New York State's Clinical Laboratory Evaluation Program
Ann M. Willey, Ph.D., J.D.

DR. FERREIRA-GONZALEZ: After we disconnect, we can go to the next speaker. We'll now turn to the role of the states.

Welcome back, Dr. Willey, and this is Dr. Willey. We're happy to have you here.

DR. WILLEY: Actually it's Willey.

DR. FERREIRA-GONZALEZ: Ouch.

(Laughter.)

DR. TUCKSON: It's so good to know that I'm not the one that screwed that up.

DR. FERREIRA-GONZALEZ: Well, welcome back. We're happy to have you here with us again.

For those of you who are new, Dr. Willey is the Director of Laboratory Policy and Planning at the Wadsworth Center, New York State Department of Health. She's also Director of Cytogenetics at the same institution where she's responsible for genetic testing laboratories, including the newborn screening and regulatory quality assurance programs, overseeing the practice of genetic testing entities and related research activities and administration of the New York State Genetic Service Program and regional genetics network.

I'll turn the floor over to you so we can learn more about the role of New York State in oversight.

DR. TUCKSON: By the way, Marc, one of the things I try to do -- hopefully, you're feeling well introduced to the committee. Even for the people that have been here like forever, it's impossible to keep up with all this stuff. You're, obviously, sophisticated in everything that's going on.

I'm also reminding anybody that may not have been at the last meeting. I'm just using Marc as the example here. I think what we are getting at is what people often don't think about are the roles of the states as they have oversight. We think about it from the federal government apparatus, and we don't think about the state.

We did not have Dr. Willey on the agenda last time. She leaped to her feet and grabbed the microphone and educated us ad hoc. But what we also learned last time was that New York -- because so many of the lab companies have some relationship with New York, they have this extraordinary legislative clout. What we also learned is that they are doing a whole bunch of stuff that in some ways are the models for what the federal government ought to be doing.

So I think as we all listen to this presentation now, if you in your mind are populating that map around who does what and where are the gaps, we've got to have a big, special color for states, and specifically for New York, in terms of the part that they do and then sort of seeing how that lines up. So that's what this is ultimately about.

So thanks again, Dr. W.

(Laughter.)

DR. WILLEY: Thank you. I'm technologically always challenged and I rarely speak from slides. So we'll see if this works.

I'm frequently asked how New York State got to the position it is. We have had clinical laboratory oversight statutory regulatory authority since 1964, predating CLIA 1967. We had deemed status under CLIA '67. We have exempt status under CLIA '88.

The relevant section of our regulatory program for discussions today is 10 NYCRR, part 58-1.10, that states that "all technical procedures employed in a laboratory shall be of proven reliability and generally accepted by leading authorities in the specialties of laboratory medicine" -- and the really critical potion is this -- "and/or approved by the Department of Health." That has given this program the authority to review any and all lab tests, even those approved by the FDA, as applied to New York State.

The other piece of history I should share with you is that in 1964 when the statute was passed, it was intended to limit the practice of laboratory medicine to laboratories physically in the State of New York, therefore infringing on interstate commerce. The statute was challenged in the federal courts and overturned in terms of its ability to restrict business to labs in New York State. But the same court said that the State of New York could apply its standards, whatever they were, to any laboratory doing business in the State of New York.

So we currently regulate laboratories in Iceland, the United Kingdom, Hong Kong, and all over the United States. If the specimen is drawn in the State of New York or if it is shipped to a laboratory anywhere in the world, that laboratory is subject to New York State licensure requirements.

DR. TUCKSON: Just to make sure -- again, this question may be beyond your area of expertise. Again, just to get it right, the FDA, which is pretty scary in terms of -- it's the FDA.

(Laughter.)

DR. TUCKSON: I mean, Gutman comes in here. He swaggers with such confidence.

(Laughter.)

DR. TUCKSON: FDA says this is okay. New York can say not necessarily so for the people of New York?

DR. WILLEY: Correct.

DR. TUCKSON: Wow.

DR. WILLEY: We have rarely, if ever, done that, however.

DR. TUCKSON: But you have the ability to tell FDA to go sit down.

DR. WILLEY: No. We have the ability of the marketer of the service in the State of New York that, for New York, they may have to meet additional requirements.

DR. TUCKSON: Okay. Then also to make sure, New York considers doing business in New York, meaning any blood coming out of a New Yorkian's arm --

DR. WILLEY: A New Yorker in New York.

DR. TUCKSON: If I am in New York and I get blood drawn --

DR. WILLEY: Correct. You don't have to be a New Yorker, but if you are inside the boundaries of the State of New York.

DR. TUCKSON: Anyone who is fortunate enough to be within the boundaries of the State of New York who has blood drawn, at that moment whatever company is involved with that process is then doing business in New York. Even if it's an Iceland company who makes the lab reagent and the blood goes in a tube, at that point that company based in Iceland is doing business in New York.

DR. WILLEY: Not that company. The laboratory performing the test. So if the laboratory performing the test is in Iceland or the United Kingdom, then they are subject to our oversight. They could be buying their reagents from anywhere in the world, and we do not regulate manufacturers of kits, devices, or reagents. We regulate the user, the laboratory.

DR. TUCKSON: You regulate the user. That was the distinction I needed. I'm sorry to interrupt your flow, but thank you.

DR. LICINIO: Just a question continuing along those lines. If something is regulated like that by the State of New York, let's say, for a lab in Kentucky or the United Kingdom, because New York is such a big market, do those labs then tend to follow these guidelines for everything they do?

DR. WILLEY: Absolutely, because at least in the U.S., the tort law cases, the medical malpractice cases look very dimly upon a laboratory that holds a New York State permit and meets those standards for specimens from New York, then applying lesser standards to specimens derived from other sources.

DR. FERREIRA-GONZALEZ: I will ask everybody to hold their questions for the end of the session.

(Laughter.)

DR. FERREIRA-GONZALEZ: So we can continue with the flow and let her go over some of these issues. Thank you, everybody.

DR. WILLEY: So I've been specifically asked what is expected of a laboratory in this process. The second half of this slide says, "A laboratory shall perform only those assays that have been validated or verified at the site where the assay will be performed." This applies primarily to multi-site, large commercial entities who might want to validate an assay at one site and then simply translate it or transfer it to other sites. They can do that, but they will have to reproduce the validation data at any site they intend to offer the test. Or they can simply ship all the specimens for that assay to one site.

They must hold the appropriate permit category for the test. New York State doesn't have six specialties. We have 26 and I think all of the subspecialties give us some 70 different categories in which we issue permits to laboratories. And every test falls in one or sometimes more than one of those categories.

And they must meet all of the other requirements related to personnel and proficiency testing and onsite inspection.

The point of this is our review of the validation of a home-brewed assay or an assay using certain commercial reagents is an integrated program. We know the personnel in the lab. We know that every category has an assistant director or director holding specified credentials. They are all doctoral degreed individuals with a minimum of four years postdoctoral clinical lab experience and a minimum of two in the specialty. All of their other personnel must meet other training experience. They are physically inspected every two years for their quality assurance program, their quality control, their reagents, their equipment, their physical location. And they are required to participate in New York State's proficiency testing program and they are encouraged to participate in any other relevant proficiency test.

Assays that we require specific validation review. This is for approval prior to actually offering the test. Any assay that is commercially distributed that is either labeled as research use only -- in other words, they're avoiding review by the FDA -- or any assays developed using analyte-specific reagents. And we do thank the FDA for its recent clarification, but we think it will create some significant problems, which we have shared with Steve. FDA-approved assays or IUOs, investigational use only assays, that have in any way been modified from their intended use or IDE approval from the FDA. Any inhouse developed assays.

An intended use is anything which changes the specimen type, the type of analysis, qualitative or quantitative, the purpose of the assay -- are you doing screening, diagnosis, prognosis -- or the target populations as specified by the FDA, outlined in the package insert, or an IDE for an investigational use device.

FDA-approved assays and IUOs can be used simply by notifying the department that the lab wishes to add them.

Now, I'm frequently asked what is it we actually look at when we're looking at a validation package. We have been regulating cytogenetics labs since 1972 and genetic testing labs since 1990. But, again, I want to emphasize that our validation review process applies to any laboratory assay used in any one of the multiple categories. We do have category-specific standards by which we look at these materials, but these packages are the same whether you're doing a hematology assay, you're setting up a new cytopathology assay, you're doing microbiology, or you're doing genetics.

The materials the lab submits -- they tell us what they're calling the test, and you would be amazed at the innovation and creativity of some of the names out there. They have to tell us the manufacturer of any reagents they're using other than those they might make themselves. The majority of laboratories are not making their own reagents. They're getting them from manufacturers.

If using manufactured components, what is the commercial designation of that component. In other words, go to the manufacturer's catalog. Is it an RUO? Is it an ASR? Is it some other creative category?

What is the basic method or scientific principle behind the assay? Is this a DNA assay using PCR? Is it a cytogenetic assay using fluorescence in situ hybridization probes? What's the assay that they're proposing to do?

What New York State permit category -- and this takes great insight from the lab sometimes -- do they think this belongs in, and we'll tell them whether we think they're right or not. The implication of this is if this is a lab that was previously only doing molecular DNA assays and they want to now do a FISH assay for a chromosome rearrangement, they're going to have to qualify for a cytogenetics permit, in addition to their genetic testing permit, and they'll have to hire someone who meets the qualifications as a cytogeneticist. So there are implications as to what category of the test.

What specimen type do they intend to use? Blood, tissue, bone marrow?

What is their target population? Is this intended for individuals who are symptomatic with disease? Is it intended for general population screening? If so, what are the population parameters? Is it a diagnostic test, a prognostic test, a screening test, a predictive test? Is it qualitative or quantitative in its intent?

And how do they intend to establish its performance? Are they going to compare it to another existing assay similar to a 510(k) type arrangement for the FDA, or are they going to use clinical status of test subjects as in a new test for a rare condition? This list goes on and you have it in your slides, and I won't describe each assay.

How are they doing the test, down to the procedure manual that they would provide to the technician in the lab who would have to learn how to do the test?

They must also provide their practitioner/patient information, including their description of the limitations of the test. I think this goes somewhat to that issue of how do we disseminate information appropriate to help the clinician decide what test to do or to help the clinician interpret the test after he's done it. We do rely on the laboratories to draft this material, but we do critique this material often to great extent.

The principle of the assay. How do they know it's a clinically valid assay? And we've talked earlier that very often these new genetic tests -- it is based on literature description of some association of this analytic marker with some clinical condition. For molecular genetic tests, we want the description of the actual gene structure, if known. But clinical validity is generally for genetic tests a literature-based observation, at least initially.

What equipment do they need? What reagents? Where are they getting them, and where are they getting their controls?

How are they going to calculate or interpret the result? This goes to that question of IVDMIAs. We don't care whether it's a single analyte simply reported as a quantitative value or a gene sequence or a chromosome rearrangement by ISCN nomenclature or it's multiple analytes taking demographic characteristics and put through a statistical equation. If it's the latter, we want to see the equation and the statistical basis on which that equation is derived. But how is the laboratory going to interpret the result?

What compounds or substances interfere?

What are the limitations of the test? This frequently goes to the issue of what patient population has the laboratory studied. Now, some of these assays are rare. Access to a known positive patient is sometimes close to impossible, and the laboratory will wish to offer the test having never seen an abnormal. We will approve a laboratory to offer an analytically validated test if

they can detect the target, whatever it is, so long as they inform the practitioner who's going to order the test, prior to ordering the test and again at the time of interpreting the test, that the laboratory is reporting the result, but by the way, they've never seen an abnormal. And therefore, their ability to interpret these results is greatly limited.

We want to see their test requisition. How do they actually describe the test?

For germline genetic tests, they have to also, in New York State, document their compliance with our privacy and confidentiality statute which is Civil Rights Law 79L. It applies only to germline genetics and applies only under statute to predisposition testing, that is, nonsymptomatic testing, but most laboratories figure they'll just apply it to any genetic test.

We want to see their sample reports for both normals and abnormals, including all necessary disclaimers. If they're using ASRs, it must be the FDA-prescribed disclaimer. And we want to see their scientific references. They can simply give a list.

And finally, the critical component of this package is where's their data. How many specimens have they actually tested and what were those results and what are they comparing those results to? On what basis are they calling these normals or abnormals? How are they recording the data? But I would caution, we frequently review and approve packages in genetics that have tested 10 normal patients.

Analyte and specimen matrix stability, reagent source, quality, particularly for RUOs. If they buy an ASR, they can rely on the manufacturer to tell them it's that piece of DNA that came from that gene of that size that encompasses those sequences because the FDA has agreed that that manufacturer is a GMP manufacturer and they know what they're making.

If they buy an RUO, they can rely on the manufacturer for nothing. And if they buy a piece of DNA, primer, a FISH probe, whatever, they will have to establish some means by which they verify either the DNA sequence or the genetic component or the fluorochrome or whatever. We try to make the point to manufacturers as well, if you're going to sell reagents to laboratories that are developing clinical tests, you are not doing them any favor by being an RUO vendor. If you're a GMP ASR vendor, at least the laboratory can rely on the product for whatever it is.

They must then establish the performance characteristics of the assay. What's the accuracy, the precision, the reportable ranges, sensitivity, specificity? And you would be dismayed to know how many genetics labs don't know what those terms mean.

Where performance evaluation is based on clinical outcome of test subject status, we need to know how they've established that. It isn't just the result of this test that tells them that they're normal or abnormal. They have to have had pathology, histopathology, clinical evaluation, symptomatic evaluation, however they're calling this a normal or abnormal patient. And when they're doing their validation, the analyst should not know who's normal, who's abnormal. It should be blinded to the analyst.

And when they get discrepant results, how do they resolve them? And how do they calculate their predictive values?

They must interpret the test. Our standards require that cytogenetics and genetics laboratories report with an interpretation suitable for a nongeneticist physician. If we bore the geneticists,

well, that's too bad. They can skip it, but we want to make sure that those other physicians see something that they might be able to understand.

If there are reference ranges for germline genetics of single gene disorders, what are the heterozygote, homozygote results?

And does it predict disease state? Because a lot of assays are indicative of some risk factor, but they don't actually predict disease.

The assay data for actual runs, and what is their quality assurance plan and internal PT design? In New York State, we offer our own cytogenetics proficiency test. We occasionally test the ability of a lab to perform FISH, fluorescence in situ hybridization, but it would be for one or two target probes at any given proficiency test event. We ask all of these laboratories to have some form of proficiency assessment twice a year for every analyte. No commercially available proficiency test will provide them with materials to do every gene that they're doing, and for some of these labs, there is no commercially available PT material for the gene that they are doing. So they will have to have developed their own blinded proficiency assessment, probably using materials derived from previous specimens. The difference is that when our surveyors visit, they actually will ask to see the data and the design of that assay.

We're frequently asked about workload. Here are the statistics since we've been keeping them since 1995. This program actually started primarily for genetics, although it applied to every assay, in 1990 because there were no FDA-approved assays and there was no comparability testing.

In 1995, when we started keeping the numbers, we actually looked at eight assays. They were all genetics.

In 2006, we looked at 586 assays. The majority of them are genetics, but this includes not only genetic testing, biochemical genetic testing, DNA-based genetic testing, cytogenetics, it also includes for us the categories of preimplantation genetic diagnosis, forensic DNA technologies, paternity identity, histocompatibility, and oncology molecular markers. They just get thrown in there as genetics.

So for genetic testing workload, in 2006, we looked at 86 DNA-based, primarily single gene disorders; 5 biochemical types of assays. This would be enzyme assays, metabolites. I personally looked at 44 FISH assays. We looked at 3 paternity identity assays, 81 forensic identity assays. These would be different STRs, different markers, mitochondrial markers. And 92 molecular oncology markers for acquired changes or expression in cancer.

We're often asked what is the impact of the New York State program on testing in this country. We currently have 70 laboratories in the country, cytogenetics laboratories. Five of these are preimplantation genetic diagnosis labs. The "genetic testing" should be bold print. I'm sorry. My PowerPoint technology is limited. And 32 of those perform biochemical genetic assays. That could be anything from quantitative amino acids to tandem mass spectroscopy for various metabolites to enzyme assays. Seventy-one molecular genetics labs, including four that perform preimplantation genetic diagnosis. I include those because that's a category that I believe only the State of New York examines their assays.

So the impact in New York State is all major reference laboratories solicit and receive specimens from New York. None of them have their primary labs located in New York. They're, therefore,

subject to New York clinical lab permit requirements, including approval of inhouse assays. It has been estimated by others, not by us, that as much as 75 percent of all cytogenetic and genetic testing performed in the U.S. -- and that's in terms of numbers of specimens tested. It's not in terms of the number of labs. GeneTests estimates there are something over 300 labs. I've given you a list of about 170. And it's not in terms of number of analytes because there are lots of rare gene testing that goes on in labs that do one or two diseases or one or two genes that may not fall -- so it's not number of labs. It's not number of tests, but it is in terms of number of specimens tested -- are subject to New York State oversight. As I said earlier, tort law medical malpractice cases have not looked favorably on laboratories that are subject to New York State standards trying to get away with using lesser standards.

Now, I was also asked to review what I know about other states and their applications. There are 26 states that have statutory authority for oversight of the practice of clinical laboratory medicine in some respect or another. There is only one other state that has CLIA exempt status. That is the State of Washington. They do not, as far as I know, have specific standards for genetic testing in the State of Washington.

The State of California, through its Genetics Disease Branch out there and its newborn screening and prenatal screening program, has rigorous review of the assays related to newborn screening and newborn screening follow-up and prenatal screening that go on as part of that program. That oversight does not generally extend to other genetic testing.

The State of New Jersey does apply some personnel standards related to the American Board of Medical Genetics to their labs that perform genetic testing.

But I know of no state that actually requires validation data for individual assays to be reviewed, other than perhaps in the context of a physical onsite inspection which, at least for most state programs, does not involve peer review. It's not another geneticist visiting the laboratory.

I was also asked to address the issue of do we know about bad tests and harm that might have happened. Now, again, if specimens are going from New York to one of these labs that wishes to offer unvalidated assays or assays that we believe are problematic, we are aggressive in sending to that laboratory a cease and desist letter, and we warn them that we do have the authority to fine them $2,000 a day for continued operation or $2,000 a specimen.

Some of the recent examples have been a laboratory in New England that was offering to predict the gender of fetuses for moms when they were about five weeks pregnant. There we believe the significant problem with the assay is of analytical validity. They claim to be able to detect male DNA markers in maternal blood at the fifth week of pregnancy and therefore predict male fetus and in the absence, predict female fetus. The clinical validity -- if you could do that, you might be able to detect gender, but we've never received any validation materials from them.

The other laboratories have been those that offer to do SNP profiles and offer to provide the clinician with a CD which has the patient's entire SNP profile. And they tell you that your physician will then be able to provide interpretation and predict all of your medical needs.

(Laughter.)

DR. WILLEY: Since they've not been able to document the actual clinical validity for the vast majority of those SNPs, they are authorized in New York to market testing -- I believe at the moment it's only four of their thousands of SNPs.

We've had serious challenges from laboratories that wish to perform nutrigenomics. They will do a DNA profile primarily of SNPs that they claim are linked to particular genes that may predict your response to certain nutritional products, not unlike the survey that was done by the GAO. Again, lack of clinical validity. There's no association with disease. And yet, we would say that they are testing a specimen derived from the human body for the assessment of some component for purposes of health assessment. It doesn't have to be disease assessment in our statute. It can be health assessment. And the consumer expects to be advised as to their state of health, their response to their nutrition, and therefore, we say to the laboratory they should not be doing this.

The other area of great concern is hobby genetics. It may not be the topic of primary interest to this group. But there are entities out there who are offering profiling for your ancestry, profiling for paternity. You know, you've got the kid for the weekend. Just send us a little cheek swab. And you always wondered and we'll tell you if.

And since we regulate forensic DNA done in private laboratories, the personal private eye, you know, if you wanted to know if there was a little infidelity going around, just send us some sheets.

(Laughter.)

DR. WILLEY: And in New York State, consumers cannot legally order laboratory tests other than those which have been approved by the FDA for over-the-counter self-testing. So laboratories cannot accept the bed sheet, the cheek swab, whatever. And in genetics, they cannot accept any of those tests without the written consent of the person being tested. So we also tell the laboratories they must cease and desist on the grounds that they're violating the patient-ordered testing.

There are issues then. New York State restricts who can order tests -- it does not include genetic counselors, by the way -- and who can receive test results.

The greatest challenge to the New York State program is this is expensive. The program cost for the personnel and the expertise to undertake all of these reviews is significant. We currently have a lawsuit pending because the laboratories would like to not pay for that part of the program.

And the cost to the laboratories is also expensive. The preparation of the documentation of these validations in a format that is readily reviewed by the staff in the department takes laboratories time. Of course, the major criticism is -- there's a turnaround time. We try very hard for 45 days, but I have packages that have been in my office for a year. Very often they go back to the laboratories a couple of times before they get one approved.

So it's costly in terms of time. It's costly in terms of expertise, and it's costly to the laboratories.

The biggest problem is labs frequently ignore previously critiques. They are poorly organized submissions. So they end up going back a couple of times.

We talked earlier about postmarket surveillance. It's generally been our experience that, if you will, the health care market drives the survival of assays. If the assay isn't good or it's not predictive or it's not meeting needs of the medical community, the laboratory will withdraw its permit or at next inspection tell us they're no longer offering the test.

We do have an active program for receiving complaints and we do investigate all of our complaints. As I said, we do have the capacity to fine laboratories. If they told us they were going to follow one protocol and they're now using another one, they can be told they must cease testing until we review the test.

There's a lot of enthusiasm for new tests. As a cytogeneticist, I would say three or four years ago the big new test was subtelomere FISH probes that were going to detect all these cryptic translocations. We only have three laboratories that are approved to perform subtelomere FISH. Only three laboratories bothered to make the effort to validate the ASRs. They're not really ASRs because they're packaged as multiple probes in five tubes. So there are three labs that are approved to do it. The assay costs about $1,000, and the numbers of assays being performed is very small.

The new test that has great enthusiasm that's sort of related to cytogenetics is array comparative genome hybridization, and there are a few labs that are saying, oh, we're getting so many positive hits, but we don't know what they mean. So after you get the array CGH result, you have to go back and verify it by conventional FISH assays on metaphase chromosomes, and we don't really know how that's going to play out. So we have four labs that are waiting to have their validation approved. None of them are yet approved.

We also have a system in New York. We don't make physicians wait until we get around to reviewing all these assays. If a physician for a medical necessity wants to order a test that is not offered in an approved laboratory or is offered only in a lab waiting in the quay to get their assay validated, they can make a specific request to the department for what we call a non-permitted lab approval. It's a one-time, that patient, that test in that lab. And the letter that goes back to the ordering physician says, you can send the specimen. A copy goes to the lab that says you can do the test -- we won't fine you $2,000 -- for this patient, for this purpose, for this time. But the letter to the physician also says we don't know anything about this lab. We don't know anything about this test. We don't know whether you'll ever see a result.

So we do handle quite a few of those requests. We have a 24-hour turnaround time on those requests. So when labs argue that this is so slow, it's keeping them out of the market, they can't offer the test, well, no, you can offer the test, put all the right disclaimers into it.

I'd be happy to take questions if there's time.

DR. FERREIRA-GONZALEZ: Thank you, Dr. Willey. This was very comprehensive, very interesting.

I have a couple of questions. In the materials submitted for review, you commented that when performed, evaluation is based on clinical outcome, and you made an allusion that laboratory testing will be compared to the histopathology of other clinical laboratory testing. Is that a clinical validation, or do you actually look at the clinical utility of the testing before you approve some of this?

DR. WILLEY: No, we do not examine clinical utility. By clinical outcome, I mean is this patient symptomatic of the disease for which you're establishing the test.

DR. FERREIRA-GONZALEZ: There's a clinical correlation.

DR. WILLEY: It's clinical validity. Are you calling this patient a known positive, or are you calling this patient a known negative when you're doing your validation?

DR. FERREIRA-GONZALEZ: So you do not cover the clinical utility of the test.

My second question is it was very interesting to see that you are able to identity the direct-to-consumer laboratories and you're able to go after them. I was just curious to see how you identify them. How do you know they're going after the --

DR. WILLEY: Our biggest challenge is the Internet, the direct-to-consumer marketing of anything, health care in general, pharmaceuticals, and laboratory tests. There are ones like the Gender Mentor that are quite obvious that it is a laboratory entity soliciting the submission of specimens.

There are also several companies out there that have established themselves as test facilitators. They are not actually performing any tests, but they are marketing to the consumer population for a significant markup, oftentimes 10 times the money that the lab would cost. Sometimes they're using legitimate labs for legitimate validated assays. And New York State also has some lab practice general business laws regarding direct-to-patient billing. We do not allow third party facilitators. The laboratory must bill the patient and not bill through a facilitator. That's an other history.

DR. FERREIRA-GONZALEZ: One more question before we open it up. You mentioned that a company had submitted a test with a number of different SNPs. I don't know. It was genome-wide or so forth, SNPs profile. And then you only approved the use of four of those SNPs. I was wondering what was the rationale for approving only four versus the rest of the SNPs.

DR. WILLEY: For those four, they were able to document from the literature that there is a known association of that SNP in that region with a known physiologically active gene product or whatever that is associated with a particular risk or disease predisposition.

DR. FERREIRA-GONZALEZ: So you take peer-reviewed literature.

DR. WILLEY: Those four meet the criteria of being clinically valid and all of these SNPs are analytically valid. It's not hard to detect the SNP.

DR. FERREIRA-GONZALEZ: Now we'll open for a couple of questions before we have to break. Marc?

DR. WILLIAMS: You mentioned that you review reports for positives and negatives. One of the big issues with molecular is, obviously, a dreaded variance of unknown significance. Has your department begun to develop any standards about what the laboratories should be reporting back on variance of unknown significance in terms of what has been done to leave them in that sort of ambiguous classification? In other words, do you require certain steps to be done before one can stop determining whether it's a true positive or a true negative?

DR. WILLEY: Yes, for variance of unknown significance for DNA. And I'm looking at something one of my colleagues provided. I think they have to be able to describe how are they going to resolve the issue. Are they going to sequence the gene? Are they going to send it to another laboratory that can perform that? How are they going to report it and how are they going

to resolve it? And are they going to put it in a data bank and follow it up at a later point, or those kinds of things?

That's not just for DNA-based. We see that in cytogenetic FISH assays, all kinds of things.

DR. TUCKSON: Terrific.

I guess the question then boils down -- were you here earlier?

DR. WILLEY: Yes. I've been here all day.

DR. TUCKSON: Terrific. So it would be great if you could help us, as Andrea and her committee of two now, the strong, the few, the proud, can pull together this map of what exists now and what are the gaps. If you could just sort of give some thought to that, it might help Andrea's team out a little bit as you sort of see the activities.

First of all, I'm going to write a letter to your boss because you're devoting a lot of extra effort to this stuff. So we need to write a letter of thank you as we ask you to do more and more and more here.

(Laughter.)

DR. TUCKSON: So you've kind of gotten roped in.

DR. WILLEY: I've been coming to these committee meetings since 1997.

DR. TUCKSON: Well, we're going to write a letter of thanks.

But if you could sort of also think how you would advise, in the best of all worlds, what we should be advising to the Secretary in terms of this so that we don't have this redundancy. We don't want to spend the money of the people of New York and the people of the United States twice. And it seems a little bit unfair for citizens in New York to get hit twice because I assume New York still pays taxes even though you've told the FDA that they're not --

DR. WILLEY: This program, you should know, is supported by fees collected from the regulated laboratories. Unlike CLIA, we do not have a capped fee structure. We charge a very small percentage. It's currently less than .6 percent of the annual gross revenue of each of the regulated laboratories.

DR. TUCKSON: I'm sure they are still probably not pleased with that, though.

DR. WILLEY: No. They're suing us.

(Laughter.)

DR. TUCKSON: I am prescient.

So anyway, to hurry up, I think we really do want to try to lay that out and help to make sense. We can talk to you offline, but if you would be willing to do that, I think that will sort of speed this up a little bit.

DR. WILLEY: And I do think these collaborations and cooperations are very good. We rely very heavily on professional organization lab standards, the ACMG standards. When laboratories want to argue about how to go about validating an assay, we point to the documents that that professional group --

DR. TUCKSON: Let me just sort of ask it this way, and it is unfair. If you could be the head of CMS for a day, if you had a blank piece of paper and you could just do this the way it ought to be done so that it all lined up right, I'd be very interested to see what would come back from that point of view. That's what I'm looking for. If you could be in charge of fixing this, what would you say?

DR. FERREIRA-GONZALEZ: Thank you, Dr. Willey. I believe we're due for a break, and we can have a short break. Five minutes?

DR. TUCKSON: Ten-minute break, but it's got to be only 10 because she asked for 5, and I'm being nice.