Existing Genetic Technologies and Their Integration into Health Care and Public Health

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DR. McCABE: The purpose of these informational briefings is really to give all of the members of the committee the same background and so that we start our discussion with a common understanding of the issues. Bio sketches are provided for the presenters under Tab 2. I'm not going to give extensive information on each of them, but you should read about them. You'll be quite impressed with their bios.

Our first presentation is existing genetic technologies and their integration into health care and public health. That will be presented by Dr. Wylie Burke, who is Chair of the Department of Medical History and Ethics at the University of Washington in Seattle, and also served as a member of the Secretary's Advisory Committee on Genetic Testing.

DR. BURKE: Thanks very much. I really appreciate the opportunity to be here at your opening meeting. My goal is going to be to take a quick tour through the use of genetics currently in health care and in public health.

I want to start by pointing out that as a general scheme, there are two ways to use genetics to get to health benefit. One is to use genetic testing to identify people that have specific needs, make a genetic diagnosis, identify genetic susceptibility, and ultimately create the opportunity to tailor care to a person based on their genetics.

The other is to develop new treatments based on genetic knowledge; that is, to use the tools of genetics and genomics to understand disease biology and thereby increase our ability to treat a variety of health conditions. These two paths are not mutually exclusive and both might apply in a particular condition, but they are two different pathways with two different implications. Most of what we have now is the use of genetic information.

I seem to be missing a slide. I'm sorry. Let me talk, then, about one of the most dramatic examples of the use of genetic susceptibility to identify people with special needs, and this also refers to the most prevalent use of genetic information in a public health setting, and that is the process of newborn screening using phenylketonuria as an example.

One of the fruits of understanding some genetic diseases -- that is, diseases that are predominantly determined by the genetics of an individual -- was to identify some children who would benefit by the initiation of early treatment, and that led in the '60s to the development of a program of newborn screening staring with phenylketonuria, and we now have an increasing number of conditions being considered for this genetic testing model.

The basic idea is that we identify the individuals very early in life and are able then to provide a specific treatment, in the case of phenylketonuria a phenylalanine-poor diet because these individuals on a genetic basis can't handle much phenylalanine in their diet, and the dramatic benefit of preventing mental retardation. This reflects the potential opportunities that we have at one end of the spectrum of the contribution of genetics to disease; that is, that end of the spectrum where genetics is the predominant contributor.

I show the full spectrum here because increasingly genomics is going to give us tools to move down the pathway and identify genetic factors that contribute to common diseases as one of multiple factors, potentially multiple genetic and multiple environmental factors. That's where diabetes, heart disease, cancer, and most common diseases reside.

Sticking with the genetic end of the spectrum for the moment, we have other examples that are comparable to PKU but where genetic testing is used not in a newborn screening program but in the course of clinical care, and a very clear example is provided by the genetic condition called multiple endocrine neoplasia type 2, or MEN2. This is a condition in which people inherit a very high predisposition to develop medullary thyroid cancer, a particular form of thyroid cancer that is difficult to treat. We now know that this particular condition is inherited as what we call an autosomal dominant condition, which means the mutation, the gene variant that predisposes to MEN2, can be passed on from parent to child. Each child has a 50 percent chance of inheriting it.

We also fortunately know what gene is involved. So MEN2 is due to mutations in the RET gene. So we have a family like the one shown here, where the grandfather died of medullary thyroid cancer, his son was diagnosed with medullary thyroid cancer, and because genetic testing was available, it was done and we now know him to be RET-mutation-positive, and this creates a new prevention opportunity. We can identify his children, all of whom are at 50 percent risk, determine which of them, if any, inherited the RET mutation, and current standard of practice for this condition would be to offer a prophylactic thyroidectomy in early childhood, thus preventing thyroid cancer.

Now, as we develop this potential for predicting genetic disease risk, we also have a conundrum that I think is with us and will stay with us for some time to come, and that is the conundrum of identifying a person with genetic risk but not having anything to do about it. So with MEN2, we have a clear action we can take in order to prevent disease. With Huntington's disease, we have exactly the same kind of genetic situation, autosomal dominant condition; if a parent has it, children have a 50 percent chance of inheriting it. But Huntington's disease is a neurological degenerative disease that typically starts in the early 40s. There's a progression over a 15- to 20-year period of loss of control over muscle action, involuntary muscle action, and also loss of cognitive ability, progressive dementia.

So it's a very tragic disease. We have the genetic test. We can identify in early adulthood whether or not a person has inherited the Huntington gene, and if a person has a normal lifespan, we can predict a virtually 100 percent chance that they will at some point develop Huntington's disease. We have no treatment. What we see in the clinical setting is that this kind of information is of interest to some individuals but not most. So the majority of people at Huntington's disease risk do not choose to pursue this information.

Now, if you think about the distinction between MEN2 and Huntington's disease, an extremely important one, the same kind of genetic prediction is possible but we have treatment in the one case and not in the other. There is a tradition in medical genetics practice that becomes very clear, and that is the tradition of non-directive counseling, which applies very forcefully in the case of Huntington's disease. The choice to be tested is ultimately the choice of the patient. It is a very personal decision. It is not a medical decision in the way that MEN2 testing is, and we recommend MEN2 testing because of what we can do for benefit. With Huntington's disease, we provide the opportunity and let individuals choose whether they want to pursue that.

The same concept of non-directive counseling applies when we use genetic testing for reproductive decision-making. So this is a family with Duchenne muscular dystrophy. The arrow points to a young boy who has recently been diagnosed to have Duchenne muscular dystrophy. He presented with

difficulties walking around the age of 2. The pattern was consistent with muscular dystrophy, and a genetic test can provide a firm confirmation if the genetic test reveals a deletion in the Duchenne muscular dystrophy gene.

It turns out that his mother's brother was also affected. We can be certain that his mother is a carrier of this condition, but what we don't know is whether or not his sister is a carrier. At this point, as a child, that's not a burning issue, but as she becomes an adult it may be very important for her to know whether or not she is a carrier for Duchenne muscular dystrophy, and she might make different decisions about whether or not to have children, whether or not to have prenatal diagnosis if she does decide to have children based on her knowledge about her carrier status.

The same test for Duchenne muscular dystrophy gene that's used diagnostically in her brother would be used to determine whether or not she's a carrier, but the implications of testing are strikingly different. In the one case, it's a pretty straightforward use of a test for diagnosis as we do in all sorts of branches of medicine. In the other, it's like the Huntington's disease question, a highly personal matter whether or not to pursue the information and whether or not to use the information in reproductive decision-making.

We now have currently within the past year an example that will be affecting or will come up as a matter of discussion for most pregnant women, and that is testing for the cystic fibrosis carrier state. Cystic fibrosis is an autosomal recessive condition, so this is a condition where parents are healthy but can be carriers of the condition. If two carriers marry, each of their children has a 25 percent chance of inheriting the cystic fibrosis gene variant from each parent, and if they get the CF variant from both parents they will have cystic fibrosis.

It's been recommended by an NIH consensus conference and subsequently by the American College of Obstetrics and Gynecology that all pregnant women be offered this carrier test, and clearly it is important for them to understand, as they consider whether or not to do testing, what the options are. The options are going to be reproductive decision-making options and personal decisions that some people may wish to make and others may simply not wish to pursue.

One of the important implications of CF carrier testing as we now have it is shown on this slide. If two parents are tested and both are found to be carriers for cystic fibrosis, as I mentioned, there's a 25 percent chance with each pregnancy that they'll have a child with cystic fibrosis. If one parent tests positive and the other tests negative, the risk to have a child with cystic fibrosis is very low, by my calculations well under 1 percent, but not zero, and that reflects a very important property of genetic tests, which is they are rarely 100 percent sensitive.

There are actually 900-plus mutations in the CF gene. Current recommendations are to start with the 25-mutation panel. We would probably follow up with additional testing in the apparently unaffected parent in this kind of situation, but there are good reasons to start with a 25-mutation panel, and bottom line, it is impractical to test for all 900, and there may yet be more CF mutations that we haven't yet identified.

The American College of Medical Genetics has recently developed a guideline on CF carrier testing, and they have a number of things to say about the recommended testing strategy. The first, of course, is that they highly recommend pre-conception screening whenever possible. This increases people's options to know about their carrier status before they become pregnant, though they recognize that the reality is that this usually will not happen. They recommend that pre-test education be provided, and actually the American College of Obstetrics and Gynecology has produced a very nice brochure that goes through a variety of details and starts with the important message, "The Choice is Yours," as the title of the brochure, and this includes understanding that this test creates opportunities for reproductive decision-

making, including the opportunity for prenatal diagnosis and a potential decision to terminate a pregnancy for parents who choose that option if testing begins in pregnancy.

The American College of Medical Genetics has put great thought into their recommendation and recommends a screening panel of 25 mutations to start with what they call "reflex tests," additional tests to clarify the initial positive result if there is a positive result on that screening panel. This particular issue was at the heart of a news flurry about a month ago, and it really reflects the fact that there are certain variants in the CF gene that are important only if other mutations are present but in and of themselves not terribly important. If you test for too many mutations to begin with, you may get a finding of a mutation that, by itself, is not clinically significant and may generate a whole lot of confusion about what you should do.

Again, I think this reflects the complexity of genetic test information, one that is very characteristic, I would say, of genetic tests generally. Then the recommendations, I think, would be obvious for careful post-test counseling if test results are positive for both or even just one parent.

Let me now turn to another genetic disease and talk about genomics beginning to give us new opportunities for therapy. Here is another X-linked recessive disease that is following exactly the same inheritance pattern as Duchenne muscular dystrophy. The mom's a carrier. Her son is affected. Her daughter may be a carrier. There are the same kinds of carrier testing issues that arise with Duchenne muscular dystrophy.

But with hemophilia, we've been studying this, we the scientific world, since the mid-century and have had very important breakthroughs in understanding this disease that illustrate how useful it is to understand disease biology. First of all, in 1952 there was a differentiation of Factor VIII from Factor IX, and it turns out that those factors, which are factors in blood clotting, represent or are related to two forms of hemophilia. So the classic hemophilia is a deficiency of Factor VIII, and people have bleeding problems because they don't have Factor VIII and don't clot normally. Factor IX produces a separate, different kind of hemophilia.

But once we knew that about hemophilia, we could begin to think about the logical thing, which is factor replacement. If you know what factor a person is missing, you can potentially replace that factor. Starting in the 1950s, there was a lot of experimentation with plasma product supplementation and initial, at least marginal, successes that caused people to keep going forward. In 1965, there was a breakthrough. The technique of cryoprecipitate, which was basically a method of precipitating large amounts of serum in order to concentrate large amounts of factor, resulted in the ability to treat people with hemophilia in a meaningful fashion. Enough Factor VIII could be given that people's bleeding problems could truly be treated.

Now, this needed to be done on a repeated basis. Gathering enough serum in order to create the cryoprecipitate of Factor VIII that was needed was a significant task, but this was a dramatic breakthrough. If you read memoirs of families, this was a major turning point, an important and wonderful turning point in the history of hemophilia. But it did have unintended consequences, and I think it's important for us to think about technological development in the context of this story.

The unintended consequence here is the story of hemophilia and AIDS. The first case was reported in the early '80s. Most exposures occurred between 1983 and 1986 because, starting in 1986, methods to treat blood products in order to minimize, to basically kill HIV virus, were initiated at that point, and the blood supply gradually improved in safety. But as a result of that period of time, a large cohort of people with hemophilia became HIV infected. About 40 percent of hemophiliacs receiving blood products, about 80

percent of those with severe disease, developed AIDS. The consequences of that are still being felt amongst the hemophilia community and amongst families in which people had hemophilia.

Now, genomics has led the way to moving beyond that. So we now have recombinant Factor VIII, Factor VIII made in vitro with DNA recombinant techniques. It's normal, pure Factor VIII. It's a much safer way to make Factor VIII than to concentrate it down from serum. In fact, now methods for making Factor VIII that require no serum at all are being developed. This is now the standard of care in the United States, so this represents a way in which genomics has provided a new and much better treatment and solved a problem.

There are some issues. The cost is $72,000 or more per year. Even in this country with good health insurance, people with hemophilia can run out of their health benefits paying for treatment. It's not an option in most of the world, so 80 percent of hemophiliacs do not benefit from this therapy.

What's coming next? This is obviously not an existing therapy but it's one in clinical trials, so I wanted to mention it, gene therapy for hemophilia. Here's a study that was reported in 2001 in the New England Journal, and this was one in which fibroblasts taken from the skin are used as the method for implanting a normal gene to produce Factor VIII and then implanting those cells back in and actually having normal production of Factor VIII -- again, still under study. One might hope that this is ultimately going to be the solution because even with recombinant Factor VIII, you need repeated treatments. What we really hope, of course, is that this will ultimately be an effective and safe and even relatively inexpensive treatment, although I think getting to that point is way in the future, but there's hope.

Let me return to the spectrum of genetic contribution to disease and now talk about the other important new wave in the use of genetic information in clinical settings, and that is the use of genetic information to predict risk for common disease. So if we move to the middle of this spectrum, we know that genetic factors are tremendously important in the development of cancer, heart disease, and a variety of other common diseases, and increasingly we're able to find gene variants in many diseases that identify people at increased risk. The question is how do we use that information effectively in clinical care.

I want to talk about the challenge involved just briefly, using the example of venous thrombosis or blood clots, a very common medical problem. There are a variety of gene variants. I've listed only a few, including the two most common, on this slide. Factor V Leiden occurs in 1 to 5 percent of the population. A variant of prothrombin occurs in 1 to 2 percent of the population. There are a variety of much rarer genetic factors that contribute to increased risk for blood clots.

There are a variety of potential interventions for people who have an increased risk of venous thrombosis. One might use anticoagulant treatment, either use it more long-term after a blood clot than with the average patient, use it episodically at times when people are at particularly increased risk -- surgery, pregnancy -- use it preventively in people who haven't had a clot yet but you know they have a genetic factor, instruct people also in the avoidance of other risk factors where that's possible. In particular, hormones, oral contraceptives, and hormone treatment therapy might best be avoided in someone who has a predisposition.

So you can see, although this isn't as dramatic as the MEN2 story, there is a very comparable picture here of the possibility of identifying people at risk and then doing something to help them, to minimize the risk. Now, the problem is that approaching blood clots with anticoagulation therapy, you take on a major risk of therapy. So current estimates are that people on anticoagulation therapy have a risk of major bleeding events of about 3 percent per year, and 20 percent of those major bleeding events may be fatal. So we are talking about non-trivial risks.

Now, there might be other ways to approach this -- reduce the anticoagulation. Then we have to see if we get the same effect. The point is we've got a very major risk with the therapy, and we need to make sure that we're really helping people if we use these therapies differently in someone at increased risk.

So when we're talking about predictive genetic testing for common diseases, in order to assure benefit, we're going to have to ask rigorously a series of questions. What test? That is, exactly who is it that we want to identify? What treatment are we then going to apply? At what level of risk is that treatment reasonable to apply?

One of the interesting things about venous thrombosis risk is that the people that are at highest risk are not the people with a single genetic factor but the people with multiple genetic factors. So, for example, here's a study of relatives of people with blood clots. There were people with blood clots who were found to have a genetic predisposition, and their relatives were studied. The initial patients had either prothrombin variant or Factor V Leiden.

What this study did was estimate the relative risk of blood clot in their relatives, calling the relative risk 1, or the neutral risk for those relatives who had no genetic factor. There was an increased risk if a relative had Factor V Leiden. There was an increased risk if a relative had prothrombin of about two-fold; less than that, three-fold, for Factor V Leiden. But the relatives that really had the big risk were the relatives that had both Factor V Leiden and prothrombin variant. They had a greater than six-fold risk. Maybe those are the ones who are going to benefit from an aggressive preventive therapy with anticoagulation therapy.

Similarly, Factor V Leiden, as I mentioned, has a prevalence of about 1 to 5 percent in the general population. That's people who are heterozygous for Factor V Leiden, have one copy. Their relative risk of blood clots compared to the average is somewhere in the range of three- to seven-fold. But if you're homozygous, and that's not a very common state, but if you're homozygous your risk is 80-fold. So I think it's quite clear that we would like to find people who are homozygous for Factor V Leiden and treat them with anticoagulation, because even the risks of anticoagulation are outweighed by the very high risk of clots. It's not as clear that we want to do that with people who are heterozygous.

Because there are a variety of unintended harms, or potential I should say for unintended harms for genetic information, there's been a lot of talk about stigmatization and discrimination, but I would argue also that unnecessary or unproven therapy would also be a very significant risk of identifying someone at risk without a clear path for what to do with that risk.

I want to finish this discussion of risk with a brief mention of Apo E4 testing, which is a means to predict Alzheimer's disease, just to make the point that we have, in the genetic risk factor category, an entity that's comparable to the Huntington's disease testing for high risk. That is, we have a factor that is Apo E, and specifically measurement for Apo E4, a variant of the Apo lipoprotein E gene that identifies people at an increased risk of Alzheimer's disease. With two copies, your risk is five times higher, and your Alzheimer's disease, if it occurs, occurs earlier, 10 years earlier than average. With one copy of Apo E, you have a more moderate increased risk. But there is no treatment available.

Actually, three separate expert panels have come to the conclusion that with this indeterminate raised risk but not certainty about risk and the lack of treatment, this is really not a wise predictive test to be using.

So what we can say is that there are a range of ethical concerns in predictive genetic testing that I think should influence how we approach clinical practice guidelines. I've categorized tests into four boxes for

the purpose of discussion. If you've got a highly predictive test and you have an effective treatment -- the PKU example, the MEN2 example -- what you really want to do is assure access. We really do want to recommend testing and we want to make sure people have testing.

If you have a highly predictive test but there is no specific treatment -- the Huntington's disease example -- there we're very concerned with adequate counseling, protecting individual autonomy, making sure that people make their own decisions based on full knowledge and their own preferences.

If you have a test that is somewhat predictive but not absolutely predictive and yet there is a treatment, and I would argue the Factor V Leiden example falls into that category, what we have is something we have commonly in medicine, which is a careful weighing of risks and benefits and coming to a careful judgment about who it is we want to identify and what treatment we want to give them, and I think that's going to be a very important topic in clinical practice guideline development over the next 10 and 20 years.

If you've got a low predictive test and no treatment, I think it's hard to justify the test, and we should identify and be clear about those tests so that we don't use them. I should say I put Apo E4 testing in that category. The minute we've got a treatment, it changes. So the issue with Apo E4 in that category is that currently we don't have a treatment to avoid risk.

I'm just going to talk very briefly about what's coming down the pike. Pharmacogenetic testing is clearly coming down the pike, and I've got an example here. This is where we identify gene variants that predict people to have a higher risk of adverse consequences to a therapy, or possibly we may have genetic tests to predict people who are responders or non-responders. CYP2C9 has two variants, the 2 and the 3 variant, that predict people who are going to have an increased risk of anticoagulation. I should say this observation does add complexity to the Factor V Leiden example, because it's possible that you're more interested in finding people with Factor V Leiden and treating them if they're not CYP29*2*3, whereas if they are CYP29*2*3, they're going to have increased risk for anticoagulation, makes you a little more cautious.

So that gives us a window, I think, into genetic profiling and its potential value in sorting out what is the best action for individual patients.

Clearly, we're going to see a lot of tests, there are already a lot of potential tests under study, and we're going to see a lot of potential use of this kind of information in clinical practice. Again, we'll have to think very carefully about risks and benefits.

I have a couple of examples just to say that we know that genome-based therapies are coming. There are two examples that I found. Others are in study. This is going to be the next wave. So Gleevec has been a major drug developer for the treatment particularly of chronic myelogenous leukemia. It looks like it will now have action and value for other cancers as well.

I just want to point out this is a selective inhibitor of a particular enzyme, a particular tyrosine kinase. The point here is that the genetic research was crucial in identifying this specific kinase, starting with patients who had a particular chromosomal abnormality, and then subsequently working with mouse models of disease to clarify the importance of this particular enzyme and therefore the key value of finding a drug that would inhibit this enzyme.

I think this is at least one model of how genomic therapies will help us, genome research will help us with new therapies.

The other is just a fascinating example that I discovered recently, and that is that there is a novel genetic therapy for a particular eye infection, a cytomegalovirus infection of the eye which is a particularly important complication in HIV infection. In this particular therapy, an antisense oligonucleotide, so basically a transcript, an RNA transcript inhibits the messenger RNA that is a crucial piece of the production of an essential protein for this virus. This virus makes a messenger RNA, that RNA codes for an essential protein, and this particular nucleotide fragment binds to the messenger RNA and blocks it and thereby blocks the production of protein.

So this is a very interesting way, I think, in which an understanding of genomics leads to a novel therapy. I'm sure we're going to hear lots more about this kind of trend as time goes on.

I'm just going to finish by saying I think we have three central questions in the era of genomic health care. The first and most unique to genetics is the question of when does the harm of a genetic label outweigh its benefit? This is going to be an important question with all uses of genetic information, particularly for prediction.

Then the second set of questions is who decides when new technologies have sufficient safety and efficacy for use, and on what basis? What are the criteria for saying we're now ready to use a genetic test or a genome-based therapy? These are not questions that are different from other health care technology, but we certainly will need the right kind of expertise at the table as those decisions are made.

Then finally, how do we ensure fair access as we develop those therapies?

Thank you.

DR. McCABE: Thank you.

(Applause.)

DR. McCABE: We'll have discussion of this, along with the next paper, at the end of this session.