundation in '99. So about

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1 13 years of research and about eight years of product  
2 development genotyped over 8,000 women around the  
3 country under an IRB and informed consent in five  
4 different geographic regions. It's one of the largest  
5 case controlled studies of breast cancer risk  
6 genotyped.

7 We then developed OncoVue, which is the  
8 first genetic based breast cancer risk test, which  
9 does take into account personal history measures, or  
10 the Gail model.

11 In 2002 when we were working to refinance  
12 the company and set up the CLEA lab, I approached the  
13 FDA to be sure that a multigenic test that had an  
14 algorithm with a software program imbedded into it  
15 operated out of a CLEA lab was, indeed, covered under  
16 CMS.

17 My response at that time was, of course,  
18 to the affirmative, and based on that and also our  
19 other guidance with knowing the history of what was  
20 going on in the industry, we raised about \$15 million  
21 for continuing development of this program.

22 That's a picture to tell you we're in  
23 Oklahoma City, and you don't see any cowboys or  
24 Indians there. It is actually a research park with  
25 almost a million square feet of Class A wetland.

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1           So what you see here is the way medical  
2 practice is currently being done: diagnosis,  
3 detection, new treatments, monitor therapy, and if it  
4 doesn't work you change the treatment. Outcomes are  
5 what we get today.

6           What the IVDMIA will most likely cover are  
7 tests that involve genetic predisposition, where you  
8 intervene and try to prevent or avoid the disease  
9 entirely or prognostic testing, where you're looking  
10 to actually find a better way to treat the patient  
11 such that the medications that are given will, indeed,  
12 be truly helpful.

13           This is how we went about developing the  
14 test. We had almost 10,000 patients through this in  
15 cases and controls, and we looked at 125  
16 polymorphisms, combined them with the current Gail  
17 model. These are questions that have been used in  
18 medical practice for 20 years now, found epistatic  
19 interactions between the personal history measures and  
20 the genes that are used.

21           So we created and found combinations of  
22 these algorithms that produced age specific risk wars.  
23 Now, I'm not talking about having frank, undetected  
24 cancer. I'm talking about susceptibility to a  
25 disease, the old theory of find a gene, find a disease

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1 has been very unfruitful, but what we're finding is  
2 that combinations of genes that taken together can be  
3 subverted when other genes are available to stop the  
4 body from going towards disease.

5 But if you look at combinations of genes  
6 and combination with personal history measures, you  
7 can accurately predict the susceptibility to certain  
8 complex diseases. So, therefore, we've developed this  
9 test in 2006 that a woman will take a mouthwash. The  
10 side effects are minty flavored breath. We then  
11 analyze the DNA. We put them through this algorithm  
12 that was created in our laboratory information  
13 management system and produce a risk score.

14 The effect is that about 90 percent of  
15 women who get breast cancer don't have a strong family  
16 history of the disease. A previous speaker talked  
17 about calculate the loss of lives. Right now the Gail  
18 model is being used out there, and this performs at  
19 least twice as good as the Gail model. Yet it's still  
20 being used without anything else available. You get  
21 a report for three stages of your life, your genetic  
22 risk compared to the average risk.

23 What do you do with it? You can either  
24 look at ways which are being done now to prevent the  
25 disease, reduce the risk, identified early through

1 more comprehensive screening, change life styles or  
2 low risk patients' peace of mind.

3 What I really want to talk about though is  
4 some of the economics and then some of the effects on  
5 InterGenetics, which I'll bring it back to.

6 Michael Goldberg talked about economics.  
7 Well, if you look at traditional diagnostics costing  
8 between 25 to \$50 million, medical diagnostics in the  
9 molecular diagnostic industry range from 40 to \$100  
10 million. If you look at as he talked about, novel  
11 medical testing originates in small biotechnology  
12 companies. It doesn't mean that all do, but most of  
13 them have been, and they get into clinical use once  
14 you've completed your validation and your clinical  
15 testing.

16 It's funded by venture capital. Most  
17 venture capital groups will tell you if you hit a  
18 ceiling of \$60 million, they will not invest in the  
19 company at the beginning because the returns, the  
20 multiples just don't work.

21 So if you add another regulatory process  
22 at the end when the company is fully staffed up like  
23 we are today and we talk about most likely a PMA and  
24 a real time effect of about 18 months, you're looking  
25 at about 60 to 120 million development costs and most

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1 likely that just will not occur because there will not  
2 be capital to be infused into the company. It's not  
3 the intent, but it's the effect.

4 The purpose of the regulation is safety of  
5 the public, efficacy of tests to be validated,  
6 proficiency, and then prevent the bogus test from  
7 getting in here. We do believe that these can be  
8 accomplished by modifying existing CLEA regulations  
9 and the FTC regulations currently in place. We are  
10 saying that we do not want to penalize the companies  
11 that are trying to do this correctly, taking the time  
12 and validating it, but then shore up the existing laws  
13 that can help prevent what you're looking for.

14 The new guidance is creating confusion.  
15 We received a letter in January or a call from the  
16 compliance officer in January of 2006 that the FDA did  
17 not believe we were in compliance.

18 In February we received a letter that said  
19 we would need to come and visit. We came for a visit.  
20 We were then told that our test would not be allowed  
21 to enter commercial market without an application, and  
22 therefore, we had to figure out a way, which the FDA  
23 did allow us to file an investigational device  
24 exemption that allowed us to collect the additional  
25 data on psychological analysis and medical impact.

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1 We're not talking about more genotyping, but to  
2 collect that in order to help suffice a filing.

3 So that took about seven to eight months  
4 of real time, including our time to respond. We  
5 though are aware that other companies during that  
6 period of time with prognostic tests did go into the  
7 market, and so therefore, the inequitable treatments  
8 among companies is also a confusion. We did not have  
9 time to respond, and we did not have time to go into  
10 compliance, and because there's inadequate guidance on  
11 how to regulate laboratory services, we're still  
12 trying to figure out and we believe that the FDA is  
13 working very closely to try to work with us, how we  
14 can get there.

15 But in some cases, potentially companies  
16 will go out of business. We were expecting funds. At  
17 the launch most of our investors backed out. Now, it  
18 does create a real problem for an organization because  
19 a test like this does require additional funds to get  
20 there. We know that clarification is necessary. The  
21 FDA has said that our device is a significant risk  
22 device. Our IRB says it is not a significant risk  
23 device. We have conflicts because one of it means it  
24 will be a Class 3 versus a Class 2 or a Class 1 and  
25 require IRB versus no IRB approvals.

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1           How do you get a 510(k) if there's no  
2           substantial equivalence?

3           The other really is who trumps whom. In  
4           essence, do we have to meet both CLEA and we meet FDA  
5           regulations? And then who will mediate the conflicts  
6           when these conflicts do and will come up?

7           And then how do you modify it? Because  
8           laboratory based tests try to get to a result. The  
9           way in which you get there can be improved very  
10          frequently. Do you need to file another 510(k) to do  
11          that?

12          So our recommendation is that we make  
13          modifications to CLEA if there's inadequate  
14          protections for public safety. Our desire is for  
15          public safety, which is why we did not offer this over  
16          the Internet. We did not go out in 2003 when we had  
17          about 150 patients that seemed to indicate this. We  
18          went and got 8,000 women, and then we only allowed  
19          this to be used in properly trained clinics where we  
20          only hand selected them that had genetic counseling  
21          capabilities, and we required that they have  
22          proficiencies in doing this.

23          If oversight is still deemed necessary, we  
24          need guidance on how do you deal with device design  
25          GMP, device master records, et cetera, allow time for

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1 feedback. The compliance has to have time in order to  
2 be able to get there, and I would say consider making  
3 it voluntary.

4 If you think about it, you did just  
5 approve a test that is going to necessitate another  
6 company having to do the same thing in order to gain  
7 market share. If you allow the market forces to  
8 dictate that, it can be another way of making sure the  
9 companies that have money can do this and those that  
10 have niche places to fill don't go out of business,  
11 and then enforce the FTC laws.

12 So in summary, it's an area of medicine  
13 that will grow. This is an area that will change. We  
14 do believe it will reduce health care costs, prevent  
15 disease. America is getting older. If we don't stop  
16 people from getting sick, health care costs will  
17 always go up.

18 If the hurdle is so high, no funding will  
19 be directed there. If you look at the NIH, American  
20 has one of the best countries for medicine health care  
21 in the world. It's also the highest cost.

22 And in conclusion, we're going to find  
23 solutions to accomplish the goal of safety and  
24 efficacy rather than just implementing a particular  
25 objective, which is regulation.

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1 Thank you for your attention.

2 DR. KESSLER: Thank you.

3 For scheduling reasons, a couple of folks  
4 from the afternoon need to move their presentations  
5 now. So we're going to do that. We'll then have some  
6 time for a few of the afternoon presentations to be  
7 brought forward, and then at approximately 11:30 or  
8 11:40 we'll take questions and comments from the  
9 floor.

10 I will ask at that time that the questions  
11 and comments be kept to approximately two minutes so  
12 that we have adequate time for everyone who may want  
13 to speak from the audience.

14 I'm going to turn now to Helen Schiff from  
15 the Breast Cancer Advocate group in New York City.

16 MS. SCHIFF: My name is Helen Schiff. I'm  
17 a breast cancer survivor and advocate from New York  
18 City. I work as a consultant for the City for Medical  
19 Consumers, and I am a member of SHARE, a breast and  
20 ovarian cancer organization in New York City.

21 I'm also a patient consultant for the FDA.

22 The potential for complex biomarkers known  
23 as IVDMIAs to change the face of breast cancer  
24 treatment is tremendous. For too long we have been  
25 plagued with a one size fits all approach to

1 treatment. Even though many women are cured with  
2 surgery, they have to suffer through radiation,  
3 chemotherapy, and five years of a hormonal treatment  
4 because there is no way to know with certainty what  
5 treatment a woman really needs, if any.

6 While this treatment strategy has had a  
7 small impact on breast cancer mortality, it has meant  
8 that many women have been needlessly exposed to the  
9 lethal and life altering effects of all these  
10 modalities.

11 Just to name some of the worst ones,  
12 leukemia, cardiomyopathy, endometrial cancer, stroke,  
13 pulmonary embolism, infertility, lymphedema,  
14 hemobrain, and loss of libido.

15 So we welcome a new technology that has  
16 the potential to customize our treatments, to give us  
17 only what we need, to even tell us which chemotherapy,  
18 hormonal treatment, monoclonal antibody, or small  
19 molecule, will be optimal for our specific tumors.

20 And we know that in the future, IVDMIA's  
21 will also have the potential to find breast cancer  
22 earlier than is now possible and to do a better job  
23 than the Gail model at determining who is really at  
24 high risk for breast cancer.

25 Nevertheless, it is very important to be

1 aware of the pitfalls that have plagued biomarker  
2 research over the years. In almost half a century of  
3 breast cancer biomarker research, only two biomarkers  
4 have proved to have clinical value: ER and HER2. The  
5 significance of what PR means is still disputed. We  
6 know for a fact that problems with assays have led to  
7 erroneous assessments, less than optimal treatment  
8 and, more importantly, premature loss of many lives.

9           Unfortunately recent studies indicate that  
10 there are still problems, for example, with accurate  
11 ER and HER2 assays. For example, the cut point for  
12 ER positivity varies from lab to lab, from one percent  
13 to 25 percent of cells with estrogen receptor.

14           You heard what Carolyn Compton said about  
15 the problems with the HER2 assay.

16           Other countries, by the way, for the  
17 estrogen receptor use a 50 percent cut point. As many  
18 have said, a treatment is only as good as its  
19 biomarker, and hence, they need to be rigorously  
20 regulated. One of the most important recommendations  
21 of the National Breast Cancer Coalition's strategic  
22 consensus report on breast cancer biomarkers is,  
23 quote, to incorporate the best components of drug  
24 development to guide the development and validation of  
25 biomarker assays.

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1           This new FDA guidance for IVDMIAs is an  
2 important first step in that direction. It will  
3 assure that IVDMIAs are, one, examined before they are  
4 marketed; two, that their results are reproducible by  
5 an independent body; three, that they are tested for  
6 accuracy; and four, and most important, that they have  
7 clinical relevance.

8           The writing of the IVDMIA label, as with  
9 new drugs, must be overseen by the FDA to insure that  
10 there are no false claims and that the results of an  
11 IVDMIA assay are understandable to both doctors and  
12 patients.

13           It is clear to me that neither CLEA nor  
14 the Federal Trade Commission or any other HHS agency  
15 has the depth of experience, the capabilities or the  
16 resources to undertake such a job, nor do they have  
17 the regulatory power.

18           One only need look to the Over Check  
19 experience to see why this kind of regulatory power is  
20 so important. Over Check was developed as a blood  
21 test for the early detection of ovarian cancer in high  
22 risk women by Coralogic, a private company in  
23 partnership with scientists from the FDA and the NCI.

24           The FDA said, however, that it would not  
25 allow Over Check to be marketed to be marketed until

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1 it published clinical evidence that it worked in  
2 patients.

3 Keith Baterly, a bioinformatics specialist  
4 at M.D. Anderson, when trying to replicate the study,  
5 found among other problems that test results were  
6 influenced by the order in which the assay was run.  
7 According to an article by David Ransohoff in the  
8 Journal of the National Cancer Institute, Over Check  
9 had not been properly validated, its findings in an  
10 independent data set, and there were possible problems  
11 with over fitting and bias.

12 Three years later, it has still not been  
13 approved to be marketed, confirming its problems were  
14 serious. If it was up to CLEA or the FDA, Over Check  
15 would have been on the market because they do not have  
16 the power to stop it. And we all know how hard it is  
17 to get something off the market once it is on, not to  
18 mention the irreparable damage that would have done to  
19 women.

20 To me the argument that FDA regulation of  
21 IVDMIAAs will hinder development and commercialization  
22 or that this new regulation is unfair are  
23 nonsequiters. Don't we want to find out which IVDMIAAs  
24 work and which don't regardless of when they were  
25 developed or for whom?

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1           If anything will hold up development in  
2 this field, it will be the premature marketing of more  
3 Over Checks. As we see, this is not just a matter of  
4 colorful characters or fly-by-night companies, as  
5 suggested in a recent GLA report. Reputable  
6 scientists can make honest mistakes.

7           As an advocate I think we need to  
8 introduce rigor and oversight into the biomarker  
9 field, and I think the FDA guidance on IVDMIAs is an  
10 important first step in this regard. I certainly  
11 don't follow the logic that because IVDMIAs are home  
12 brews they should not be regulated by the FDA. My  
13 logic leads in the other direction. All biomarkers,  
14 including home brews when used in the clinic should be  
15 regulated by the FDA. Otherwise we leave the  
16 successful commercialization of IVDMIAs to companies  
17 who write the best press releases, do the most  
18 advertising, or try and court advocacy groups.

19           Thank you.

20           DR. KESSLER: Thank you.

21           We'll turn to David Levison from Cardio  
22 DX.

23           MR. LEVISON: Thank you for the  
24 opportunity to speak here today.

25           I'm David Levison, the president and CEO

1 of Cardio DX.

2 Craig Shimasaki did a very nice job of  
3 providing a case study in the oncology area. I'm  
4 going to do a similar thing in the cardiovascular  
5 area to really demonstrate how companies are  
6 developing products in this area and why regulation  
7 needs to go hand in hand with innovation.

8 First slide, please.

9 Cardio DX is a molecular diagnostic  
10 company based in California. We're developing a  
11 series of diagnostic tools to allow physicians to make  
12 more appropriate treatment decisions for their  
13 patients.

14 The scientific tools we have at our  
15 disposal today provide the opportunity to improve  
16 patient care in new and unique ways. We believe there  
17 are many very safe and very effective treatments  
18 available to patients in this country.

19 Unfortunately, in many disease areas we  
20 have not had the diagnostic tests necessary to guide  
21 physicians in finding the right treatment for the  
22 right patient at the right time.

23 Said another way, Cardio DX is trying to  
24 help physicians take some of the practice out of the  
25 practice of medicine.

1 Next slide. Keep going. Another one.

2 Our focus is on cardiovascular disease,  
3 specifically three of the largest areas within  
4 cardiovascular medicine. If you think of the common  
5 things that can go wrong with your heart starting with  
6 the top left-hand part of this slide, you can either  
7 have a plumbing problem, coronary disease; you can  
8 have a pump problem, heart failure; or you can have an  
9 electrical problem, arrhythmias.

10 Cardiovascular disease is widespread and  
11 affects millions of patients and families in this  
12 country. These diseases are prime candidates for new  
13 types of diagnostic tools being developed by companies  
14 like Cardio DX.

15 Specifically, Cardio DX is working in  
16 disease states where patient stratification can  
17 improve clinical outcomes and lower total health care  
18 cost.

19 let me use one example. If you look at  
20 the third bullet point on this slide, we can use  
21 sudden cardiac death to illustrate a large unmet  
22 medical need to better risk stratify patients. Today,  
23 Thursday, February 8th, there will be about 500 ICD  
24 devices implanted in patients in hospitals around the  
25 country. If you track these patients that receive the

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1 defibrillators today for two years, less than 30  
2 percent of them will receive therapeutic benefit  
3 during that period of time.

4 That leaves the door wide open to improve  
5 our techniques for stratifying patients that should  
6 receive this remarkable ICD therapy.

7 The ICD case is just one example of how we  
8 might be able to use our understanding of the human  
9 genome to improve the delivery of care. You've heard  
10 other examples today during others' testimony.

11 Next slide.

12 While we can all agree on the need for  
13 better risk stratification, I think it's important to  
14 highlight the rigor and redundancy that must go into  
15 the research and development of these diagnostics.  
16 Cardio DX has taken an intensive clinically focused  
17 approach in the development of our products. We will  
18 spend several years and millions of dollars to bring  
19 each product to market.

20 We begin to carefully choosing the  
21 clinical decision where there is a significant need  
22 for patient stratification. We then design clinical  
23 protocols, collaborate with academic and community  
24 based cardiologists to collect thousands of samples.

25 In addition to samples, we collect all of

1 the relevant clinical data necessary for our analysis,  
2 and in many cases the clinical data is more  
3 challenging to collect than the sample itself.

4 With the samples in hand, we use provided  
5 nonproprietary technology to generate millions and in  
6 some cases billions of data points from these samples.  
7 It's that data that drives the development of our  
8 diagnostic products. This process takes a dedicated  
9 group of scientists, clinicians, statisticians, and  
10 business people to bring a product through the many  
11 hurdles of the development process.

12 In this slide I've provided just a general  
13 outline of the development phase that we go through to  
14 bring a product to market. We believe that it's a  
15 proven and reproducible process that will lead not  
16 only to clinically useful products, but also to  
17 acceptance within the scientific community through the  
18 publication and peer reviewed journal articles.

19 Next.

20 One of the things we'd like to emphasize  
21 is that Cardio DX products are designed to provide new  
22 information to physicians that are not available  
23 today. I believe that our work and that of others  
24 will provide new tools and new insights into the  
25 delivery of patient care.

1 I believe that molecular diagnostics  
2 provide a new flashlight, if you will, to illuminate  
3 disease in a new and exciting way.

4 I've got to the level of detail on Cardio  
5 DX because I believe it's important for the agency to  
6 know the rigor and thoroughness which many are  
7 approaching the development and use of IVDMIAs. Let  
8 me now turn my attention to draft guidance in its  
9 current form.

10 Ironically, if the guidance had been  
11 issued two years ago, I doubt I'd be standing here  
12 today. It's unlikely that Cardio DX would have  
13 received its initial funding if the draft guidance had  
14 been in place at that time.

15 Going forward, the guidance will force our  
16 company to be much more selective in our development  
17 projects and to significantly scale back our research  
18 and development efforts. This reduction stems from  
19 the economics of the market. Diagnostic products do  
20 not enjoy the same high revenue and high margins as  
21 pharmaceuticals and medical devices.

22 Therefore, diagnostic firms cannot afford  
23 the development of regulatory cycles that take five to  
24 ten years to get a product to market. If the guidance  
25 were to be implemented as is, Cardio DX would be

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1 forced into a difficult decision. Should we focus our  
2 resource on a single product rather than continue to  
3 drive the development of three programs? That's a  
4 choice that is one of the many unintended consequences  
5 of this draft guidance.

6 We're very supportive of the appropriate  
7 level of regulation to insure the public safety, but  
8 the draft guidance is too significant a jump from the  
9 current regulations to avoid significant disruptions  
10 in the flow of new and innovative diagnostic products.

11 Cardio DX is just one example, but you've  
12 heard others talk about the consequences of their  
13 programs as well. My biggest fear is that the draft  
14 guidance will have the opposite impact of what is  
15 intended. It could have the impact of keeping  
16 thousands of physicians from having the information  
17 necessary to deliver the most appropriate care to  
18 millions of patients.

19 I believe that companies like Cardio DX  
20 will be the source of innovation in the area of  
21 molecular diagnostics. Both the academic research  
22 centers and large laboratory companies are missing  
23 critical components necessary for the development of  
24 the new types of tests. Academic centers and  
25 established labs will be valuable partners for

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1 companies like Cardio DX, but they are unlikely to  
2 drive innovation.

3 We encourage the FDA to continue to foster  
4 innovation through forms like today's session where we  
5 can find creative solutions to the challenging issues.  
6 Specifically, we would like the FDA to continue  
7 working with companies and coalitions like the ones  
8 represented here today to find common ground. We  
9 firmly believe that the existing CLEA regulations are  
10 appropriate and adequate to bring tests to market.

11 If there is to be regulatory authority  
12 over IVDMIAAs, let's drive innovation by focusing on  
13 risks and not complexity, by creating low volume  
14 exemptions similar to orphan drugs, and by giving  
15 credit to those tests that have withstood the scrutiny  
16 of published research by the scientific community.

17 Regulation can go hand in hand with  
18 innovation.

19 Thank you for the opportunity of  
20 discussing these issues with you today.

21 DR. KESSLER: Thank you very much.

22 We're going to turn to Sharon Terry from  
23 Genetic Alliance, please.

24 MS. TERRY: Thank you for the opportunity  
25 to address you this morning.

1 Next slide.

2 The Genetic Alliance was founded in 1986.  
3 It's an international coalition of over 600 advocacy  
4 organizations covering about 1,000 diseases which  
5 affect about 25 million people. We basically work to  
6 transform the leadership of that community and to  
7 build a capacity in those organizations.

8 I'm concerned with some of the rhetoric  
9 around the IVDMIA guidance from all the stakeholders,  
10 and as a parent of children with a genetic disease and  
11 as an advocate I'm deeply concerned that we have not  
12 struck the correct balance and are currently engaged  
13 in inadequate dialogue to serve the end users of  
14 IVDMIA.

15 The first concern I'd like to address is  
16 process. I think that we should stick to regulation  
17 by rulemaking and not by guidance. The unrealistic  
18 public comment period was very difficult and is  
19 difficult for us to get especially advocates up to  
20 speed enabling them to respond during this time.  
21 Draft guidances are not binding or enforceable and so  
22 we're concerned about their ability to advance the  
23 FDA's aims.

24 The FDA process could lead to litigation  
25 and artificial procedural delays that would impact the

1 kinds of qualities that we want to see at the end and  
2 disjointed regulatory strategy from the FDA and CMS  
3 and others could also impede this area. We're a part  
4 of the citizens petition with Genetics and Public  
5 Policy Center to look at enhancing CLEA.

6 We'd also like to address whether we're  
7 talking about services or devices, whether this is  
8 about process or product or whether we need to even  
9 look at some reclassification in general, and how does  
10 this work in practical terms and pragmatically I think  
11 that maybe in this age of innovation there needs to be  
12 some consideration of that.

13 Is this an over extension of the Medical  
14 Device Safety Act and its amendments into an area that  
15 was not originally contemplated in the original intent  
16 of the regulations. In other words, has science  
17 advanced to a place where we really need to  
18 reconstitute some things? And it appears that there  
19 are unintended consequences or potentially harmful  
20 effect from the enforcement of these draft guidances.

21 We also wonder whether this is technology  
22 based rather than risk based, and we've heard several  
23 other people address this. In general, consumers are  
24 far more concerned about risk than the method of  
25 delivery or the technology, and they look forward to

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1 coming innovation in this field, as we've heard. We'd  
2 like to know if there are findings or wrongdoings  
3 that would be good examples of what motivated this  
4 approach because that would be certainly important in  
5 understanding why a technology approach might  
6 supersede a risk approach, and we believe that what is  
7 at stake and what truly matters to us as community,  
8 which is availability, access, affordability,  
9 innovation and transparency are not served in this  
10 approach, and we would agree that the more  
11 transparency we could have, for example, with  
12 registries, et cetera, that are open would be very  
13 important.

14 So I think in summary we have issues  
15 around whether or not the guidance shows us that FDA  
16 is getting up to speed and keeping pace with discovery  
17 and commercialization, including focus resources, your  
18 staffing and training, your experience in clinical  
19 laboratory operations, the general knowledge base and  
20 genetics, genomics and proteomics, and the  
21 technological aptitude.

22 So patient access to tests, basically the  
23 individuals that we work with, and we are working with  
24 a consumer task force on genetic testing asks  
25 questions about will this impede access. What are the

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1 associated costs? What are the associated delays for  
2 commercial adaption? How to facilitate timely access;  
3 is FDA balancing access to powerful innovation with  
4 regulation that would improve clinical outcome? Is  
5 the FDA creating new processes that will facilitate  
6 the integration of these new technologies into  
7 traditional markets as these markets change?

8 Innovation and information and  
9 technological renaissance in health care, we've heard  
10 a number of speakers address this, that the existing  
11 industrialized manufacturing regulatory model for the  
12 19th Century will not overlay well in a new era of  
13 information based or personalized medicine. We want  
14 federal authorities to be looking forward to this new  
15 age. We stand at the tipping point for dramatic and  
16 powerful advances in our understanding and potential  
17 management of these disease pathways and the  
18 regulatory paradigm can either promote or stymie  
19 innovation, access, affordability, and transparency.

20 So we feel that this guidance fails to  
21 adequately deal with this dynamic reality, and in our  
22 community a great deal is at stake, and we feel we  
23 really need to get this right now.

24 We would recommend that the guidance be  
25 withdrawn, that a formal rulemaking process be

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1 initiated, and that we request a formal public  
2 engagement initiated to be established by HS across  
3 the federal agencies involved in this in establishing  
4 a process that will deliver a regulatory pathway to  
5 enable 21st Century health care.

6 So our challenge to every entity involved,  
7 and it's across the board, all the agencies and the  
8 companies and the advocates, is to consider the system  
9 not only from your own perspective but from the whole  
10 system's needs, essentially forgetting turf; create  
11 methods for supporting innovation, access,  
12 transparency, and accountability that will support  
13 novel solutions for the men, women and children who  
14 depend on you to get it right so that they may live in  
15 health and strength and comfort and plan and execute  
16 actions from what matters for patients and not from  
17 the limited perspective of advocacy of research  
18 regulation, laboratory or industry.

19 Thank you.

20 DR. KESSLER: Thank you very much.

21 We're going to turn to Stuart Hogarth from  
22 the University of Cambridge from the U.K.

23 You came all the way here for this?

24 MR. HOGARTH: And another meeting in San  
25 Francisco. So --

1 (Laughter.)

2 MR. HOGARTH: Yeah, and I should declare  
3 a conflict of interest. I'm getting a lift to the  
4 airport this afternoon from Steve Gutman.

5 (Laughter.)

6 DR. GUTMAN: I really want to hear your  
7 comments.

8 MR. HOGARTH: So I'm a research associate  
9 in the Department of Public Health and Primary Care at  
10 the University of Cambridge, and I'm part of a  
11 research team who has spent the last three years  
12 exploring the policy issues around the evaluation and  
13 regulation of genetic tests.

14 Next slide.

15 Our forthcoming report will explore two  
16 key questions. What are the incentives test  
17 developers need to generate good evaluative data on  
18 new tests? And what are the appropriate regulatory  
19 mechanisms for evaluation of such data?

20 We've looked at the regulatory regimes in  
21 Europe, the U.S., Canada, Australia, and we've spoken  
22 to 80 individuals from key stakeholder groups, policy  
23 makers, regulators, diagnostics companies, clinicians,  
24 and patients groups.

25 We've had the good fortune to enjoy active

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1 FDA involvement in our research, and we've held two  
2 policy workshops here in D.C.

3 Many of the people we've spoken to  
4 expressed the view that the public confidence in  
5 genetic testing can only be maintained if there's a  
6 clear and coherent framework of regulation. There was  
7 general agreement that the status quo was not  
8 adequate, that new tests should be subject to some  
9 form of systematic, independent, premarket evaluation.

10 Many U.S. participants expressed some  
11 frustration that despite the detailed policy work of  
12 successive task forces and advisory committees, there  
13 was still no progress in these issues. Much of this  
14 concerns centers and the lack of a level playing field  
15 between test kits and in-house developed tests. The  
16 clear certification process relapse is an important  
17 and necessary part of insuring the safety and  
18 effectiveness of pathology tests, but it is not  
19 enough. Premarket review of novel tests to assess the  
20 analytic and clinical validity if also required.

21 Next slide.

22 If we look at this internationally, we can  
23 see a clear trend in the regulation of IVDs towards  
24 explicitly bringing in-house developed tests into  
25 device regulations, exemplified by Australia and

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1 Europe.

2           However, the situation in the United  
3 States is not quite as clear-cut as this little table  
4 suggests. A significant proportion of in-house tests  
5 are subject to premarket review in the U.S. not by the  
6 FDA, but by New York State Department of Health under  
7 their clinical laboratory evaluation program.

8           I am told that the New York State system  
9 of premarket review is not dissimilar to requirements  
10 for a 510(k) review by FDA. What can we learn from  
11 the New York State model?

12           Clearly there is a concern that FDA  
13 regulation of in-house tests may become a block in  
14 innovation. Yet companies like Quest, LabCorp and  
15 Genomic Health are at the leading edge of diagnostic  
16 innovation. the fact that they are NY licensed, which  
17 suggests that premarket review of in-house tests need  
18 not be a major block in innovation.

19           In passing I would also comment that we  
20 have very little data on the relationship between  
21 innovation and regulation. A negative correlation is  
22 often asserted, but usually in the absence of  
23 evidence.

24           Innovation is important. I believe in  
25 order to discuss the IVDMIA guidance we need to place

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1 it in the context of changing models of innovation in  
2 the IVD industry. The industry has traditionally held  
3 IP and test platforms not in biomarkers. This means  
4 it's very competitive industry with low profit margins  
5 compared with PhRMA, with little protection and  
6 investment, relatively low margins and little  
7 experience or infrastructure for clinical evaluation,  
8 the traditional sector is ill equipped to undertake  
9 large scale clinical studies.

10 This model of weak IP in biomarkers has  
11 meant that no one party is responsible for developing  
12 the data on the clinical validity of a new test.  
13 Academic studies and professional advocates have  
14 filled the gap often promoting tests in the back of ad  
15 hoc clinical experience.

16 Next slide.

17 There's some evidence that the emerging  
18 field of molecular diagnostics has disrupted the  
19 traditional model in a number of ways. A number of  
20 companies developing genetic tests based on patent  
21 protection of the gene and its association with  
22 disease have emerged with products near or on the  
23 market, Decode, InterGenetics, Solera, devoting some  
24 or all of their R&D activity to heritable risk  
25 predictors and, of course, bringing tests to market,

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1 often with IP in the biomarkers and/or the  
2 interpretive algorithm which creates a clinical result  
3 from the analysis of multiple analytes.

4 The emerging market for gene expression  
5 and proteomic tests is based on similar strong IP  
6 rights. Strong IP allows company to charge higher  
7 prices for the test because it gives them longer in  
8 the market before they arrive off competing products.

9 IP gives small companies the leverage to  
10 access the money needed for clinical studies. they  
11 can raise money from catalysts or find a bigger  
12 partner, such as a major reference lab.

13 So IP is an incentive to fund large scale  
14 clinical studies. It is a good thing, and it is not  
15 just the technology which is changing. It's just the  
16 business model and the innovation process.

17 Next slide, please.

18 Do IP protected tests such as IVDMIAs  
19 present special regulatory problems? IP biomarkers  
20 can lead to monopolistic provision of test and the  
21 home brew loophole has made it more attractive for  
22 companies to develop their tests as in-house tests  
23 which are carried out in a monopolistic basis by  
24 either the test developer or two or three exclusive  
25 licensees.

1           Many clinicians and lab directors have  
2           opposed this arguing that monopolistic provisions  
3           circumvents the traditional informal methods of test  
4           evaluation whereby a test is subject to peer review in  
5           the field. They are concerned that it creates a  
6           situation where the only people who can perform the  
7           test are those with a vested interest in its  
8           promotion, and this creates anxiety that in order to  
9           recoup their R&D investment companies may make strong  
10          clinical claims for their test at a stage when the  
11          evidence base is still developing.

12                    Controversy over emerging IP protected  
13          tests has been seen repeatedly in recent years and  
14          we've just had discussion of the correlogic (phonetic)  
15          Over Check example.

16                    The novelty and complexity of many of the  
17          tests involved only heightens concerns. The point is  
18          not that all companies producing IVDMIAs are bad  
19          players making dangerous tests. No. The point is  
20          that with that independent evaluation by FDA there is  
21          no way for doctors and patients to distinguish good  
22          from bad.

23                    Next slide.

24                    Over the last few years, the FDA has  
25          written letters to several companies about

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1 irregular status of their in-house tests. Many  
2 industry people we spoke to felt that there was a  
3 clear pattern emerging about when FDA might intervene,  
4 if there's an algorithm involved in the test, if  
5 there's strong utility claims or if it's for a high  
6 risk use.

7 Last year we wrote a report in  
8 Pharmacogenomics for the Canadian government. We  
9 noted this trend and suggested that it was likely to  
10 increase in pace and would eventually have to be  
11 resolved by a formal guidance document or even a rule  
12 akin to the AASR rule.

13 Next slide.

14 Our research has indicated the importance  
15 which companies place on regulatory guidance  
16 documents, providing clarity on both the review  
17 processes and standards of evidence required, vital  
18 information for those taking strategic business  
19 decisions about product development.

20 This was clearly an area where  
21 clarification was needed. There may be doubts about  
22 whether guidance is sufficient and concerns about  
23 ambiguities in the document, but the draft guidance  
24 has provided a rationale for FDA's recent activities  
25 in this field. It represents a major step forward,

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1 yet it raises as many questions as it answers.

2 The new guidance does not cover all  
3 monopolistic providers. Manufacturers still compete  
4 with in-house tests which do not need to go through  
5 FDA review. Having asserted its authority over in-  
6 house tests, FDA must accept it may be called upon to  
7 exercise that authority.

8 What will the agency do if it receives  
9 complaints about a test which falls outside the IVDMA  
10 guidance? It cannot state that the matter is outside  
11 its jurisdiction, and there's no other authority to  
12 whom the matter can be referred.

13 Yet for the FDA to respond by  
14 investigating other tests on an ad hoc basis would  
15 simply add to the confusion around this issue. This  
16 is not a hypothetical situation. Witness the current  
17 controversy surrounding direct consumer genetic tests,  
18 some but not all of which may fall under the new  
19 guidance.

20 The only solution as Gail Javitt indicated  
21 earlier is for a comprehensive approach to in-house  
22 tests, one which leaves test developers in no doubt  
23 about the regulatory pathway they must follow and  
24 which gives doctors and patients the assurance that  
25 the tests on which they rely are both safe and

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1 effective.

2 Next slide.

3 This is not the forum for a detailed  
4 discussion of how FDA could develop its approach to  
5 the regulation of in-house tests. However, it is  
6 worth noting that the agency has at its disposal a  
7 range of regulatory tools which might be applied to  
8 insure FDA review is not unduly burdensome.

9 In Australia the TGA have adopted third  
10 party review, authorizing the professional pathology  
11 bodies as reviewers, but with TGA retaining ultimate  
12 authority in a standard setting role. Orphan status  
13 can be given to rare disease tests to address the  
14 unique challenges faced in this area.

15 The SACGT identified an approach to  
16 premarket review which focuses on insuring truth in  
17 labeling as one which may be of assistance. This may  
18 be consistent with the use of the 510(k) review  
19 process and FDA has asserted that they took this  
20 approach in their reviews of both the raw  
21 (unintelligible) and third wave UGD-181 test.

22 Another approach is conditional licensing,  
23 although at present it would appear that this can only  
24 be done for PMAs, and there may be some scope here for  
25 enhancing the role of post marketing surveillance for

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1 Class 2 devices.

2 A move towards PMS could be consistent  
3 with a shift in favor of responsive regulation. That  
4 is, companies which clearly play by the rules are  
5 given relative freedom, but those who transgress come  
6 under greater regulatory scrutiny.

7 Finally, the U.S. has in the N.Y. State  
8 model an alternative free market review process which  
9 is already applied successfully to in-house tests, and  
10 it may be that the FDA can learn from this model.

11 Finally, in conclusion, I believe there's  
12 good reasons for the FDA to bring IVDMIA's under  
13 regulatory scrutiny. The guidance has brought greater  
14 clarity and consistency to the agency's previous  
15 piecemeal approach to this class of tests. FDA's  
16 decision to assert its authority over lab developed  
17 tests begins to bring it in line with the regulatory  
18 approach of both Europe and Australia, creating  
19 greater consistency across the international market  
20 for IVDs.

21 However, as has been made clear this  
22 morning, much remains to be done. The guidance is not  
23 the end of the process. It can only be the beginning.

24 Do I still get a lift to the airport,  
25 Steve?

1 (Laughter.)

2 DR. KESSLER: Thank you very much.

3 DR. GUTMAN: We're going to the same  
4 meeting.

5 DR. KESSLER: The last speaker for this  
6 morning will be Jonathan Cohen. Then we'll have some  
7 time for an open discussion on the floor. Jonathan  
8 Cohen is from 20/20 Gene Systems.

9 MR. COHEN: Thank you.

10 It appears that I'm the last. I'm between  
11 you and lunch. So I'm going to try to be very brief.

12 I'm Jonathan Cohen, President of 20/20  
13 Gene Systems. I serve as in-house patent counsel and  
14 General Counsel for two publicly traded diagnostics  
15 companies, one of which got the first FDA approval for  
16 the HER2 test, which has become the poster child of  
17 personalized medicine.

18 Before starting 20/20 in 2000, we're an  
19 emerging diagnostics company that among other things  
20 is developing a blood test for the early detection of  
21 lung cancer which looks at a panel of autoantibodies  
22 in serum, and based on the published data to date, it  
23 appears that the tests can identify lung cancer in  
24 high risk smokers with up to 80 percent sensitivity  
25 and specificity several years earlier than it is

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1 detected on the CT scanning.

2           Some of what I'm going to cover, I'll be  
3 brief because it has been touched on by others, but  
4 I want to kind of give you my perspective of where  
5 diagnostics is today from the standpoint of a small  
6 company entrepreneur, anticipated consequences of  
7 these guidelines, and perhaps most importantly what  
8 the FDA should do because I do believe that the FDA  
9 plays a critical role in advancing products like the  
10 one that we're trying to develop, although it's not  
11 the role I believe that you are currently playing.  
12 I'd like to see the FDA be more of a referee than a  
13 gatekeeper, and I will return to that.

14           And finally, talking about incentives, a  
15 number of people have called for incentives. I'd like  
16 to give some specific ideas on that, with a little bit  
17 more detail.

18           As has been articulated, you know, this  
19 has historically been a commodity based industry.  
20 Most of the innovation has been on instrumentation and  
21 automation, and as a result, you have low margins.

22           But a lot of the products are essentially  
23 generic. In generic products, as you see with the  
24 drug side, typically are reimbursed at a substantially  
25 lower amount than innovative products.

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1           So we're caught in a bit of a Catch-22.  
2           There are a few incentives for substantial investments  
3           both by companies, large or small, or venture  
4           capitalists. There was a statistic in BioWorld that  
5           I read that in 2004 only three percent of the venture  
6           capital, life science venture capital went to  
7           diagnostics, and I have no reason to believe that that  
8           has increased.

9           In fact, we heard from one VC this morning  
10          that if these regulations were to be implemented as  
11          written, he predicts that there will be even less  
12          venture capital. So its hard to believe it could be  
13          any harder, but perhaps with these guidelines it could  
14          actually be that.

15          And I really think it's very important  
16          because a number of entrepreneurs have touched on  
17          this, that for those that are advocates of higher  
18          guidelines, whether they be in government or in  
19          patient advocacy or in academia, really take to heart  
20          this point because ultimately what brings products to  
21          markets are companies, and companies need to be funded  
22          to do things the right way, and that funding comes  
23          from investors.

24          And if you're hearing from investors and  
25          you're hearing from entrepreneurs the same thing, that

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1 needs to really be absorbed. So I think that's  
2 extremely important.

3 Next slide.

4 This sort of says it a different way, and  
5 this is why I believe that pharmaceuticals and medical  
6 devices, as traditionally defined, such as stents and  
7 the like, do attract more investment relative to  
8 diagnostics. In short, the risk and rewards for both  
9 drugs and medical devices are, by and large, balanced.  
10 The burdens are very high, but the rewards are high.  
11 There are blockbuster drugs. There are blockbuster  
12 stents. There really are no blockbuster diagnostics.

13 And as a result, when you have medium  
14 level risks but low returns, there's little  
15 investment. My concern is that with if you with these  
16 guidelines only increase the risks or increase the  
17 burdens, but we're not addressing the return side, and  
18 that will mean fewer products and perhaps more  
19 inferior products. Again, less investment, fewer  
20 products.

21 Static tests, again, this was touched  
22 upon. Again, the perception of those of us in  
23 industry, especially in the area of multiplex  
24 biomarkers because things are evolving, and I can't  
25 say that the five or six markers we have today will

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1 necessarily be the optimum ones. It's a very early  
2 stage process, and the fear a lot of us have is that  
3 we will need to lock down our panel, and there will be  
4 little incentive to improve. It could create what I  
5 would call a race to the bottom. In other words, the  
6 pathologist this morning talked about the EGFR marker,  
7 very important for a class of new targeted cancer  
8 drugs, and currently there's an FDA product that's a  
9 single analyte, and it's by and large viewed not to be  
10 very effective.

11 What incentive would that company or  
12 others have to then create a panel test that could be  
13 effective. And actually the FDA is singling out the  
14 multiplex testing for higher scrutiny. You're, in  
15 essence, punishing the innovator, and that could  
16 create a race to the bottom where companies retreat to  
17 safer ground, which in the end could be worse and will  
18 be worse for patients. We'll have fewer products, and  
19 the products will ultimately be less effective.

20 So what should the FDA do? I believe  
21 that, again, referee, not gatekeeper. There is a  
22 critical role, and I definitely hear that the views  
23 from the cancer advocates and the academics and so  
24 forth, that there does need to be something done to be  
25 able to help these doctors and the patients determine

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1 what really is the right product.

2 And can you believe these claims that  
3 entrepreneurs and the companies are making? The  
4 database concept, some call it a registry, I think is  
5 really where we want to go at least for now for the  
6 next few years. I think the FDA is the right agency  
7 to manage that process and allow, essentially empower  
8 the marketplace to pick the winners. And as I'll talk  
9 about furthermore, to provide incentives and, if  
10 necessary, go to Congress and ask for legislation to  
11 provide incentives to help accelerate diagnostic  
12 development.

13 The database concept, again, well, you  
14 know what? Let's go to the next slide, yeah.

15 This is just sort of an example, quick and  
16 dirty, but this concept of where you would have  
17 Internet accessible not unlike the food labeling  
18 concept that you have for food, where physicians and  
19 even patients could make apples to apples comparisons  
20 between a lab test done that would clearly spell out  
21 the sensitivities, the specificities, validation of  
22 the studies that were done, all with links to the  
23 published data, and even allow the FDA to comment  
24 because I think the FDA can play an active role.

25 The FDA could in some cases even criticize

1 companies if they think that they are making inflated  
2 claims or that the cohort of patients tested was too  
3 small to be statistically significant. So there would  
4 be the opportunity for the FDA to play an active role,  
5 but again, acting as a referee and not a gatekeeper.

6 This would not have -- there would be no  
7 premarket approval required here. This would allow  
8 the marketplace to be able to compare tests, and if  
9 you say you have a test with 85 percent sensitivity,  
10 you need to reference the studies that support that.

11 Next slide, please.

12 Again, to the extent that FDA does require  
13 a formal PMA type approval, it would really be for the  
14 high volume, high risk test, and this illustrates it  
15 graphically. Here when you have a test that addresses  
16 a small population, it simply doesn't make sense to  
17 develop a kit. It can be done in one lab with one set  
18 of technicians, with one set of equipment, and it  
19 doesn't need to be done under GMP with all of the  
20 burdens that traditional FDA approval has. It just  
21 doesn't make sense.

22 On the other hand, there will be certain  
23 tests that do because of the market size warrant that  
24 the test be done in multiple places, and then there  
25 should be a higher level of regulatory scrutiny. As

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1 a practical matter because it's high volume, the  
2 manufacturer or the developer would have the economic  
3 resources for this type of regulation.

4 So this makes sense, I think, both  
5 scientifically and economically, this kind of model  
6 where the high volume, high risk test would be  
7 regulated, and the others would be regulated under the  
8 CLEA model as well as this proposed database concept.

9 I want to touch on accelerators because  
10 really -- and a number of people have touched on this,  
11 but I think we need to really start thinking of real  
12 ideas.

13 The orphan drug model is by and large a  
14 success for the FDA where, in essence, combinations of  
15 exclusivity tax credits and grants, in essence,  
16 created a robust market where one did not exist. In  
17 part, I think that is applicable to diagnostics today.  
18 I think there needs to be expanded reimbursement, but  
19 not for all tests, but truly the innovators. Let's  
20 reward the risk taker. Let's reward the person that  
21 substantially improves the state of the art. There  
22 needs to be a new DARPA-like or BARTA, the new BARTA  
23 for biodefense-like entity at HHS to fund Valley of  
24 Death development in diagnostics.

25 The number of peer review publications is

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1 exploding. Apparently there was 100,000 publications  
2 on biomarkers last year and zero FDA approved  
3 products. So we have a lot of publications, but very  
4 few products. We need funding for that Valley of  
5 Death. We need to collectively ask Congress for it.

6 Finally, income tax credits for both  
7 investors and developers is a proven and effective  
8 mechanism that works at the state level. I think it  
9 has worked at the orphan drug. This is really where  
10 we need to advance diagnostics so that we can have the  
11 kind of accuracy that that we need to deliver the  
12 patients without putting companies out of business.

13 Thank you.

14 DR. KESSLER: Thank you, Mr. Cohen.

15 I think in your last comments talking  
16 about the gulf between the large number of biomarker  
17 discoveries and the lack of new products may make an  
18 advertisement for some of our critical path  
19 initiatives.

20 So thank you.

21 The floor is open. If you do want to make  
22 comments, please come to one of the microphones in the  
23 center, the microphone at the podium, and please make  
24 your comments brief and to the point and try and keep  
25 it under two minutes.

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1 We're not paid by the minute up here.

2 (Laughter.)

3 DR. KESSLER: Sir. Please don't forget to  
4 mention your name clearly.

5 DR. LEADER: Mention my name?

6 DR. KESSLER: Mention your name.

7 DR. LEADER: Hi. My name is Ben Leader.  
8 I'm an emergency physician and I did have a -- I  
9 apologize. I've got a cold -- but I did a Ph.D. where  
10 I started to develop a genetic diagnostic, and I've  
11 been encountering some of the challenges to try to  
12 bring this to patient care.

13 So I wanted to just ask maybe a naive  
14 question. Would it be possible to maybe take a non-  
15 traditional approach of an interaction between the FDA  
16 and industry where you actually say to industry,  
17 "We're going to help you get FDA approval or we'll go  
18 through the process for free, but we'll just take a  
19 percent of the profits."

20 (Laughter.)

21 DR. LEADER: And, I mean, that way there's  
22 no argument to say that there's any cost up front, and  
23 those that have a good idea, you know, it's a  
24 business proposition, and I'm not sure. Then there's  
25 the alignment of goals. So I put that out there for

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1 business experts.

2 DR. KESSLER: If you'd like a ride to the  
3 airport, I'm sure Steve will give you one.

4 (Laughter.)

5 DR. KESSLER: Other comments from the  
6 floor?

7 (No response.)

8 DR. KESSLER: It's approximately quarter  
9 of 12. Let's all retire for lunch. An hour and 15  
10 minutes. We'll convene back here at one o'clock  
11 promptly, and we should be finished this afternoon in  
12 case any one of you are planning approximately we're  
13 looking at 3:30 to four o'clock, maybe even a little  
14 earlier.

15 Thank you.

16 (Whereupon, at 11:45 a.m., the meeting was  
17 recessed for lunch, to reconvene at 1:00 p.m., the  
18 same day.)

AFTERNOON SESSION

(1:01 p.m.)

1  
2  
3 DR. KESSLER: Good afternoon. If we're  
4 fortunate and this afternoon's speakers are as careful  
5 with their time as this morning, we're going to take  
6 all ten presentations straight in a row. That should  
7 take us to a little before three o'clock, a little  
8 time for open mic, and then Dr. Schultz will be back  
9 in a minute, our Center Director, and I will have some  
10 closing comments.

11 I'm going to start with Sherry Salway  
12 Black from the Ovarian Cancer National Alliance.

13 Thank you.

14 MS. BLACK: Thank you.

15 Good afternoon. I'd also first like to  
16 thank the FDA for holding this public hearing and  
17 providing the opportunity to testify on this very,  
18 very important issue.

19 The Ovarian Cancer National Alliance has  
20 no financial interest. Our interest is in the  
21 millions of women who are at risk for this disease,  
22 and the close to 200,000 women who are survivors, who  
23 are alive today in this country.

24 My name is Sherry Salway Black, and I am  
25 Executive Director of the Ovarian Cancer National

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1 Alliance.

2 I was diagnosed five years ago with both  
3 ovarian and endometrial cancers. Both cancers were  
4 detected in Stage 1 where I had the best chance of  
5 survival. Actually this month is my fifth  
6 anniversary, something only 25 percent of women with  
7 ovarian cancer can claim, being diagnosed in early  
8 stages.

9 I was lucky to be diagnosed early.  
10 However, it was not the result of having access to an  
11 early screening test. My good fortune was only the  
12 lucky result of my perseverance with my doctor and  
13 subsequent treatment by the appropriate specialist,  
14 the gynecologic oncologist.

15 Two years ago I joined the Ovarian Cancer  
16 National Alliance as Executive Director to insure that  
17 other women can have the opportunity to be as  
18 fortunate as I have been. We cannot rely on luck for  
19 our survival. We must have the research to develop  
20 early screening tests, diagnostic tests, and new and  
21 better treatment and the spread awareness to women  
22 about the risk factors and symptoms of ovarian cancer.

23 The alliance is an umbrella organization  
24 with 50 state and local groups representing more than  
25 a million grassroots advocates, activists, and health

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1 care professionals. I'm testifying on behalf of those  
2 survivors, women at risk, advocates, and professionals  
3 to express my concern regarding draft guidance on  
4 IVDMIA.

5 According to the American Cancer Society,  
6 in 2007 22,430 women will be diagnosed with ovarian  
7 cancer and 15,000 will lose their lives to this  
8 terrible disease. Ovarian cancer is the deadliest  
9 gynecologic cancer, and the fifth leading cause of  
10 cancer death among women in America. Currently more  
11 than half of the women diagnosed with ovarian cancer  
12 will die within five years.

13 When detected early, the five-year  
14 survival rate increases to 90 percent, and when  
15 detected in the late stages, it drops to 28 percent.

16 A valid and reliable screening test, which  
17 is an important tool for improving early diagnosis and  
18 survival rates unfortunately does not yet exist for  
19 ovarian cancer. Since the alliance was founded ten  
20 years ago, close to 250,000 women have been diagnosed  
21 with ovarian cancer, more than 85,000 of those  
22 diagnosed in Stages 3 and 4 because there is no early  
23 screening test and no diagnostic test.

24 Only a small portion of those women are  
25 alive today. We recognize that it may be years before

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1 there is a highly sensitive and specific early  
2 screening test for the general population, but we do  
3 know there is significant research going on sponsored  
4 by both government and industry to develop effective  
5 diagnostic tests using multiple markers. These tests  
6 are the future for early screening, but they may be  
7 today and in the very near future the best hope for an  
8 early diagnosis for women who are at a higher risk  
9 than those with an existing pelvic mass.

10 These women's lives cannot be held hostage  
11 by a process that creates barriers getting a safe and  
12 effective test for early diagnosis and screening.  
13 Some of the issues and concerns for advocates are:

14 Does FDA's intervention and process  
15 improve safety and efficacy of these tests? Is the  
16 FDA the right body to regulate these tests?

17 Advocates have called for a specialty  
18 under CLEA that would create certain standards for  
19 this test. Is issuing guidelines the right process  
20 for the FDA to take in establishing the regulation of  
21 these tests?

22 The impact of this guidance is a totally  
23 new approach to how these tests are regulated and how  
24 the FDA interacts with labs.

25 What is the big picture plan for

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1 regulation of these types of tests to insure their  
2 quality and thus the health of the public? It is  
3 clear that standard need to be established -- we've  
4 heard that this morning -- for these kinds of tests  
5 which address their clinical validity. The FDA does  
6 have this expertise.

7 But this approach is a slide of a much  
8 bigger issue. There are dangers in taking a piecemeal  
9 approach to such a significant issue, and we really  
10 don't feel there's an overall strategy that is clear.

11 It's not clear what the procedures will be  
12 for the regulation of these tests. The FDA indicated  
13 it will take a risk based approach in determining what  
14 kind of review will be required. In fact, it seems to  
15 be taking a technology based approach with this more  
16 complicated algorithm and more variables require  
17 longer review.

18 The guidance appears overly general.  
19 There are a number of outstanding questions regarding  
20 what the FDA policies will be, and I won't go into  
21 more specifics because I think it was covered quite  
22 adequately this morning.

23 We feel the draft guidance is vague and  
24 opening to varying interpretations. We urge the FDA  
25 to resolve this by creating a clear, predictable

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1 process with remedies. The process must allow rapid  
2 access to diagnostic or screening tests, as well as  
3 increased safety and efficacy. I know it's a delicate  
4 balance, but this is what we're asking.

5 Such a process will encourage entry in  
6 research and the tools that will increase survivorship  
7 while protecting safety. Already ovarian cancer is a  
8 rare disease, not always at the forefront of medical  
9 research. Further discouragement into the ovarian  
10 cancer area will have great consequences for the lives  
11 of women.

12 The process required by the FDA must be  
13 clear, must be predictable, fast, and protect the  
14 lives of women because our lives depend on it.

15 Thank you.

16 DR. KESSLER: Thank you very much.

17 We'll next hear from Robert Erwin-Marty of  
18 the Nelson Cancer Foundation.

19 MR. ERWIN: Thank you. It's Robert Erwin  
20 of the Marti Nelson Cancer Foundation, but that's  
21 okay.

22 DR. KESSLER: I just realized where the  
23 hyphen was.

24 MR. ERWIN: Yes, thanks.

25 Well, I appreciate the opportunity to

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1 speak and also your setting up this meeting. I've  
2 worked as a patient advocate for about 12 or 13 years  
3 now. I also have been involved in commercial biotech  
4 for even longer than that, and by this time in the day  
5 there's probably not a whole lot new that you'll hear  
6 from me, but I thought I might see if I could frame my  
7 view of the problem and then offer a few suggestions.

8 I think the problem in the broader context  
9 is really the attempt to balance two realities, one,  
10 the reality that there are a lot of scumbags in the  
11 world who will take advantage of people who are in  
12 desperate situations, and that the attempt to keep  
13 them out of the market will create significant  
14 obstacles to the honest, legitimate, creative people  
15 who want to enter the market.

16 I don't like reading slides, but sitting  
17 in the back earlier I realized they can't all be read.  
18 But basically that conflict between the willingness of  
19 people to cut corners and the desire of people to have  
20 the government prevent that is the essence of a very  
21 serious challenge, I believe.

22 Looking at how we got to where we are,  
23 clea regulations came about because consumers were  
24 harmed by sloppiness, poor quality control, and corner  
25 cutting. FDA regulations arose from basically the

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1 same reasons, death and injury caused by products that  
2 were dangerous or faulty or that were completely  
3 misrepresented.

4 And it goes far beyond health care. I  
5 think that there is a very real problem that the FDA  
6 in general does a very good job of addressing, and  
7 that is what happens if capitalism is totally  
8 unfettered, and the examples I have up here are not  
9 health care specifically, but auto makers selling  
10 minivans as passenger cars without meeting passenger  
11 car standards was a rather cynical attempt to drive  
12 through the loopholes which they did successfully for  
13 a long time.

14 I don't think I need to comment to this  
15 audience on the problems with nutritional supplements  
16 and the fraud in that industry.

17 More recently, breakfast cereals being  
18 essentially advertised as containing fruit when they  
19 don't, and how many of us have seen the young, healthy  
20 models flitting through the fields of flowers? If  
21 anything, that should at least increase the sales of  
22 anti-nausea medication.

23 (Laughter.)

24 MR. ERWIN: So I believe that the  
25 regulation of claims made for products is very

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1 important. I agree with the comments that have been  
2 made earlier about regulating the analytical  
3 reliability, the clinical validity and all of that,  
4 but from simply a consumer standpoint, understanding  
5 that what is claimed for a product can be believed is  
6 an extremely important government service which, left  
7 to the free market, frequently unfortunately is not  
8 done.

9 And my concern is that as CLEA currently  
10 operates, that's not being done and that validation of  
11 claims for products sold directly to consumers,  
12 especially as the technology becomes more and more  
13 complex, is especially critical.

14 So I believe that FDA should regulate  
15 claims made for these products, and I do not think  
16 that the Federal Trade Commission and CLEA, despite  
17 the good work they do, are the answer. As  
18 personalized medicine, I hope, become more and more  
19 the norm, the importance of overcoming the natural  
20 tendency that would ensue if only direct to consumer  
21 advertising guided the choice of medicine and the  
22 choice of diagnostic tests, even direct to physician  
23 advertising would be a real problem.

24 I think that the pace of technological  
25 innovation certainly is high, but despite the

1 protestations of a lot of people, it's not so fast  
2 that a rational regulatory process cannot provide good  
3 quality controls and good assurance to consumers.

4           However, there are some problems, and it  
5 basically has to do with the potential for government  
6 regulation to stifle innovation and to delay consumer  
7 access to the things that they need. I believe that  
8 the FDA currently does not have the resources to keep  
9 the review time line short enough if it takes on the  
10 full breadth of materials, products that are covered  
11 by this draft guidance. Depending on how it's  
12 implemented, a good product could be withdrawn from  
13 the market, and certainly the ambiguities between CLEA  
14 and FDA will make a lot of money for the lawyers, and  
15 I don't think that's necessarily a good thing.

16           Delays in marketing approval as has been  
17 pointed out before will definitely inhibit investment  
18 in innovative technologies, and that will result in  
19 innovation being slower to reach routine medical  
20 practice.

21           In addition, something that I'm very  
22 concerned about is that an added regulatory burden can  
23 significantly increase the prices of these products  
24 and the costs to consumers.

25           So one solution is to provide more

1 resources to the FDA. I think that 15 years ago if  
2 you had asked me, I would have said the FDA were the  
3 bad guys. After a lot of interactions with a lot of  
4 people in the FDA on a lot of different projects with  
5 many companies, some quite controversial, I've revised  
6 that opinion substantially. I have a lot of respect  
7 for the quality of the staff, and I particularly like  
8 the researcher-reviewer model where there are very  
9 good scientists staying on the cutting edge of work  
10 who participate in the reviews. I don't think there  
11 are enough of them. I think there needs to be a  
12 reallocation of resources.

13 The federal government has plenty of  
14 resources. It's a question of allocation. I think  
15 the FDA staff should be expanded so that it can do  
16 this job well. More resources would reduce the risk  
17 of costly delays, and it would also reduce the need  
18 for selective enforcement, and I know that that's been  
19 a concern addressed in various ways today.

20 I agree that selective enforcement is a  
21 bad thing because it creates uncertainty among  
22 investors, even among physicians and researchers.

23 So a few slightly more specific  
24 suggestions, although these are somewhat "lay" in  
25 orientation. I think they get at a lot of what we've

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1 heard today.

2 Products that are already in clinical use  
3 that have already been validated through third party  
4 efforts or peer reviewed processes I think should in  
5 some way be grandfathered or exempted from any sort of  
6 deadly change, withdrawal from market or what have  
7 you.

8 I've listed two examples here, which are  
9 products that I believe, based on the peer reviewed  
10 medical literature, are good examples of things where  
11 the risk-benefit of a grandfathering or a temporary  
12 but adequate exemption from immediate compliance would  
13 make sense, and the examples I chose are Oncotype DX  
14 for breast cancer and AlloMap used in heart  
15 transplantation.

16 I also agree with an earlier comment that  
17 existing tests should not suddenly be labeled  
18 experimental because, going back to my skepticism  
19 about capitalism, we know exactly what the insurance  
20 companies will do if that happens.

21 And I do think that the standards need to  
22 be clarified a little bit across the rather diverse  
23 range of technologies that are covered here so that  
24 it's a little easier to understand.

25 To get at what is probably a red herring,

1 but could be an actual health issue, there should be  
2 a special provision for IVDMIAs that specifically  
3 address rapidly emerging or mutating infectious  
4 disease. This is a very different kind of biology  
5 from a genetic test, a cancer test, or something else  
6 where the progression and the treatment occurs over a  
7 much longer time period than the potential need to  
8 react quickly to an emerging infectious disease.

9 Some type of a provision to put this in a  
10 special category will also reduce the income to the  
11 lawyers who will feed off of this otherwise, and I  
12 think that at least as a person who is not an expert  
13 but who has read a lot of this stuff, I had a hard  
14 time figuring out what would fall into Class 2 versus  
15 Class 3, and there are huge financial implications for  
16 that difference for the companies that have to fund  
17 it.

18 And my suggestion is to reconcile  
19 conflicts between CLEA and FDA and to use plain  
20 English. The Securities and Exchange Commission has  
21 figured out how to do that reasonably well, and it's  
22 probably a good model for other government agencies to  
23 follow.

24 So just to wrap things up, I think that  
25 the draft guidance is a good start. I would encourage

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1 a few modifications stated very clearly and with as  
2 many words as it takes, but clearly so that ordinary  
3 people can understand it.

4 And I do think that if it's properly done,  
5 this will represent a benefit for consumers, and it  
6 will also have the effect of assuring that profits  
7 flow to people who actually earn them.

8 Thank you very much.

9 DR. KESSLER: Thank you, Mr. Erwin.

10 At the beginning of the talk Dr. Schultz  
11 leaned over and wanted to offer you another minute.  
12 When you got to the resources, we wanted to offer you  
13 another half hour.

14 (Laughter.)

15 DR. KESSLER: However, we got three notes  
16 from the lawyers in the audience. They wanted us to  
17 cut you off.

18 (Laughter.)

19 DR. KESSLER: And finally, with regard to  
20 the SEC and plain language, we'll be calling Martha  
21 Stewart to see what she thinks of plain language with  
22 the SEC.

23 Elda Railey, you're welcome. You're from  
24 the Research Advocacy Network, and we'd like to hear  
25 your thoughts. Thank you.

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1 MS. RAILEY: Thank you.

2 I'm Elda Railey from Research Advocacy  
3 Network who is the sole supporter of my presentation  
4 today.

5 We hope that makes a strong statement of  
6 how we feel about this issue because we do feel like  
7 for an organization with limited resources to fund my  
8 travel here today and to be able to speak to you, and  
9 we thank you for that opportunity.

10 It's also providential that this is  
11 happening on my son's 24th birthday. To me it's  
12 important for us to remember that it's for our next  
13 generation. It's not only for ourselves, but it's for  
14 our next generation that we will be enacting some of  
15 these regulations.

16 At the Research Advocacy Network, we're  
17 focused on demystifying the science behind cancer  
18 research and providing advocates with the tools they  
19 need to participate effectively in the research  
20 process. This is in an effort to insure the inclusion  
21 of the patient perspective in clinical trials as they  
22 are designed and conducted and as new diagnostics and  
23 therapeutics are developed.

24 As advocate we believe that IVDMIA's play  
25 a critical role for patients and the health care

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1 providers that use them to better understand a  
2 prognosis or to provide insight into treatment  
3 decision making.

4 In addition, these tests and this field of  
5 genetics and genomic research also represent the  
6 overall direction that research is rapidly moving,  
7 holding the promise of earlier diagnoses more  
8 effective treatments and better patient outcomes.

9 However, we also acknowledge that because  
10 the information provided by these assays leads to  
11 critical decision making on the part of the patient  
12 and the physician, it's imperative to insure that  
13 genetic and genomic tests are both scientifically  
14 accurate and can be reliably performed by the testing  
15 laboratory.

16 We recognize that there is a very fine  
17 balance to be achieved protecting safety while still  
18 enabling patient access and promoting scientific  
19 innovation.

20 It's from this perspective then that we  
21 ask the agency to address the following issues and  
22 questions as it considers how to effectively provide  
23 oversight of IVDMIAs. Because all of these are not  
24 created equal, it doesn't make sense to us for all of  
25 these tests to be regarded in the same way simply

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1 because they fall into the same category.

2 There could be significant difference in  
3 the quality of the science being conducted by the  
4 individual companies who develop and manufacture these  
5 tests, how well FDA distinguished between the  
6 companies to develop their assays with rigorous  
7 research practices and those whose clinical data is  
8 subpar.

9 What standard FDA used to determine the  
10 sufficiency of a company's scientific evidence? And  
11 when has a company fulfilled its research obligations  
12 with regard to demonstrating the clinical accuracy and  
13 the validity of its tests?

14 We feel that some of the developers have  
15 already provided a breadth of clinical data attesting  
16 to the scientific utility of their assays. Will these  
17 companies be forced to go back and do their clinical  
18 studies under this new regulation?

19 Since some of the assays were already  
20 scientifically validated and readily available, does  
21 the FDA plan to allow patients continue to have access  
22 to those tests throughout these changes to the  
23 process?

24 We believe that it's important for these  
25 tests to be grandfathered in as Bob Erwin mentioned to

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1 any regulatory process, providing that adequate  
2 clinical data exists to demonstrate scientific  
3 validity.

4 Otherwise patients and health care  
5 providers who have come to rely on these tests will  
6 lose out on the important information that they  
7 provide.

8 These are just a few of the complex issues  
9 our organization would like addressed through the  
10 draft guidance issued by the FDA. As the science of  
11 genetics and genomics advances rapidly, we anticipate  
12 that the agency may be challenged to develop  
13 regulatory policies and procedures that keep pace with  
14 the research, and as new policies and procedures are  
15 developed, we urge the FDA to create a clear, fair,  
16 balanced, and scientifically informed process so that  
17 new regulations are rational and truly support the  
18 best interest of patients.

19 Additionally, it's important that the FDA  
20 and the community come together to work out the  
21 details of new regulation in this arena. We all want  
22 the new science to move forward as long as it is safe  
23 and effective and results in better patient outcomes.

24 Thank you for the opportunity.

25 DR. KESSLER: Thank you. Thank you for

1 spending your time with us today.

2 I'd like to introduce Carol Berry from  
3 Aviara Diagnostics.

4 MS. BERRY: Thank you.

5 And we appreciate the opportunity to talk.  
6 I am the Vice President of Sales at Aviar Diagnostics.  
7 We are a molecular diagnostic company focused in on  
8 oncology based genetic tests.

9 today what I wanted to do, many of the  
10 points that I had in my presentation have been covered  
11 in the morning session. So I'll highlight just few of  
12 those, but I'd like to talk about one of our tests  
13 that has been licensed to Labcor and Quest and exists  
14 on the market today.

15 This is a 92-gene RTCPR test that  
16 classifies 39 different tumor types. The sample that  
17 is used is generally taken out of a metastatic cancer  
18 patient is a fine needle biopsy, and it's used  
19 formalin fixed paraffin embedded tissues. So these  
20 are samples that are very small because these patients  
21 generally go through these fine needle biopsies. So  
22 the test was developed to accommodate those small  
23 sample sizes.

24 The medical situation today that exists is  
25 that one out of every four metastatic cancer patients,

1 the primary classification cannot be identified. So  
2 this is about 15 percent of around 300,000 cases. So  
3 this is a very serious situation, and the physicians  
4 really depend upon the knowledge of what that primary  
5 cancer type is to be able to make a sufficient  
6 treatment decision.

7 And the traditional work-up is extremely  
8 costly, but more important, the time that it takes to  
9 diagnose these patients is critical because these  
10 patients don't have time. Every day is important to  
11 them.

12 So through successful cancer  
13 identification the patient can receive the best  
14 treatment to either help cure their cancer or extend  
15 their lives.

16 So this is the clinical decision tree, and  
17 one of the points I want to make is that this test  
18 today and how it's applied does not stand alone in  
19 clinical decision making as many diagnostic tests do  
20 not. The physician, the pathologist usually starts  
21 with immunohistochemical staining. If they can't --  
22 sometimes they do get an answer and they go straight  
23 to a treatment decision, but in many of these cases  
24 these patients are not identified. So you have  
25 diagnoses like adenocarcinoma. It's just this general

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1 classification of cancer.

2 But what we suggest is that when we work  
3 with the pathologist is that they come back and  
4 confirm with their IHC or they confirm with an imaging  
5 test. So it's not like the test acts alone.

6 So just to give you an example, in one of  
7 our recent studies, we were looking at 50 cases of  
8 what's called cancer of the unknown primary or CUP  
9 patients, and they blinded the 50 patients for us. So  
10 the pathology group knew the results and when they  
11 unblinded it, seven of the cases were actually CUP  
12 patients. They could not determine the case, and when  
13 they applied the CUP test to those seven patients,  
14 five of the seven were identified properly.

15 So this is a test that is really  
16 encouraging because now these people can receive  
17 treatments that are very specific to their primary  
18 cancer type.

19 But another piece of this, too, is it's  
20 also about an economic look at the disease, is that  
21 some of the treatments that are available are very  
22 expensive and managed care companies are not going to  
23 pay for those expensive treatments unless you can get  
24 a proper diagnosis. So if you do get that diagnosis  
25 and you do get that treatment, then it will be

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1 covered, whereas in general what these patients  
2 receive today is just general chemotherapy, which is  
3 usually not successful.

4 So some of the questions which have been  
5 very well covered in the morning session we stand in  
6 the same situation and that is what do we do. This is  
7 a laboratory developed test at the present time.  
8 We've actually been to you all and talked with you.  
9 You like our science. You like all of the peer  
10 reviewed articles that we've -- all the science that  
11 we've generated.

12 But we stand in a situation that is very  
13 difficult because we want to follow the guidelines.  
14 We want to comply, but we're unsure because of the  
15 ambiguities in the current draft guidance.

16 So as I sat here this morning and I  
17 listened to many of my colleagues and many of the  
18 patient advocates, what I came away with, and this is  
19 not on the slide, is there are a lot of smart people  
20 in this room, and you guys were M.D.s, were Ph.D.s,  
21 were MBAs. Good heavens, I would hope that as a group  
22 we could figure this out and not have the FDA standing  
23 on one side, CLEA standing on the other, and our  
24 industry sitting out here listening.

25 I mean, good heavens, we need to come

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1 together as a group and figure this out. I really  
2 think that we can. I think we can make it reasonable.

3 The CLEA guidelines as they exist today,  
4 it's kind of interesting from a perspective of a  
5 business person in this industry for 20 years, is that  
6 we sometimes generate more clinical data and  
7 validation studies on the CLEA side because when you  
8 go to a physician to get them to use your test, they  
9 ask for lots of information, and that's the sign of a  
10 good physician.

11 And then on the other side, we can take  
12 that data and somehow apply it to FDA and not have to  
13 recreate studies, which creates a lot of cost. So we  
14 would really hope for a transition period to be able  
15 to look at new regulations that address laboratory  
16 developed tests, not devices.

17 There should be guidelines for devices.  
18 There should be guidelines for laboratory developed  
19 tests, and let's make them appropriate so that we can  
20 then take our tests and have patients benefit from  
21 those tests.

22 So go ahead.

23 So this is really one of the issues that's  
24 been covered quite well, is about risk and benefit to  
25 the patient, and really what are we trying to do? Are

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1 we trying to look at the way now we use multiple  
2 markers versus single markers? And really looking at  
3 it, is it because we're bringing new platforms and  
4 technologies to market?

5 These are all good things, but we need to  
6 have some balance, and that is risk and patient  
7 benefit.

8 So thank you for the opportunity to speak,  
9 and hopefully as a group we can work this out  
10 together.

11 DR. KESSLER: Thank you very much.

12 Elissa Passiment from the American Society  
13 for Clinical Laboratory Science.

14 Did I get the pronunciation correct?

15 MS. PASSIMENT: No, that's okay. No one  
16 does.

17 My name is Elissa Passiment. I'm a  
18 clinical laboratory scientist, and I'm here today to  
19 talk to you about the concerns of the members of the  
20 American Society for Clinical Laboratory Science.

21 Our organization is made up of the  
22 individuals who not only manage laboratories, but  
23 perform the laboratory testing, and we have over the  
24 years spent our time watching technology evolve and  
25 have grappled with the problems that occur in the real

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1 world both in implementing laboratory testing and also  
2 helping physicians and patients understand the results  
3 of their testing.

4 Next slide.

5 Our members have two major concerns, and  
6 both of these have been expressed. So they are simple  
7 statements, but they are still the huge hurdles that  
8 have to be overcome by whatever documentation and by  
9 whatever process FDA and the industry and the  
10 community decide to use.

11 The advances in science that are coming  
12 hold incredible promise for all of our patients and  
13 for patients and consumers in every point of the  
14 health care continuum, not just during acute phases,  
15 but also in prevention wellness and in chronic  
16 disease, and these advances cannot be stifled by more  
17 regulation that is truly nothing more than a burden.

18 On the other hand, there are a lot of  
19 claims that have been made that we have seen over the  
20 years that have not been able to be validated when put  
21 into practice in a routine laboratory, and it is very,  
22 very important that the science that we use in our  
23 laboratories be as validated as possible.

24 We believe that laboratories and  
25 laboratorians in general have a fairly good

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1 relationship with clinicians and with patients, that  
2 most of our laboratory tests have proven over time to  
3 be accurate, and that most physicians especially place  
4 a great deal of weight on what we produce in the way  
5 of information.

6           However, it will take very little to  
7 compromise that relationship. It doesn't take much  
8 for a physician or for an entire community of  
9 consumers to suddenly decide that there's something  
10 terribly wrong because we are putting out information  
11 that we cannot clearly state or validate and then have  
12 to retract.

13           You see this in the drug industry all the  
14 time, and this is not the way we want to see the  
15 practice of laboratory services evolve.

16           The guidance document that has been issued  
17 is an interesting one. We applaud FDA for attempting  
18 to frame the issue surrounding these assay, and we  
19 appreciate this attempt to give some clue as to your  
20 thinking. We agree with the agency that these assays  
21 are devices that should be regulated and that they do  
22 not fall under the ASR rule.

23           We support the characteristics that you've  
24 enumerated to define IVDMIA's, but we need some  
25 clarification. We assumed when we read this, and it's

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1 interesting to me listening all day today how we could  
2 all have read the same document and come away with  
3 different ideas about what it said.

4 But we assume from the language that all  
5 three of those characteristics had to be in place  
6 before it was considered an IVDMIA. If that is not  
7 the case, if that is not the correct assumption, we  
8 have a problem because there are some very common  
9 algorithms and calculations that were developed in  
10 house over time by laboratories that would be in  
11 jeopardy.

12 So there needs to be clarification on this  
13 point, exactly what encompasses the definition, how  
14 much of those three characteristics need to be in  
15 place before it becomes an IVDMIA, and if there is any  
16 ambiguity, that needs to be clarified.

17 We recommend that the FDA include  
18 descriptions of the 510(k) and PMA processes in  
19 whatever guidance they issue and that the URLs for  
20 additional information be supplied. Now, this sounds  
21 like possibly a silly thing to ask, but for most  
22 laboratorians who are going to be involved in trying  
23 to meet this guidance, they have no background in  
24 either 510(k) submissions or PMA, and they don't  
25 understand at all what it is that the FDA is even

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1 asking for.

2 So as much information as possible that  
3 can be placed in one place where people can go and  
4 that information concisely stated and then referred on  
5 with URLs rather than trying to find things on the FDA  
6 site would be appreciated.

7 The other thing that we request is that  
8 FDA develop more examples and, frankly, over time a  
9 process that better defines what's Class 2 and Class  
10 3. This has been said multiple times in many  
11 different ways. It is a very important part of this  
12 process. It will make the difference between how  
13 people will approach their in-house lab test  
14 development.

15 The current document does not provide  
16 enough guidance for laboratorians, and after listening  
17 to the industry reps and their comments today, I've  
18 come to realize it give us enough information at all.

19 We are very supportive of FDA's intent to  
20 work with laboratorians, to be in compliance with the  
21 QSR and with CLEA. There are differences between the  
22 two. Those differences have to be worked out. They  
23 have to be enumerated.

24 We're asking that you not wait for  
25 laboratorians to identify the instances where they

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1 believe there is a particular requirement that may  
2 demonstrate compliance for QSR that's already being  
3 done under the CLEA's quality systems, but rather,  
4 give those examples to us within the framework of the  
5 document now because people will need, laboratorians  
6 are going to need some idea of what it is you're  
7 talking about. Again, this is a process that's very  
8 foreign to most laboratorians.

9 And then we would like to see a compendium  
10 developed over time. We commend the FDA's plan to  
11 provide laboratory professionals with further guidance  
12 about MDR provisions since many of our members and  
13 many laboratorians out in the field really, frankly,  
14 do not spend a great deal of time with the MDR. They  
15 rely on the manufacturers for that.

16 We believe that this guidance document  
17 provides an approach that will insure that our  
18 services are medically and scientifically sound. Now,  
19 we recognize that this is a very complex issue. This  
20 is not something that's going to get done tomorrow.  
21 We are looking forward to working with the FDA over  
22 time to review multiple iterations of this document  
23 before we have anything that we can call final.

24 There is certainly a need to continue to  
25 develop and expand the document, and we must at all

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1 times keep in mind that the complexity of testing that  
2 will be covered by this is testing that is so cutting  
3 edge that for many physician, clinicians and patients,  
4 it becomes and will continue to be confusing.

5 So the more guidance and more structure  
6 and more standardization that occurs will make it  
7 easier for all of us.

8 Thank you very much for your time.

9 DR. KESSLER: Thank you.

10 The next speaker is Colette Saccamanno,  
11 Dr. Saccamanno from Gene Express.

12 DR. SACCAMANNO: Good afternoon, and thank  
13 you for this opportunity. I'm actually here by proxy  
14 for my colleague Dr. Jim Willey, who is the inventor  
15 and co-founder of Gene Express, inventor of the  
16 technology that I'd like to discuss with you today,  
17 which is called StaRT-PCR.

18 The position of Gene Express as a company  
19 has been always to be aligned in philosophy with the  
20 goals of what the FDA is trying to do here today, and  
21 with the issuance of the pharmacogenomic data  
22 submissions guideline back in 2004 or 2005, rather,  
23 the company really started to try to define its  
24 technology around the guidelines that were spelled out  
25 back then as looking for an analytical system within

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1 which a biomarker would be considered valid under the  
2 conditions specified here.

3 Gene Express was actually founded back in  
4 1992 and spent the first decade of its existence  
5 coming up with validated assays for various genes and  
6 developing a technology platform that would be not  
7 only high throughput, but would remove much of the  
8 human intervention needed in the kind of precision  
9 that is needed in the pipetting steps and such in  
10 reverse transcription PCR processes, quantitative PCR  
11 processes.

12 So in keeping with the approach to try to  
13 find the least burdensome approach -- next slide,  
14 please -- the technology that we have developed is  
15 known as StaRT-PCR. Standardized reverse  
16 transcription polymerase chain reaction is simply a  
17 variation, a very what I call an elegant twist on the  
18 competitive template PCR by which each gene is  
19 measured relative to its respective internal standard  
20 within a mixture of internal standards.

21 And the elegance of this becomes clear  
22 shortly, but the features of the technology that  
23 actually allows me to say that we believe we have what  
24 could be characterized as a least burdensome approach  
25 is that the method itself inherently controls for the

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1 sources of variation that contribute to some of the  
2 difficulties that have been well acknowledged over the  
3 years with looking at various gene expression  
4 measurement technologies.

5 The internal standards and normalization  
6 to a reference gene of choice produces numerical data  
7 that is standardized and is quality controlled  
8 inherently. It allows the development of what we call  
9 interactive transcript abundance indices that have a  
10 beauty in and of themselves as providing a very simple  
11 and relatively easy and quick approach to defining a  
12 set of biomarkers, a small subset of biomarkers that  
13 can possibly diagnose a condition or monitor response  
14 to therapy, and so forth.

15 And we are very confident that the  
16 clinical chemistry aspects of what this StaRT-PCR  
17 brings to the table do meet the FDA requirements for  
18 genomic data submissions, as well as the requirements  
19 set out by CLEA for analytical performance  
20 characteristics.

21 This is a little busy. I'll just focus  
22 your attention right here. The standardized mixtures  
23 of internal standards that I referred to is literally  
24 a mixture of the standards that are pulled from the  
25 genes of interest, normalized against a reference

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1 gene, in this case beta Actin.

2 and you can see by the relationships here  
3 that Sample A and Sample B in the presence of the SMIS  
4 mixture can be related based virtually infinitely  
5 across the matrix not only to each other, but to any  
6 of the subsequent samples that are taken, and this is  
7 all documented in published literature, including the  
8 recently published results of the FDA's own microarray  
9 quality control Phase 1 project.

10 Down the right-hand side of the slide we  
11 can see some, again, of the characteristics that allow  
12 this to be characterized as a least burdensome  
13 approach. The intrinsic quality control in each of  
14 these measurements virtually eliminates any  
15 possibility of a false negative or false positive  
16 reading because you must see that internal control.  
17 Otherwise there's no result.

18 The lower limit of detection is  
19 established a priori in the development of the assay  
20 itself. The numerical data that is generated will  
21 allow the scientists interpreting this the knowledge  
22 that would basically rule out or at least understand  
23 the stoichastic sampling errors, especially on the low  
24 expression level end.

25 It also definitely simplifies the

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1 development of these diagnostic interactive  
2 transcriptive indices that I mentioned earlier.

3 The standardized data. Here's a power  
4 that is being brought to the industry that is  
5 unprecedented, and that is by virtue of, again, the  
6 SMIS reagents. Every laboratory that does an  
7 experiment with a particular gene will be able to  
8 measure that result against every other.

9 We just got word that Clinical Chemistry  
10 has accepted for publication some work that we did  
11 jointly with Pfizer that shows that we have used  
12 StaRT-PCR to generate normal human reference ranges  
13 for gene expression.

14 Next slide, please.

15 I mentioned the MAQC project. We did  
16 participate as one of the quantitative PCR platforms.  
17 Again, I guess one of the questions I had even in  
18 coming here today, seeing the news that came out  
19 yesterday, I like so many of people here am a little  
20 bit confused about the need, the recognition for  
21 standardization, for clear regulation, and yet I  
22 would like for the record to ask the question what  
23 criteria were invoked that enabled the clearance of  
24 the Mammiford (phonetic) test yesterday.

25 So I think everybody in the room deserves

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1 possibly in the closing remarks to hear a little bit  
2 directed toward that, especially in light of the fact  
3 that MAQC Phase 1 basically gave rise to the need for  
4 MAQC Phase 2, which is currently in the planning  
5 stages.

6 So the FDA recommended analytical  
7 performance characteristics that were defined by that  
8 work and even earlier by the guidance that came out  
9 did define for us what the performance characteristics  
10 are.

11 Next slide, please.

12 Those that are intrinsic to StaRT-PCR, and  
13 virtually all other quantitative PCR platforms are  
14 listed here, sensitivity, specificity, a linear  
15 dynamic range that covers the known range of human  
16 expression, and appropriate signal to analyte  
17 response, but those inherent to StaRT-PCR that are  
18 missing in other measuring platforms are the  
19 following: quality control, namely, internal  
20 standards in each measurement to control for false  
21 negatives and positives, and for interfering  
22 substance, and the ability to produce numerical  
23 quantification that gives rise to these indices that  
24 I've mentioned.

25 Here is a unique example of averting a

1 false negative reading. If we do not see the internal  
2 control peak, then we cannot call that a result at  
3 all. It's not measurable.

4 By noticing that what should have been a  
5 highly expressed gene not being expressed at all gave  
6 the laboratorian the ability to go back and say what  
7 was going on here, dilute the cDNA, the sample, and  
8 the SMIS tenfold, dilute out the inhibitor, and get a  
9 reading of 160,000 molecules of ERB-2 per million  
10 molecules of beta Actin.

11 That same sample first time through was  
12 able to pick up a very lowly expressed gene at 2,300  
13 molecules per million beta Actin because there was no  
14 gene specific inhibition in that particular sample.  
15 This is not possible with any of the other current  
16 technologies.

17 We recently licensed our technology to  
18 Gene Logic right here down the street and have started  
19 compiling some data that is beginning to show the  
20 ruggedness of the technology being able to compare lab  
21 to lab, gene to gene all of the transcription  
22 abundance measurements that were done. These are just  
23 representative, high, medium and low expressing genes,  
24 the average CVs that are coming out.

25 Admittedly a small sample size right now,

1 but over time this will grow.

2 The power to produce molecular diagnostic  
3 products. These all have been well characterized in  
4 the published literature. We do have a diagnostic of  
5 lung cancer that would improve the diagnostic accuracy  
6 from 80 percent to something in the order of 93 to 95  
7 percent. Again, money is the object. We don't have  
8 it to move forward with the clinical development of  
9 these tests right now.

10 We are working, looking at FFPE samples  
11 with Eli Lilly to protect pemetrexed resistance.  
12 That's soon to be advanced and published. We do have  
13 a test that can look for resistance to cisplatin,  
14 again, bladder cancer progression, all using our  
15 technology.

16 Next slide.

17 So in conclusion, the performance  
18 characteristics does affect the quality of the data  
19 obtained, properly controlled transcript abundance  
20 measurement methods such as StaRT-PCR is standardized,  
21 is sensitive and poor performance in any area of these  
22 things will be reflected in our results.

23 So I echo the comments of the previous  
24 speakers as well. There's enough brains in this room  
25 to get this right.

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1 Thank you.

2 DR. KESSLER: Thank you.

3 The next comments, we'll hear from  
4 Carolina Hinestroza from the National Breast Cancer  
5 Coalition.

6 And, Carolina, you can mention.

7 MS. HINESTROSA: Okay. Thank you very  
8 much for the opportunity to speak today, and I'm going  
9 to focus really on the issue of the importance to  
10 consumers of the evidence based use of biomarker  
11 assays.

12 The National Breast Cancer Coalition was  
13 founded in 1991, and we have the nation's largest  
14 grassroots advocacy organization dedicated to ending  
15 breast cancer.

16 NBCC recognizes the tremendous potential  
17 that biomarker research has to impact risk assessment  
18 for the prevention and early detection of breast  
19 cancer and for the clinical care of those diagnosed.  
20 However, despite enormous investment and decades of  
21 research, there have been few successes and many  
22 disappointments so far.

23 With this in mind, the National Breast  
24 Cancer Coalition convened its first strategic  
25 consensus conference shaping the future of biomarker

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1 research in breast cancer to insure clinical  
2 relevance. This is the report I was referring to.  
3 There are some copies outside, and a few others.

4 This meeting took place in November 2005  
5 with 50 world experts representing five key  
6 stakeholder groups, consumers, practicing clinicians,  
7 academic researchers, industry, and federal regulatory  
8 and research agencies in the U.S.

9 The group developed consensus on five  
10 general principles that serve as the framework for six  
11 priority areas and 18 recommendations. The five  
12 principles focus on the need for research on and the  
13 clinical use of biomarkers to be patient centered and  
14 aimed at substantially improving patient outcomes.

15 In other words, for biomarkers to be  
16 clinically useful, their use must reliably result in  
17 marked improvements in patient outcomes, chiefly  
18 survival, balance with quality of life, minimal  
19 toxicity and no over treatment.

20 Ultimately, a clinically useful biomarker  
21 will arguably identify those individuals likely to  
22 benefit from specific intervention and those who will  
23 probably not benefit from those interventions.

24 The other principles in the report call  
25 for biomarkers to be conducted in a socially