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SYSTEMS TO DETERMINE TREATMENT EFFECTIVENESS IN NEWBORN SCREENING

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DR. HOWELL: Max, thank you, very much. It's my pleasure to be here today to talk about newborn screening with this distinguished group of LC researchers and clinicians.

This afternoon, what I'm going to do is to spend the time I have talking with you about some systems that are in place and that are being put in place nationally, to decide, whether or not, indeed, conditions are treatable in the newborn screening panel. And I'll go through some of the rationale behind that as we proceed.

These first comments are well known to all of you. Newborn screening has been around for a long time. I think, fundamentally, however, once a serious but apparently treatable condition has been identified, it has been felt that controlled studies in those conditions would be not ethically sound. And this has resulted in the fact that they are extraordinarily meager studies in outcomes and, particularly, in peer-reviewed journals. The amount of information on these rare conditions has continued to be meager. And the result is that in very few of the conditions do we have, really, what we would consider perfect information about the effective treatment in the long-term outcomes.

This has been discussed extensively and this panel is very much aware about the American College of Medical Genetics panel that came up with the recommended uniform panel. This has been widely discussed. This group, as you know, recommended a core panel of 29 conditions. The secondary targets were a number of 25. We could spend a month talking about this and I'll be glad to discuss it with anybody in private. There are a few conditions that are excluded and a considerable number of conditions that were not on the panel because there was no test available.

I might point out this report has not only been groundbreaking as far as changing the practice of newborn screening in the United States,

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it has, arguably, been one of the most discussed documents, of, certainly, my lifetime. And many folks in this room, as I sit around looking, have written highly critical documents about this. I can see two without changing my eye. What I might point out is that there were 29 put on primary conditions and 25 secondary targets. But I will include one article from a scientific journal that is Nature Genetics and I have quoted this in view of the company present today. Nature Genetics said in 2007, "perhaps we can learn from one of the most impressive recent exercises in evidence-based medicine, namely the American College of Medical Genetics Systematic Prioritization of Genes for Newborn Screening." I will not further comment about that.

Now, what are some of the challenges that we have to deal with in the area of newborn screening? Number one, there are enormous expansions of potential targets and that's just been emphasized in Don's recent presentation. Poor understanding of the clinical significance, scalability, affordability, invariability of complexes of policy, but we come down to the bottom line again, of striking lack of published peer-reviewed articles. And I might point out there were more than 100 people that worked on the ACMG report that you've seen here for a couple of years. And it was the people whose careers have been devoted to this, but families were involved. There were legal people, ethicists, et cetera. The basic fact was is that there was not a lot of concrete, long-term information about many of these conditions and everyone was very much aware of that.

What are some of things that are going on that I think will impact our information about the conditions that are on the panel? I'd like to discuss, briefly, the recent collaborative screening and genetics collaborative groups around the country. Many of you are very familiar with this in that the HRSA has established this group of folks, whose goals were to address mal-distribution of genetic resources, promote genetics, promote translation of genetic medicine in the public health and healthcare services, cooperate in studies to establish best laboratory practices and the appropriate cut-off phase. I'm going to spend a good bit if time with that in the later panel. But also to work with national groups to effect, to evaluate treatment outcomes and long-term follow-up. There are seven of these regional collaborative groups and one national coordinating center that is operated with HRSA.

This is the map for those of you – many of you work within these and you're very familiar with these, but basically, you have the United States, divided up into seven regions. The great value of this, aside from the sharing of information and so forth, is that these groups are closely involved with the state health departments in all of the regions

and they have contact with the folks who are collecting the patients and the information and so they provide an extraordinarily good opportunity to do a large number of things and there are many things going on.

The groups are encouraged to establish cooperative programs. Region 4 is one region that is currently working very, very hard in an international collaboration. It has actually, expanded beyond the seven regions and now has people from all over the world to look at cut-offs and false positives. And the other regions around the country are developing individual projects. But the reason I go into this system is that the next part of my discussion is going to be discussing a recently announced NIH program that will be dealing and will be built on top of the original collaborative programs. I might point out that Jeff Botkin today asked about the action sheets that are handed out through the regional collaborative networks to address one of the key problems with newborn screening. As this group is intimately aware, the conditions, individually, are rare, and it would be unrealistic to expect any practitioner to be aware of all of these conditions. The typical situation that happens is that on Friday afternoon – it'd be a day like this – about this time of day on a rainy Friday afternoon, you get a call in your office that you have a child that has just been screened positive in the state health department with the condition that you, literally, have never heard of. That is the paradigm that we deal with.

I might point out, these ACT sheets are designed to be available online and they, actually, are online and they have been developed for all the core and secondary targets. They are really designed to provide immediate point of learning, education and so forth. And they also are currently included in the American Academy of Pediatrics' plan at the newborn clinical report in their task force.

Let me just show you one of these. Many of you are familiar with these, but this happens to be the one for thyroid disorders. And it, basically, provides a differential diagnosis. It tells you exactly what to do, immediately. It has some comments about the diagnostic evaluation and it then has some additional information you can click on and go there. We have not yet talked about the genetic home reference, and I am not going to talk about that today, but the National Library of Medicine, working with the parts of the NIH, has on its Genetic Home Reference site all of the conditions that are included in the panel and it's done for parents. And so, it is a very nice source for, really, highly vetted information. I might point out that certain states have their own ACT sheets that are customized for their specific program. But it is also intended that these national Act sheets will also be customized for the local site.

The thing I would like to talk about next is the fact that NICHD has recognized that there is a very meager amount of information about these conditions and so, fundamentally, one that they have funded a variety of programs that I have listed here about innovative technologies and strategies. One of the things that they are currently involved in is to set up a NICHD newborn screening translational research network. There is some background information about the need, et cetera and NICHD proposes to establish this network, and it is far beyond a proposal at this time in that the contract for the coordinating center of this network will be awarded in the current federal fiscal year. So, it will be awarded before October of this year. These are the kinds of things that this network is expected to do. Number one, it is planned to develop a virtual repository for residual dried blood spots, as appropriately stored by the states, that they would develop and oversee laboratory and practice standard guidelines and work with the laboratories for the clinical diagnosis included in the panel so there would be specific discussions about diagnostic confirmation; that they would develop policies and recommendations about informed consent that might be appropriate for newborn screening. We are all aware of the fact that informed consent documents must be developed at the institutional level, but we are also aware of the fact that national collaborative groups such as the Children's Oncology group make a great deal of progress by having a nationally vetted informed consent that applies – that then can be worked on at the institution locally.

Fundamentally, the long-term plan is that this network would provide a mechanism by which research can be initiated and there can be long-term follow-up of patients with rare conditions, et cetera, as a research effort. This is a five year proposal for the coordinating center and, as times goes along, it will have additional activities to coordinate between other state and federal estimates and develop standard protocols and research. It will also be working on a data-sharing policy so that there can be nationally acquired data on the various and sundry children who are being diagnosed and how they will be followed-up in some of the research protocols. This is, in general, what it would look like: the translation research coordinating center in the center, but working with various and sundry grants, and coordinating many activities. There will be a steering committee and this will be closely tied to the states' newborn screening programs.

Let me comment just briefly in my final remarks about the advisory committee on heritable disorders and genetic diseases in newborns and children and the law that was just signed last week has shortened the name, mercifully. That committee has been just renewed for another five years. Fundamentally, this is a broadly based

committee that provides recommendations to the Secretary of Health and Human Services about the appropriate application of universal screening, newborn tests, technologies, policies, guidelines and programs. Now, many of you are aware of this committee and many of you have been involved with the committee, but it has medical, technical and scientific people. It has a broad group of public members and representatives from the federal agencies, such as the March of Dimes and other professional groups who have relevance to newborn screening.

The committee is currently looking at new nominations for newborn screening and the nomination process, as outlined here, is to be a very broad process where anybody can make nominations. It would be streamlined; it would be transparent and there are consistent criteria. And the main areas for consideration by the group will be the condition, the test and the treatment. This is the form that is on the web site of HRSA and it is a very simple form, I might point out. It takes a lot of time to fill it out properly, but basically, there is information about the condition, the incidence, the timing of onset and severity, the test, such as the screening test to be used and the modality of screening, validity, confirmation and the risk of false positive and carrier detections and things of that nature, the treatment, modality, urgency, efficacy, availability, risk and then the references.

This nomination then comes to the committee. But one thing that recently has changed, and that we think that will be a very big issue, is that once this report comes to the advisory committee, if the advisory committee thinks that yes, this looks like a perfectly reasonable proposal, it then will go to a totally external evidence-based committee. And that committee is operating under a contract with HRSA, but it is totally independent from the advisory committee and it is headed by a group of distinguished folks at Harvard who are involved in evidence-basis research and is headed by Dr. Jim Perrin. And that group will do a formal review of the evidence about these rare conditions. And I might point out that formal evidence review in these rare conditions just has not been done before and they have really spent a lot of time thinking about it. They have identified some issues that we are aware of, the lack of randomized trials, they are rare. There is limited information on the cost. They are concerned about access to the evidence; the published evidence is meager, as you know. There are unpublished results that they will look at. They are going to try to get as much as possible FDA data, such as when you introduce a new therapy, such as Myozyme, where you have an approved drug; the FDA will have those data. And they are going to use proprietary data, when possible. They will review the thing just to be sure that the form is filled out and so forth.

And I might point out, as of this moment, the Maternal and Child Health Bureau has already received five nominations for conditions, as I have shown here. Two have been seen sufficiently by the committee to send to the evidence group and so forth. And those two that have been seen by the committee and sent out for evidence review, is Pompe disease and Severe Combined Immune Deficiency (SCID). Those are the two conditions that have gotten to that point.

The evidence review is going to publish all of their material, but they will have a clear conflict of interest policy. That is a very interesting issue, because most of the people that recommend conditions of this nature are heavily conflicted because they have either been involved in research or they have families with the condition. And it is a very small community. They recognize that; they want to have that clearly stated.

Let me zip through some of the things. They are going to review the natural history, including variations in phenotype, the prevalence, impact and severity, methods of screening and diagnosis and things of that nature; the feasibility and acceptability of screening. They are going to look at the benefits of treatment, screening positive individuals otherwise diagnosed persons. Harms or risks involved in the screening, diagnosis and treatment and the cost.

They are publishing their search methods, such as the time frame and the search engines that they have used. They are going to use peer-reviewed English literature, English only. Gray literature, they are going to review. They are going to exclude case reports. I think that this will be an interesting problem, because so much of the material in here tends to be individual or small numbers of the cases. They are going to review consensus statements, but not for abstraction. They are going to, once they have finished with all the data abstraction and quality assessments and so forth, and analyze the raw data that they have. They are then going to have focus groups that will discuss their findings and they will make the input public, which would include families and investigators.

And severity estimates are particularly important. For example, for those of us who have been taking care of your children for a long time, we tend to think that, well, you know that, the diet, the PKU is a very straight forward treatment. Families do not think so. It is a big deal; it is very complicated. And so severity will clearly have a very different view depending on whether or you're living with it or at a distance.

Finally, once this evidence review, it will come back to the advisory committee. All the decisions will be made by the advisory committee and some of the possible recommendations from the advisory committee will be that this is recommended for universal screening,

that there should be some targeted screening done, or some pilot studies done. They will identify studies that will be done and, hopefully, that will feed back to the NIH who will say, if there are studies that need to be done, these should be proposals that are sent out as RFAs and so forth.

No recommendation is listed here as an outcome, which I think is an unfortunate turn, because I think if you do not make any recommendation that tends to be a recommendation of sorts. And you can recommend against newborn screening.

But anyway, I think that one of the – I will close with this. That is, I will comment briefly about public law, 110-204, that was signed on April 24th by President Bush and the working document was the Newborn Screening Saves Lives Act. That legislation authorizes 58 and a half million dollars to improve, expand, coordinate and evaluate federal research, education, programmatic activities. It is intended to help the state and local health agencies to provide screening, counseling, healthcare services, state laboratories, parents, families, and fund new technologies and follow-up treatment. So we will be very interested to see what happens with that.

I think that it was widely felt that there was not a chance that would get through the Senate. It was further confirmed that there was not a chance that it would get through the House. And thirdly, it was felt there was not a chance the President would sign it. And all three of those happened. And I might point out, almost exclusively, because of very active parent and advocate procedures. Now the same people that told me all those three things, there is not a chance that any money will be appropriated, but we will have to see.

Thank you very much. (Applause).

(Presentation concluded.)