Primer on the Oversight of Genetic Testing
Wylie Burke, M.D. , Ph.D.

DR. TUCKSON: So we'll just take just a second to see if Wylie has joined yet. Hey, Wylie. Can you hear us?

DR. BURKE: Well, can you hear me?

DR. TUCKSON: We do now. You look marvelous. Thank you.

DR. BURKE: Great to be here virtually. Sorry I can't be there in person.

DR. TUCKSON: Yes, but this works out pretty well. So feel confident that you can speak in a normal tone and behave normally because you are front and center. We see you well and hear you clearly.

DR. BURKE: Great. So, Reed, I need to explain that although I sent a slide show, I don't have it here with me. So I believe the slides are not going to be projected for you. I think everybody has a copy of them, and I don't think that's going to present a problem. But I'm just going to go ahead and give my presentation without slides.

DR. FERREIRA-GONZALEZ: Wylie, the presentation is in our packet. So we have copies of your slides.

DR. BURKE: Okay. I think that will work fine for this presentation.

DR. FERREIRA-GONZALEZ: Thank you very much. Go ahead, Wylie.

DR. BURKE: Well, I was asked to kind of give an overview of the oversight system. Before I begin, let me say that particularly when it comes to details of the federal agencies involved, I am well aware that there are ex officio members who know far more than I do about the details. My effort is going to be to give you a kind of big picture of where oversight occurs and what the potential interactions of different kinds of oversight mechanisms are. And I'll be happy to be corrected on any details, if need be.

Let me just start by saying that I think the reasons for oversight are clear and have been discussed now for many years, basically for a decade. We see coming out of the Human Genome Project many new genetic tests and a lot of complexities in thinking about how best to use those tests, many different technologies, often difficulties in determining or at least complexities in determining who is a candidate for a particular test, and genetic test results can be difficult to interpret. Superimposed on that is the difficulty that many clinicians at this point in time have limited knowledge of genetics. Surveys tell us that many clinicians are uneasy about interpreting or using genetic tests. All of this leads to concern about appropriate oversight.

Sources of oversight are multiple, and I really want to emphasize four different areas where we can take actions for oversight. What I want to reflect on in particular with you is how we might think about the interaction of these different methods.

So there is statutory regulation, and I know that that's received a lot of discussion in your committee and in the prior committee, the Secretary's Advisory Committee on Genetic Testing.

There's also public leadership, and I'm going to talk a little bit about, I think, the very important role that public leadership can play.

And then, as a separate issue, decisions about health care funding, which in our society can make a profound impact on how tests are used.

And then, finally, professional leadership.

So talking about statutory regulation of genetic testing at the federal level, I think we can say that there have been two major areas of focus. One is on CLIA certification and its implications, and the other is on the potential and actual role of FDA, particularly in premarket review.

So the well-established model for regulatory oversight is that for laboratory oversight, the CLIA system that provides certification for laboratories that provide test results for clinical use. What this oversight system does is it provides oversight regarding laboratory procedure, the documentation of it within laboratories, standards for the training of laboratory personnel, and also the credentials needed for test interpretation.

As you know -- I know it's already received discussion in your committee -- when we think about the CLIA system, which I think all agree is a very well functioning and effective system, there is a question about whether there should be a genetic specialty; that is, whether there need to be specific enhancements of the oversight with respect to genetic tests, particularly genetic tests that might involve complex technology. And I understand that that is still an issue that people are discussing.

I want to mention another issue with laboratory oversight, and that is the issue of results obtained in research. I know that this has been a discussion now for several years, and I guess I want to bring this to your attention because I don't think it's a resolved issue at this point.

Both the NBAC in 1999 and a working group of NHLBI a couple of years ago have set out criteria by which we could identify those results that should be disclosed to research participants. In general, I think there's a consensus from those statements that when research studies produce validated results that have implications for health and for which there is a health care intervention, that these are, in essence, results that have clinical utility and should be disclosed to research subjects. But what to do if the laboratory that generated those results is not CLIA-certified?

I'm well aware that CLIA offers opportunities for small labs that are primarily focused on research to develop CLIA certification, but I also hear from colleagues that this is not always a feasible way for researchers to go and that researchers are troubled basically about exactly what their responsibilities are. So I think this is a particular small piece of the laboratory oversight picture that perhaps still needs further discussion.

I want to talk now about the regulatory oversight of the use of tests in clinical care and just start with the historical note that in 1997, when the NIH/DOE Task Force generated its report -- this was a task force co-chaired by Tony Holtzman and Mike Watson -- one of the things they called for to support the safety and effectiveness of genetic testing was what they called evidence-based entry of new genetic tests into clinical practice. What they acknowledged was that there were not necessarily concerns with all genetic tests, but certainly that some genetic tests needed more attention than they were currently getting to assure the right kind of evidence base when they entered clinical practice.

And so they called for criteria to identify those tests where special measures should be taken, special measures specifically to require validation and clinical utility data before the tests entered the marketplace. They envisioned that this process would include an independent external review of tests, basically premarket, and that professional organizations might potentially play a role. They also considered that the FDA might have a role because the FDA does have a role with premarket review of test kits.

So that was a recommendation from the task force, and the Secretary's Advisory Committee on Genetic Testing, which preceded your committee and met between 1999 and 2002, took this recommendation very seriously and gave it a lot of consideration, as Reed and others can attest.

What the committee did was to try and figure out a way to categorize tests, basically building on the NIH/DOE Task Force call, and they did try and think through what are the circumstances when a test should receive higher scrutiny looking, for example, at diagnostic versus predictive tests. That, in a lot of the early discussions, seemed to be a critical distinction.

But the short version of the effort that went on for many months is that there was no simple way to categorize genetic tests, or the SACGT could not find a simple way to categorize genetic tests that enabled them, in a clean and simple way, to say these are the tests that require higher scrutiny and these are the tests that don't.

There are a few reasons for this. One of them is that many genetic tests have multiple uses. Most do, arguably. There are different definitions. If you say we're more worried about predictive than diagnostic tests, you get into the issue of what's a diagnostic test. I can remember, for example, a conversation about whether pharmacogenetic tests should be considered diagnostic, that is, diagnosing a particular susceptibility state, or predictive, that is, predicting a particular drug response. Obviously, there would very appropriately be incentives to test manufacturers to go with whatever characterization of their test was going to be least onerous from a regulatory perspective.

So where did that take the SACGT discussion? Well, in the end, the committee recommended that all genetic tests, including home brew, which is where the large discussion occurs, should undergo some form of premarket review. But the committee was very concerned that that premarket review not be onerous, and the ultimate outcome of that discussion was to create a template, a template that laid out basically, in words often quoted, "what we know and what we don't know."

And I'm not sure exactly who to attribute that quote to. I think Muin Khoury was the first person to use that phrase. Others claim that other individuals were the first people to use that phrase

But the point is the SACGT review suggested that what we would get from premarket review primarily was information about what the test was, accurate information about what we know about the analytic validity, which we assume will be well established and we believe CLIA oversight assures, clinical validity, information often limited about clinical validity at a time when the test comes to market, and clinical utility where information is often even more limited. The idea was that a premarket review would enable health care providers and patients to know exactly what they had with the test. And that was the recommendation, and the Secretary of HHS accepted the recommendation and asked FDA to consider what would be involved in implementation.

I know that you've heard a lot of testimony in your tenure around FDA activities. So I'm just going to highlight a few issues that I think have been really important in actions taken by FDA since that time.

First, there have been several draft guidance statements related to pharmacogenetics and particularly focusing on the voluntary collection and submission of data, what Steve Gutman described in testimony to the committee about the idea of creating a safe harbor in which to explore interesting data that might help to inform manufacturers and the public ultimately about appropriate uses of drugs, guided by pharmacogenetic data, potentially appropriate development, use of pharmacogenetic data in the development process as well.

More recently, we've had a statement from FDA about the intent to change the clinical pharmacology section of the drug label, and one of the points in that change is to create the opportunity to showcase pharmacogenetic information when it's relevant to the use of the test. I think these efforts on the part of FDA signal what I think is a very appropriate decisionmaking process.

Obviously, I can't speak for FDA, but what I see in their actions is the decision that pharmacogenetics is a particularly important area for the FDA to be looking at as it's looking at guidance that it can provide about the appropriate use of genetic testing. And that's important, in part, because the use of pharmacogenetic testing is obviously tightly allied to the safe use of drugs. But I think it's also important because it seems pretty clear that pharmacogenetic testing is going to be a really important early product of genomic research in terms of impact in the clinical arena.

Other FDA efforts. Well, obviously, in the past several years, FDA has approved a few genetic test kits and that's been a very important process, creating precedents.

But also, what I think has equal importance to the efforts that FDA is making in pharmacogenetics is efforts with respect to in vitro diagnostic multivariate index assays. I'm speaking about the draft guidance that came out last fall proposing the extension of oversight to these assays. As you know, these are tests that utilize both laboratory data and analytic tools to generate results, and we're talking about things like the gene expression profiles that might predict cancer prognosis and be very important in guiding the use of chemotherapy.

What I take from the FDA's efforts is that they are identifying two areas of priority. One, as I've said, is pharmacogenetics, and the other is test complexity. I think that may be a much more functional way to think about what tests need higher scrutiny than the diagnostic/predictive kind of categorization that SACGT was working with a few years ago. So I think this is a very interesting approach.

I want to go on to the next topic and just say that clearly another area for very interesting discussion is the area of direct-to-consumer tests. The question there that's raised is, is there room for additional or different kinds of statutory regulation when we're talking about tests going directly to the consumer? And I know you're well aware of the General Accounting Office report on nutrigenetic testing in which it raised questions about whether websites offering nutrigenetic tests were misleading consumers and, in fact, concluded that this was so.

There are other potential sources of regulation around, for example, truth in advertising that might be important here, but it also raises the question whether a test that is proposed to be offered directly to the consumer should be another category, raising questions about regulatory oversight.

Let me talk briefly about genetic discrimination. For some years, there was a hope that the ADA would provide protection against genetic discrimination, and the EEOC action against Burlington Northern some years ago -- I think it was 2001. This was related to workers who had work-related claims for carpal tunnel injury and were subjected to genetic testing without their knowledge. In bringing a claim against Burlington Northern for these activities, EEOC did invoke ADA and claim protection from that bill against genetic discrimination.

But I think we have to say that when we look at how the courts have interpreted ADA claims in nongenetic cases, that it seems likely that the ADA will be interpreted as primarily providing protection against people with disabilities that actively interrupt their life and that genetic susceptibility itself is not likely to be something that would meet that standard.

So the other opportunity we have for oversight around genetic discrimination is laws that prohibit genetic discrimination, and at the federal level, as you know, GINA is now before Congress, and I know that you'll be hearing an update on the status of that later.

At the state level, statutory regulation can also be very important for genetics. In particular, some states actually have more stringent laboratory oversight than is called for by CLIA. Many states -- I think the count is now 41 -- have enacted genetic nondiscrimination legislation, although it's fair to say that this legislation has not been tested in the courts yet. So we're not really sure what the scope of protection provided by this legislation is. And obviously, newborn screening is a state function that is under oversight of states.

Let me conclude these remarks about statutory regulation by saying that I don't think the role of statutory regulation and oversight of genetic tests is yet clear. I think we see conversations that are very important going on at FDA. I think we have an ongoing concern about whether or not there should be more regulation around performance of genetic tests in laboratories, and I think we have uncertainty about certain kinds of delivery of tests like direct-to-consumer and exactly what measures we should take to make sure that consumer safety is protected.

I do think that statutory regulation is a potential vehicle to standardize reporting and labeling of information about genetic tests, and we should think seriously about how best to use statutory regulation for that purpose. I think it's not a route to establishing a standard of practice around the use of genetic tests, and other mechanisms, I think, are likely to be much more effective. So let me talk about some of those other mechanisms.

First of all, public leadership. So in addition to the regulatory responsibilities of many federal agencies, federal agencies have the opportunity to provide leadership in a variety of ways, and I think we have many very positive examples occurring now. As I've outlined in my slides, these include promoting best practices, education and training, practice guidelines, and research, all of which are important efforts.

Just picking out a few examples, because there are many, I wanted to mention the Division of Laboratory Sciences at CDC. When we're talking about genetic testing, this particular division of CDC and particularly the Lab Practice Evaluation and Genomics Branch within that division has a variety of roles that I think are making a very positive impact. It provides leadership for quality control, quality assessment in the development both of technology and of practice. That, obviously, includes proficiency testing.

I think also as an example of very interesting work that has come from this agency, there has been an interesting project looking at genetic test reporting. When we think about the complexity of

genetic tests and the fact that there are going to be many new ones and the fact that many providers are not necessarily well-grounded in genetics, this represents, I think, a very interesting kind of example of how appropriate use of new genetic tests can be enhanced simply by looking carefully at how information is provided to providers to guide them at the point of service, at the point where they need to know.

And this division has many other activities, education and training, research activities, and also does take a role both nationally and internationally in policy development, including obviously an interaction with CLIA in terms of standard setting.

But public leadership extends to other areas as well, and I want to mention the role of public leadership and the support of processes as a very important one in guideline development.

So EGAPP -- I know you'll hear more about EGAPP later today -- I think is an important initiative on the part of CDC and AHRQ to not just provide guidance about the use of some genetic tests, but really to work on establishing methodologies for evaluating genetic tests and, hopefully, also addressing what I think is a really important, unresolved question, and that is, what kind of evidence do we need, what kind of evidence is sufficient for us to be ready to say this particular genetic test is now ready for clinical use?

The U.S. Preventive Services Task Force has also provided some important guidelines, notably their guideline around BRCA testing a couple of years ago, and the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children is also active, particularly in the newborn screening area.

What I think is really important, as we step back and think about where public leadership should go, where opportunities for contributions can be made, we need to think in terms of the translational pathway. And I've shown you my diagram of the translational pathway, the idea being that we've got a huge amount of research going on that's helping us to understand with increasing detail the genetic contribution to disease, and that's one end of the pathway. And over at the other end of the pathway, what we hope are improved health outcomes.

Clearly, federal research support is a critical component in the early part of that pathway, and NIH, AHRQ, CDC, HRSA, all make important contributions to the research enterprise.

When we think about oversight of genetic tests, what I think is important to emphasize is that there is a crucial need for educational research, research on educational interventions, what really does help providers, what really does help patients to assure appropriate use of genetic testing, the creation of educational resources, an ongoing focus on clinical utility, which starts, not least, with clarifying what we mean by that term, and as I've said, what kind of evidence we need to support clinical utility for different kinds of tests, and then also research into the ethical/legal/social implications and policy options.

I think it's fair to say that federal agencies are providing support in all of these areas. I think it's still an open question of whether more support might be provided or perhaps more focused support, identifying particular crucial areas where more work might be needed.

And now I'm going to turn to funding decisions as an alternative to statutory regulation, and I don't mean by that that funding decisions can replace statutory regulation. But I think it's really important to recognize that funding decisions play a crucial role in the use of genetic tests or, for that matter, any medical tests in our society; that is, whether or not a test is funded will have a

powerful impact on whether or not that test is actually used. A test might be made available for clinical use, but if it's not funded, it's not likely to be used.

There are a lot of challenges here. What we want is for funders to make wise decisions about what they fund and what they don't fund because this will help to ensure appropriate use of genetic testing. But in trying to address this issue, the challenges that funding agencies encounter are, first of all, how they should be thinking about delivery of genetic services. For example, when is counseling essential? When should it be part of the package? And what kind of counseling should it be? When should it be a certified genetic counselor or a medical geneticist? When is the counseling appropriately given in primary care?

We do know the answer, I should say, for some tests. I think it's clear that the kind of counseling provided by genetic counselors is the most appropriate kind of service to offer, for example, with Huntington's disease testing. But as we see more and more tests coming, pharmacogenetic tests, tests for susceptibilities to common diseases, the answer to that question is not clear. But if we had a clear answer, it would be possible through funding decisions to help to ensure that services are delivered in the right way.

I think another interesting and problematic area for funders is how they should think about genetic tests which have as their primary endpoint information. So mostly we think about tests in health care as providing information for the provider and the patient that guides treatment decisions. Tests help us to manage patients in order to improve outcomes.

But in genetics, historically the majority of tests have had information as their endpoint, information that establishes a prognosis of a disease like Duchenne's muscular dystrophy or X-linked retinal dystrophy where there's a tremendous health impact on the family, where it may have very important social implications, where it may help to design the appropriate kind of supportive care to provide, but information really is the endpoint as opposed to an improved health outcome, which is what we hope for most medical testing.

How should funders think about that? In general, funders are quite willing to test the Huntington's disease type of test where we say this is a highly penetrant genotype with very important implications in terms of the information about an individual's health. Are other genetic tests that provide information, for example, about a probabilistic increase in risk for Alzheimer's disease or diabetes also appropriate for health care funding? How should health care funders think about that problem I think is quite challenging.

And as health care funders try to make rational decisions, they're confronted with a tremendous problem of lack of evidence, which gets us back to research and also to this issue of thinking through what evidence is necessary in order to say whether or not a test is ready for prime time clinically.

So let me showcase a couple of other problematic issues when funders become, in essence, the regulators of access to genetic testing.

One, of course, is that coverage of genetic counseling historically has been poor. So we have many circumstances where the patient can get the expensive test covered but not the genetic counseling that we tend to agree should go along with that. And I know you're well aware of that as a problem.

Funders also try to create rules that help to standardize use and can easily get into inflexible rules. We see this, for example, when we're looking at a potential candidate for BRCA testing. There are often family history rules that are perfectly rational; they make sense. But if they're adhered to too rigidly, certain patients that we can argue, often based on second-degree or third-degree relatives, really are candidates for testing, but they don't quite fit the rules.

Then, obviously, funding as a regulation of genetic testing doesn't address a really core problem in our society, and that is inequitable access to genetic services which comes from people lacking insurance or being underfunded, the underfunding part being a particularly important issue for genetic services because often these are kind of viewed as more marginal services that may be less likely to be funded.

Now I'll move on to the role of professional organizations and collaborations. In the same way that public leadership I think can play a really powerful role in creating standards of practice, so can professional organizations. Professional organizations can help to identify for their members the importance of genetics issue. An interesting example a couple of years ago was the American Association of Family Practice which identified genetics as an area that its membership should know about and created a series of educational videos, in partnership with federal agencies and other sponsors. They can provide education both at national meetings, as well as standalone educational programs.

We also see professional organizations playing a very important role in laboratory oversight, working with or within the context of CLIA to standardize, create proficiency testing, et cetera.

And then professional organizations play an important role in developing practice guidelines.

So practice guidelines. Practice guidelines are what most docs look for when they're faced with a new area of practice. They look for guidance and they look for guidance from sources that they can trust. This is why professional organizations play a very key role in practice guidelines.

The problem, if you look at what we have today in terms of practice guidelines, is that they're kind of all over the map. Many different bodies set themselves up to provide guidelines. They use different processes. Some processes are more transparent than others. Some processes are more evidence-based than others. We've had some reports that suggest that interests may sometimes insert themselves into the process in a way that's not good, and methodologies vary. They're not always disclosed.

Of course, with all these sort of process problems, that is, what kind of processes should we have to produce good practice guidelines, we also have the ongoing frustration, on the part of guidelines panels, that even if their processes are good, the evidence may be lacking. And I think this just speaks to the importance of both public and professional leadership, making sure that we're doing the research we need to do to get the evidence we need, but also providing leadership to ensure that practice guidelines follow rigorous procedures so that they can provide valid and legitimate guidelines.

Of course, as we do so, we have to acknowledge that standard of practice is an evolving concept. In fact, you can make a guideline, and then there's going to be new data, which means you have to rethink the guideline. This is, obviously, a tremendously important area in genetics where technology is evolving and the quality of evidence is, hopefully, increasing over time. We've certainly seen that with BRCA testing, for example. The first guidelines came out when virtually no evidence existed, and all recommendations were made on expert opinion. We now, 10 years

later, have a body of data and can, with increasing assurance, make evidence-based recommendations for people that are test-positive. And obviously, case law also will influence a standard of practice.

I will just finish by mentioning health professional education. I've already alluded to this as a very important issue at the federal level where we're looking for support for educational research and resources, at the professional leadership level, at the public leadership level as well. Health professional education has the potential to enhance other efforts by enabling health care providers to make good judgments in gray zone areas.

But there are a lot of challenges. We know that the traditional methods of calling a conference and giving a lecture don't necessarily have much impact on physician practice.

We know that many genetics curricula, as a colleague of mine said, have been created and then they sit on the shelf collecting dust. And that's probably because a lot of curricula have been created without a preliminary phase of needs assessment. We really need to go out to the individuals that we hope to bring genetics education to and talk to them about what's going to be most helpful to them. I think when people have those conversations, they discover that genetics education for health care providers needs to be intensely focused on relevance and, from the primary care perspective, ideally focused on health outcomes. That's what primary care providers see as their mission.

I'll just finish by saying that I think all of the different ways that we can provide oversight for genetic testing are complementary or hopefully complementary. They have the potential to be complementary. And I think that's one of the challenges, trying to think through what reasonably should we expect from statutory regulation and how can we make that happen, but not expect statutory regulation to do everything. What can we accomplish with a combination of public and professional leadership? What can we accomplish by working on the research agenda? What can we accomplish by making practice guidelines processes better, pushing on those standards? And what can we accomplish by education? I think that that issue of thinking through the role of different oversight mechanisms and trying to promote a complementary use of them is where a lot of attention is needed.

I'll stop there and be happy to discuss more with the committee.

DR. FERREIRA-GONZALEZ: Thank you, Dr. Burke. Right on time. That was great.

DR. TUCKSON: Dr. Wylie, as Andrea drives the train here, I do want to make you aware that we did have a -- Wylie. Well, that's fine. I messed up and called Wylie Burke "Dr. Wylie." So, you know, now they're going to write me a letter and a note and I'll get yelled at.

DR. BURKE: No problem, Dr. Reed.

(Laughter.)

DR. TUCKSON: I actually write a health column that's called "Ask Dr. Reed." So that's great. And then we have Dr. G. here, as well.

(Laughter.)

DR. TUCKSON: Anyway, just to let you know, as you participate in the discussion with us in case it comes up, we had a long session this morning with some guidance that we got from the Secretary's office regarding oversight tests and some questions they wanted us to address. Your presentation was prescient in that it anticipated a lot of the things that came in the discussion earlier. So people may refer to that.

The point I'm raising sort of with you is that the activity that we are engaged in now as an advisory committee to the Secretary is, in a way in which it has not been before, really specifically advising the Secretary around very granular issues that we had not been asked before. So, again, just giving you a sense of the importance of this activity as it goes forward.

I'll turn it back to Andrea.

DR. FERREIRA-GONZALEZ: Thank you, Reed.

Dr. Burke, thank you so much for that, and I want to echo Dr. Reed's comments earlier that it really falls within some of the discussion that we had this morning. I think you have done a very good job of looking at a comprehensive way of the oversight of the federal, state, and even professional organizations in different issues, but also to bring to the attention of our committee some of the efforts that have been occurring at the federal level through different advisory committees to these specific issues.

I think also, like you said, there is room maybe for additional oversight for specific areas such as direct-to-consumer testing, but also improving how we report the testing that we do to be a vehicle to educate these.

I really liked the questions that you have framed in the last slide because these go really well with some of the comments that we heard this morning from the Secretary and some of the other areas we'll be discussing this afternoon.

But I would like, at this moment, to open it for questions, if anybody has questions for Dr. Burke. Marc?

DR. WILLIAMS: Thanks, Wylie.

One of the issues that we touched on briefly but really haven't talked about in great detail is what might be in the drug parlance termed postmarket oversight because I think what we've surely learned, with the release of genetic testing into clinical practice, is that we learn much more after the test is out there and being used about the potential impact. I'd like to hear your take on the role of postmarket data collection and surveillance.

DR. BURKE: Thanks very much for bringing up that point. I think it is a very important point for discussion. It's, obviously, the other half of the discussion about what evidence do we need before something comes to the marketplace, something becomes clinically in use. The simple, I think, answer is the less evidence you have when it enters the clinical arena, the more evidence you're going to need postmarket to understand how things turned out.

And I think that is the reality. Most genetic tests come into the clinical realm based on partial evidence, based on a strong presumption that they can provide benefit, but not necessarily full proof.

And there are some questions that can only be answered over time because there has to be a duration of following people who are test-positive before you're certain that you know, for example, what management they should be offered or what the clinical validity of the test is.

So, yes, I do think that's a very important question, and of course, it leads to sort of the practicalities. To what extent would it be possible, for example, for premarket review to generate conditions for certain kinds of postmarket collection. That would be one question.

Another question, though, I think is realistically what kind of partnerships might we want to think about putting in place to maximize the quality of the information we get postmarket and perhaps also the speed with which we answer questions. I think you can imagine a circumstance where a partnership that included participation of the lab offering the test, or the labs, participation of some large health care systems that really have a stake in using these tests properly, and some appropriate public participation through funding. If you could create these kinds of partnerships, you might be able to create systems where, as tests come in, you can prospectively plan on gathering certain kinds of data to be sure that you understand the uptake, outcome, and ultimate clinical effects of new tests. I think how to construct and promote those kinds of partnerships is a very important question.

DR. FERREIRA-GONZALEZ: Any other questions for Dr. Burke?

DR. WILLIAMS: The other question I had is looking particularly at your slide on the translational pathway. Having participated on a review panel for the CETT program, which I think most people here are familiar with, I've been very impressed with that model as walking through all of the pieces of that from the gene/disease association to interventions and implementation with incentives built in to translate this into the clinical arena with the caveat that there be transparency, that there be educational materials for patients and for providers, but also that there's a requirement tied to that about collecting data after the test is in clinical practice for a five-year period of time that is able to be used to answer some of the questions.

It's, obviously, a rare disease test model. Do you think there's any possibility of taking that model and translating that into something that would work for more common disease-based genetic tests?

DR. BURKE: Yes. I think you're getting to a crucial issue. I guess my short answer to it would be all the questions are going to be the same, but some of the logistic issues that arise in answering the questions will be different. And they include thinking about a critical evaluation of a genetic test versus alternatives.

So just for the sake of an example, there's been a lot of interest in the last year/year and a half, about gene variants that identify individuals with a moderately increased risk of type II diabetes. So the relative risk might be 1.5 or 2. Substantial numbers in the population will have these variants, and there certainly are some claims of potential clinical utility. These tests might be used, for example, to motivate individuals toward healthier lifestyles.

So I think when you think about the CETT model and then applying that to a test like this, not only is the potential locus of data collection much broader -- there are many more places where you might want to collect data -- I think you also have to think about collecting comparative data that will be crucial to answering the question.

So those data include just how well do we do motivating people with a healthy lifestyle to begin with. What measures work? What measures don't work? Is identification of genetic risk the best way to go versus other nongenetic risk factors like, for example, body mass index? And how do we measure the impact of different strategies for achieving the same outcome at the level of patient experience and acceptability, you know, taking into account the possibility, for example, that genetic results might have fatalistic impacts on people's motivation, and actual clinical measures of outcome and, hopefully, short-term and long-term measures of health outcome?

I guess what I'm saying is I think the questions will be the same, but how to answer them will be a much more complex undertaking.

DR. FERREIRA-GONZALEZ: I don't want to go over the next speaker's time, but I have a quick question. You touched upon a little bit about the reasons of concern about oversight. You started alluding to some of these issues.

We heard this morning from the Secretary's office, which has given very specific questions on what they would like us to be considering, and one of the questions is what distinguishes genetic tests from other laboratory tests for oversight purposes. I was just wondering if you could elaborate or give your perspective on that particular issue.

DR. BURKE: Well, yes, the issue of genetic exceptionalism. That's a really tough issue.

I think we can say a couple of things about genetics. One is that genetics certainly does provide us with a subset of tests that have extraordinarily high predictive value. You don't find medical tests that have the predictive value, say, of a Huntington's disease test. That would be very unusual in other medical arenas. So I think the notion that genetic tests require maybe a different approach to oversight starts with that fact, that there are some tests that really are by degree, if not by nature, different in the kind of information that they provide.

Clearly, as a corollary of that, genetic tests and genetic testing processes raise often questions about the family that other tests don't raise. So an example there would be testing for mutations associated with hereditary nonpolyposis colon cancer. A cost effectiveness study showed that the greatest value of that kind of genetic testing comes not at the point where you've tested the person who's affected, but at the point after that where having the positive test result, you're then able to go out to the family and test individuals within the family who are at risk and could benefit. I think you reach extraordinarily greater cost effectiveness if you're able to reach two or more relatives than fewer.

So that kind of testing paradigm is different and raises questions about appropriate use of tests and, obviously, corollary issues about confidentiality and privacy. So I think that's another reason why maybe there are some oversight issues unique to genetics.

And the third is probably a cultural one; that is, we live in a society that at this point in time accords a huge amount of power to DNA, a huge amount of power to genetic information, and people are concerned about that. I think many state nondiscrimination laws reflect that concern.

So I think those are the reasons to think about genetics as somewhat different.

And I will say, having said that, that I think we should also be extremely cautious about not pushing that concept too far. So if you look at the example I just gave you of a genetic test for increased risk for type II diabetes that predicts a 1.5 to 2-fold higher risk compared to a person

who doesn't have the gene variant, I'm not sure that test should be viewed differently than any other risk factor in determining how to use it in clinical care. At the same time, I think it is true culturally that it's likely to be viewed as different, and we have to take that into account.

DR. FERREIRA-GONZALEZ: Thank you.

DR. LICINIO: A quick question related to that, which is this. I think that there is an issue with Mendelian diseases in which everything that you said is very accurate. But for a non-Mendelian specialty, I mean, if you increase the risk of the disease, like 50 percent, that's one story, but for common and complex diseases, there are many risk factors that are like 3 percent of the genetic contributor and having that marker has no predictive value in terms of whether you're going to really develop the disease in the future. It may have some, but very limited. It's not like having the genes for Huntington's disease. If you have one of the variants that gives some susceptibility to some of the common and complex diseases, you may easily have the disease, you may not.

How is that going to be dealt with in terms of this? Does that deserve a special, even different kind of protection or not? And I think the potential for misinformation there is tremendous because having a specific variant that's associated with depression, diabetes, or arthritis doesn't, by any means, mean that you're going to have the disease or not have it.

DR. BURKE: I think you're identifying a tremendously important issue. I really do worry that the variant predicting a small increased risk of type II diabetes is going to be viewed as having the same power as a test for a Mendelian disease. I think that's a great concern, and I think there is reason to be concerned about that when you look at how genetics is covered in the media, you know, where you see a headline that says "gene for Crohn's disease," but actually it's a variant that increases risk a little bit.

I'm not sure what are going to be the most effective actions, though it would seem that if we can figure out how to craft the right kind of messages, that's an area for public and professional leadership, and if we can think about how to approach education properly, both public education, as well as health professional education, that might be where we need to put some energy. I think we really need to figure out how to communicate this notion of multifactorial disorders better than we do.

DR. FERREIRA-GONZALEZ: Thank you. I think these are very important issues that will help us later on frame up the work that we will do. Again, thank you very much, Dr. Burke, for being with us.

DR. TUCKSON: Actually, as you do that, Dr. Wylie, can I assume that as we go forward, that we would be able to draw upon you and your expertise from time to time as we journey down this road?

DR. BURKE: Certainly. I would be happy to do that, and I appreciate the chance to be here.

DR. TUCKSON: Great. You're terrific because one of the things that I mentioned I thought was prescient on your part is the request from the Secretary's office did sort of ask about looking at issues beyond the pure HHS regulatory issues. And they brought up the thing about professional societies and so forth and so on. And you sort of spoke to those issues in your presentation. So I think following up with you on some of those is going to be important.

Thanks again for doing this.

DR. BURKE: Thanks very much. I'm glad to be here.