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ROUNDTABLE DISCUSSION: REGULATORY, SCIENTIFIC AND ETHICAL ISSUES RELATING TO GENETIC TESTING

ROUNDTABLE DISCUSSION

BEFORE THE

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ROUNDTABLE DISCUSSION: REGULATORY, SCIENTIFIC AND ETHICAL ISSUES RELATING TO GENETIC TESTING

THURSDAY, JUNE 12, 2008

U.S. SENATE
SPECIAL COMMITTEE ON AGING
Washington, DC.

The Roundtable was Commenced at 2:16 P.M., in room G-11, Dirksen Senate Office Building, Hon. Gordon H. Smith, Ranking Member, presiding.

Present: Senator Smith.

Also Present: Christina M. Hinkle, Chief Investigative Counsel.

OPENING STATEMENT OF SENATOR GORDON H. SMITH, RANKING MEMBER

Senator SMITH. Welcome, everyone. We appreciate so much your coming to this very important roundtable. We want it to be somewhat informal, but make it helpful for this very important topic. It's a topic that we had a hearing on in the Aging Committee 2 years ago. It is obviously the issue of genetic testing and direct-to-consumer sales and the impact that that may have on consumers as they may or may not be exploited or misled or defrauded.

My investigation in this area has revealed to me and to my staff questionable clinical practices of laboratories performing these tests, despite the fact that a number of these labs purportedly were CLIA-certified. While at that hearing we focused on a particular subset of DTC tests, the concerns raised at the hearing apply across the board to genetic testing and chiefly to these three areas:

No. 1, do consumers have adequate assurances of the safety and accuracy and usefulness of genetic testing, be it the DTC or physician-ordered tests?

No. 2, what protections exist for consumers' DNA, genetic test results, and other sensitive information provided in the course of genetic testing, particularly in the DTC arena?

No. 3, does CLIA provide adequate oversight standards for genetic testing laboratories?

I have invited you all here as panelists today because from what I have seen there remains much work for regulators and for the Congress to do to protect consumers to ensure the privacy and confidentiality of personal genetic information. CMS has abandoned plans for a CLIA genetic testing specialty. To my knowledge, the FTC has done little to pursue enforcement actions, despite clear evidence of fraud in the marketplace. Confusion abounds regarding

the roles of CMS and FDA in regulating certain aspects of genetic tests, especially DTC tests.

For 2 years I have been sounding the alarm, calling for more stringent oversight, a call that is echoed in the recent report from the Secretary's Advisory Committee on Genetics, Health, and Society. In the 2 years since this committee's 2006 hearing, genetic tests have continued to proliferate. According to genetest.org, there are now available genetic tests for over 1500 diseases. This proliferation continues to fuel concerns about the oversight of genetic testing and the protection of consumers' health data.

I'm hopeful that today's panelists will address these and other issues relating to genetic testing. Since we have a lot of ground to cover in a short period of time, you'll have to excuse me. I won't be here for the entire roundtable. My staff will take over. I'll be here for just as long as I possibly can, because this topic I think is very, very important and it's a subject that is growing.

Our panelists today include. Tom Hamilton and Judy Yost from the Centers for Medicare and Medicaid Services. Tom serves as Director of the Survey and Certification Group. Judy serves as Director for the Division of Laboratory Services and the CLIA program.

Steve Gutman and Catherine Cook are here from the Food and Drug Administration. Steve serves as Director of the Office of In Vitro Diagnostic Device Evaluation and Safety in the Center for Devices and Radiological Health. Kate is the Acting Senior Associate Center Director of the Center for Devices and Radiological Health.

Also we have Greg Feero, who serves as the Senior Advisor to the Director of Genomic Medicine at the National Human Genome Research Institute at NIH.

Kathy Hudson is the Director of there Genetics and Public Policy Center at Johns Hopkins University.

Elaine Lyon is here on behalf of the American Clinical Laboratory Association. She serves as an Associate Professor of Pathology at the University of Utah School of Medicine and is the Medical Director of Molecular Genetics for ARUP Laboratories.

Finally, we have Linda Avey, Co-founder of direct-to-consumer testing company 23andMe.

Thank you all for coming. I want you to be at home, relaxed. This is not an inquisition. This is a serious inquiry by the U.S. Senate to find out where we are and what this means, what this means to consumer protection, what this means to people's privacy, and what holes there are in our regulatory system, to make sure that we're doing right by the American people with this proliferating product.

So why don't we start. Any particular order here?

Why don't we start with—when we speak of regulatory gaps—and here we go to CMS—what seems to me is in some instances consumers are basically signing away their rights to their own DNA information, the test results and any scientific discoveries from research on their DNA. I understand that 23andMe require consumers to consent to the use of their DNA samples in unspecific research.

My question is what aspects of DTC testing are regulated, where are the holes, and what protections exist for consumers. I throw it open. Would you like to answer that one?

STATEMENT OF LINDA AVEY, CO-FOUNDER, 23andME

Ms. AVEY. The whole idea of research is something that we're very interested in at 23andMe. We actually just launched a new extension of our platform that we call 23andWe, because what we're hearing from our customers, who voluntarily sign up to be part of 23andMe, is that they're very interested in being active participants in research, which really doesn't happen right now. When someone is presented with the opportunity to be a subject in a research project, they're not necessarily given the option to have access to their own data that is generated.

23andWe is an extension of that idea of being part of a research project, again very voluntarily. When people sign up for 23andMe, yes, we say that we're going to do a limited amount of research with their genetic data. But until they give us additional information about their phenotype, we can't do a study with them anyway. So it's all voluntarily submitted.

From what we're hearing people are really eager to be part of research projects where they can actually have a voice. Just like we see with autism, there are still parents out there who believe that their child was affected potentially by their vaccines. Those are the kinds of things we want to open up and give parents and consumers and patients, cancer survivors, anyone who's interested, the opportunity of being a participant in research.

Senator SMITH. Do they know when they sign this over that it might go out more broadly as to them specifically?

Ms. AVEY. One of the promises we make to each and every customer is that we will never sell an individual's data. We will never do that or make it accessible. If they want to download their data and give it to a researcher, they can do that. That's within their rights to do that.

But our intention is to keep the information very secure and private within 23andMe, and then when outside researches approach us and propose queries of our database, our bioinformatics experts internally will do that query for them. But the data will never leave 23andMe, again unless a consumer says, "I want my data to go to my doctor or a researcher I know at UCLA who's doing a study and I want to be part of it."

So they own that decisionmaking process.

Senator SMITH. You feel like they have sufficient control over it, then?

Ms. AVEY. Absolutely. That's the whole design of the platform.

Senator SMITH. Any of our regulators have a different opinion on that? [No response.]

If you don't that's fine; that's good news.

At the 2006 hearing we heard testimony regarding companies providing DTC nutrigenetic tests that indicate various risk levels for developing cancer, Alzheimer's disease, kidney disease, macular degeneration, rheumatoid arthritis, high blood pressure, and heart disease. In one instance a company even claimed to repair DNA, a claim that the company is still making as of this morning, even

though we heard testimony that this claim is scientifically unfounded.

Tom and Steve, at the hearing you both expressed concerns about these health-related claims being made by these companies. Given that these companies, along with many new entrants into the market, are still in business and still making similar, if not identical, claims, you have to wonder how concerned the agencies are about consumer safety. Any response?

STATEMENT OF THOMAS HAMILTON, DIRECTOR, SURVEY AND CERTIFICATION GROUP, CENTERS FOR MEDICARE AND MEDICAID SERVICES

Mr. HAMILTON. I think when you look at direct-to-consumer testing it is extremely broad-ranging, and I count seven or eight dimensions. There's the advertising and-or education, there's the sales, the test ordering, the analytical validity—was the test accurately administered—clinical validity, and clinical utility, the interpretation of results, and then the communication of those results to consumers.

With regard to any test that involves the analysis of human specimens for health care purposes, those would fall under CLIA and would be examined with regard particularly to the analytical validity. Whether or not they've engaged in false advertising on the front end transcends CLIA and I think that one of the things that is quite obvious about this all very challenging but very exciting field of ever-growing genetic testing is that it's much larger than any of us. I think any one agency or entity that tries to address all the public policy issues here immediately confronts what our children may have learned as Miss Piggy's fifth law. Never try to eat something that you cannot lift. No one agency has the heft to bring into solution, a solution to all of these issues.

So that's why I think the right tune here is not a solo, but a choir, if you will. If we can get all of our agencies and public-private partnerships to be a tune in harmony, a choir in harmony, then I think that would be ideal, and I think that's why the groundbreaking hearing that you held, Senator Smith, was so important, and your continued leadership in this arena, because I think it takes someone such as yourself to bring everybody together to move this agenda forward.

Senator SMITH. Do you know, Tom, in the last 2 years has there been any greater coordination between CMS, FDA, the FTC? They're not at the table here, but we may have some FTC folks in the audience who can participate in the roundtable.

Mr. HAMILTON. I think there definitely has, and we've been holding regular conference calls with CDC and the Food and Drug Administration and have been particularly working with the Centers for Disease Control. We've added a staff person at CMS, acting on one of the GAO's recommendations, and she's sitting behind me and that's Penny Keller, specifically focusing on genetics, beefing up our capabilities to work in this area. She is working with the Centers for Disease Control on a best practices publication that will be coming out in their morbidity and mortality weekly report.

We are working together with the Centers for Disease Control to make a recommendation to the Clinical Improvement Advisory

Committee at their September meeting to form a work group on proficiency testing to bring advances and more proficiency tests, to make them more available and put them into greater use.

We are convening a work group, a convocation amongst the accrediting organizations in November to work on ways in which we can promote the availability and the use of proficiency tests.

Those are a few examples of things coming together. I think Federal agencies are all pretty attentive to this now.

Senator SMITH. The conference call you speak of, is that the inter-agency task force that we spoke of at the hearing, that there's going to be an inter-agency task force to tackle this?

Mr. HAMILTON. Well, there's multiple inter-agency groups working on this. The proficiency testing would be not only inter-agency amongst the Federal agencies, but involving the accrediting organizations, someone from New York State since they are pretty advanced in this arena, and public-private organizations that can all collaborate to figure out the best ways to move the agenda forward.

Senator SMITH. The best practices the thank you speak of and that we're striving for—this is a legitimate field of medicine. I'm not suggesting that. What I am suggesting, though, with the proliferation of this category of direct sales to consumer, I wonder if there are best practices out there that are actually being followed.

I wonder maybe, Steve, you've got a comment on that?

STATEMENT OF STEVEN I. GUTMAN, M.D., DIRECTOR, OFFICE OF IN VITRO DIAGNOSTIC DEVICE EVALUATION AND SAFETY, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH, FOOD AND DRUG ADMINISTRATION

Dr. GUTMAN. Well, I think there are. I think that there are best practices that are general, so I think a lot of what's in CLIA applies directly to the testing of genetics. But I think that the idea of the best practices is that there are enough nuances in this particular area that there needs to be perhaps some more specific guidelines or recommendations.

I can speak to the interaction, not on a formal basis, but on an informal basis, and I can assure you there probably isn't a week that goes by that there's not some kind of informal or semi-formal interaction between our group and the CLIA group, either asking them for help in our premarket compliance program or offering them help in their inspection or compliance program. So there's actually on an informal level, there is perhaps some outsiders might view it as a disturbing amount of communication and coordination.

Senator SMITH. Is there a disturbing amount, Linda? [Laughter.]

Ms. AVEY. We're not disturbed.

Senator SMITH. I'm curious, Linda. With your company, do you have a sense that the industry is developing with some best practices and standards that are designed to protect consumers from what they're doing?

Ms. AVEY. Yes, certainly we're very engaged with all the agencies, I would say, as much as we can be, and open about what we're doing and very open to the idea that we need new regulation. I think trying to fit this round peg, if you will, into the square hole of existing regulation is probably not a good fit.

But that said, we're very open, and we applauded the hearings you had 2 years ago because we recognize, and I think coming from the scientific community, we saw what some of these other companies were doing and were appalled by that. We feel, very similarly, that this does need to be regulated in a very strong way. It's just a matter of how can we do it and still allow the United States to be a leader in this field, because getting more genetic information and providing more people access to their genetics will move the field of personalized medicine forward, and if we block that we're going to be stymied and stuck with the existing health care system that we have.

Our overriding mission is to gather more data so that we can make these connections between people's genetics and their health outcomes and translate the great research that's going on into the clinic more readily. The SACGHS writeup really showed that there's a gaping hole in this translational aspect, that we don't really have a way to take the results that are now coming out in a flood from the research community of all these genetic associations and move them into clinical practice. How do we get those data into the clinics? If we don't have a way to demonstrate clinical utility and validity, we're never going to get there.

That comes from having many, many people involved. We think the consumer has to be engaged in the process or it's just never going to happen.

Senator SMITH. Is yours a public company? I'm curious.

Ms. AVEY. It's a private company now.

Senator SMITH. A private company.

Ms. AVEY. We're small. We're a startup.

Senator SMITH. If I were to own stock in your private company and I heard what you just said, that you were horrified about some of the new entrants into this field, how do you distinguish yourself from somebody selling snake oil versus somebody putting out a legitimate product?

Ms. AVEY. The bottom line, it comes down to what the genetic associations are really—what's out there, what do we know and what's real, and what is not real, what's been proven and what has not been proven.

The research labs and our science team are working very closely together to say, look, this is all new, we don't really know what this means yet. We need to start asking our customers. It looks like you're at higher risk for type 2 diabetes based on your genes. Do you have type 2 diabetes or not? So that's where we're going to start putting out surveys to our customers to say, let's start connecting the dots here.

So we just see some of those other companies as putting their claims out way ahead of the science, where we don't know yet, we have no idea what foods you should eat based on your genes. We just don't know that yet. Some day maybe we will, but until we get there we're going to be very true to the science and very responsible about that.

Senator SMITH. So you would be welcoming the agencies' efforts to try and formalize some of this so you can distinguish your company from some of the others that may just be selling a lot of prod-

ucts to the injury of their customers or of creating false hopes in their work product?

Ms. AVEY. Any claims about these data we think are really pretty premature. That's why we put that out there that this is research data. We do feel like it's best to engage with consumers through their own genetics because they get so much more interested and they really want to be educated when you're talking about their own DNA, what they're born with, what they're going to die with, what does that mean for them.

But we put it out there that we just really don't know a lot yet. We keep saying, we need to do more research, we need to get more people involved.

Senator SMITH. Kathy, I see you anxious to say something.

STATEMENT OF KATHY HUDSON, PH.D., DIRECTOR, GENETICS AND PUBLIC POLICY CENTER, JOHNS HOPKINS UNIVERSITY

Dr. HUDSON. Senator, you asked a very straightforward question at the beginning, which is, are consumers protected, are genetic tests safe? You asked that same question 2 years ago when you had your hearing and had the GAO investigation. I would argue that there have been no improvements in the oversight of laboratory quality, in the oversight of genetic tests themselves, and in the oversight of the claims made about those tests in the intervening 2 years.

There are conversations and working groups and meetings and conference calls, but we actually have not seen any actions. Despite your call for actions and continued attentiveness, which we appreciate, and the recommendations of now four expert secretarial-level advisory committees that there be changes in CMS, changes in FDA, changes in FTC, we actually haven't seen so much as a notice of proposed rulemaking.

So it's great that the agencies are working together, and talking is really great, but action is even better.

Senator SMITH. Any proposed rulemaking coming out of the advisory group?

Ms. YOST. Definitely, yes.

Senator SMITH. Go ahead, Judy.

STATEMENT OF JUDY YOST, DIRECTOR, DIVISION OF LABORATORY SERVICES AND CLIA PROGRAM, CENTERS FOR MEDICARE AND MEDICAID SERVICES

Ms. YOST. On proficiency testing requirements, but we've got to gather data, we've got to work with the experts in the field, we've got to determine a negative, and to identify which tests should have proficiency testing using scientific and technical expertise. So it's going to take a little time, but the plan is definitely to propose new proficiency testing requirements, not only which tests are covered, but how they're graded, how they're monitored, how the PT providers are approved, and so forth.

So the entire scope of proficiency testing is being reopened and reevaluated through our advisory committee process.

Senator SMITH. Can you give us a sense of a time line? How much time do we need to gather all this information, all the data

that will make the difference to allow some rulemaking to go forward?

Ms. YOST. Well, we've initiated a process starting in March and we have a plan to meet with the proficiency testing providers by November of this year. We've already gathered some preliminary data on the most frequently performed tests. We're going to also look at tests that are clinically relevant and where proficiency testing materials might be available. We have a meeting scheduled with our accrediting organizations and with our advisory committee in September to develop a recommendation and to convene a committee to begin the deliberations on that process.

So it will take some time on the front end, but the idea is that hopefully we will have a quality product then to be able to move forward with.

Senator SMITH. Kathy, do you have a comment, or Steve?

Dr. GUTMAN. Yes. You asked me the question about whether we thought we had authority over these tests at the hearing. Actually, there had been some ambiguity, so that was a well placed, well chosen question. I answered that we did.

We haven't made a lot of progress. I won't pretend that we have. We have, however—we haven't initiated rulemaking. We have initiated guidance to—again, we're a risk-based organization, so we start with things that are the most worrisome to us. We've chosen a particular product line called in vitro diagnostic multi-variate index assays. That's a mouthful, but what that is is——

Senator SMITH. Don't ask me to repeat it.

Dr. GUTMAN. What it is, you take a bunch of signals, you put them in a non-transparent black box or black blender, you grind them together and you come up with a magical score that's somewhat not intuitive to the health care user. We thought that would be an interesting place to start in terms of changing that pattern in which we have applied enforcement discretion to these tests and deferred entirely to CLIA, to perhaps becoming partners in more active regulation.

Senator SMITH. So would it help you to have Congress give you more statutory direction in this?

Dr. GUTMAN. Yes.

Senator SMITH. It would, OK.

Yes, Elaine?

STATEMENT OF ELAINE LYON, PH.D., ASSOCIATE PROFESSOR [CLINICAL] OF PATHOLOGY, UNIVERSITY OF UTAH SCHOOL OF MEDICINE, AND MEDICAL DIRECTOR, MOLECULAR GENETICS, ARUP LABORATORIES

Dr. LYON. The issues we're discussing here will be directing us in the laboratory community. We definitely have a stake in this. I want to discuss CMS's comments on what is being done. I disagree with Kathy's remark that nothing is being done because there is significant activity.

We've been working with the CDC on a reporting initiative, how to communicate genetic information back to physicians. We've worked with the CDC in terms of getting reference materials for the validation of tests and for the proficiency testing. The CDC is

also going forward with a study looking at the clinical utility of these tests.

So I believe in the genetics community and the laboratory community that there has been a lot of work moving forward to address some of the issues, to make testing better and safer for the public.

Senator SMITH. I'd love to get the FTC up here too, if there's anybody from the FTC here.

Mr. DAYNARD. Do you mind if I stay here?

Senator SMITH. That's fine.

One of the questions, along with the clinical practices and best practices, one of the other issues I'm concerned about is obviously privacy. Linda's company says they only use it in a very limited way, with their permission. But what happens if somebody is selling the genetic information to somebody?

STATEMENT OF MATTHEW DAYNARD, SENIOR ATTORNEY, DIVISION OF ADVERTISING PRACTICES, BUREAU OF CONSUMER PROTECTION, FEDERAL TRADE COMMISSION

Mr. DAYNARD. Well, two points. I was going to answer the first question about our coordination with other agencies and what the FTC is doing. But we're also very involved in privacy and security issues. That would be a serious problem. If there is a privacy policy that says, for example, "under no circumstances do we sell or rent or give away your protected health information," and if in fact they did or in fact they didn't have well-established security measures the FTC might take a very close look at it.

On the claims issue——

Senator SMITH. You can see the damage that would be done to an individual if their genetic information was sold and it's out there in the insurance market——

Mr. DAYNARD. Certainly.

Senator SMITH [continuing]. They have some test, whether valid or not, that somehow says they have a predisposition to cancer.

Mr. DAYNARD. Yes, absolutely. At the moment we don't have evidence of that happening, but it may be happening.

But what I'm looking at, and what we looked at very shortly after your hearing 2 years ago, was the claims issue. What we did quickly, in conjunction with the Food and Drug Administration and Steven Gutman's staff and the staff at the CDC, was to issue a consumer alert warning them about issues that they should be aware of when they consider direct-to-consumer advertising.

That we could do quickly. A law enforcement investigation can't be done quite as quickly. But I can confirm that we have a couple of investigations in this area looking at the subject.

Senator SMITH. So you've got all that you need?

Mr. DAYNARD. Yes. I mean, the statute which declares that unfair and deceptive practices in or affecting commerce are illegal is pretty broad. We have done wonderful things with it, and I think we have jurisdiction in this area as well.

Senator SMITH. You're on the case.

Mr. DAYNARD. Yes.

Ms. YOST. I'd also like to mention, because the impetus for your hearing last time was the four DTC laboratories that had been

identified by GAO. Since that time I'd like to mention that we have collected a series of at least eight or nine of them, so we have been very closely monitoring them, and in addition, as the ACLS statement indicates that those that we identified aren't doing testing that falls under CLIA. Some are just marketing. All of them have very different various functions and they're all organized very differently. Sometimes they're interrelated.

But that said, those that are actually performing testing that fall under CLIA have been required to obtain a CLIA certificate and obviously assessed as to their compliance status. So we have made a tremendous amount of progress, I would think, since then, and we continue to do so. Now that we have expertise and we are working much more closely with FDA, we have the ability to look at the types of tests that they are performing and verify their validity.

Senator SMITH. The four labs we identified at the time, you're on top of that?

Ms. YOST. Yes.

Ms. AVEY. I'd like to add to that, Senator Smith. This is something that we interacted with CMS on as well. When we first started, it was unclear whether or not CLIA was the right oversight for what we were doing, because we don't really claim ourselves to be a specific clinical test. We look at 600,000 data points in your genome and then tell you what we know based on the research. So it's not a test per se, but nevertheless we were notified by CMS.

We were working with a very high quality laboratory, but it was not CLIA-certified. But after the interaction with CMS, we did switch to a CLIA-certified laboratory. Then we did tests back to see how well the data correlated. We ran the same people in the previous lab and then in the CLIA lab and got over 99.9 percent concordance between the two labs. So we felt very good about our previous lab, but now we're working under CLIA oversight, which we do think is the right thing.

Senator SMITH. I've got a question for you, Greg. But before I get to it, Kathy and Elaine, you disagree on a point, whether anything is being done or not. I wonder if we can explore that just a little more.

Dr. HUDSON. I applaud the efforts that CMS has undertaken to identify what laboratories are offering these tests and to bring them into CLIA compliance. The problem is that CLIA, as it stands today, just isn't enough.

It's great that they're moving now toward proficiency testing requirements. The Secretary's advisory committee made a very straightforward recommendation, which was that if a proficiency testing program exists, and you perform that test, you must participate in that program. Proficiency testing is like a pop quiz for a laboratory. You get a sample, you have to do the test for the disease, cystic fibrosis, sickle cell anemia, send the result back, and if you get it right you pass, and if you don't get it right, authorities are alerted that you're sub-optimal.

That's important. Getting the right answer is important, and knowing the meaning of that test result is important as well.

I'm encouraged that CMS is moving in the right direction, but again, it's been 10 years since the first recommendation for proficiency testing requirements.

In terms of the claims that are made about tests, I agree with Linda that the platform that she is you're using is incredibly, incredibly reliable. But the information that's made available about the tests is more uncertain. Let me give you an example.

Robert Green, who's a neurologist at Boston University, spoke at an event earlier this week. He has had his genome done, and he showed the results. He had his genome done—sort of like you get your hair done and your nails done, you get your genome done—at both 23andMe and a sister company, Navigenics. For his variations for heart disease one company said, "You have a heightened, greater than population risk for heart disease." The other company said, "You have less-than-population risk." So they gave absolutely contradictory information. It turns out that he had an incredible risk for heart disease because in fact he had a major cardiovascular event and a triple bypass.

So if two companies testing the same variation's give you two different answers, we've got a problem on our hands.

The head of the genome office at CDC, Muin Khoury, recently published a paper in which he said there's insufficient scientific evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases.

Senator SMITH. This is the point of the hearing to begin with. The information that can come out of this is so explosive and can be interpreted so differently. My concern with direct-to-consumer sales, not that they can't be made appropriate, but that they can be used in a very destructive way, and people will go get the wrong treatment when they ought to be getting the opposite treatment, and their information can be disseminated in the insurance market in a way that would make them uninsurable.

That's why this is an exciting new field in medicine and we need to pursue it, but we've got to have—time is of the essence to put up the kinds of standards and best practices and regulatory barriers so that we're not leaving the consumer behind in this.

Dr. LYON. There is room for improvement and I won't deny that. I think that what we do as a CLIA-certified laboratory, we can really make improvements under CLIA and under CMS, and I don't believe that there really needs to be additional regulation. However, there can be additional improvements.

It is true that for these genome-wide associations, the science is just coming out with them and it may be not be strong enough right now for me to be able to interpret what the tests mean. That doesn't mean we shouldn't go forward with the science to get that understanding.

On the other hand, a lot of new genetic testing is being thrown in with the mix which is really standard medical care. That needs to be differentiated. We design, perform and validate laboratory-developed tests. I brought some of our validations and can show you what we do as laboratories to validate these tests.

As new issues come into play, which is really where we are—we're on the verge of going from single gene disorders—such as we know the gene that causes cystic fibrosis; I know to look for mutations in this gene and for the most part I know how to interpret it—to looking for all of the genes that may cause some type

of lung disease. We need to go forward with that. There are definitely reasons to do so.

But that shouldn't be confused with what we are doing right now in the practice of genetic testing.

Senator SMITH. Greg.

STATEMENT OF W. GREGORY FEERO, M.D., PH.D., SENIOR ADVISOR TO THE DIRECTOR OF GENOMIC MEDICINE, NATIONAL HUMAN GENOME RESEARCH INSTITUTE, NATIONAL INSTITUTES OF MEDICINE

Dr. FEERO. I'd just like to first make the comment, I think we all are sort of in a privileged position right now to be dealing with a wealth of information that we don't exactly know what to do with. I'd say that what we have right now is a lot of data and somewhat less wisdom as to what we should actually do with that information.

I think there are a couple of things that really need to be thought about. One is the science is evolving very, very rapidly, and I think the systems we have for dealing with that rapid evolution don't—can't really keep pace with that evolutionary process. Over the last few years, we've seen discoveries for literally hundreds of new genetic associations in I believe 40 common disorders. That pace is accelerating.

It's, I think, a natural outgrowth that various elements in industry would see potential advantage in working with that wealth of information. In many ways, some of those companies, the responsible ones, may be on the vanguard of figuring out how to exactly deal with that information at the end.

There's a really broad spectrum, of groups offering testing some that are clearly doing things that are very egregious. However, are folks on the other end of the spectrum that are doing diagnostic testing that's well established.

Then there's this great grey zone in the middle that we don't really have a good handle on how to deal with at this point in time. Simple questions like what defines a medical test are very difficult to answer when you start talking about these things. Do you draw the boundary at Ann's asking questions about Ann's ancestry? Do you draw the boundary when you start to talk about things like eye color or your muscle fiber types? Do you draw it at the boundary of predictive, potentially predictive genetic testing for late onset disorders? Clearly I think most people would agree that that's where you start to think that, yes indeed, you're on the medical end of the spectrum, But answering where that starts is I think a real challenge.

We really need ways to be as nimble as possible as this area rolls out to deal with these topics. Which is a great challenge. The larger issue of measuring the utility of these types of tests is going to be critical as we move down the line, because we'll have the opportunity to do many things in our health care system and it'll be less clear as to the added value of each of those items.

Right now I think we're just sorting out what the pipeline looks like for this area as it moves forward for determining that utility.

Senator SMITH. Greg, in February of this year there's a company that started issuing, selling a genetic test to determine bipolar dis-

ease. Mental health is an issue that matters a lot to me and I'm trying to push it forward as a coequal part of health care. I understand you're aware of this, that you've lent tacit approval to the company's test. That's what I've been told.

Dr. FEERO. I would disagree. When that article came out, I have to say I was chagrined. I was even more chagrined when it came to me last night that that might potentially be on the discussion today.

Senator SMITH. Can you genetically test for bipolar disorder?

Dr. FEERO. Bipolar is a clinical diagnosis at this point in time.

Senator SMITH. Not a genetically determined——

Dr. FEERO. Not a genetic—well now, it has a genetic component to its causality certainly.

Senator SMITH. OK.

Dr. FEERO. But it is not diagnosed using genetic testing—I was trying to make a fine point with the reporter in that case, that using a test in a totally predictive manner in an asymptomatic person is different than using a test in an individual who already has symptoms that make them more likely to have the disorder you're talking about. So sort of the analogy might be to use a white blood cell count. In somebody who's perfectly healthy interpret what an elevated white blood cell count means, is very different than in the use of somebody who has a fever and a cough which is productive of sputum. It means a very different thing when you see a high white cell count in that person.

I think they didn't quite get the distinction I was trying to make.

Senator SMITH. Does it concern anybody that there's a company out there selling genetic tests to determine bipolar disorder? Should that be done with a doctor or through the mail?

Dr. FEERO. I would say that if you look at their site they've qualified it. But the question is do people understand the qualifications that they've put into it. That's really the big question when I look at this type of thing, is will the consumer and the health care provider, frankly, be able to understand this area sufficiently to make a determination as to the value of the proposed application.

Senator SMITH. Yes?

Dr. LYON. When I heard this from Chris, I went to the Internet site to see if I could find out what was going on and what it was. In doing that, I needed to go back to the scientific literature and read to see what the science really was.

There is a modest association, according to the published abstract. That does not mean that it's ready for prime time.

The unfortunate fact is that when I went to that web site I couldn't get to the details of their test in order to make a judgment on whether it was actually good or not.

Senator SMITH. Yes, Kathy?

Dr. HUDSON. That actually raises a really important point about the transparency of information. So even if there's not a heavy hand of regulation for these tests, we need to make sure that consumers and physicians and others have access to information about the scientific evidence on which you are basing your claims, so that we can all tell the truth to one another, at least know what the truth is.

Right now you can't. It's very difficult in many cases to know what's the scientific evidence underlying the claims that a company is making in selling a particular test.

Ms. AVEY. I want to go back to what Kathy said earlier about the seeming discontinuity between the heart disease predictive markers between the two companies, Navigenics and 23andMe. That is something that we are going to address. The good thing is both companies are very transparent about how we do these risk calculations. You can do these in very different ways. There are a lot of assumptions that we have to base it on, whether it's average risk in a population, whether it's lifetime risk.

Again, we're very clear about that, but that might be partly why Bob Green ended up with two different end points through these different services.

So we're meeting with Navigenics on the 17th of July to start working together to develop our own internal standard so that we're not confusing people, and that we're at least using some of the same criteria for how we come up with these risk assessments, if you can even call them that, because it's based on research data.

Senator SMITH. I have to—that buzzer you heard means I've got to go vote. Unfortunately, the leadership doesn't check with me on my schedule when they schedule a vote. But that's life in the Senate.

I'm not doing anything today more important than this. This is really exciting stuff. It's a whole new era that we're in. But it can be dangerous. That's why I've asked you to come together and to keep the focus on this, because we're focused on it. If we need more legislation, if you need more authority to get this right, we'll help you with that, because again it's exciting, it can be troublesome too. We've got to get this right. The sooner we do it, the better off the American people will be and the better off health care will be.

So with that, if you'll excuse me, and with my apology for having to go answer this vote, I'll turn it over to my staff. I thank you all for being here. You've added measurably to moving this forward in a constructive way and to the record of the U.S. Senate. So I thank you all for your time.

Ms. HINKLE. Well, so we jumped right into the questioning and I'm wondering if now, an hour into it, we might be well served by backing out a bit and covering maybe some of the broader aspects of genetic testing, and then we'll dive into a few technical and nitty-gritty bits.

For the audience, there will be an opportunity for you to engage in some Q and A during the last 15 minutes or so of the roundtable. We've passed out some cards on your chairs. You can hand those to our staffer in the back there who's waving her hand if you have questions. Or you can just feel free to come up to the middle here, where there was supposed to be a microphone, but isn't unfortunately, and ask the question yourself, whatever you prefer.

Let's back out. Let's take an overview of genetic testing. Anyone who wants to jump in and set the stage, just very succinctly tell us, where have we been with genetic testing, what advances have we seen over the past couple of years? Who's really using genetic tests and in what capacity?

We know that patients, doctors, researchers, even law enforcement are using genetic testing. So maybe someone could just give us a quick overview? Anybody? Greg?

Dr. FEERO. A quick overview of what defines a genetic test. I think there have been probably week-long arguments over what exactly defines a genetic test. Is a genetic test simply a molecular diagnostic assay that you might use to determine whether or not there is hepatitis virus present in someone's serum? Or is it only testing for rare genetic disorders in the context of someone's germ line?

There aren't clearcut answers for that. I would say that in the main, the vast majority of genetic testing with a fairly strict definition of what you mean occurs in the realm of relatively uncommon to rare diseases. For this type of testing there is much less question, I think in general, about the sort of systems that are in place to deal with the topic.

What we've seen in the last few years is a profusion of sort of this new type of testing, which looks at variants across the genome that are merely associated with the disease, rather than necessarily causal, and then an attempt to use those variants in sort of a predictive prospective manner to inform people about various things, ranging from, as I mentioned, eye color and ancestry to whether or not they're going to develop Alzheimer's disease or cardiovascular disorders.

I think the profusion of this sort of predictive testing with associations is really one that has brought this question to the fore. We've been waiting a very long time, I think, in the scientific and medical community to finally crack into the understanding of common chronic diseases that have a component of both genetics and environment contributing to their causality. We finally made that crack and—the rush is to try to use that information in a way that's beneficial.

Ms. HINKLE. I know that clearly one of the frequently cited concerns about genetic testing in the DTC arena is the absence of a qualified medical provider to help patients interpret the results. The American Medical Association is going to be voting on a resolution at its meeting again I guess restating and further enhancing, further expounding upon its opposition to DTC testing.

I guess my question to you particularly as the provider at the table is, who is qualified to interpret these tests? What is a qualified medical professional?

Dr. FEERO. I think that that is a question which is very dependent on the context and the type of test that you're talking about. There clearly, even now with the more rare conditions, is a spectrum of who's qualified to interpret what type of test.

So for example, a general internist might be quite capable of interpreting a test for clotting abnormality in the form of Factor V Leiden. It's a relatively straightforward test. Internists and family physicians order these quite frequently. However, I would say that the average internist at this point in time is probably not adequately trained to fully interpret a complex result from a BRCA–1 or BRCA–2 testing. In that case, it would be best handled by someone who has formal genetics training in the form of a medical geneticist or a genetic counselor or a nurse geneticist.

Ms. HINKLE. Do most patients have access to that level of care?

Dr. FEERO. There is a great disparity, I think, right now in the current genetics community between the sort of profusion of new types of tests that will need to be dealt with and the actual amount of manpower that's present to deal with the information as it comes out. Hopefully I'm not misquoting this, but this year in the match in the United States, which is the process by which medical students select their residency, the statistics for those people matching in medical genetics, suggested that there was one U.S. medical graduate that matched for medical genetics.

Ms. HINKLE. One?

Dr. FEERO. Yes. So there's clearly a big manpower issue.

For example, I was in a talk earlier today where a family physician was presenting some data from a survey that they did that showed that 11 percent of family physicians that they surveyed reported that their patients had to drive over 2 hours to get to the nearest medical genetics professional. So there's a great disparity.

Dr. LYON. We have realized that what used to be ordered by geneticists is now being ordered by other physicians, and because of that it's very important to communicate well what the results mean. So a laboratory's role is not just to give a result, but we do need to give an interpretation of what that result means.

One of the programs that I've worked with at the CDC is their reporting initiative to get the information so it is understood by a general practitioner or a family practice physician.

Ms. HINKLE. So let's say I go on line, as I have here to 23andMe, and this is just their demo site here, so this isn't any real health results. But I get a whole profile like this. Let's pick something at random. I ordered it here on the web page by what 23andMe has listed as the most established research for. How about restless leg syndrome. So I'm going to learn some genetic information.

As I'm logging in, tell me. So I go on line, I get these test results. To whom do I take them if I want assistance in understanding what these results mean?

Ms. AVEY. We actually have some information now back from our customer base, because we launched in November and we have thousands of people who have signed up and who are now using our service. We take all of their questions. Most of the questions are about ancestry, or "I forgot how to log in," or "I don't know how to get to my data." It's been more about the use of the web site.

We have to get better and better at how we direct people on how they go through the service so they get the information they're looking for. We have found that people are not really asking questions like "What do I do with these data, who do I go to talk to? But we're following this closely.

In the mean time, we're aligned with other companies in this space, and we agree that this information is going to start getting into the hands of a lot of people, and the medical community, especially the medical genetics community, will not be prepared to really catch this on the other side if a lot of people are having questions.

So we're having webcasts with the Genetic Counseling Society. We're reaching out to physicians. We're working with NCHPEC, we're talking to Muin Khoury at CDC. We think we have to do this

in a very broad way and a very scalable way, because if we just have a few people who are educated about this information it won't be a system capable of handling the load of people who might start having questions.

We try to pack a lot of information about the fact that most of the diseases you see are not just genetically determined; there's a big environmental component. So for type 2 diabetes we put that out there. It's only about a 25 percent genetic disease. Your environment plays a much bigger role.

So once people read through that information, a lot of times they say, OK, it is what it is, but they may not have increased risk for a lot of the diseases, because I think a lot of our customers are, luckily, very healthy. Then they go and they look at their ancestry information and that's where they start having the questions, because it's something that they've never seen before and it's not something they've really thought about before.

Ms. HINKLE. Linda, earlier in speaking with Senator Smith and actually in our earlier conversation as well, you certainly distinguished what you offer from the nutrigenetic tests that were the focus of the hearing 2 years ago. While I think certainly maybe the type of testing or the labeling of the testing is the same, I also find many things in common with the results that you offer. That is, though, much like on those web sites, you disclaim making any sort of diagnostic services and that this is strictly for educational purposes, as a consumer when I read something that is telling me what type of odds I have of getting a condition, and as we see up here, an odds calculator, when that's telling me increased risk, decreased risk, that to me sounds like a health diagnosis.

This was exactly the same question that we posed to the FDA and CMS with respect to the nutrigenetic testing and whether or not these really were the type of health care claims that would fall within the ambit of your jurisdiction. So are these types of results to you really different than the nutrigenetic tests? Is there really a distinction there? I guess where do we draw the line in genetic testing, where one type of genetic test falls under a different type of regulation, or the laboratory would?

Dr. GUTMAN. Well, actually I would probably—I do think Greg is right, it's nuanced when you start moving toward whether you like particular apples or vegetables or where your grandfather might be from. I don't think it's so nuanced when you say, well, whether it's a definite possibility, a reasonable possibility, a possible possibility. Are you starting to associate—from FDA's—I'm not a lawyer, but from FDA's perspective, it seems to me the definition is pretty clear. We have a very broad interpretation of "diagnostic." So that's clearly a health claim. You can put for informational purposes, you can put not for real use, this is pretend. You can't duck it. It's the old thing, if you quack and you have a beak and you waddle, you're probably a duck; you're probably not a horse.

Ms. HINKLE. So these look like diagnostic claims?

Dr. GUTMAN. Yes. But it begs the issue. I think it's an incredibly complex issue. I think the fact that we at FDA haven't moved faster or that others haven't moved faster or, you know, we've only got the SACGHS report for 8 weeks. To reinforce, as Kathy pointed

out, it's not exactly a fundamentally new construct that suddenly popped up.

Actually, what was striking about the SACGHS report from my perspective is, one, it did reinforce what had been said before at least a couple of times. Then it opened this incredible door that somebody finally figured out that the utility was actually important. I feel sorry for whoever gets stuck with that.

From the agency's standpoint, while we're from the government and we're here to help, it is a big task, so we would be careful about what we wish for. I remember saying that at SACGHS as they struggled over whether to put FDA in or not, is that we're not terribly worried about job security right now, we're not sitting around. But we do think—I do think; I shouldn't represent the agency in this comment—that there is some value to independent review, whether FDA does it, whether CMS does it, whether it turns over and 23andMe becomes an accrediting agency for ACLA. There is some value to independent, financially independent, intellectually independent, absolutely agnostic in terms of technology and claims—there is some value that somebody might want to step in here and look at independent review.

I think that's hidden in the 200 pages of the SACGHS report—not that well hidden, it's actually kind of obvious. So I personally think that's a good idea. I don't know who should do it, but that's a good idea.

I think on the issue of confusion—I thought the point was made—certainly I do think the average doctor is having trouble figuring out what a pro-time means, much less what a new genomic marker for brain cancer or Alzheimer's disease or bipolar disease, which I think is absolutely a medical claim that's very confusing. I can't imagine a direct-to-consumer patient actually sorting through that and starting to self-diagnose bipolar disease. That's just absolutely frightening.

I think doctors have problems, maybe even the genetic counselors. When you take the brand-new cutting edge molecular signatures that have no literature, are brand-new, or literature from a single source, they're going to have trouble. I think that speaks to Kathy's request for transparency and that the leitmotif both among people who swear at FDA, or swear by FDA, is that nobody seems to speak against the idea of more disclosure, of having transparency, of having registries. Nobody says who'll fund it, whether it will be mandatory or voluntary, who will administer it, how do you assure financial and intellectual independence, how do you communicate the results.

So there are some niceties that haven't been addressed, but nobody seems to speak against that. The more you can get information out there, then the more likelihood that, whether they be a Ph.D. from Harvard in genetics or my mother-in-law, that they might have some chance at least of reading and getting a straight answer on whether there were three samples or 3,000 in the credentialing of the test, whether the test was established using well-established goals, standards, and brilliant literature that map a course or using an article in the "Gutman Journal of Unusual Results."

So I think that——

Ms. HINKLE. We'll get a subscription to that.

Dr. GUTMAN [continuing]. It's a timely topic to bring up and we from the FDA, from the government, we are interested in understanding how we can help and not hurt.

Ms. HINKLE. We've talked a lot about the genetic tests that we sort of have a sense are not appropriate for direct-to-consumer use—I guess I would ask you what genetic tests are appropriate for direct-to-consumer use right now? Or are there any?

Dr. HUDSON. Can I respond?

Ms. HINKLE. Oh, absolutely, Kathy.

Dr. HUDSON. I think ultimately there's going to be a large number of tests that will be appropriate for consumers to access, and there may be some now. If there was a test that could tell me which over-the-counter medicine would work best for me, why do I need to have a doctor order a test to tell which over-the-counter drug to use?

Ms. HINKLE. We'll come back to pharmacogenetics and pharmacogenomics in a bit.

Dr. HUDSON. So I think that the tests that we need to worry most about in terms of direct-to-consumer access are those tests that are high risk. We can talk about what risk really means. I think high risk means when you're going to make an important health-related decision based on the result of that test.

So if you're going to go to the gym a few more times, who cares? If you're going to start buying more Q-tips because you have sticky earwax and not dry earwax, who cares? But if you're going to make important health-related decisions based on that test, then I think that sort of moves it over to a more important category. It would be impossible, and will become even more impossible, for Judy and Tom and Steve and Kate to oversee all tests. There were 40 associations last year, or we're up to 40 validated? So this is going to become a tsunami that's going to drown these guys. So they have to be able to be selective about what's important. I think what's important is what's important to the consumer and the consumer's health.

Ms. HINKLE. Yes?

Dr. FEERO. A quick point. I'm a little reluctant, I think, to paint the types of associations you see up there in the same category as things that went on in the past with nutrigenomics, because to some extent the fundamental scientific underpinning of the actual association is actually very sound now. The science——

Ms. Hinkle. In just 2 years it's evolved?

Dr. FEERO. It's evolved considerably. So these associations are quite robust. The difficulty is that they provide relatively meager predictive capabilities. So any one marker, for example, associated with, say, type 2 diabetes, may elevate your risk only by 1.2 or 1.4-fold.

Ms. Hinkle. Don't you think that's why most people are getting these tests, though, because they want to know, am I going to get cancer, am I going to get Alzheimer's?

Dr. FEERO. The difficulty is in how do we interpret and utilize those very small risk increases. There may come a time ultimately where we have, say, 40 markers identified, we know how to assemble them into a panel, we know how to compare that to the envi-

ronment the individual's in, and we can give them an accurate risk prediction based on that.

But we're very early on in sorting out what to do with those bits of information. But that doesn't mean that ultimately there may not be utility in this. We're just so early on.

Ms. AVEY. Again going back to my earlier comment, what we see lacking right now is the ability to translate this tsunami into something clinically relevant and clinically useful. That's really the role we see ourselves playing. If you go back to the list of all 70 different traits that we're showing, we have now the little icon for surveys that we have along these disease lines. So what we're going to start doing is asking our customers to give us information back, answering questions such as "Do you have type 2 diabetes?"

My brother-in-law has type 2 diabetes, but he wouldn't know it from his risk profile through his genes. It likely means his environment has had the most impact on his getting the disease. So he looks at this and he feels empowered to say, no, these genes, even though I have the disease, don't look like they light up in me. So that means either we don't know enough about the genetics of this or I've got the environmental gun loaded and pointed at me and I have to do as much as I can to change my environment. It's not a genetic thing for me personally.

So it's about gathering up all this other information and empowering our customers to tell us and have them be active participants in the continuation of these studies, rather than having it go on in the research community and the Science and the Nature papers come out and the scientific community reads all of that, the New York Times picks it up, maybe sometimes the Wall Street Journal writes about these studies, and people think, "Well, what does this mean for me? I want to know what this means for me personally?" That's the sentiment that we're hoping will help drive additional studies and get more people involved directly.

Ms. HINKLE. It's interesting you picked type 2 diabetes. If I recall correctly, maybe just a week or so prior to the 2006 hearing NIH had issued a press release regarding genetic testing and type 2 diabetes and, although they acknowledged some of the predictive testing computers, they actually discouraged consumers from undergoing routine testing, genetic testing for diabetes.

Has the science evolved on that particular condition enough in order to make routine genetic testing now more sensible?

Dr. FEERO. You didn't ask me directly the question would I subscribe to one of these services at this point.

Ms. Hinkle. I was going to actually ask everyone if anyone at this table had undergone genetic testing, if anyone wanted to actually share.

Dr. FEERO. So if a patient came to me right now and asked me this question in my office, what I would say is that there is great promise in this area in general, but we are at a time that's too premature to fully utilize this information. We're really in a discovery phase, and that if you are looking to use this to change your health care at this point in time, it's probably not appropriate.

Ms. Hinkle. Then I'll ask you in public now, so hopefully you won't feel too put on the spot. The question I asked to you when we chatted on the phone is. Why should consumers spend $1,000

on your test if you yourself admit that the scientific claims are a little premature at this point? It seems like you guys get a good deal out of it. You get lots of DNA for research purposes, and even the disclosures on your web site basically say that your DNA sample is ours once you give it over, that you guys claim ownership in the spit sample that I sent in to you, and I think that that's probably something that most consumers maybe don't realize.

I mean, let's face it. How many people in the room read the fine boilerplate? I'm an attorney and I don't half the time, shame on me. But I did actually sit down and read all the disclosures on your web page and I have to tell you, at this point in time I wouldn't be prepared to submit a DNA sample to you because I'd be very nervous about the research that was being done on it.

So assuage my concerns. Tell me why my DNA is in good hands when I turn it over to you?

Ms. AVEY. Well, the first thing is that you don't have to participate in extended research.

Ms. Hinkle. Any research?

Ms. AVEY. The research requires us to collect additional information from you. If you never fill out a survey, we're not going to be able to have you be part of the studies that we conduct, because we need the phenotypic information. We need to know whether or not you've had breast cancer or if you've been diagnosed with autism.

That's the information that we will use and that will be voluntarily submitted by customers who are very interested in participating in the research projects.

Similar to how you see people signing up for the Susan G. Komen walks people who have a family member, co-worker or a friend who has breast cancer are wanting to do these things. So when we talk to people that say, yeah, I don't have breast cancer, but my sister did, and if I'm a healthy control for a study that I could be part of, sign me up.

So it's really more when someone has a disease and they're very interested in sharing that information. That's partly who we're seeing signing up for our service, because they get the message that not only do you get this preliminary view of what's going on in the research community, you will be able to be enrolled in these projects, in these studies.

But hey, if you're healthy and your life's going along great, this probably isn't for you. It's completely voluntary. So we say that right off the bat, that this isn't for everybody.

Ms. HINKLE. So I spit in the cup, I send the sample off to the lab, and the sample's destroyed?

Ms. AVEY. At this point, yes. All we do is we extract the DNA out enough to do the genotyping and then we discard the sample.

Ms. HINKLE. The results or the data from that, if I don't want you to ever use it for anything other than just returning the results to me, it will never be data banked, you'll never use it for any further analysis or research, even if it's anonymized and in the aggregate?

Ms. AVEY. If you choose, you can get your initial snapshot. So you could go in, sign in to 23andMe, print out all of the information that we have on the web site that's pertinent to your data, and

then you can download your data. You can take your whole data set, and then you can come to us and say, delete my file, and we'll delete it.

So you have that choice. If you don't want to get the continual updates—every month we have more and more information coming out. So what we're finding is our customers are saying, give us more, we want more information, what about that study that came out about "such and such" that's why we added the other category of preliminary research, because things do end up in the New York Times and then our customers say, well, why didn't you guys cover that one?

There was one study that came out about how well you learn from your errors. It was in a major journal. But we didn't think that was appropriate because it was a very small sample size and we thought the study was way, way, way too preliminary; not bad or good, just not enough information yet. But because of that we put it in our preliminary research category and we put one star on it. So we have a way now to categorize what's preliminary. Maybe a study will prove the test of time. Maybe we will actually find genes for whether or not you can learn from your mistakes. But we don't want to be the judge to what our customers are interested in learning. But we just have to put the right caveats around the data.

Ms. HINKLE. Let me ask you a question a bit about maybe sort of the future of genetic testing. I posed this question to many of you already. Are we looking at a scenario where some day, perhaps even soon, we'll be having genetic tests sitting on the shelf next to, say, pregnancy tests or diabetes testing strips? Where are we headed for genetic testing?

Or maybe I'm going to get the perfect genetic match in my love life, so I should invest quickly and establish a genetic sort of dating service. Danny and I, actually that's going to be our million dollar idea, so nobody steal it from us. Well, there you go. Someone already scooped me.

What do you guys think? Thomas, you've been terribly quiet today. I'll put you on the spot.

Mr. HAMILTON. Well, I don't think you want the government making predictions about the future.

Ms. HINKLE. Everyone's on the edge of their seat waiting for you to speak, the great oracle. Come on.

Mr. HAMILTON. You were asking if we had ordered tests. I haven't personally, but I probably will order the Alzheimer's test because on one side of my ancestry it's not just rampant Alzheimer's, but Irish Alzheimer's.

That's when you forget everyone you know except those against whom you hold a grudge. [Laughter.]

I just haven't seen this particular phenotypical variant show up in the questionnaires. But when it does, let me know.

Ms. HINKLE. Maybe we can get some grant funding for that research for you, Tom.

Maybe we'll chat a moment about some ownership issues, since I grilled you so mercilessly on the DNA samples. Who should have rights to the DNA material when I do actually either provide my—when I provide a blood test or saliva or a cheek swab, be it a physi-

cian-ordered test or a direct-to-consumer test? Who owns that DNA? Who should own it? What good use should we be able to make of it as clinicians, as researchers?

I have a rare health condition and there could be great medical cures developed from my DNA. Do I have the right to say no? Does the government have the right to come take it from me? What are we looking at as far as the future there?

Dr. LYON. I can talk about what we are doing right now. With the samples that come in, the residual samples that we have are very important for us as we continue to validate and continue to work for new tests coming on. There is a way for anybody who sends their sample in to us to opt out of using their sample for validation and education purposes.

There needs to be a distinction between research and what the laboratories need to do to keep tests validated. So we make the assumption that we can use that DNA unless we are asked to discard it. If we are asked to discard it, we do so.

If we want to do research on it, we work with an internal review board, the IRB. We need to go through the entire IRB process, which includes the informed consent and the understanding of the study. So we have this dual process. One is to be able to keep our tests validated in the clinical laboratory—those are anonymous and we cannot go back and link any new information or finding to the patient—or research, where we go under a research protocol which does ensure confidentiality and ensures what the internal review boards require.

Ms. HINKLE. Yes?

Dr. HUDSON. Elaine raises a really important point and it's interesting, because I suspect that your laboratory is governed by the privacy provisions of HIPPA because you probably bill electronically. So while people can criticize the privacy regs under HIPAA, they do govern the more traditional genetic tests.

I don't believe that HIPPA covers many of the direct-to-consumer companies. So there's the issue then of what assurances of privacy protections do you have, and how do they compare to HIPAA, and should we expand HIPPA to follow the information and not the entity? So that's one issue.

The second issue is that there are a set of accepted norms of the ethics governing research in terms of whether a research participant is informed and understands what they're getting into, whether or not somebody other than the researcher is looking out for the research participants' interests and making sure that the benefits outweigh the harms, etcetera, etcetera.

But if I read the regulations right, these ethics regulation also don't apply to pic genetic testing companies, although you could voluntarily comply with those research regulations.

So we have this interesting situation where we have sets of entities that are subject to ethics standards, and sets of entities that aren't subjected to those standards. In some cases people are opting to meet the higher standard, but some are opting not to.

Ms. HINKLE. From our regulator's perspective?

Mr. HAMILTON. This isn't really a CMS question——

Ms. HINKLE. Right.

Mr. HAMILTON. But we do a great deal of health care purchasing and we do want managed care entities, health care providers, to compete in the domains of good quality, efficiency of services, effectiveness of services, not to be competing to get unfair advantage to do favorable selection, to use genetic information in a way to gain market share by cherrypicking.

So we think that the protections in this area are quite important. That means the protections that are put in place amongst the providers of genetic information, because there will always be some health care provider out there trying to get—no matter how strong the laws are, there will always be some provider trying to access some indication about potential consumers so that they can get market share. We want them to get market share if they're providing good services, but not through the use of genetic information.

Ms. HINKLE. Well, since you're at the mike and talking about finances, maybe you can talk about the converse of that, reimbursement for genetic testing. What is CMS's policy right now, particularly under Medicare, for reimbursement for genetic tests?

Mr. HAMILTON. I'll have to beg off on that question since I represent the quality assurance side of Medicare, but not the payment side.

Ms. HINKLE. Judy.

Ms. YOST. I'm sorry, I don't know.

Ms. HINKLE. That's all right.

Anybody at the table have some background or expertise on that? [No response.]

Everybody just looks at you, Kathy, as the default.

Dr. HUDSON. That's one area we haven't spent a lot of time on yet, although let me make one quick comment. There is an important piece that's been not really talked about here, which is the translation into clinical practice and the need to collect enough evidence. There's a weird imbalance right now where we have tests for 1500 diseases, and then a zillion variations that we can look at, but a tiny, tiny number of health professional guidelines.

What the health care professionals say is that they need evidence, and they need somebody to look at that evidence, and weigh that evidence and then give it to them so they can develop guidelines. There is a CDC-funded effort under way to do that, where they are carefully looking at genetic tests and then doing the evidence reviews, drawing conclusions, and making recommendations. Hopefully, health care provider organizations will be able to pick up that evidence base, translate it into guidelines, and get it into the hands of health care professionals, so they'll know what tests are good tests and where the evidence base is strong and what tests are a shrug. At the end of the day it's going to be the useful tests that really benefit.

Dr. FEERO. I would extend that point, that the EGAPP process is a very valuable process for reviewing evidence, but you actually have to have evidence to review. Developing the sort of translational evidence that's needed is going to be a challenging and costly endeavor, and will be a moving target. That's what I was trying to refer to previously. This concept of developing a pipe-

line in this area to figure out how to develop that evidence in a cost effective way is a major challenge, I think, moving forward.

Ms. AVEY. That's something that I can't expect that the government would take on solely. That's where I think the public-private partnerships are really going to make a huge difference, and that's exactly the role we want to be playing with our partners, with the technology providers, with the labs that have CLIA oversight.

So I think all the pieces are in place and then it's just a matter of us working together and not halting something that could be very positive for health care.

Then I just wanted to mention, going back to the privacy issue, we are a for-profit company and we would not have a business model if we did not protect the privacy of our customers. We know that. That's a fundamental thing and an element of this company. So protecting that privacy is, of penultimate importance to us.

So we do that, but we also give our customers the option of sharing their data. If they want to download it and give it to a researcher at their favorite institution to do studies, they can do that. But we would say that we are even beyond HIPPA compliance without the unintended consequences of HIPPA which we hear about all the time from physicians, who say they can't look at the same medical record in their office that they can see at the hospital, and it really hinders their ability to take care of their own patients.

So we don't think HIPPA is perfect, but, that said, we totally believe in the privacy of this information. When you see what UCSF did when they sold the record of 6,000 patients recently—it was in the papers everywhere. HIPPA does not prevent those types of things from happening.

Ms. HINKLE. What resources currently are available to consumer or perhaps even medical providers who have patients coming in either wanting genetic testing or wanting help in interpreting genetic tests? Where are the resources? Do the agencies have information on their web sites that's digestible? A third party, or is there a hole there right now as far as public education?

Dr. FEERO. A number of years ago NHGRI, in collaboration with a number of other entities, created or helped to create an organization called the National Coalition for Health Professions Education in Genetics, to try to begin to create an infrastructure for delivering information on genetics to the health professional community.

That organization has been working diligently with a number of groups, most recently physician's assistants, prior to that in the nursing organizations, to try to deliver the information.

There are a wide variety of efforts on various web sites that are funded by the government at least. A good example is Gene Tests and Gene Clinics that provide information for the less common disorders.

Ms. HINKLE. I have to say, I don't find that a particularly helpful web site from a consumer's perspective.

Dr. FEERO. It's not designed for consumers. It's designed for the health professional.

At this point in time, the resources that are available in the public space to help with the interpretation of these association studies are much more scarce. In fact, the NIH is working on this right

now. There's a trans-NIH communications group on the genetics of common chronic disease, that is working to formulate a response to that sort of vacuum of publicly available information on this topic.

But it's clearly something that I think a number of different agencies, the CDC included, have their eye on.

Ms. AVEY. Just to mention that we're in discussions with them as well, because if we're already aggregating this information and creating our own tools, we're happy to share those and work with NCHPG directly if that makes sense, if the information we're providing is something that they're also interested in.

Ms. HINKLE. Kathy, you offered your perspective much earlier in our conversation that there has been a real lack of progress with respect to genetic testing oversight. Of course, not everyone at the table shares that opinion. So I guess my question to you is, what particular progress would you like to have seen the agencies be undertaking at this point? What would you really like to say this must be your top priority over the next 1, 2 years in order to ensure adequate consumer protections?

Dr. HUDSON. I appreciate you pulling this roundtable together because I learned a lot from my fellow panelists. I was stunned to hear Steve say that he welcomes new authority, and that'll be interesting to follow up on, exactly what authority is he welcoming.

Ms. HINKLE. I was going to ask in a moment what authorities he would like from Congress and we're just going to get that written up.

Dr. HUDSON. I'm excited about the efforts that CMS is making in terms of moving forward with proficiency testing, despite their lengthy rejection of our petition requesting proficiency testing last year. So I think we need to move quickly on proficiency testing. I don't think it's that difficult. I don't think it should take that long. My colleague Gail Javitt put together a notice of proposed rulemaking to implement the Secretary's committee's recommendation and it took her about 4 hours in her office alone. Of course, she's extraordinary, but it's not that hard.

The most important thing second to proficiency testing is creating a genetic testing registry and creating that transparency. Nobody's against it. Yes, the details are hard. It absolutely must be mandatory. It absolutely must be at an agency that has proven informatics and genetics sophistication. But I think that that could move forward quickly and help a lot.

Ms. HINKLE. Where should that be housed?

Dr. HUDSON. I personally believe it should be either housed at FDA or NIH, because both have a track record of success in making information instantly publicly available and easily searchable. CMS, sadly—and I understand their resource constraints—2 years ago Tom testified that you could find out the CLIA certification status of labs on their web site. I checked yesterday and still can't. So I think——

Ms. YOST. It's coming.

Dr. HUDSON. It's coming. It's coming.

Ms. YOST. It's almost there. I saw it yesterday. It's almost there.

Ms. HINKLE. So it's not online?

Ms. YOST. It's almost there.

Mr. HAMILTON. It's almost there. The wheels of government grind finely but slowly.

Dr. HUDSON. At different rates in different agencies.

Ms. HINKLE. So we're not quite there yet.

Mr. HAMILTON. In contrast to Gail's 4 hour piece, we worked for a year to get permission to get exceptions to our hiring freeze and a year to fill the position. So government—the Federal Government is purposely designed with the famous checks and balances. But notwithstanding, we're making slow progress. I think we had the web site ready to go and then——

Ms. YOST. For like a day.

Mr. HAMILTON. For that cameo time. Then the directives came down to make it all 50 compliant, which it should be, of course. But if you've ever had the pleasure of trying to make a large enterprise 50 compliant so that individuals who are blind can read it——I don't use charts. That's all I can say. At any rate——

Ms. HINKLE. So could we anticipate that this year some time?

Ms. YOST. I'm saying weeks.

Mr. HAMILTON. Kathy is right in so many ways. We support the registry idea and it ought to be within an agency——

Ms. HINKLE. So long as somebody else houses it.

Mr. HAMILTON. If we were good at it, we'd jump at the chance, frankly.

Ms. HINKLE. Well, Steve, Greg, here's your opportunity to take up the mantle and go to bat at your respective agencies. So who wants it?

Dr. FEERO. That's above my pay grade. [Laughter.]

Ms. HINKLE. Show some initiative. Get that promotion you've been bucking for.

Dr. FEERO. I don't think that's what I'd get.

Ms. HINKLE. Is FDA well equipped to handle a registry like that?

Dr. GUTMAN. Well, as I said before, we're from the government and we're here to help. So we're always anxious to do what's appropriate. I think when I was talking about authority it might be really not so much authority, because I believe we have the authority. I think Congress could perhaps express some interest in direction. If you look at the SACGHS report, it's a very complex report. It offers more than one path to Rome. So a path to Rome could be more reliant on CMS, it could be more reliant on FDA, it could be more reliant on a public-private partnership, or it could be reliant on other out-of-the-box thinking, all of which might fall within existing authority.

It would be a matter of how you emphasize that authority. So I think that there might be a role for, after a factfinding by Senator Smith or by anyone in the Congress, to express advice and interest. There are no easy answers here. These are very complex problems. I think what Thomas said at the beginning is that really, in order to do it right it really does require the involvement of multiple stakeholders, not just FDA, not just CMS.

I think the idea of a public-private partnership has to be carefully thought out and carefully orchestrated, but it is probably necessary.

Ms. HINKLE. Judy, I'll put you on the spot for a second, since I know you frequently speak in public about the CLIA genetic testing

specialty and PT. So I think everyone in the room is very familiar with the agency's history in abandoning the genetic testing specialty. So can you tell us a bit more about your plans for PT, because even just as recently as this December when my boss met with Administrator Weems and questioned him as far as the agency's plans for enhancing oversight over genetic testing, I would say we got what was a less than specific response about the agency's enthusiasm toward mandating proficiency testing for genetic tests.

Maybe you could just——

Ms. YOST. Well, actually there's a very simple answer. You don't need a specialty in order to change the proficiency testing requirements. So we feel it gives us actually an easier way to proceed to use the existing infrastructure to develop proficiency testing, because currently it depends on how you define a genetic test and, as you heard, no one has the same definition, no two people.

But even so, that said, the genetic tests that could be potentially genetic tests if you define them that way are interspersed among all the current specialties now. So we just envision that that would just continue, with the change that we would make. So it makes that part of the process a lot more simple.

As we progressed through the discussions with the SACGHS oversight review and thought about what the options were and what were the things that were most important and what were the things that we could do and could not do, and what were things better done through other vehicles, we felt that PT was something that not only for genetic testing but overall the regulations needed to be updated, because they hadn't been done since 1992.

So that has become our priority, that's next if we can ever get the cytology PT out. We are well under way with a plan and players in order to accomplish that.

With regard to some of the other concerns about CLIA, I know there's discussion about personnel and quality control and some other areas. We feel that there are probably ways that we can accomplish that through use of professional guidance and incorporating it into our guidance documents and still get there from here.

We've found in the past, because we have experience in that, in doing that, that once you start to put a professional standard, as long as it's within the scope of our authority, into our guidance, people tend to follow it because it's an easy route to compliance, and then it standardizes the standard of practice as well. It becomes the standard of practice.

We saw it in microbiology with cut points for susceptibilities and using a consensus standard, and it has worked extremely well.

Ms. HINKLE. So you're confident that if you issue those as sort of sub-regulatory guidance that you're still going to have adequate enforcement authority or there's just going to be adequate enough compliance, that you're not going to have to worry about bringing down the stick against people?

Ms. YOST. You would always have outliers. There will always be an aberration. There will either be circumstances or individuals who either willfully or unknowingly will not be in compliance. That's a fact of our lives on a daily basis. So you can never say never. But we believe that for the most part it does become——be-

cause in many of these cases too we're talking about competition. So the idea is that if you're in compliance you can use that as added value to your services to be able to work in the marketplace as well.

Ms. HINKLE. Is there anything you can share as far as specifics about this guidance or when we might look for that to be issued?

Ms. YOST. I think again this is an area where we have to—there is a lot of material currently available that a number of the professional organizations have already developed. It's a matter of vetting that information, working with the experts in the field to provide us perhaps some additional guidance with their expertise.

Ms. HINKLE. Wouldn't most of that work have already been done, though, with the 6 years that you spent laboring on the CLIA genetic testing specialty? I mean, how much more up to speed does CMS really need to get at this point?

Ms. YOST. Well, I'm not talking about up to speed. I think we have to decide what we really want and what are the most important things. I don't think we can do it all yet tomorrow. But clearly we've agreed that proficiency testing is important. We have the work that's been done with CDC on the best laboratory practices document that will be published next year.

In addition, I believe we should work with partners. Rather than we being the selectors as the Federal Government, I think we need to have private entities provide additional advice to us to——

Ms. HINKLE. Well, Kathy and—they've been very free with their advice.

Ms. YOST. The invitation's been open for 2 years. We've asked—we don't claim to be the be-all, end-all. So we want to have folks buy into whatever it is that we select to use, rather than send—picking something and then have people not happy. So it's better, again, to work on the front end rather than the back end.

Mr. HAMILTON. Well, if we can think about this strategically, we've got 1500 genetic tests.

Ms. HINKLE. The number increasing every day.

Mr. HAMILTON. Expanding every day. How many proficiency tests do we have? 50, 60, 70? The number of tests is growing faster than the proficiency tests. So we will always have this enormous gap.

Into that gap come two things. One is alternative quality control, alternative assessment, that needs to be pretty robust and needs to be adequately enforced. That's our piece under CLIA, to make sure that it is. There are current requirements that apply when a proficient test is not being used, that the laboratory twice a year verify. So that needs to continue to be applied and made as robust as we possibly can.

With regard to the proficiency tests themselves, we need an adequate strategy. These things do not just magically appear. We had a 17-year history trying to get national proficiency tests for cytotechnology. That's a very long saga, but in 2005, 17 years after CLIA was passed, we finally got national proficiency testing there.

So what we really need for proficiency testing is a real strategy. Instead of thinking about this as an all or nothing, either proficiency testing exists or it doesn't, if we think about it perhaps as a ramp, where you start in sequence with the education, then with

possibly quasi-volunteer, quasi-voluntary participation, and then ultimately the legally mandated national participation.

That's why in that sequence we want to work with particularly the accrediting organizations and the professional societies, both of which do a great deal of work on the educational side of things. But on the accrediting organizations, they have the ability to require their members to do proficiency testing where they make the proficiency tests available. So on the one hand, that's short of a universal government mandate, and it's voluntary for an organization to decide whether or not to be accredited. But having made that voluntary decision, the accrediting organizations can make the participation in PT mandatory.

So that's a step up from just education. From that ramping up it's a shorter step to us either doing sub-regulatory guidance, which is just short of a full mandate. We can make it a full mandate by changing the regulation and adding these various analytes to the regulation. So Ithink that's the strategy. That's why Judy's got planned a November meeting with the accrediting organizations, to really focus on this, and we want that CLIA work group.

Ms. HINKLE. Why wait until then?

Mr. HAMILTON. Excuse me?

Ms. HINKLE. Why wait until then?

Kathy, I'm sure you have some thoughts on this. My question to you is, Steve indicated earlier that some direction from Congress might be welcome or needed. Do you guys need a little help from Congress, some direction here steering the ship in this respect? You know, people are just chomping at the bit. They're just waiting for CMS to do something. Clearly you heard my boss express his frustrations at the very glacial pace at which CMS seems to be moving here.

So there's certainly some frustration, I think, about the stakeholder community as well as on the Hill, just kind of waiting for CMS to do something.

Mr. HAMILTON. Again, look at the nature of the proficiency tests. We do not have a group of sallow scientists hidden in the basement concocting proficiency tests. These come from the professional community. So we want to work with the professional community to develop those.

Now, which comes first, a mandate for proficiency testing or the proficiency test itself?

Ms. HINKLE. Well, you know if CMS required proficiency testing there'd be plenty of people willing to provide proficiency testing to capitalize on all the people now who have to undergo that testing. It's the whole "build it and they will come" philosophy that we talked about.

Ms. YOST. That is very marketplace-driven, too. The proficiency testing providers currently will not develop the PT material if in fact they don't have a market to sell it in. So that you can see that by the difference of——

Ms. HINKLE. But if they know CMS is going to require it, then——

Mr. HAMILTON. Well, you asked what Congress could do. If Congress provided up-front funding and said don't worry about any

marketplace uncertainty, here's reimbursement, the marketplace is guaranteed.

Ms. HINKLE. I've got 20 dollars in my wallet over here. We'll start with that.

Mr. HAMILTON. I'll match you and——

Ms. HINKLE. Yes, right, matching funds.

Yes, Elaine?

Dr. LYON. Can I comment with that? As Mr. Hamilton has said, what CLIA requires is to demonstrate the accuracy of your tests. When there are proficiency programs available that we can be a part of, we are a part of it. Some of the tests we do are not in those proficiency programs. However, that doesn't eliminate the lab's responsibility for doing proficiency testing.

We will then get with other laboratories doing the same test. We will work together. We will exchange samples. We have these set up to be able to do.

If that doesn't work, we still have the responsibility to make sure they are accurate, and we do it by what we call an internal proficiency. So one cannot say that the proficiency testing isn't being done; it is being done. For some tests, it may not be under a formal program right now.

Would we be in favor of expanding that program? Yes, because it makes it easier for us. We don't have to find another laboratory to work with. But the proficiency testing is being done. The requirements from CLIA to show that your test is analytically accurate is being met for every test that we do in our laboratory.

Ms. YOST. That's a requirement, that's a regulatory requirement currently in place that we very closely monitor because, interestingly enough, it's one of the most frequent findings we have on surveys. So that obviously means we're actually looking at it.

The thing to remember here, though, as folks are losing perspective, is everything's hanging on proficiency testing. CLIA is a package deal. CLIA has quality control. That means every day you do a test you have to check to see that it has worked before you report any results, and you have to have qualified people, you have to have trained people. You have to check their competency on an annual basis. You have to have a quality monitoring program in place that you monitor every test and every system in place in your laboratory to ensure that your test results are accurate, that they're reliable, and they get to the person who's going to use them reliably, and confidentially, by the way.

So those other requirements, as well as having recordkeeping requirements for every step of the testing process, so that if somebody needed to go back and check to see what happened from the time the specimen was collected through the analysis until the result is reported, you could track that test. All of that is part of CLIA and, together with proficiency testing or alternative assessment, as this is called, that is what makes an accurate result.

You have to really look at the whole picture and not just focus on one requirement. Yes, it's a lovely measure of outcome, it's a lovely measure of test accuracy. But frankly, you don't get PT results until 3 months after you reported that patient's result. What good does that do you? You've got to know on a daily basis that your test is working.

Ms. HINKLE. I appreciate you making that point. I think that's a point well made. I think we could probably spend the entire 2 hours together talking about proficiency testing, but it would be incredibly remiss of me not to talk about a couple of the SACGHS task force report recommendations. I see that Tom has brought his trusty copy there.

Instead of me sort of picking through various recommendations, I think people would probably be much more interested to sort of hear what your perspectives were on the report recommendations. Was there anything that surprised you by being included or not included? Is there anything from the agencies' perspectives you think particularly feasible—I know you've already talked about PT—particularly feasible to implement or just completely, can't do it, that's crazy talk?

Anyone jump in. I know you touched on a couple points as well, so anyone just jump in. [No response.]

All right, we'll go around the table. Kate, you've been very quiet today. How about you? Give you a chance to get on record and some camera time.

Ms. COOK. I'm actually here to carry Steve's bag.

Dr. GUTMAN. Well, I will reiterate what I said before. Actually, I'll be more personal than perhaps I should, because it was an incredible report, so I'm just in awe that they had 30 people who worked, beat their time line, argued over every word and paragraph and sentence, and came out with something that was reasonably intelligible. So I'm extraordinarily impressed.

Ms. HINKLE. That's credit where credit is due.

Kathy, you were on that.

Dr. HUDSON. Yes. Steve was there as well.

Dr. GUTMAN. Yes. I wasn't trying to praise myself.

I was actually quite peripheral.

There were a couple of things that amazed me. It amazed me that after the report was written when you looked at the press it was as though there was only one paragraph in the report and that was the paragraph describing FDA. So I found that disheartening, that we are so fearsome. You could have had that written in one afternoon. You didn't need the whole report. So you look at the press and it just completely missed the point.

The report was rich in that it actually wasn't just the FDA issue. It was the education, the reimbursement. The only thing that was—everything was reiterating from—you got a snapshot, but I think if you want to look at the big problem, the whole field hasn't quite addressed maybe all of these complex issues, education, reimbursement, analytical validity, clinical validity.

The new one in town—I don't remember, but I certainly don't remember it in the SACGHS report; it wasn't in the tax report for genetic testing—was this notion it is 2008, so we're a little bit further along than we were even 8 years ago. People are worried about evidence base of medicine and they are worried about value base of tests. How could they not when 16 percent of health care dollars are being spent on—16 percent of GNP's spent on health care and it looks like in my lifetime it will be 20 percent and my kids will be paying 25 or 35 percent. We're a very rich country. I don't think we're that rich.

So I think the epiphany in the report was that it's not just FDA, it's not just CLIA. There's a problem here. AARP's trying to work on the problem. Blue Cross-Blue Shield technology evaluation center is trying to work on the problem. But you've got to figure out a problem. Do we actually have money to spend on these tests? Which tests should we be spending the money on? How should we be deploying them and how should we be making sure that they are improving the quality of performance?

So it's a rich report. I hope everyone in the community doesn't shelve it. I hope that—they can agree with it, they can disagree with it, but I hope they respond to it and it stimulates. It's worth not being ignored and not being shelved.

Mr. HAMILTON. I was not in the group, so I can be completely fulsome. It is an awesome, awesome report. Congratulations, Kathy, Steve, and Chairman Toich, and before him Reed Tucker, and everyone who participated. It created a forum to bring very disparate points of view together to fashion a very constructive set of recommendations that do make it very clear that this is going to take all of us working clearly together and for quite some time to make progress.

But it's an optimistic report because I think it charts a pathway. We can all have our particular viewpoints about what the solution or a technique might be, but I think the report keeps the vision before us of, regardless of the approach, here's the destination. So that's why I am carrying it around. I think it ought to be required reading.

Ms. HINKLE. They should have that in the pocket size, like the Constitution that the members carry.

Judy, what was your take-away from the report?

Ms. YOST. It was actually——

Ms. HINKLE. By the way, I'm assuming that you've all read it from cover to cover.

Ms. YOST. It was actually a very enlightening experience to work with such wonderful people. Truly I learned, I learned as much as I complained. So I did find it highly valuable. Clearly we are doing our very best to look at those things that we can accomplish within the scope of our authority and to work through them. We've begun in a number of different areas. They're already under way.

We'll do our best. But again, it is pretty awesome because it shows you a full picture of what's happening. It's not just isolated to one aspect of genetic testing because it's a continuum, it truly is. So it was an honor to be able to work on it.

Again, I always learn more than I give. So it's always worthwhile time.

Ms. HINKLE. Kathy.

Dr. HUDSON. I already shared my top priorities. The one area that didn't get addressed—and a lot got addressed by this committee but the one area that I think may have gotten less attention than it should have was how we need to move nimbly to get information into drug labels about diagnostics. This is already saving lives. There's a genetic test that can tell if a person will suffer severe reaction if they take a particular antiviral for HIV and it's not yet, as I understand it, on the drug label. So how can you move

really fast? How can we move really fast so that we can get the benefits as fast as possible?

Dr. GUTMAN. Yes, I do want to respond to that, because the agency is cognizant of that and we think that a policy statement we need to clarify is that when you do have a—when you do have a diagnostic and a drug linked so tightly that the selection of the drug or the avoidance of selection of the drug is related to use of the diagnostic, we at least in my neck of the woods would say that the drug becomes a slave to the diagnostic, so that the cross-labeling becomes critical, that cross-labeling has to be based on data. In fact, Dr. Woodcock has been fairly explicit in suggesting that those tests do require pre-market review if they're going to make drug decisions.

We have a very colorful, inconsistent past history. I suspect the transitional period will be rocky, but I do think we are going to move in the direction of having higher expectation when you have a really tight link. When you have a weaker link, then I think—I still think we ought to be looking at that policy, but I don't think it's as compelling.

Ms. HINKLE. Elaine.

Dr. LYON. What I saw in this report was, first, they still couldn't define a genetic test. It makes it very hard for us to move forward if genetic testing is defined so broadly that it goes into every aspect of medicine.

Then the question that they had brought up is whether there is an exceptionalism about genetic testing that is different than the rest of medicine. I don't think that there is a complete agreement with that, either. I think overall the tone was that there is not an exceptionalism, that genetic testing does fall into the realm of other types of clinical laboratory testing.

Those were the two ideas that need to be clarified for us to really move forward.

Ms. HINKLE. Greg.

Dr. FEERO. So first, going back to my comment about being above my pay grade, what is not above my pay grade to say in NHGRI is that we are very supportive of the idea of a registry and think that there is great potential value in that.

Particularly with regard to this report, I think that the introduction of the concept of utility as part of that registry is something that is very valuable. Clearly, genomic applications span the health care system. They're coming out at a tremendous pace and, as much as any technology, they have great promise for improving the health of the general population. But they also have a cost associated with them and I think we have to be cognizant of that as we move forward.

I guess my overall comment, and perhaps this is because I haven't been in government quite long enough to understand this, it is a report, and that ultimately a report is only good as its implementation and how people's toes are held to the fire over time for its a product. That would be my comment, that I think it is an excellent report; the proof will be in the pudding.

Ms. AVEY. For us, we broke it up into chunks and everybody got assigned their reading, and then we came together and had a meeting about it, which was great. Our scientists all reported back what

they got out of the section they read. I think at the end of it we all thought this is such a huge opportunity for 23andMe to be involved, to be part of this public/private partnership with all the different agencies, because it was very clear that genetics education is really lacking for the medical community and for lay people. If that's a role that we can play, we're very excited about that. That's really one of the missions of the company, is to just get genetics out into the mainstream.

But it was very clear that, even on testing that isn't genetic, there's still a huge disconnect between what comes out of a testing lab and what a doctor is able to report back to their patient. So it's not just us—I don't think we've created this problem by coming out and creating this new industry. I think it existed before we came along. But certainly as far as genetics goes, that's where we're going to be focusing and we're very excited about the educational opportunities.

Ms. HINKLE. Since I promised everyone in the audience an opportunity for Q and A, is there anyone in the audience who has any questions for any of the panelists?

Ms. FOMOUS. My name is Cathy Fomous. I thank you for all the wonderful things that you said about the report. I really appreciate it and I will bring it back to the staff.

My question is for Linda, because I know the least about what your company does. You have mentioned a few times during the conversation today that you are very enthusiastic about doing research with the database that you have and the voluntary nature of the additional information. My question is, do you think that you'll voluntarily follow guidelines for human subjects research protection, such as an informed consent process?

Ms. AVEY. Absolutely. This is something that's coming up a lot in our discussions with researchers and with other organizations about the stifling stranglehold IRBs have over the research process. We have a consent form and we've met with a commercial IRB to have them kind of bless it. Because we break the paradigm, we don't know what questions we're going to ask yet. Frankly, coming from Perlegen and Affymetrics and Applied Biosystems and working with researchers over the last 25 years, I can tell you that the current research paradigm requires that you know what questions you're going to ask in advance most of the time, other than things like the Framingham study, where it's prospective and you learn information over time that you might not have even thought to ask in a study.

So we're very open-ended in that we don't know what questions we're going to ask and we don't know even what information we're going to find. So the IRB scratched their head like, "This doesn't fit our mold." You have to be able to say what is the end point of your protocol and what is your protocol.

So for us it's frustrating. They've been very honest to say, this just doesn't work the way we review protocols. What was interesting to me, though, is at the end of the meeting one of the people on the executive team of this IRB came up to us and said, "I have a daughter with a genetic disease and she's going to love what you're doing."

So we really need to work together with the IRBs, I think, as well to see how do we do this, how can we make these non-protocols, if you will, fit into an IRB paradigm.

Ms. HINKLE. Any other questions from the audience?

Mr. DAYNARD. I may be biased, but since I have all the experts here and we're talking about this, Greg, I think you mentioned that the associations seemed to be robust over the last few years depending upon the polymorphism you're looking at. Linda, you said that you may not disagree about the associations, but you still can't tell people what to eat. I think what we may be seeing in terms of claims with some of these companies is the claim that having a susceptibility and gaining information about your genotype and maybe even getting recommendations about lifestyle and diet changes is going to impact your health outcome.

What kind of evidence supporting the claim would you require if it's not a clinical trial?

Ms. AVEY. That's where we want to work with the agencies to make those definitions. What does become information that has clinical utility? I think as a society we have to come to an agreement of how we get to those end points. I don't think we have all the answers. I don't think FDA has all the answers or CMS. But I think together we can come to some kind of conclusions, because doctors are going to need to know this. They're going to have patients coming to them time and again with the reports and say, here, doc, what do I do? I don't think we know what to say yet.

That's why we sound like a broken record. We keep going back to the fact that we need more data, and that's really what the mission of 23andMe is to get many, many, many people, hundreds of thousands of people hopefully, involved answering the same questions, that we can then make those clinical connections and connect the dots.

But we don't know the numbers we'll need for that. It depends on the condition, it depends on the genetic association. It's really complicated.

Mr. DAYNARD. Exactly.

Ms. AVEY. But that doesn't mean we shouldn't do it.

Mr. DAYNARD. What are respondents going to say to me when I present them with a draft consent agreement to comply with the Federal Trade Commission Act is, boy, this is complex, and we're not quite there yet. We don't know. Maybe these association studies are good enough. Then someone will say, well, even a strong association is not good enough because you don't know that the recommendations are genotype-specific. But here's the FTC that's going to tell someone, you need this kind of evidence and you don't have it; your association studies aren't good enough if the claim is that this is going to impact your health outcome, not just that there's an association. That may be right, and that's a distinction that we're continually trying to hone.

Yes, we'd love to talk to you.

Ms. HINKLE. Anyone else?

Dr. FEERO. I would just add the comment that certainly that whole question is an active area that the NIH is looking at carefully, in conjunction with other groups. It is a huge challenge. It's going to be dependent on the particular disease, the particular

markers, the particular invention you're proposing. But that really is I think the $64,000 question for any registry that is going to use utility as one of the bars that you set. A, what is the bar; and B, who's going to set it, is really going to be a challenge.

Mr. DAYNARD. Well, I hope the FTC doesn't become premature in this area, because the FTC very definitely, although it enforces the law against unfair and deceptive practices, it doesn't want to chill an emerging science, and that's our standard. It's a rigorous standard, but it's flexible. So either I see it the way it is or I make it up. Just kidding.

Ms. HINKLE. Any additional questions from the audience? [No response.]

I have received one question via email from John Rockoff with the Baltimore Sun and he was just curious to know about the volume of genetic testing. Does anyone here at the table know how many patients each year undergo genetic testing? [No response.]

No one?

Or how might we get that answer? Is that something that's even really tracked or identifiable?

Dr. FEERO. The fundamental problem is we haven't defined exactly what we mean by "genetic tests." So it's very hard to count when you don't know what you're trying to count.

Dr. LYON. One point that I could say is that most of the genetic testing that we do right now, is for the relatively common genetic diseases, the Factor V Leiden, the cystic fibrosis. I had the numbers pulled from our laboratory and about 70 percent of them in volume have FDA-cleared reagents to do them.

Ms. HINKLE. Well, I promised you all that it would be about 2 hours and in lieu of opening statements we would afford the panelists an opportunity to make closing remarks if you wish. So would anyone care to make any type of closing statement before we adjourn?

Dr. LYON. I just wanted to emphasize that the knowledge that we've gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of diseases and its care. I want to emphasize that genetic testing does have value. It has tremendous value to diagnose difficult and rare diseases. It has value in detecting people who are highly susceptible to disease before symptoms begin and hopefully that we can do something to intervene. With pharmacogenetics we are able to target the appropriate medication.

Genetic tests are being regulated, as are all clinical laboratory tests. We appreciate CLIA's stand to allow us to do laboratory-developed tests. I believe they are critical for many of these rare genetic diseases for which manufacturers will not making reagents and the laboratories are responsible to make sure that their tests are valid. We do participate in the proficiency testing and we follow the CLIA and professional standards.

There are some guiding principles that I think that we should include. The tests do need to be developed based on medical knowledge and should be ordered by a knowledgeable health professional that can help in their use and interpretation. All laboratories performing these tests should be CLIA-certified for high complexity

testing; and that any exaggerated or unsubstantiated claims then could be investigated by the FTC.

The innovation in molecular testing is extremely sensitive to regulation and reimbursement. Too much of the former and too little of the latter could prevent or delay the hoped-for medical advances. I believe that we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise in diagnosing, treating, and preventing disease.

Thank you.

Ms. HINKLE. Anyone else?

Ms. AVEY. I don't have a formal response, but I just want to thank everyone for being invited. It's been great to be here. It's been really illuminating. We're very excited about the future. We think the United States can play a big role in personalized medicine and can be a leader in this. I think we've fallen short in the last few years in things like stem cell research. I really think it's time for us to step back up to the plate again.

The great thing about the U.S. is, especially in California, we have a very diverse population. We're already talking to places like the South Asian Heart Center. At a hospital in Sunnyvale they're looking into why do Indian men who have vegetarian diets and take care of themselves, die of heart attacks? If we can do a study in the U.S., but that information can translate to India, we can start a global effort that could help other countries that may not have the same resources as the U.S.

So we're very interested in signing up a very diverse population of people and having them be enrolled in studies, because when you look at these gene journals that we have, there's a drop-down menu that you have to select which population does it apply to, and a lot of times it's just Caucasian. Research is done in a very Caucasian-centric way and we want to change that. We want to enroll people of all backgrounds.

The other issue we have is that people are of mixed race and won't know how research results apply to them—if they're like Barack Obama and he's looking at his results, does he pick Caucasian or African? He doesn't know because we haven't done studies in multi-ethnic people.

So we're very excited about the opportunity and we just hope by working with the regulatory agencies that things don't get stifled, but that we do it in a very responsible way.

Thanks.

Ms. HINKLE. Yes?

Ms. YOST. I just wanted to quickly say that the "I" in "CLIA" stands for "Improvement," and so we realize that that goes for us too. We know that we can do better and we have intentions; and I think mostly just to extend again the offer to please work with us to help us get the things that you need to improve and enhance the oversight over genetic testing.

Dr. GUTMAN. I'll just reiterate the message that I conveyed at the very beginning. This is an area that we all have a role to play. We all have a responsibility, and sometimes when everyone has a responsibility that can sometimes be a recipe for no one. So I particularly appreciate the role of you, Chris, and Senator Smith in bringing us together and the SACGHS for performing the same function;

and to say the "I" in "CLIA" does not stand for "you." We look at it as being "I" as well. So we want to be part of the solutions here. Thanks.

Ms. HINKLE. FDA?

Ms. COOK. We heard today about the fact that there isn't an identified definition of genetic test. But I think that people can agree that there are some tests that clearly are. Even though the borders might not be clearly identified, there are some that are.

Steve mentioned earlier that FDA has taken a risk-based approach in some of its regulatory efforts with regard to laboratory-developed tests. So I think it's worth observing that here, and even though we may not have really the full definition of genetic tests, there are identified genetic tests, there are identified risks, and bearing those two things in mind, it might really help this effort move forward to address the most significant risks.

Ms. HINKLE. Well, I would extend my thanks personally and certainly those of Senator Smith to everyone here. Senator Smith is very engaged in this issue. We had a difficult time getting him out of his seat. If you saw us frantically passing notes to him behind, it was like, the vote's coming, you have a meeting, you're missing your meeting, the vote's coming. He did not want to leave.

So clearly this topic is very engaging. As you know, it can be very difficult to engage the interest of a Senator. So I think that speaks to how just compelling this topic is and really how engaging you all are as panelists as well.

I have to say I was a little surprised when I first sort of bounced this idea off of some of my colleagues here on the Hill. Everyone was quite skeptical about the concept of getting everybody together at a table. They were like, you're never going to get the agencies to sit down with all these stakeholders and have a conversation and do a roundtable on this topic. I was completely surprised at that sentiment.

Certainly you're all very agreeable people, very well intentioned, very knowledgeable, and it is always such an education. Every time I have the true privilege of speaking with any one of you, you are all always very generous with your time with respect to staff and the members. This is the second time you've come before this committee and you've given up hours of your time today to share with us and the public, and we very much appreciate that. You have added immeasurably to the record today.

For those of you who are interested, an archive of this will be webcast on the Aging Committee's web site and a transcript will be available at some point in time, too.

I look forward to following up with all of you, and thank you so much.

With that, we are adjourned. Thank you.

[Whereupon, at 4:25 p.m., the roundtable was adjourned.]

APPENDIX

WRITTEN COMMENT FOR THE RECORD

ELAINE LYON, PhD

MEDICAL DIRECTOR OF MOLECULAR GENETICS

ARUP LABORATORIES

ON

GENETIC TESTING

BEFORE

UNITED STATES SENATE

SPECIAL COMMITTEE ON AGING

GENETIC TESTING ROUNDTABLE

JUNE 12, 2008

American
Clinical Laboratory
Association

Senator Smith, other Members of Congress, staff and guests. I am Dr. Elaine Lyon, Medical Director of Molecular Genetics at ARUP Laboratories. As a medical laboratory geneticist, I would like to set the backdrop for today's discussions on the appropriate regulation, validation and medical necessity of genetic testing.

Knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and its care. Molecular testing improves patient care today and holds promise to further advance care in the future.

Molecular testing allows us to

- Diagnosis difficult and rare diseases (Rett syndrome)
- Detect people highly susceptible to disease before symptoms appear (cancer, colon, breast, ovarian)
- Target which medication to use and when to use it (Tamoxifen, TPMT)
- Manage and monitor diseases effectively (leukemia)

I would like to present examples of mutations known to cause disease, demonstrating the value of appropriate genetic testing. Contrast these to tests for one or more genetic markers that simply show an "association," often weak, with a disease, and for which there has been so much concerned public debate in recent months. More studies are needed before these are ready for "prime-time".

We perform a common genetic test for cystic fibrosis (CF). Since 1989, when Dr. Francis Collins, director of the Human Genome Project, discovered the gene, over 10,000 scientific publications have described its role in this disease. CF is a classic study, not only of the value of genetic tests, but of how the Clinical Laboratory Improvement Amendments (CLIA) allow for the rapid inclusion of new scientific knowledge. I hope there is time later to discuss this in more detail. Several states have now added CF testing to their newborn screening. Without this testing, the diagnosis may be delayed for years because the symptoms can be so vague. Early diagnosis can help prevent malnutrition and diminish lung damage improving longevity for this devastating disease.

One hereditary form of colon cancer—Lynch Syndrome—can be identified in individuals who have a strong family history. For those at risk because of a mutation, cancer screening at a much younger age than is recommended for the general population can improve survival if the cancer is caught early. It will also reduce the anxiety of family members who learn they do not have the mutation and enable them to follow the screening recommended for the general population.

Time does not permit me to share other common examples of clinically important molecular tests in cancer diagnosis, infectious diseases management like HIV and diseases of the blood. We have provided a longer written comment as an attachment that does provide more examples and information.

It is important to address common misconceptions about genetic testing, particularly with respect to validation and regulation.

Validation for analytical accuracy is required for all laboratory developed tests and must be made available to laboratory inspectors. For our CF test we worked closely with the manufacturer to collect data for FDA review.

For the clinical validation of the CF test, we relied on published scientific literature. A standard that I as a laboratory geneticist adhere to is that there must be at least three scientifically sound peer reviewed studies demonstrating a causal or strong link to disease. In some instances, other means of validation are initiated by the lab, consistent with medical practice guidelines and in collaboration with clinicians.

There is a particular challenge to validate tests for rare disease. The NIH encourages laboratories to develop and validate tests for rare genetic diseases that are unlikely to be developed by manufacturers. Their Collaboration, Education, and Test Translation (CETT) program combines the expertise of clinicians, researchers, clinical laboratorians, genetic counselors and patient advocates. It ensures educational material, appropriate testing protocols and good reporting practices.

Molecular tests are available for over 1,500 diseases and conditions and are performed in over 1,200 clinical laboratories in the U.S. Although the FDA has approved relatively few of these individual tests, by volume the cleared tests represent 60-70% of genetic and molecular tests in common usage. The pie chart below graphically depicts this finding. In addition, it has been estimated that as much as 75% of all genetic testing volume performed in the United States is subject to oversight by the State of New York, which carefully examines the clinical validation of new tests. Furthermore, all genetic tests ordered by health care providers are performed in laboratories regulated under CLIA by the Centers for Medicare and Medicaid Services.

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly, our industry association, ACLA, has proposed both strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS.

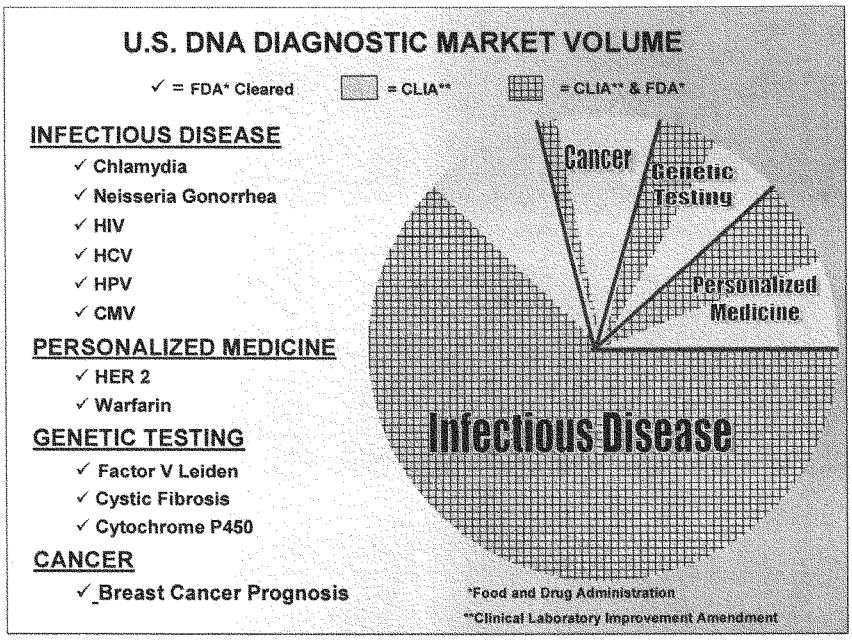
I want to contrast the examples of well established and validated tests with some tests being marketed directly to consumers that make unsubstantiated claims related to disease and provide advice that borders on the practice of medicine. A web based company offers to analyze 5 genes to determine insulin sensitivity. They state that loss of insulin sensitivity may play an important role in common health disorders including type 2 diabetes, high blood pressure, and heart disease. The gene testing result is provided back to the consumer, without any physician examination, glucose testing or HbA1C testing, with suggestions for diet and lifestyle choices – including marketing of vitamins and minerals.

Senator Smith's hearing in 2006 did much to bring attention to certain online companies who market genetic tests directly to consumers and make misleading claims. CMS has properly enforced regulation of those that claimed they need not be CLIA licensed. For those companies that merely market genetic tests performed by other laboratories, any misleading claims about these genetics tests should be investigated by the Federal Trade Commission (FTC). We applaud Senator Smith for raising this issue and support actions to stop these activities.

Let me close with my thoughts for guiding principles to apply to genetic test services:

- Tests should be developed based on sound medical knowledge
- Tests should be ordered by a knowledgeable health care professional who can guide their proper use and interpretation.
- All laboratories which perform these tests should be CLIA certified for high complexity testing
- Exaggerated or unsubstantiated claims should be investigated by the Federal Trade Commission

Innovation in molecular testing is extremely sensitive to regulation and reimbursement. Too much of the former, and too little of the latter, could prevent or delay the hoped-for medical advances. I believe we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.



American
Clinical Laboratory
Association

Genetic Test Fact Sheet

Executive Summary

Knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and its care. It has led to a new era of "personalized medicine" replacing a trail and error approach. Genetic tests are powerful – they allow for the selection of the specific medication that will best treat disease, predict the risk of disease before symptoms occur, and manage the disease more effectively with better information.

Recent media reports could lead one to question the value of genomic based medicine and be concerned that the field is not regulated. That is unfortunate because it sends the wrong message to the public and decision makers. The fact is, the majority of genetic tests by volume are cleared by the Food and Drug Administration or are performed in a laboratory regulated under the Clinical Laboratory Improvement Amendments by the Centers for Medicare and Medicare Services—or both. In addition, clinical laboratories performing genetic tests are regulated by states, and most are additionally overseen by other accrediting bodies.

A concise definition of genetic test remains elusive because genetic tests can refer to analysis performed on human DNA, RNA, genes, and/or chromosomes, human proteins and certain metabolites used to detect inherited or acquired disease and conditions. It is incumbent on all of us to be mindful of this inherent limitation as we discuss important issues such as regulation and validation of genetic tests.

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly the American Clinical Laboratory Association has proposed strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS.

There are a few bad actors marketing lifestyle, nutritional deficiency, and other tests directly to consumers online with inappropriate and misleading claims. By alleging these tests are for screening and not medical diagnosis, some of these web based companies skirt the CLIA requirements and do not require a physician to order the test and do not provide genetic counseling to help interpret the findings. It is important to distinguish between well established and validated tests with tests being marketed directly to consumers that make unsubstantiated claims to disease and provide advice that borders on the practice of medicine. Companies marketing genetic tests directly to consumers utilizing non CLIA-certified laboratories or making unsubstantiated claims should be investigated by the Federal Trade Commission.

Innovation in molecular testing is extremely sensitive to regulation and reimbursement. Too much of the former, and too little of the latter, could prevent or delay the hoped-for

medical advances. ACLA believes we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.

I. What is a Genetic Test?

There is no generally accepted definition of "genetic test". A concise definition remains elusive because genetic tests can refer to analysis performed on DNA, RNA, genes, and/or chromosomes, proteins and certain metabolites used to detect inherited or acquired disease and conditions. In some cases there is cross-over between a disease that is inherited and one that is acquired through lifestyle, nutrition and other factors.

This complexity and lack of specificity in the definition can lead to confusion in communication and increases the chance of unintended consequences with regulatory and legislative oversight efforts. It is incumbent on all of us to be mindful of this inherent limitation as we discuss important issues such as regulation and validation of genetic tests.

Setting aside the lack of a precise definition, knowledge gained from the Human Genome Project has resulted in meaningful discoveries in our understanding of disease and in our care for patients. It has led to a new era of "personalized medicine" opportunities that identify genetic differences among individuals and in many cases, customize treatment which holds promise to significantly advance medical care.

One way to look at genetic testing is to consider tests by the laboratory techniques used to examine material taken from blood, urine, cheek or skin cells or tissue samples. These can be considered in three categories:

- Cytogenetics is used to detect chromosomal abnormalities such as the number and shape of chromosomes within a cell by microscope examination, detection of fluorescent probes, or microarray CGH testing (common test is chromosome analysis for trisomy 21(Down syndrome) or fluorescent probes for leukemia's).

- Molecular genetics is used to detect changes at the level of a single or multiple genes or DNA sequence within cells (single inherited gene examples are Cystic Fibrosis or Fragile X syndrome; multiple gene examples are familial colon cancer (Lynch syndrome), an oncology example is bcr/abl monitoring for leukemia, and an infectious disease example is HIV genotyping for drug susceptibility.

- Biochemical Techniques are used to detect markers of changes inhuman proteins and certain metabolites based on genetic function (common examples are phenylketonuria (PKU) the first newborn screening disease and Tay-Sachs disease, an oncology example is HER2 protein detection in tumors).

II. Genetic Tests Have Significant Healthcare Value

These multiple applications of genetic testing allow for the customized treatment or "personalized medicine" approach, which is replacing the trial and error care to diagnosis and treatment. Sales of DNA tests represent about 5% of all diagnostic tests ordered in

the US, and they are the fastest growing segment at about 15% a year. There are many and rapidly growing examples of how genetic tests provide real health care value. Genetic tests are increasingly being used to;

- Select the specific medication that will best treat the disease
- Predict the risk of disease before symptoms occur, allowing earlier treatment or lifestyle changes to avoid disease
- Manage the disease more effectively with better information

Condition	Problem	Personalized Medicine Approach	Result
Selecting the specific medication that will best treat the disease…			
Breast Cancer	Overabundance of HER2 protein on the surface of breast cancer tumors prompts excessive cell growth	Genetic test measures HER2, identifying patients who will benefit from a drug that inhibits its growth	Significant improvement in survival rate. Reduces cancer spread by 50%
HIV	Viral genetic variations make the HIV virus resistant to some anti-retroviral drugs	Tests determine the genetic makeup and rapid mutation of an individual's virus and pinpoint most effective drug	Dramatic improvement in quality, length of life. Patients now can now live for decades
Cardiovascular disease	Genetic variations in the ability to metabolize warfarin, a common blood-thinning drug, often lead to clotting or bleeding	Genetic tests identify the variation	Allows more precise and individualized dosing. Broad use could reduce strokes by 17,000, costs by $1 billion annually
Colon cancer	Due to a gene variation, patients experience life-threatening side-effects from certain colon cancer drugs	Genetic test identifies the variation	Allows physicians to choose other drugs to address cancer
Predicting the risk of disease before symptoms occur, allowing earlier treatment …			
Breast cancer, ovarian cancer	Variations in the BRCA1 and BRCA2 genes increase risks for breast and ovarian cancer	Genetic test identifies the variation	Allows preventive measures, such as closer monitoring and preventive surgery
Colon cancer (Lynch syndrome)	A gene mutation in one of several genes increases the risk for hereditary colon cancer	Genetic tests identify the variation	Allows early and regular screening to enable early detection and treatment
Blood clotting	Individuals with a variation in the Factor V gene and	Genetic test can identify unique variation that increases risk	Allows preventive strategies and medication

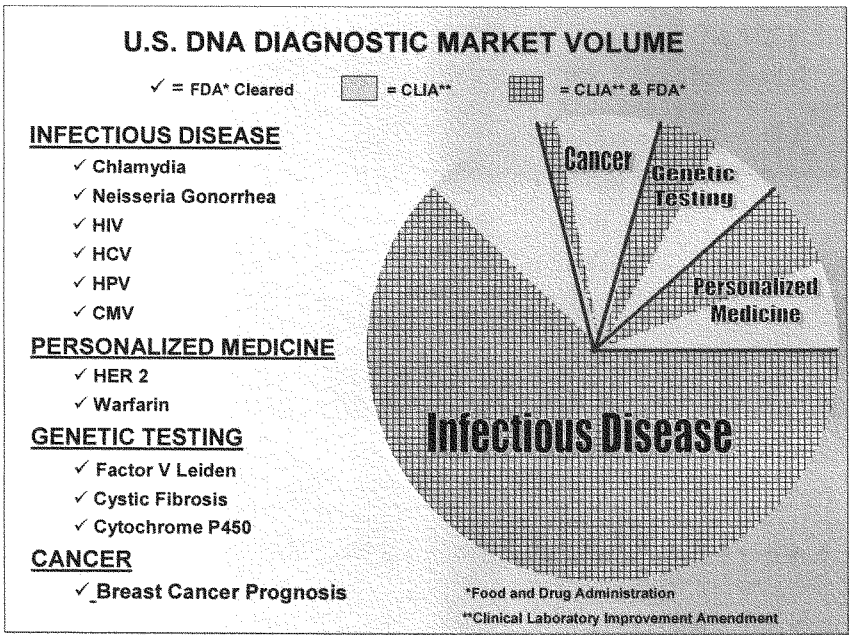
	other genes have five times greater risk of a developing blood clots		to manage clotting
Heart disease	Gene variations increase susceptibility to heart disease and heart attack	Gene tests identify the gene variation	Lets physicians increase the dosage of statin drugs, thus significantly reducing risk of heart attack and coronary heart disease
Melanoma	Gene variation leads to up to 40% of hereditary melanoma cases	Test identifies increased susceptibility to melanoma	Allows preventive steps such as surgery on suspicious lesions, less exposure to sun
Emphysema	Gene variation increases likelihood of liver cancer in patients with emphysema	Genetic test identifies the variation	Allows diagnosis without biopsy; early identification also enables preventive actions
Diagnosing the disease more precisely, leading to more effective treatment...			
Childhood leukemia	Various genetic subtypes of the most common form of childhood leukemia makes "one-size-fits-all" treatment ineffective	Gene tests identify subtypes	Enables physicians to choose drugs and treatment protocols that are geared to the specific genetic subtype. Today's cure-rate for children exceeds 80% vs. 4% in the 1960's
Adult Leukemia	Chromosomal changes create an abnormal protein that increases white blood cells	A genetic test detects the abnormal protein, which can then treated with a genomics-based drug that slows its growth	Better response rates, less toxicity, complete remission in many patients. 5-year survival rate increased from 69% in '01 to 89% today
Cervical Cancer	Certain high-risk strains of the Human Papilloma Virus (HPV), which causes cervical cancer, are difficult to identify	Genetic test identifies the high-risk strains of the HPV	Allows earlier decisions about treatment and frequency of follow-up monitoring
Managing the disease more effectively with better information...			
Breast Cancer	The traditional treatment following surgery for early stage breast cancer is chemotherapy, but it may provide little or no benefit to many women	Gene tests identify an overabundance of specific genes in the tumor itself. This information can be used to quantify the likelihood of cancer recurrence—and the likely need for chemotherapy	Provides more information for physicians and patients to decide whether the benefits of chemotherapy outweigh the side-effects and cost

Cancer	Chemotherapy is often prescribed once cancer has progressed beyond the early, localized stage—yet cancer patients do not respond to chemotherapy 70% of the time	Functional genetic tests can identify with extremely high accuracy those drugs to which the patient's cancer is resistant	Helps in prescribing the most effective treatment, sparing patients unneeded toxicity and saving valuable treatment time
Hereditary hemochromatosis	Hereditary gene variation causes the body to absorb excess iron, leading to liver failure, heart failure, and diabetes	Gene test identifies the variant	Replaces liver biopsy as the first-line confirmatory test for most patients; alerts family members to need for monitoring, preventive therapy
Metabolizing Medications	Gene variations can mean an individual absorbs drugs too slowly or too quickly—leading to "too little" or "too much" of the drug	A molecular test detects the group of enzymes that influence metabolism of about half of all drugs	Allows physicians to make more precise, individualized dosing decisions
Screening to determine if the disease is present...			
Sexually transmitted diseases, hepatitis	Older methods including culturing the bacteria or virus can take days for results	Genetic tests identify these conditions in hours, rather than days	Enables rapid intervention and treatment
Staphylococcus infections	A rapidly-morphing group of bacteria—called Methicillin-Resistant Staphylococcus Aureus—is resistant to drugs	A genetic test can identify this form of Staphylococcus infection rapidly	Helps detect and stop costly, dangerous infections that patients acquire in the hospital

III. Genetic Tests Have Extensive Regulatory Oversight

There are genetic tests for over 1,500 diseases and conditions offered by over 1200 clinical laboratories in the U.S. The Food and Drug Administration has cleared or approved several dozen of these tests, and those approved represent approximately 60-70% of the molecular genetic testing by volume ordered. Genetic tests are performed in laboratories regulated under the Clinical Laboratory Improvement Amendments (CLIA) by the Centers for Medicare and Medicaid Services. In addition, laboratories are regulated by states, and most are additionally overseen by other accrediting bodies.

The pie chart graphically depicts this finding. Furthermore, genetic tests ordered by health care providers are performed in laboratories regulated under CLIA by the Centers for Medicare and Medicaid Services.



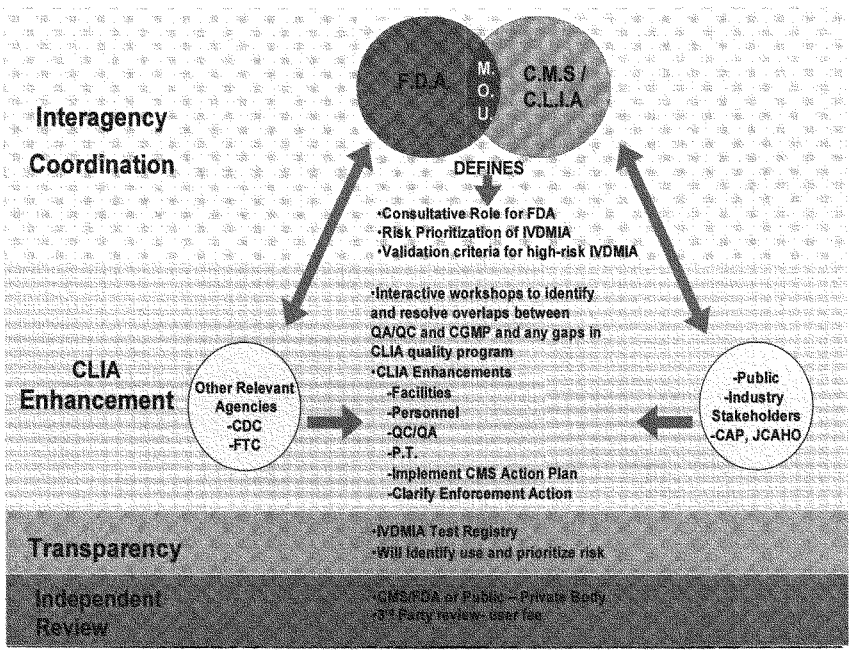
IV. A Proposal to Strengthen CLIA and CMS Oversight

As an industry, we recognize that the existing regulatory paradigms of CMS and FDA need to be updated to keep pace with the rapid advances in genetic testing. Accordingly the American Clinical Laboratory Association has proposed strengthening CLIA and CMS oversight, as well as greater interagency coordination between FDA and CMS. An important aspect of the proposed model is an interagency Memorandum of Understanding (MOU) defining a significant consultative role for the Food and Drug Administration while maintaining the Centers for Medicare and Medicaid Services and CLIA as the exclusive regulatory authority for laboratory test services. The key elements of the proposal are summarized below as bullets; a graphic displaying the key components follows. The key points of the proposal are:

- It is consistent with principles of least burdensome regulation thus avoiding overlapping and potentially conflicting regulatory oversight by maintaining CMS as the sole regulator under CLIA while identifying a significant FDA role.

- It is intended to remedy known concerns by including a mandatory test registry maintained by CMS or by a public-private entity and accessible by the public.
- It can be implemented under law as it exists today through the MOU process and use of interpretive guidelines.
- It is a participatory approach that draws on the expertise of industry stakeholders, CMS, and FDA.
- It does not involve significant new costs for the agencies to build internal expertise or fund a parallel laboratory regulatory oversight structure. User fees would fund third party review of validation packages

Overview of Model



V. What is Needed for the Validation of Genetic Tests

It is important to address common misconceptions about genetic testing, particularly with respect to validation and regulation.

In enacting the Clinical Laboratory Improvement Amendments (CLIA), Congress clearly intended CLIA to be the controlling mechanism for regulating laboratory testing services. CLIA constitutes a comprehensive regulatory scheme that governs nearly every aspect of a laboratory's testing performance. As the agency responsible for CLIA, CMS is responsible for each aspect of validity of laboratory developed genetic tests. The FDA is responsible for ensuring both the analytical validity and clinical validity of commercial genetic test kits manufactured as devices for commercial distribution to third parties, which are not regulated as such under CLIA.

CLIA is fully accepted and recognized as providing a comprehensive, robust approach to all aspects of analytical validity. The requirements and specific approaches to clinical validity should also be an internal function of the laboratory offering the test, if offered as a laboratory developed test. If the laboratory uses an FDA cleared or approved product without modification, it is sufficient for the laboratory director to rely upon the FDA's determination of intended use and clinical significance. If the laboratory offers a test that represents a modification of the FDA cleared or approved product or a laboratory developed test, the laboratory director must ensure that such tests have been appropriately validated. This can be demonstrated by means of peer reviewed papers that report on clinical studies and/or actual clinical studies to the extent that the laboratory performs them to establish clinical validity in different patient subsets.

ACLA supports the principle of data transparency as it relates to making available to clinicians data relevant to the genetic tests they may order, including data regarding the clinical validity of such tests, to the extent that such information is readily available. Data that would be sufficient to demonstrate clinical validity includes that reflected by existing medical guidelines or contained in peer-reviewed literature derived from clinical research. When it is suggested that clinical laboratories should "document current evidence" concerning the clinical validity of tests offered, adequate documentation includes assembling existing medical guidelines or peer reviewed literature derived from clinical studies, but does not necessarily require the clinical laboratory itself to conduct clinical trials. At a minimum the supporting documentation for the clinical validity and utility of a genetic test should include multiple references that provide a reasonable basis for concluding that the test is valid and effective for patient care.

There is a particular challenge to validate tests for rare diseases. The NIH encourages laboratories to develop and validate tests for rare genetic diseases that are unlikely to be developed by manufacturers. Their Collaboration, Education and Test Translation (CETT) program combines the expertise of clinicians, researchers, clinical laboratorians, genetic counselors and patient advocates. It ensures educational material, appropriate testing protocols and good reporting practices.

VI. Problems Raised by Some Direct to Consumer Genetic Tests

There are a few bad actors marketing lifestyle, nutritional deficiency, and other tests directly to consumers online with inappropriate and misleading claims. By alleging these tests are for screening and not medical diagnosis, some of these web based companies

skirt the CLIA requirements and do not require a physician to order the test and do not provide genetic counseling to help interpret the findings. It is important to distinguish between well established and validated tests, on the one hand, and tests being marketed directly to consumers that make unsubstantiated claims to detect disease and provide advice that borders on the unlicensed practice of medicine.

Interest in these direct-to-consumer (DTC) genetic testing companies was enhanced following a hearing by the Senate Special Committee on Aging in 2006. This hearing did much to bring attention to certain online companies who market genetic tests directly to consumers and make misleading claims. CMS has properly stepped up enforcement of those that claimed they need not be CLIA licensed. The Federal Trade Commission (FTC) has released an alert warning consumer's about DTC marketing of genetic tests. Some states have increased the regulation of these tests. But more needs to be done.

ACLA's guiding principles should be applied to all genetic test services:

- Tests should be developed based on sound medical knowledge
- Tests should be ordered by a knowledgeable health care professional who can guide their proper use and interpretation.
- All laboratories which perform these tests should be CLIA certified for high complexity testing
- Exaggerated or unsubstantiated claims should be investigated by the Federal Trade Commission

Innovation in genetic testing is extremely sensitive to regulation and reimbursement. Too much of the former and too little of the latter could prevent or delay the hoped-for medical advances. ACLA believes we can target the problems of marginally useful testing while allowing testing based on good science to accomplish its promise of diagnosing, treating and preventing disease.

These aberrations should not confuse the public or policymakers. Genetic tests performed in CLIA certified laboratories are safe and are saving and improving lives daily.

For more information on the value of laboratory testing, go to www.labresultsforlife.org or call 202-637-9466.

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