TRANSCRIPT

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
ADVISORY COMMITTEE ON HERITABLE DISORDERS AND GENETIC DISEASES IN NEWBORNS AND CHILDREN

Monday, June 7, 2004

Horizon Ballroom
Ronald Reagan Building and International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

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P R O C E E D I N G S (9:05 a.m.)

DR. HOWELL: Good morning. I'm Rod Howell, Chairman of this new Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. I'd like to first turn over our program to Dr. Dennis Williams, who is Deputy Administrator of the Health Resources and Services Administration.

DR. WILLIAMS: Thank you. Good morning to all of you. It is my pleasure to welcome you here today. I bring greetings from HRSA Administrator Betty Duke. She regrets that she couldn't be here this morning, but asked me to thank each of you for participating in this first meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

Let me begin by thanking Dr. Rodney Howell of the University of Miami School of Medicine for serving as Chair of the committee. I'd also like to thank Dr. Peter van Dyck, HRSA Associate Administrator for Maternal and Child Health, for serving as HRSA's representative to this committee. Most of HRSA's genetics programs reside in Peter's bureau.

As members serving on an inaugural advisory committee, please be advised that you must follow federal rules on conflict of interest. Additional standards of ethical conduct are issued by the Office of

Government Ethics and the Department of Health and Human Services. Pam Kelley and Jennifer Jordan of HRSA's Ethics Office will provide training on this matter later this morning.

Tab 6 of your book has a colorful, useful handout detailing these rules and regulations, and I encourage you to read them. If you have any questions, the contact information for both Pam and Jennifer is listed in your briefing book.

All of us here know that the life-threatening or disabling impact of many heritable disorders can be prevented if detected early. This committee will advise the HHS Secretary on the most appropriate application of screenings, health services, and counseling in identifying and treating these disorders.

The national guidelines you recommend to the Secretary will help Department officials develop policies to encourage advances among our partners and state and local public health agencies on many crucial issues. These include improving quality screening programs, promoting equal access to genetic testing by all newborns and their families, and standardizing treatment and follow-up from state to state.

The Department of Health and Human Services has supported the development of newborn screening programs since the 1960s, primarily through the trailblazing of HRSA's Maternal and Child Health Bureau, and researchers at the National Institute of Child Health and Human Development. CDC's Newborn Screening Quality Assurance Program has improved quality practices among state laboratories, and its national Center on Birth Defects and Developmental Disabilities provides expertise in the areas of epidemiologic surveillance and evaluation.

More recently, the Agency for Healthcare Research and Quality has supported research that helps health care professionals use advances in genetics to improve the care they provide. Strengthening the scientific bases for newborn screening is one way the federal government can support state newborn screening programs, and my agency, HRSA, has been a leader in translating the findings of genetic science into practice.

The discretionary grants portion of HRSA's Maternal and Child Health Block Grant Program is the primary federal source of newborn and other genetic screening, counseling, and information projects. In 2002, two years after release of the task force report on newborn screening and genetic testing, Dr. Duke appointed a HRSA genetics workgroup, consisting of representatives of all of HRSA's bureaus and offices.

The workgroup, chaired by Dr. Sam Shekar, HRSA Associate Administrator for Primary Care, was asked to inventory all genetics-related activities across the agency. The group was also instructed to develop a strategic plan for future genetic activities and to strengthen partnerships to advance genetic education and service. We expect the workgroup's report to be released soon.

HRSA also trains health care and public health professionals in genetics through the Genetics in Primary Care project, which targets the next generation of health care professionals by introducing genetics to students in health professions, and through our new Family History project, in partnership with the March of Dimes and the Genetic Alliance, HRSA educates consumers so that they understand more fully the benefits, risks, and limitations of genetic testing.

As new discoveries and technologies emerge, the future impact of the genetic testing of newborns cannot be fully glimpsed. On Wednesday, for example, HHS Secretary Tommy Thompson addressed a summit in Williamsburg on the obesity epidemic.

That same day, the Atlanta Journal Constitution ran a story entitled "Too Big For Your Jeans?" — that is spelled J-E-A-N-S — "It Might Be Your Genes," G-E-N-E-S. The story quoted a Duke University researcher who said that obesity is not just a problem with people having no willpo wer. If you combine the wrong genes with the wrong environment, the researcher added, you have big problems. Today's

teenagers are three times as likely to be overweight than they were in 1980, so one would surmise that changes in behavior and nutrition have played the major role in this startling increase. What is the influence of genetics in this rather sudden health crisis? We're not sure. Stay tuned.

Advances in genetics testing and understanding are leading us into the future where scientific gains strained against the moral and legal boundaries that have guided us up to now. Your role, and it is one of significant importance, is to help the Secretary and the nation understand these challenges, and the choices that await us.

I wish you good luck. Thank you.

DR. HOWELL: Thank you very much, Dr. Williams.

At this time, I'd like to go around the table and ask each person to please introduce themselves to the group here. I'll start with Dr. van Dyck on my left.

DR. VAN DYCK: Good morning, everybody. I'm Peter van Dyck. I'm Director of the Maternal and Child Health Bureau in HRSA. I'm a pediatrician and long-time MCH person, and was a state director of MCH in Utah for 15 years or so before I came to the federal government, so I like to claim knowledge of both the federal and state mechanisms for delivery of service. I'm very pleased the Secretary appointed me to the committee to represent HRSA and the broader public health community, and really look forward to the input of the committee, and its output.

DR. WILLIAMS: I'm Dennis Williams. You already know me. I'm the Deputy Administrator from HRSA, and I welcome you all here.

DR. RINALDO: Good morning. I'm Piero Rinaldo, I'm a pediatrician and biochemical geneticist, and I am a professional of laboratory medicine at the Mayo Clinic.

DR. TUCKSON: My name is Reed Tuckson. Unfortunately, I'm an internist and not a pediatrician, but I did work for Jennifer Howse at the March of Dimes. I am now a Senior Vice President in UnitedHealth Group, a very large and multi-disciplinary health and well-being company, and I spent some time as an administrator for mental retardation developmental disabilities here in this city before I served as the Commissioner of Public Health here in Washington.

DR. BECKER: I'm Bill Becker. I'm a pathologist, as we're moving down the medical specialties. I'm Medical Director for the Ohio Department of Health Laboratory in Columbus, Ohio. We do the newborn screening for the State of Ohio.

DR. BOYLE: Hi. I'm Coleen Boyle. I'm actually an epidemiologist, and my primary work has been in the area of developmental disabilities and newborn screening. I am currently the Chief Scientist for the National Center on Birth Defects and Developmental Disabilities, and I'm very pleased to be able to represent CDC in a number of different capacities in newborn screening here at this committee.

DR. BROWER: Hi. I'm Amy Brower, and my training is in medical genetics. I have spent the last few years understanding more about genomics and high-throughput screening across the genome. I'm also a parent.

DR. COGGINS: Good morning. I'm Peter Coggins. I'm President of Life and Analytical Sciences for PerkinElmer. Part of that encompasses the genetic disease screening business, where we develop, manufacture, and distribute systems, such as hardware, software, and reagents, globally for newborn screening.

DR. HAWKINS: I'm Greg Hawkins. I'm Assistant Professor at Wake Forest University School of Medicine. I'm also the Director of DNA Sequencing in the Center for Human Genomics.

DR. EDWARDS: I'm Steve Edwards from Raleigh, North Carolina. My background is that of a pediatric practitioner, and I'm Immediate Past President of the American Academy of Pediatrics.

DR. HOWSE: I'm Jennifer Howse. I'm President of the March of Dimes Foundation. I'm very pleased to be here this morning on the subject of newborn screening, which is a very high priority for our prevention organization, so we're looking forward to that work. I also had the privilege of working with quite a number of you around the table in various capacities. It is good to be with such a talented and committed group.

DR. LLOYD-PURYEAR: I'm Michele Puryear. I'm a pediatrician and Chief of the Genetic Services Branch in the Maternal and Child Health Bureau, Division of Services for Children with Special Health Needs. I'm here as the Executive Secretary for the committee.

DR. HOWELL: I'm Rod Howell. I'm Professor of Pediatrics, Miami School of Medicine. My background is as a pediatrician, and I'm trained in biochemical genetics. I have been interested in newborn screening for longer than many of the people in the room have been alive, having worked originally with the State of Maryland Newborn Screening Program in the mid-1960s when I was at Hopkins on the faculty.

I currently am spending much of my time on an interagency personnel agreement arrangement at the University of Miami, and I am working at the NICHD on some of their interests in the research arena.

Let me also comment that Dr. Duane Alexander, a member of the committee, is unable to be here today because of a meeting that I understand involves all the directors of the NIH institutes having to do with the budget, and I think we can always appreciate that that is not something you would miss. But Dr. Alexander will be with us tomorrow and will comment about that.

We are off to a wonderful start, because we are far ahead of schedule, which I think is a great way to start this thing. I wonder if we could just go ahead and do the ethics rules at this point. We have a good bit of instruction that we need to hear from HRSA about the ethics rules for special government employees. I think we'll go ahead and do that before we take a break, since we just got here.

Who is going to speak first on this issue?

MS. KELLEY: I will. Pam Kelley. Hi.

DR. HOWELL: Hi. It looks like we have both Pam Kelley and Jennifer Jordan. They are both arriving to tell us the proper behavior.

MS. KELLEY: First of all, I want to thank all of you for how kind and patient you were in answering the numerous questions that I had. I thought your cooperation was just very wonderful. Just in talking with you, the expertise reflected in this committee is extraordinary, so I'm really hopeful for you all to have a real productive two days here.

Jennifer and I work in HRSA, and we do ethics there. What we have for you this morning is about a

20-minute videotape from the Office of Government Ethics. Basically there are some objectives that I want to make sure we attain here in our talk. One is twofold. It is that you all obtain a general familiarity

with the conflict of interest rules that are applicable to you all. The other important thing is that you know who to call if you have any questions. It would be Jennifer and myself.

Now, you have a designated federal official, which is Dr. Michele Puryear, so she might be your first line, and then she could come to us. Or if you feel comfortable, you can just come to us directly. But at least you know some folks that you can speak to.

There are criminal conflict of interest statutes, and there are ethics rules, and they are applicable to you throughout the term of your appointment. There is the Hatch Act, which is in Section 6, Tab 6. It is about 11 pages of rules for special government employees and committee members that I really encourage you to take a look at. It is critical that you look at that. The last page is on the Hatch Act.

Now, the Hatch Act is only applicable to you for the exact time that you're serving on this committee today. So from now until when the committee is over today, you're under the Hatch Act. Tonight, you're not. When you leave this committee, you're not. So that is the only one that is specific to sitting right here. Does that make sense to you? So just for the time nine to whatever time it ends today, Hatch Act you're under. Outside of that, you're not.

The other ones are applicable to you for the length of your term. I believe it is four years overlapping. I think that's right. Why don't we go ahead and show the videotape? After that, I'll field questions.

(Videotape shown.)

MS. KELLEY: What we have is a gentleman who filled out a form 450, which you all completed. On the form 450, what Jennifer and I do when we review, and in fact, that is the first step we come to when we're taking a look at you all in terms of ethical issues and conflicts of interest.

On the 450 form, there was a notation that there was a stock apparently that this gentleman had. Well, the stock was his stock, and he is an engineer, he builds planes, or a plane engineer. He was going to be speaking in an advisory committee, I believe, for the Navy. His stock made the parts that he was going to be on a committee about from the Navy, so he would actually have a conflict. Here he has money in an entity that he is going to be on an advisory committee to review, to look at. So do you see the conflict there?

The ethics person said, you have some choices. Depending on how much money is in this stock, we could write a waiver, or he could recuse himself and not deal anything at all with that particular matter. Or he could sell his stock, if that is what he chose to do. Apparently, that is what he had wanted to do.

The next example is his wife. Now, his wife, he didn't know this, but his wife's stock — let's try it again.

(Videotape shown.)

MS. KELLEY: This committee is unlikely to consider issues that would focus on the interests of a particular employer, or a particular party, it is my understanding, in terms of how specific it was in this film, reviewing a grant, and then having somebody related to that grant offer them work on that topic. Do you know what I'm saying?

The specifics of this tape may not translate into this committee, but we did want you to know that that does exist. You want to know about the restrictions and the rules.

Are there any questions that I can take? Any comments? Some points I could accentuate if you'd like? Dr. Tuckson?

DR. TUCKSON: Actually, I think it makes sense.

MS. KELLEY: Oh, grand. That's grand.

I have a few points I'd like to make. When we talk about teaching, speaking, and writing, a lot of you most probably do that. Did you understand what they were speaking of? Clearly if it is your area of expertise and it is not related specifically to this committee, you are free to do that, and you can talk generally about this.

Do you remember when the aeronautic guy was speaking, and the woman asked him about hey, I hear you're working for the Navy? He said, yes, it is pending, I can't speak of anything specific right now because it is nonpublic. But he could speak generally and talk about yes, there are problems because of the rust due to the Marine environment. So he got very vague, he didn't get specific, and it was clear that it is non-public. So that's something to remember. I don't know that that would apply here, but you are certainly free to do your teaching, speaking, and writing on your particular area of expertise. You can't accept compensation if your speaking, writing, or teaching deals in a specific way with this particular committee, so there is the distinction there.

Representing folks back to the government. As committee members in your personal capacities, you are not prohibited to make representations on behalf of others back to the government on particular matters involving specific parties that you were involved in as committee members. In the film, the gentleman that was the Ph.D. teacher guy, the museum woman came to him and said hey, I heard you were on this committee and you have this NEH expertise now. We got that grant, can you come now and work for us, and help us with that, since you know how NEH runs? He says no, I can't do that. She said, well, there is this other thing, the Van Gogh exhibit. Well, that's brand new, that has nothing to do with what he reviewed on in his committee. He can do that, it is brand new. It is not related to what he worked on.

So what you've got to remember is what you work on here is what you do here, and it isn't what you can carry out in specific matter outside in your personal life. If there is something that comes up in this committee that involves financial matters on your own, or input to you by your spouse, dependent, or your employer on any action you would take on this committee as a special government employee, you need to let Michele Puryear know, or Jennifer and I know.

Yes?

DR. BOYLE: I have a question.

MS. KELLEY: Sure.

DR. BOYLE: Is there a statute of limitations on some of these issues?

MS. KELLEY: Sure. These rules are applicable to the SGE, these conflict of interest rules, and these ethics regulations, for the length of your appointment. So that whatever your length of appointment is. The only one that is real short is the Hatch Act. If you look at that Tab 6 at the last page, there is a nice breakdown. That's a good question.

Dr. Rinaldo?

DR. RINALDO: Do you make any distinction between people who make decisions, and people who advise others?

MS. KELLEY: Well, it depends on the situation. You are doing advising here. Well, I don't know, if you were doing advising, there could be an appearance problem if in fact what you'd worked on in a committee would be something that you may be asked to do in your personal life.

It really depends on the circumstances. There could be a distinction, and again, there could not. If you come up with something like that, let us know, and we'll work it through with you. That's a good question.

DR. HOWELL: Let me ask one other question.

MS. KELLEY: Sure.

DR. HOWELL: That is the most likely thing that will come up, I believe, with members of this committee, that they will be asked to talk about the activities of the committee, because people are extremely interested in what is happening.

MS. KELLEY: Sure, sure.

DR. HOWELL: Since most, if not all, of the deliberations of this committee are going to be open and public, there might be something as we go along that will be "confidential," but it is basically public. I would infer from what we have heard that one would be free to talk about anything that this committee had discussed, as long as it was in the public arena.

MS. KELLEY: If it is public, right.

DR. HOWELL: So that that, I think, might be the most likely, I believe, thing that will come up, and so forth.

MS. KELLEY: You couldn't be compensated for talking about it outside. In other words, if someone wanted you to give a speech on this topic, specific to the committee, you couldn't be compensated. But it sounds like if it is public information, and someone wanted dialogue about it in general terms, is that right?

DR. HOWELL: I think so. And the other thing you and I had is we had a lot of conversations.

MS. KELLEY: Yes, Dr. Howell.

DR. HOWELL: One of the issues that came up is that many people around the table are involved in newborn screening in an extremely broad fashion, either from the industry side of the fence, the CDC, the state, or the university side. In virtually all of those instances, federal funds from HRSA, the NIH and so forth, flow through those organizations. But again, not preferentially.

In other words, we are not going to be recommending that this particular group get something, but we will recommend programs and policies, and that seems to be that that would not create a problem, as long as it was not inferred that the March of Dimes or the State of Ohio had some special interest in this project.

MS. KELLEY: Right. Talking about specific matters with specific, particular individuals coming back, yes. If it is not going to be specific party matters, then there isn't going to be an issue in that respect. Go ahead.

DR. BOYLE: Let me ask one more question.

MS. KELLEY: Sure.

DR. BOYLE: In terms of the issue that Rodney just brought up, and being able to talk about the deliberations of this committee, as an individual, I'm assuming then you can also talk about your own viewpoints? You don't talk in unison, or as a unified committee, do you?

MS. KELLEY: How do you mean that?

DR. BOYLE: The committee's opinion. I think that's part of the record anyway.

MS. KELLEY: Right, correct. You had dialogue, and that is what they would want.

DR. BOYLE: I was just going to say, outside the committee deliberations. I think I answered my own question.

MS. KELLEY: Okay. Now, what you can't do is just say the committee said so and so, and it is your own opinion. You can't represent a separate opinion than what was decided upon by the committee. You certainly are free to dialogue about what it is that you are talking about here, but if you take your own opinion and fabricate what you think the committee came up with, that wouldn't work. Does that help you?

The handout at Tab 6 is a very good handout, and it actually touches on that. It would be very important for you all to take a look at that. "Ethics Rules for Advisory Committee Members and Other Individuals Appointed as Special Government Employees." Does anybody have any other thoughts or questions?

(No response.)

DR. HOWELL: It seems that there is silence. So thank you very much.

MS. KELLEY: You're very welcome.

DR. HOWELL: Is that the end of the things that we need to hear about, that we should be doing properly?

MS. KELLEY: Yes, yes.

DR. HOWELL: Good.

MS. KELLEY: It is. The video and the handout were the main things, and then being able to talk, and letting you know who to talk to.

DR. HOWELL: Thank you very much.

MS. KELLEY: You're welcome.

DR. HOWELL: One of the things I had hoped to do if we were running well on the schedule, and we are doing extremely well, is I would like members of the audience to please introduce themselves and tell us in a very brief way who they represent. I think that would be extremely helpful for this committee to

understand the constituency that is here. We'll hear later in the program from specific people that have asked to address the committee.

Marie, could we start over in your corner, and then go across the front row?

(Audience introductions.)

DR. HOWELL: Thank you very much.

I think that Michele would like to introduce the folks who are the planners for this meeting, who can give us a little update before we go on our break.

DR. LLOYD-PURYEAR: I just thought you should know who our logistics contractors are. Martrell Kelly, standing up in the back, Laura Sternesky will be the science writer for the meeting, and Alan Friedman is here doing the transcription. Some of you may know him from other advisory committees.

For the committee's information, behind this screen is coffee and break foods.

DR. HOWELL: And it is time. Let's take a little break and so forth, and celebrate our early schedule. We'll be back in about 15 minutes.

(Recess.)

DR. HOWELL: Ladies and gentlemen, let's resume. We're doing wonderfully. We're ahead of schedule. We want to spend a bit of time now talking about the charge to this committee. I will comment about the charge, and then Michele will discuss some details about voting and things of that nature, and then I'll take questions that you might have.

Title 26 of the Children's Health Act of 2000 authorized the establishment of this Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, and this committee has obviously been duly appointed by Secretary Thompson. We're here today to meet for that first committee meeting.

I think that this is a very exciting time, because I think that this committee has the ability to make recommendations to the Secretary, and if they can be further really brought into practice in the United States, they have a substantial opportunity of saving children's lives. So I think it is a great opportunity, and it certainly is my commitment that we fulfill that really tremendous opportunity.

This morning, as I was coming, I thought it was particularly poignant that we were having this first meeting designed to save the lives of babies in this magnificent Ronald Reagan Center. Obviously as Washington and the world begins mourning over the death of our 40th President in the building that was named for him, I think that as we begin an entire week of state funerals honoring President Reagan and this building, it is in an extraordinarily important setting that we begin our meeting here.

I have outlined a few of the key issues that this committee will address, and they are outlined in the following slides. The first issue is the committee shall review and report regularly on newborn and childhood screening practices, and recommend improvements in the national newborn screening and childhood screening programs. Although we're not completely focused on newborn screening, as you know, that is really a key area.

The second is that the committee will provide advice and recommendations to the Secretary concerning grants and projects awarded or funded under Section 1109 of the Public Health Service Act,

an important part obviously of this project, to provide technical information to the Secretary for the development of policies and priorities for the administration of grants under Section 1109 of the Public Health Service Act, and provide such recommendations, advice, or information as may be necessary to expand and improve the ability of the Secretary to reduce the mortality or morbidity in newborns and children from heritable disorders.

Section 1109 of the Public Health Service Act authorizes grant awards to enhance, improve, or expand the ability of states and local public health agencies to provide screening, counseling, or health care services to newborns or children having, or who are at risk for having heritable disorders. Awards will be granted to the states, political subdivisions of the state, a consortium of two or more states, or political subdivisions of the state.

Those are basically the key issues. Now, the actual charter of this committee is under Tab 4, and it is substantial, and I'm sure that most of the members of the committee have read it. Obviously if members of the group here have not, I'm sure that we can get copies in greater detail.

I want to ask Michele if she would be good enough to talk about some of the voting and membership things.

DR. LLOYD-PURYEAR: The legislation and the charter is in Tab 4. The charter is based on the legislation. The legislation indicates the name of the committee, and the name of the committee was originally the Advisory Committee on Heritable Disorders in Newborns and Children. The Department added "Genetic Disorders" to the name, and that is explained in the charter, so there was that addition.

The legislation indicates that committee membership is limited to 15 members, and then outlines specific areas of expertise that must be on the committee. We interpreted when we wrote the charter, what kind of members we would have, so you have both voting and

non-voting members. You have members that will translate into special government employees, and members that remain as representatives of organizational groups.

I'll first speak to that. The representatives on this committee, there are three different kinds. One is representing two other advisory committees, and that is the Secretary's Advisory Committee on Infant Mortality. Dr. James Collins is a member of that committee, representing that advisory committee in a non-voting capacity on this committee, although he is a voting member on his committee. In fact, he is the Chair of that committee. He was unable to be here today. His son is graduating.

Dr. Reed Tuckson is representing the Secretary's Advisory Committee on Genetics, Health, and Society. He is a voting member of that committee, but is a non-voting member on this committee.

Then we have Dr. Stephen Edwards, representing the health care professionals broadly, although he is here as a member representing the American Academy of Pediatrics. He is a representative, and he is a non-voting member of this committee.

Another non-voting member of this committee is Dr. Jennifer Howse. She is representing the public at large through her presidency for the March of Dimes, which has a long record of public advocacy.

All the other members of the committee are special government employees, except for the four federal agencies that are represented on this committee. They are also members, and unlike most other committees, they are voting members of this committee. Congress wanted the four federal agency representatives to be voting members.

They were limited to those four federal agencies. The Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Health Resources and Services Administration, and National Institutes of Health.

To my knowledge, there is only one other advisory committee that is similar to this, and that is the Advisory Committee on Immunization Practices, where the four federal agencies that are represented on that committee also serve as voting members. That advisory committee advises the Secretary, similar to this one, on guidelines and standards for immunization practices.

Do you have any questions?

DR. HOWELL: Are there questions at this point in time?

(No response.)

DR. HOWELL: No questions from anybody. Let me tell you what. I would hope we would get this accomplished before lunch. I'm going to make a very few comments about the clinical delivery services to children in a clinical setting, and then I think we should have adequate time at that point to move on, and have Marie Mann present the overview of newborn screening programs in this country.

We anticipate that Brad Therrell will be on the telephone. Brad has recently had back surgery, and although he was hoping to get here, he is not able to be here, but Marie will present his information, and he will be with us on the telephone. Brad is on the phone now, so he is an early bird.

Let me go up and tell you a little bit about genetic services in the clinical setting.

Obviously I will be able to make just a very few remarks about delivery of genetic services in the clinical arena today, and obviously they will be focusing on what has been some of the dramatic changes that has happened in that area in recent years.

I think it is fair to say that genetic services have really been a very integral part of the medical care of children for more than 40 years. Those services have focused on what you can see, the abnormalities that you see in children, such as Down's syndrome and dysmorphology, and other things of that nature, and single-gene defects that have really been very commonly picked up through newborn screening, that you have biochemical or metabolic abnormalities and things of that nature. Basically, relatively simple single-gene defects.

The area, as I look at it, and I will be parochial, since my training is in biochemical genetics, I think that the area of genetics in children really began with the very important publication by Garrod of the Croonian Lectures that were delivered in London, and later published in this volume called "Inborn Errors of Metabolism."

Garrod's book, which is a wonderful little book, focused to some considerable extent on things that you could see, and then his visual inspections were backed up by relatively simple chemistries that were available in the early 20th Century. There is a very nice description of albinism that you could clearly see that people were different, because they had differences in pigmentation.

He described another condition that we still see today, and this Pamper is obviously not from the age of Garrod, but a little bit more recent. But again, one of the conditions that was classically described in his book was described by this mother who brought in a baby and said that when my baby's diapers sit for awhile, they turn very dark, and in time, they turn black.

Again, Garrod described this condition extremely amply as alcaptonuria, and had the simple chemistry at that time to demonstrate that these people were excreting abnormal amounts of homogentistic acid, and that in time, these materials formed black colorations.

But again, a tremendous interest in these "inborn errors of metabolism," because you could see things that were wrong with them, and that interest continued, again, all through the early part of the 1900s.

There was very little you could do about these conditions, I think it is fair to say. You could describe them, but not much beyond that point. One of the next phases that I would call in the evolution of clinical genetics and biochemical genetics in children started with these very simple screening tests that were popular 35 to 40 years ago. Basically children that had special features, or special abnormalities such as mental retardation, commonly had simple urine tests done to see if there was anything in the urine that gave a clue to the diagnosis.

These are three examples of simple tests that were widely utilized. On the left, we have the feric chloride test, and the dinitrate phenylhydrazine test that is in a patient with phenylketonuria. You can see that the feric chloride, which is ordinarily a light tan, had turned a blue-green here, and this dinitrate phenylhydrazine had precipitated a hydrazone, again consistent with phenylketonuria.

In the middle, a child with histidinemia, again, with a positive feric chloride, and a soluble hydrazone here. Then on the right, a patient with maple syrup urine disease. These were popular, and you can clearly see abnormalities there.

At the same time, there was a lot of clinical diagnoses that were being made at that time, not on the basis of newborn screening, but on the clinical diagnoses.

This is a little girl I saw long ago who, at the time this photograph was made, was six months old. She basically weighed what she did at birth, and she was a profound failure to thrive. Even those of you who don't deal with infants can see that there is tremendous wasting, with essentially no subcutaneous fat.

One of the things that was routinely done 35 years ago when this photograph was made, you do simple tests looking for what might be wrong. She had a strongly positively reducing substance in the urine, and was shown to have galactosemia, a condition that has been known for a long time to respond dramatically to removing galactose in the diet. Again, this is a picture of Karen after being on a lactose-free diet for a relatively short time.

So the point is that there were a considerable number of conditions that were recognized at that time, 30 and 35 years ago. At the same time this photograph was made of this little girl, Bob Guthrie had come along and utilized a very simple punch test, and had developed simple screening tests using dried blood spots in the situation of phenylketonuria.

This is an old slide, simply to indicate what has historically been the simplistic list of what was done for mass screening in the early days with Dr. Guthrie. The disorder should be treatable, they should be simple, feasible, the tests should be inexpensive, and the program should be justified. Even early, it was kind of in the background that you could consider screening for something if you saw a treatment on the horizon. But again, having a treatment, and treatment I might point out at that time, was visualized as a very specific treatment, one you could get your hands around, such as a diet or medication, and not some complex treatment.

What has happened in recent years, and again, Mike Watson tomorrow is going to have an extensive discussion of what has happened, but fundamentally, the mass spec and other high-throughput genetic testing is clearly changing how we look at inborn errors of metabolism, and again, newborn

screening is expanding rapidly. A considerable number of states are using tandem mass spectroscopy. But more importantly, there are other technologies evolving that I'm going to talk about a little bit at the end, that require even more sophisticated issues.

There are a variety of problems emerging. One, in addition to the conditions that we know a good bit about, and that we have treatments and awareness about, we have some data about the outcomes, and there are conditions that are being identified that we don't know a lot about, the natural history, and/or the treatment.

The other issue that is very important, and there are many important issues, but a compelling issue is that there are relatively few people in the United States to follow up, diagnose, and treat with some of these extremely uncommon conditions. So figuring out how to distribute that talent will be a very big area.

Now, the other thing is that in addition to newborn screening, I think it is fair to say with the Genome Project, we're right at the beginning of what can be predictive medicine, and there is an enormous opportunity for prevention. In other words, we really have never been a preventive society, but there are opportunities now, if it is properly rolled into that.

This group is very familiar with the Human Genome Project, and these covers of Nature and Science celebrate the private and public publication of the genome. For those of you who have looked carefully at this cover of Nature, if you look very carefully down in here, these are all photographs, and it is hard to see unless you've got a magnifying glass, but Watson and Crick are tucked down here in the bottom of that thing.

So what we know about the genome at the current time is that it is big, 3.2 billion base pairs, and then in addition to that, the mitochondria has a little over 16,000 tucked away in its circular chromosome. The goal of the Human Genome Project was to map and sequence the human genome, and it has recently been focusing, to some considerable extent, on model organisms.

I might point out that some folks have said why is the Genome Institute spending so much money on model organisms? Is it going to have any relevance to where we are and what we are doing? The answer is yes, and I'm going to show you a publication from just two weeks ago.

One of the things that has been wonderful about the data from the NIH-funded and the Department of Energy, is that these data have been publicly available, and there has been a lot of technology developed, and importantly, there has been a significant focus on ethical, legal, and social issues with regard to this, which is obviously continuing and it needs to continue.

There are a few things listed as what one might call unexpected findings. I guess some people could expect things more than others. But one is that I had grown up being told all along that humans have about 100,000 genes, and they don't. That's one of the things.

The other thing, and I'll show you a slide about this, but human genes make more proteins than other organisms, human genes have a couple hundred genes that have been adopted from bacteria, and the male mutation rate is more rapid than female. It has been called "junk DNA," which is an unfortunate and probably not correct term, but there is a lot of DNA that we don't know an awful lot about today.

Now, this slide is actually from one of the genome programs, and this is to not make anyone feel inferior, but we have just a few more seeds than a mustard weed, and fortunately, considerably more than the worm or the fly, but not a lot. So that we really have relatively few genes, compared to these organisms which we think are considerably less complex.

However, the proteins in the human, we have 90,000 type proteins, dramatically more. So the use of the genetic information in humans is obviously vastly more complicated. That adds a level of complexity that will be very difficult as we look at gene sequences, and try to predict certain things.

There are some other important things about the Human Genome Project, and that this that we're 99.9 percent identical at the DNA level. That is a very important thing, and the thing is regardless of who you meet on the street, or where they came from, the chances are overwhelming that you would just have this little one-tenth of 1 percent of DNA that is different in sequence. However, since there are 3.2 billion bases, that still leaves a lot of room for change. The frequency of these alleles can vary between populations, such as results of selection, and so forth, and obviously found effects, and so forth.

This is very interesting, and that is that except in extreme geographic isolation, people that have been on a specific area isolated for many, many centuries, there will be very little specific differences between population groups, and the difference between individual population groups are very, very different, and so forth.

As far as differences in illness among observed groups, it could be due to allele frequency, but dietary cultural and environmental factors can play a very big affair. I think that many of you know that some of the population studies that are being considered now to look at the genes and environments in children, adults, and so forth, are really focusing to some considerable extent on the environment, or other factors that are affecting illness, in concert with an extensive awareness of the gene.

Everybody, I think, certainly knows the central part of modern genetics is DNA, RNA, protein, and then a metabolite. Interestingly enough, there are some new terms that are hitting the streets, such as transcriptomics, which is basically a combination of all the RNA transcripts. The proteomics, which is the proteome, all the proteins in the cell, and the metabolome, which is all the small molecules that are within the cell.

When all of this is done, we should have information about all of the genes, all the proteins, and all of the RNA, we should have a fully functioning assembly of the human organism. I think the thing is is that the human genome had a promise of doing predictive medicine, and reactive, individual medical care, and then population screening.

We realize some of these things are going to be a lot more difficult than others, but one of the areas where I think this group has a great deal of possibility is looking at screening, and identifying certain persons at risk for significant conditions, that if early detected and so forth, can be treated. I think this is going to be far more rapid than either individual medical care, or preventative medical care. Although those clearly are going to come, they are not going to come easily, or readily.

Mike Watson tomorrow is going to review a very long program that the American College of Medical Genetics has been working on under contract from HRSA, to look at some recommendations about standardizing newborn screening and so forth, so we will not go into that. He will cover that very, very well.

I wanted to comment about the following, and I'm going to talk to you about a couple of specific things. The specific genes that underlie genetic defects are dramatically enhancing diagnosis. In other words, instead of just looking and measuring a trial and so forth, they are increasing numbers of specific genetic tests that provide accurate diagnosis, and that is obviously very important.

One of the areas that has undergone an enormous explosion in technology has been cytogenetics, where you now have the ability to do very sophisticated testing for small gene deletions and so forth, and accurately diagnose important clinical conditions in childhood.

This is actually a cover of a Nature Genetics paper from two weeks ago. It struck me as interesting for two reasons, and this is from Philadelphia. I don't expect you to see it, but it is a publication that reports the discovery of the genetic defect underlying the Cornelia de Lange syndrome. Again, the Cornelia de Lange syndrome was described by Professor Cornelia de Lange, who was Chair of Pediatrics in Amsterdam in the 1930s, and she described this group of children who had very characteristic facial features, profound retardation, and these children have been diagnosed since that time. It is quite characteristic, and geneticists, and particularly people that specialize in dysmorphology, have routinely diagnosed this condition.

Now, interestingly enough, in doing some studies of this group of children, the group at Philadelphia were able to hone down on one area of the genome in an area where they thought the defect might lie, based on studies of association. It turned out that in comparing this area of the gene to the gene of the Drosophila, which is a fruit fly, they discovered that these children lacked a gene that is identical to the gene in the Drosophila that is called the Nipped-B.

It is very interesting. I don't know anything about Drosophila, but they showed in the picture, this wonderful picture, that the Drosophila that lacks this gene has a little defect in the wing, and it looks like someone took a bite out of the wing. That's why the name Nipped-B came up, because it looks like the B got nipped.

But the bottom line, the availability of the Drosophila genome was very valuable in helping to identify the specific genetic defect in the Cornelia de Lange syndrome. Again, it is a condition that has been diagnosed for 70 years, and it is a complicated gene, having to do with human development. But knowing what the problem is, and knowing a good bit about how that gene works, clearly will provide you with the background that will let you consider, what can we do about this? Obviously with diagnoses, families and so forth, the accuracy is dramatically increased with this.

I'm going to talk it into the story about Pompe's disease, which is a condition that I have been interested in for many years, and it is a rare glycogen storage disease. But again, Pompe is the disease which was described in the Netherlands in 1932. If you read the original paper, which I have read in translation, Professor Pompe thanks Dr. Cornelia de Lange for having sent him a patient, which is kind of interesting how these things come together.

Now, the other area that has been discussed a great deal in the genetic area is pharmacogenetics. The adverse drug reactions in this country is a very big problem. Some of the data has indicated that it causes more deaths than pneumonia and diabetes. There is a lot known about polymorphisms, and how they might affect drug porters, receptors, and things of that nature, and pharmacogenomics has been a term that has been used now to talk about the whole area of genetics, of drugs, and things of that nature.

I want to talk about one that has considerable application to children, and intrigues me as a potential test. That is that if you read the insertion in the medication for streptomycin sulfate, which is an aminoglycoside that is not commonly used, but it is a member of the family that is commonly used today, the adverse reactions are listed, as required.

It says the common abnormalities are nausea, vomiting, paresthesias, and angioneurotic edema, all things that are troublesome, but not a real problem. But a less frequent one, however, is cochlear ototoxicity, deafness, and that obviously is a big problem. Although it is rare, it is a major problem.

Now, if you look at it from the other side of the fence, and that is as far as irreversible hearing loss, aminoglycoside toxicity is a significant cause of hearing loss. Now, interestingly enough, there has been identified a mutation in RNA in the mitochondrial RNA that makes the human ribosomal RNA resemble a bacterial RNA.

This particular mutation in the mitochondrial RNA causes the bonding of the aminoglycoside to this particular target, and then deafness is at very high risk. Now, the point is, this mitochondrial mutation, which is an A to G change at 1555 in the mitochondrial, is it of any relevance, and so forth? I'm not aware of any larger studies, although there may be at the current time.

There have been some screening programs looking at whether or not this particular mutation is frequent. The program in New Zealand identified one person out of 206 people, and then the other side of the fence, this group at the Annals of the New York Academy of Science found that 17 to 33 percent of people who had aminoglycoside toxicity had this mutation. So the bottom line is that you can demonstrate in vitro that you can inhibit mitochondrial protein synthesis with this particular drug.

Let me go back to that. I'm not suggesting at the current time that we do that, but we do know that aminoglycosides are very commonly used in the newborn nursery, particularly in premature infants who are considered to have sepsis, which is a big problem, and we also know that a certain percent of those will have toxicity. One could make a case that if you had a very rapid test, that before selecting a drug, you might really want to look for that mutation, since that does have a significant risk.

The American Academy of Pediatrics has issued a specific comment about testing for adult onset disorders, which will obviously come up for this group. When you start widespread testing in infants and so forth, you are going to identify conditions that have late onset. The Academy's recommendation is that you do not test children unless there is an immediate medical benefit, or there is a benefit to another family member, and no other recognized harm to that minor.

If you look at genetics in general, to this date, genetics in childhood has been the diagnostic area. In other words, you make diagnoses. Aside from a relatively few rare conditions, phenylketonuria, and some of the fatty acid disorders, you don't do a lot of treatment. One of the things that we would certainly hope to see is an evolution of diagnoses of conditions that are treatable, and for which we can provide more specific treatment.

Again, one of the new treatments is coming along that is currently in clinical trial, is the treatment for a glycogen storage disease that is known as Pompe's disease. Pompe's disease is a very rare condition involving glycogen metabolism, described by Pompe in 1932. These babies have weakness, and these are floppy babies when they are born. They have feeding difficulties, they fail to thrive, there is macroglossia, respiratory distress, and hypertrophic cardiomyopathy.

It affects the muscle throughout the body, and there is a delayed onset variant that the persons have a gradual muscle problem. Now, importantly, however, is that we have been making this diagnosis certainly during my career, and it is a diagnosis that is readily suspected clinically if you're aware of it, and this little girl is again, a patient that I saw some years ago. She exemplifies the problems.

As you can see, she is being gently raised, and she is about five months old in this photograph, six months old. She is not able to hold her head up, she is very floppy, and has very poor muscle tone, although her muscles are very, very firm. She has a big tongue, as you can appreciate somewhat there. When you make a chest x-ray of this little girl, she has a very big heart.

The diagnosis has been made microscopically, chemically, and historically by biopsying the muscle. This is the first of the lysosomal storage diseases that were identified. If you look at an electron micrograph of her muscle tissue, you'll find that the lysosomes are absolutely jammed with glycogen, and there has been considerable disruption of muscle.

This condition, the enzyme defect, has been known for more than 30 years, alpha glucosidase, and the gene has been mapped for a very long time. In recent years, it has been cloned, and a great deal is known about it. However, if we had an accurate enzyme diagnosis, we can tell you your child has

this condition, and we can also tell you, unfortunately, that the average age of death of these children is about eight months.

So the earliest suspicion is two or three months, the diagnosis is about five to six months, providing they get to good medical attention, and the average age of about death is about eight months. It is a rapidly progressive downhill course, and very discouraging.

One of the things that is coming along rapidly, and the reason I talk about this condition is this kind of condition, lysosomal storage diseases, and this is only one example, Krabbe's, the mucopolysacchariodosis, are other examples who have treatments coming along. Some of these infants were originally treated with an enzyme produced in rabbits, so that rabbit milk produced an enzyme, and that was isolated and infused, and showed considerable benefit in the children.

Unfortunately, it is not practical to produce an enzyme in rabbit milk simply because of the number of rabbits required, and the milking and so forth, so it is not a practical thing. But recently, the alpha glucosidase has been put into Chinese hamster cells, and they are making alpha glucosidase, and so clinical trials are under way. These are old data, but they are published data.

At that time, eight children had been treated, and I might point out, some of the children who were treated were extraordinarily sick, even on ventilators. But the children were surviving, and at that time, five of the five children, more than six months, were surviving and were ventilator free. But the bottom line is the results of these studies are extremely encouraging.

It is clearly lifesaving, and the children overall are doing very well. The problem is that at the current time, by the time you make the diagnosis, the disease is significantly advanced. It is almost like PKU in the late 1950s, early 1960s. In other words, prior to the advent of newborn screening. So that as technology comes along that treats these conditions effectively, there is going to be an increasing requirement for newborn screening for these conditions.

I'm not going to address that further, but they are certainly compelling arguments to think about in such areas as the Fragile X syndrome where the treatment would not be what we would consider a traditional treatment, but may be an intense intervention that would dramatically affect the outcome of the children.

I think that the bottom line is how we diagnose conditions is changing dramatically. In addition now, to making a visual diagnosis, or measuring the patient, or looking at a patient with Cornelia de Lange, you will have very specific diagnostic tests that will be much more accurate. The other thing that will happen, once you have a specific test for a condition, you will learn that the condition is considerably more variable and complicated than you thought, because you will find people that have varying expressions of that same gene.

We will obviously, over the period of time, address the challenges that some of these discoveries present. The education of professionals is enormous. The number of people that are available to parlay this new information is limited. The public, in order to take the best advantage of genetic discoveries, is going to have to have an extensive investigation in education in order to do that, and again, professional training and so forth is one of the things that will be a very big issue.

But anyway, those are just some of my very brief thoughts about some of the things about the practice of clinical genetics today. I'd be glad to answer any questions before we go onto Marie's presentation about where things really are.

DR. TUCKSON: First of all, that was a terrific summary. One comment, and actually I'm afraid to ask it in such an audience of experts, so I'll make the comment first.

I would also urge you to put on the end of your slides, some consideration for the economics and costs. In addition to the training and counseling issues, is that one of the real issues that we all have to face, of course, every day, is there is just so much stuff to do in medicine today. That's one of the great miracle wonderfulness of our system, but yet we have 43.6 million uninsured who can't get access to anything. So at some point, one of our challenges also, is how do you appropriately use resources? I think that is as important a consideration as the others on your list, all of which were important.

The dumb question is given that there is so much information about a person that could be relevant before visual cues are there, or before symptomatology appears, how do you know what to test for, and when, in this new era? Do you just have to accumulate an entire picture of everybody from the beginning, and then sort of see what's there? How do you know when to know what you should be looking for, if you know that there is stuff that you could find if you look for it before you can see it?

DR. HOWELL: Right. Let me make a couple of comments, Reed. Thank you for your kind words.

The first thing is that we obviously are going to have to talk about cost. I think Mike Watson will have some information about what his particular program asks. I think he ended up having responses from about 300 people, a little over 300 people, who were an array of people, professionals, families, and so forth. They were asked to weight cost on this, and so forth, and he'll talk about that a little bit.

One of the encouraging things about it is that if you are doing tandem mass spectroscopy, which some of the people at this table are world experts on, and you decide that it is absolutely essential to test for MCAD deficiency, and I think we all would feel that, because the point is you can diagnose it and you can treat it, and it clearly is lifesaving.

The nice thing about that is if you set up your system to test for MCAD deficiency, you get a whole bunch of other stuff that you could not afford to do individually. For instance, it comes out in the same read. In other words, you say, it would really be nice to know about this, but gosh, it is so uncommon, and we're so unsure about it, but you get a lot of information. I think most of us feel that you should use that information. How you use it is complicated, and the cost is a big issue.

One of the things is that some of the treatments are very, very inexpensive. Biotinidase comes to mind, that is very important. Some of the ones that are very expensive to treat, and the lysosomal enzymes would be in that category, are fortunately for that reason, very rare, so that the impact on the health care is not dramatic. In other words, it is not like hypercholesterolemia, where 32 percent have the problem.

So that the rarity of the thing, I think, will be a blessing.

That will be one thing, but obviously we will need to discuss this, and I think we'll also need to think a lot about what we should test for. Again, some of that will come out in the discussions of criteria. But I have a very broad view of that, and I'll speak of personal view now, and so forth. That is, I think that we should test for anything that we can demonstrate has a value, either to the child, or the family, unless it is just outrageous. It seems to me that we are at a time where we can make a big difference in a lot of these. Peter?

DR. TUCKSON: I'd just like to comment on that. There are actually two levels, to think of the economics. It may be a big blessing in some ways that on a population basis, the condition is rare, but it is also very expensive to treat. At the individual level, the family level, or the community level, it is devastating to that particular family. So while it may be on a population basis not necessarily a tremendous issue, at the individual level, it still becomes a major economic issue. We have to think of it at both levels, I think.

DR. TUCKSON: Peter, could I just also amend, and I want to make sure, I like where both of you are taking my question. In addition to the economics of the treatment, and the economic of the diagnostic costs for the individuals and the society in terms of as health care costs increase, I also want to put it in there in the sense of the issues for public health, and state and local governments, again, as they try to decide how do they use their resources.

All of these things are going to be important, and I think one of our obligations is to make the credible case, which of course people won't force us to do in real life in terms of other public health priorities that are not being met. How do you put this into the mix, also for those?

So in addition, Peter, to your very important point, I don't want to lose sight of the other cost challenge, which is to the state and local governments, and the Public Health Departments. How we make that argument as well.

DR. HOWELL: Piero?

DR. RINALDO: Along the same line, I think we often get tangled in these issues of costs and claritization. I just want to reiterate that you really have to look at the other side. On one end, there is the cost of testing, and on the other, we have the cost of a catastrophic event. I believe we have a representative here today as a mother of children, which one of them had such a thing.

Then we have the cost of the medical odysseys, where we know that patients with some of these diseases may go through a numerous number of visits to various specialists, and in fact, at times I know personally on a number of occasions where actually there were allegations of Munchausen By Proxy, because they kept going from physician to physician.

Then we have the loss of productivity of the parents and the family, the extended family. Finally, I think the ultimate point is you really have to put it in a time perspective, because we are talking about the difference between a person being completely dependent on family and society, versus being a productive member of society.

So I think we need to talk about it, but I really think that we really have to see the other side. I think at the end, you will find there is an overwhelming indication to screen.

DR. HOWELL: That's extremely well put. I mentioned briefly the Fragile X situation, and that particular community has data about the average length of their odysseys, and it is substantial. In other words, from the time that they recognized that their son was not doing well, and things were not right until a diagnosis was made, it is substantial. Again, it has cost to the family, absence from work, the whole nine yards, and it is very, very expensive.

Bill, you had a question or comment?

DR. BECKER: Yes, just a brief comment. I certainly agree with what Reed, Piero, and Peter have said. I think it points to your comments early on in your presentation that there is this opportunity. We seem to be at this cusp, or maybe we're at the edge of a cliff, I'm not sure which, but we seem to have this tremendous opportunity ahead of us to take medical care into more of what you have described as the predictive model. Probably first in the mode of prevention, which is really what the Genetic Services Branch is all about, and HRSA, and many of their programs, in leading it towards the predictive model that I think you alluded to early on. I think that's the opportunity that is ahead of cost.

Clearly cost, clearly the cost program, cost of society, cost of treatment, programmatic issues, how do we assure that we have enough well trained people to take care of the types of disorders we're

going to identify? Or even the ones we don't identify? Those are all going to be the issues that are always going to be with us, but I think it is the opportunity that is here, and what brings us all together.

DR. HOWELL: Yes, I agree. I'd like to pick up on something that Peter said, and that is that just last week, a mother got me on the phone through the NIH line. She had two children with a rare metabolic problem, and she lived in Atlanta. She herself was a graduate student at Georgia State.

Both of these children were under an experimental protocol, and the care, the hospitalization and all the medications and stuff, were covered through the research project that she was participating in. But she said, I have this terrible problem, can you help me? She said, I have got all these personal expenses. I have got to go back and forth, I'm having to miss school and so forth, and what is there around to help me? Not with the medical care and so forth, but with all the family expenses that are incurred with a complex illness, when you have to go somewhere and stay somewhere, and so forth? That is a very big issue, I think, particularly with the special children that we're talking about.

Coleen?

DR. BOYLE: This conversation, I guess, brings up for me an issue that I still need some clarity in terms of the charge of the committee. That is whether or not we are making recommendations in terms of public health, or clinical practice. I mean, is our charge the charge of coming up with some type of universal recommendation for public health authorities or agencies in terms of newborn screening? And how do we balance that against issues related to clinical medicine?

DR. HOWELL: Well, I have an idea, but Peter can probably be clearer on that than I am, as one of the agency representatives that we will be advising.

DR. VAN DYCK: Well, I think the charge is broad, and I would hate to limit the discussion of the committee before the committee even gets started and hears the issues, and hears the discussion. Plus, I don't think it is very easy to compartmentalize public health from clinical practice and all the rest. They're all intertwined.

If any system relates public health and clinical practice together, it is certainly the newborn screening area, I think, and clinical genetics. So from my standpoint, I would certainly push to include a broad mandate, which I think the legislation and the charters affords.

DR. LLOYD-PURYEAR: (Inaudible.)

DR. BOYLE: When I think of newborn screening, I think of public health mandates. A lot of the issues that we're talking about on the table in this conversation for me straddles the line between appropriate clinical practice, versus mandated public health screening.

DR. HOWELL: I certainly hope that we could do what Peter suggests, and make comments and recommendations in all of these areas.

DR. LLOYD-PURYEAR: The charge is broad. The charge specifically addresses, in the charter and in the legislation, the health care services, and not just the public health program, but the health care services.

DR. HAWKINS: One of the issues that I think as we talk here, and we talk about what we're going to do as we go forward with all the genetic information we have, one of the issues that people always ask me is we are discovering new genetic diseases and they say well, you found this mutation and it is in my family, what do I do?

I will describe it in a number of presentations, and genetics is often like being in a firing squad. You've got a bullet coming at you, and you can't get out of the way. With genetics, you know it is a disease that you may get. The real issue there is people have got a lot of questions, and I think this comes down to a point of what are we going to do with genetic counseling?

I think genetic counseling is something that rears its head. It is so important as these people find out more and more about genetics, and how it is going to impact their lives. We had the issue of the families that maybe don't understand the impact that it is going to have on them financially.

I think in the course of diseases, there will be no cure for it genetically, we just have to face that issue. We can tell them they have this disease, but they basically just go home. I think the counseling issue is going to grow dramatically as the more we do our research, the more diseases that we find, and especially if we come up with specific testing.

Say we come up with 1,000 tests that we want to do routinely. We've got to have people who are experts in all of those 1,000 areas to be able to do genetic counseling. I think if we leave that out and kind of ignore it, then we're going to be running a great risk of having people that are just not well informed about how to deal with this in their lives.

DR. HOWELL: Well, I think that obviously the charge is very broad. I think that we can come up with a lot of positive comments on all of these. I think that someone asked, and I, like everybody else, have heard so much about Reagan in the past 24 hours. But one of the things that everybody was consistent in, was that he was always very optimistic. I think that since we're in this building today, we can be optimistic that we're going to come up with something great.

Marie, are you ready? Dr. Marie Mann is going to present the state of the states' newborn screening challenges and opportunities.

I think we have Brad on the phone. Brad, are you there?

DR. THERRELL: I'm there.

DR. HOWELL: Oh, good. I hope your back is doing well?

DR. THERRELL: It is progressing slowly. I am sorry I couldn't be there, but I know Marie is going to do a fine presentation for us.

DR. HOWELL: Right. Brad Therrell is in charge of the Newborn Screening and Genetics Resource Center, University of Texas Health Center, San Antonio, which is funded through HRSA.

DR. MANN: Good morning. As Dr. Howell said, Dr. Therrell is on the phone with us, and he was responsible in pulling together this presentation, and really wanted to be here to join us. While he's not here in person, he will be on the phone, and will be available, and has kindly agreed to be available for questions after I go through the series of slides.

In talking about newborn screening, these days when people use the term "newborn screening," they could be either talking about newborn hearing screening, which screens for congenital hearing loss, or the more traditional biochemical screening for inherited and congenital conditions. For the purpose of this presentation, we're going to be for the most part talking about the traditional newborn screening.

What is newborn screening? I think Dr. Howell has already talked briefly about it, so you'll have to bear with me if I repeat some of the things he has already mentioned. Newborn screening is recognized as an essential public health program that has been lauded as an effective strategy for preventing

significant morbidity and mortality in those infants with certain genetic or congenital conditions who are identified during the newborn period, and were started on treatment.

It is also very importantly, a complex system that is dependent on many, many individuals and organizations, including the family members of the affected newborns, as well as a myriad of program officials, laboratory and follow-up individuals, and the primary subspecialty care clinicians who take care of these infants. It also involves policymakers, manufacturers, and generally, the general public.

In talking about newborn screening, we have already gone through this. We need to start from sort of the beginning, in how did it get started? In the early 1960s, and we have already heard, Robert Guthrie showed that a blood sample from the newborn could be absorbed and dried onto a standardized filter paper, and using that, analyzed for biochemical markers for metabolic disorders, such as phenylketonuria, or PKU.

Still, it took the lobbying efforts of parents who argued for the prevention of mental retardation, to convince health policymakers that this method could be used to routinely screen newborns. In 1965, the American Academy of Pediatrics Committee on the Fetus and Newborn recommended a newborn screening blood test for PKU for all newborns. Within a few years, most states in this country had passed legislation mandating PKU screening. By 1973, 43 states had formal statutes.

Over the next decade, other filter paper tests became available, and they included congenital hypothyroidism, congenital adrenal hyperplasia, and sickle cell anemia. With improvement in technology, it allowed for expanding of the program, and such technology as automated specimen preparation, testing, and data handling systems. With the expansion of the program, they started with other conditions, such as congenital hypothyroidism.

As the number of conditions for screening increased, the cumulative risk of having one of the conditions also increased. And so with congenital hypothyroidism being the higher incidence condition, when hypothyroidism screening was added to the newborn screening program, there was improved cost effectiveness. This was important, because as programs had to justify themselves, their existence, and their spending, the state legislatures began asking the programs to be self-supporting.

Throughout the 1980s, the programs continued to expand, and this expansion was assisted by computerized data management and record keeping, just to accommodate the increased testing volume, as well as the necessary follow- up that was required. Toward the end of the 1980s and into the early 1990s, the ability to extract DNA from dried blood spots allowed for genotypic confirmation of sickle cell anemia.

As well, subsequently it was also shown that DNA extraction could be used as a secondary screening tier for cystic fibrosis screening. Around this time, advances were being made in mass spectrometry technology, so during the early 1990s, the technique of linking to mass spectrometer in tandem was applied to newborn screening.

Tandem mass spectrometry, or MS/MS, allows the simultaneous detection of multiple conditions, including organic acid, amino acid, and fatty acid oxidation disorders. With this new technology, there was public pressure for the programs to adopt this technology, and thereby increased the number of conditions to be screened.

Indeed, there has been dramatic expansion of many of these programs. Meanwhile, the equipment and procedures for screening newborns for hearing loss were also being refined. Newborn hearing screening is now mandated in most states, because many of the newborn hearing screening programs have been developed independent of the blood spot screening programs, and unfortunately, the two are often not well linked.

There is increasing interest in linking the two screening programs, as well as linking these programs with related newborn and child public health programs, such as birth registration, and immunization, with such linkage to be facilitated by data linkage and integration, and keeping in mind the need to preserve and respect privacy and confidentiality of those affected.

Programs are also examining the issue of storage and use of those blood spots that have been tested, as well as the impact of HIPAA on the operations of the programs. I'm going to over the next few slides, sort of run through what the typical system looks like, and what are those components in the system.

In this schematic, it shows the newborn in the birthing facility, the specimen, or where the hearing test is obtained, with the demographic information then transported into a computerized system that stores this information. The specimens are then on these Guthrie cards, transported to the laboratory where they are analyzed. The results of these analyses are then entered back into the computerized database, and the information can be accessed by the follow-up personnel at the state level.

If the screening result is positive, the coordinator will contact the newborn's medical home, if that is known, which is not always known, and certainly provides those results back to the newborn's birthing facility, and often to the subspecialty consultant to the program. Often there may also be direct contact with the families. With just normal results, they always do go back to the birthing facility.

But in looking at this, you can see that the system is quite complex, and the components of this system need to be well coordinated for the system to function optimally. We're going to go through the various components, and the components and systems can be fit together like a puzzle.

We begin with screening, which, as you can see, involves the sample collection, the submission, and transportation of it to the laboratory, and the testing itself. There is also follow-up, where the results are then sent to the appropriate places. If the results are such that it warrants additional testing, then family is brought back, and the child is retested. Certainly the results are given to the child's provider of service.

When there is a positive result, it is up to the program to ensure that the child receive the appropriate follow-up, appropriate testing, retesting if necessary, and the referral for diagnostic testing. It is necessary for that diagnosis to be confirmed, and if it indeed is confirmed, then the child is referred to the appropriate subspecialist, and when necessary, and certainly usually, there is counseling given to the family.

As far as management, for the most part, that is involved usually with treatment, but as Dr. Howell alluded to, there will be conditions that may be considered for screening that may not have treatments. But in any case, this is an important component. Part of that, we need to be following these children over the long term throughout their life, and certainly we need to address the issue of specimen storage.

The program would not be complete unless we have continuous monitoring of that program, as well as evaluation of the effectiveness of that program. Overlaying this system is essential education involving pretesting education for the families, the parents, and the expectant families. Also the education of the hospital staff and personnel, as well as continuous education of the laboratory and program staff, the clinicians responsible for the care of the newborns, as well as the various policymakers and payers, and certainly anyone involved with the system. So when we are making policies about newborn screening, we must remember that the system must be considered in its entirety, to remain efficient and effective.

In 2002, at the request of Senators Dodd and DeWine, the Government Accounting Office was asked to examine the United States Newborn Screening Programs. Some of the findings from the report

were released in a March, 2003 report. They include the following, which I'm going to highlight some of the differences that this report provided.

Fifty-one states and the District of Columbia are mandating newborn screening. Three of the programs required consent for the testing, and those are Maryland, Wyoming, and the District of Columbia. While most programs allowed dissent, there are a few programs that do not allow dissent for any reason.

Eight programs mandate two screens. When we talk about two screens, we are talking about screening a newborn period, with a second screen in the period following that newborn period. Usually, it is between two to four weeks of age. There are several other states, that while they don't mandate the two screenings, they strongly suggest that a second screening be obtained.

Eight programs do not charge a fee for the newborn screening, but for others, the fee can be as high as $70. As noted here, it excludes the hospital and administrative costs. The amount of Medicaid reimbursements vary widely, with about one-third of all births being Medicaid. The storage time and protocols for accessing and using residual blood spots that remains after testing varies widely.

Now, moving on, I'm going to go looking at sort of what is the status of newborn screening in the country. This slide shows the most commonly screened conditions in the United States, and the number of states screening for them.

On this slide, currently all states, and the District of Columbia, screen for PKU, congenital hypothyroidism, and galactosemia. Now that we have seen the one slide, or the three conditions that every state is screening for, over these next series of slides, you will see there is quite a bit of variation around the states, in which conditions they screen for.

In this slide, you will see that all states universally screen for sickle cell diseases, except for Idaho, South Dakota, and New Hampshire. While in these three states, screening is not mandated, there is screening available upon request.

There are 36 states screening for congenital adrenal hyperplasia, with some that will be adding that condition, 32 states screening for Biotinidase, also with a couple to be added. There are thirty-one states screening for maple syrup urine diseases, and again, there will be, I assume, a couple more states adding the screening. Twenty-eight states, homocystinuria, with again, there are four optional or pilot.

Currently there are 26 states that have mandated screening for medium-chain acyl-CoA dehydrogenase, or better known as MCAD, with six more states in the process of implementing the mandate to screen.

Only a few states currently mandate cystic fibrosis screening. From what we see here, there are six, with two mandated, but not yet screening. There is even fewer states that are screening for infectious diseases, and only the District of Columbia mandates screening for glucose-6-phosphate dehydrogenase, G6PD deficiency.

On this slide, this is another way of looking at what the states are doing. Again, there is wide variation among them, so that you see there is one state that only screens for three, and there are other states that are screening for more than 30 conditions.

Not only do the states vary in the conditions screened, but they also vary in other ways. One significant variation is the entity that performs the laboratory analyses. Again, this is sort of looking at those states with MS/MS screening, and showing you those that have mandated testing, and those with optional pilots.

In the subsequent slide, we're going to show where that testing is being done. So that you will see, for example, Oregon, the lab in Oregon is conducting the testing for four other states.

Again, Massachusetts is another state lab that is conducting the testing for other states in their region. While certainly most states do utilize their own public health laboratory to conduct the laboratory analysis, often because of financial constraints, they contract out that testing to other state labs, or to commercial labs.

This is just showing you sort of what the patterns of the contracting out, and it shows some of the public health labs that are performing testing for other states.

Shortly after the Council of Regional Networks for Genetic Services came into existence in the 1980s, it began collecting newborn screening information from the state programs on a voluntary basis. With the dissolution of CORN in the late 1990s, this information gathering activity was handed off to the National Newborn Screening and Genetics Resource Centers.

What you see here is a preliminary summary of ten years of data, listing conditions in order from the most prevalent, to the least prevalent. So in this case, sickle cell disease is the most prevalent condition, according to the data that has been recorded over this

ten-year period, and to homocystinuria, which is the most rare one in over 300,000.

So how are decisions and policies about newborn screening made? First, there is no federal mandate. This is a state mandate public health activity, and as noted by the GAO, every state has a law mandating screening. Sometimes it defines and specifies the conditions to be screened, as well as who is going to be doing this testing.

Policies are generally also made by the state health officers, as well as the state boards of health, and the state advisory committees. As you see here, all but two states have standing advisory committees.

Decisions about newborn screening policies are very much influenced by the interests of the various stakeholders, as well as the cost and benefit associated with screening, and the scientific evidence of such screening with local politics, economics, and culture also exerting tremendous influence on these decisions.

Historically, the formal groups have periodically made recommendations that have provided the framework for much of the decisionmaking in newborn screening. Going back to the 1960's with the World Health Organization Scientific Group for Inborn Errors of Metabolism, there were recommendations made at that time, and what came out of that was the Wilson and Jungner's criteria for population screening.

They identify ten criteria, and basically just to highlight, they focus on treatable disorder, significant population, that would have cost-effective outcomes. There was also in 1975 the National Academy of Sciences review of genetic screening. It made several recommendations in establishing some fundamental principles for genetic testing, as well as some guidelines for newborn screenings. These guidelines, however, differ very little from the World Health Organization recommendations.

As you see here, the recommendations are generally under controlled conditions, screening is appropriate. It talks about responsibility should be in an agency representing both the public and health professions, and that there should be extensive public and professional education and involvement. Screening should not be mandatory, and privacy should be protected.

If mandated, there should be some formal body to provide the structure for such screening, and that there should be research supported, and that research should be conducted in an ethical fashion.

In 1998, HRSA's Maternal And Child Health Bureau funded the American Academy of Pediatrics to convene a national task force on newborn screening. That was chaired by Drs. Edward McCabe and Thomas Tonniges. This task force was jointly sponsored by the federal agencies and organizations you see listed here.

The task force members represented many individuals who operated programs, conducted research, persons who functioned within that system, as well as those who were affected by this system. Task force findings and recommendations were published in August of 2000. These recommendations were based on the following fundamental principles. That infants should benefit from and be protected by newborn screening programs, public health agencies should assume responsibility for oversight of newborn screening systems, standards and guidelines for newborn screening should be more consistently applied, greater uniformity would benefit families, professionals, and public health agencies, and newborn screening systems should link to a medical home.

In conducting the work, the task force divided up into five workgroups, and you see listed here, what those workgroups were. These workgroups made recommendations on several key areas, including public health infrastructure, public and professional involvement, surveillance and research, as well as financing.

Finally, the task force may recommend an agenda for action that involved public health partnering with health professionals and consumers. Basically the action agenda would model regulations for newborn screening systems, define federal and state responsibility, define minimum standards for newborn screening, model guidelines and protocols for professionals, model systems of care from infancy to adulthood, design strategies to inform and involve families and the general public, and fund demonstration projects to evaluate technology, quality assurance, and health outcome.

In 2000, the March of Dimes made a recommendation that all newborns should be screened for these nine conditions that are listed here, as well as for congenital hearing loss.

So what has happened since that time? The public interest has remained high, and in 2002, there was a Senate committee meeting where various individuals had the opportunity to make presentations. Subsequent to that, various congressional directives were made, where a committee urged the availability and accessibility of newborn screening service to apply to public health recommendations for expansion of effective strategies. It directed HRSA, in collaboration with CDC and NIH, to encourage to implement a strategy for evaluating and expanding newborn screening programs, and that tangible steps should be taken to protect patient privacy, and to avert discrimination based upon information derived from screenings.

Besides the congressional interest, federal agencies have also been very actively engaged in various activities that support newborn screening. I'm not going to go into those now, because you will be hearing about them in later presentations.

I would like to highlight one activity that has been jointly supported by HRSA, CDC, the National Newborn Screening and Genetics Resource Center, as well as the Association of Public Health Laboratories. What this activity was, it was designed to meet the needs of state programs that were implementing tandem mass spectrometry.

It provided a one-week intensive course on the basis of tandem mass spectrometry methods interpretations. They were initiated, and have been conducted at Duke, as well as the Institute for Metabolic Disease at Baylor in Dallas. These were designed to fill the training gaps for the states.

Just showing you some of the students at these courses. With continued funding from HRSA, the National Newborn Screening Resource Center continues to send an expert reviewing consultation team to states that request the review and consultation. Their team is made of members who are experts in laboratory follow-up, administration and quality assurance, clinical care, to address specific program needs of the state programs.

Since 1987, over 22 states have requested such visits. A limited external evaluation of this activity found overwhelmingly favorable response by the states visited. Indeed, there was tangible evidence that these consultations were helpful to the states.

I'm going to spend a couple of minutes talking about the National Newborn Screening and Genetic Resource Center, which is at the University of Texas Health Science Center in San Antonio. What you see here is what is available through this site. There is online genetics and newborn screening information that can be accessed.

The information includes program links and testing summaries for the various programs, the information about the individual state newborn screening programs, as well as the state genetics plan, and a searchable genetics education materials database, as well as other reports of regional and national significance.

So I'm going to briefly summarize sort of what I have been reviewing for you over the last few minutes, is that of the approximately 4.1 million babies born annually in the United States, almost all are screened during the newborn period for a number of genetic and congenital conditions, and approximately 4,000 of these newborns are detected with one of those conditions.

In recent years, there have been increasing differences among the programs. Such that more than 1,000 newborns with detectable conditions may go undetected, because they are not screened for all the conditions currently available.

There is federal and state interest, and certainly support in improving these programs to improve the equity between the programs. While there is no national mandate, there is national interest in expanding newborn screening programs.

You may not be able to see this comic strip, but this story line appeared in many newspapers this past year. The story line revolves around a mother who recently gave birth, and her question is about newborn screening. Basically this slide here sort of summarized where people are at this point, and where the national interest is. What the mother says is, "So I shouldn't worry? The tests are routine?" And the nurse says, "Right. I just wish there were federal standards so we could help every baby."

In summarizing, I just want to take another minute to just really sort of highlight some of the challenges. I know you are going to be spending a lot of time talking about challenges, but I want to just highlight a few that I think we need to address. In talking about newborn screening, certainly we've seen throughout the tenure of this program, the technology transfer to population based screening.

As many of you have already articulated, the issue is of financing and reimbursement for laboratory services, as well as for referral and follow-up, and the long-term management of these infants. Again, others have mentioned the availability of expertise, both at the laboratory level, as well as at the clinical level.

I think it is very critical and essential that we maintain education and communication with all these people who are involved in the system. So I would like to just close saying that we need to hear from families, we need to hear from the clinicians, we need to hear from the laboratorians, the researchers, and all those people who are a part of the system.

So in closing, thank you.

DR. HOWELL: Thank you very much, Marie.

(Applause.)

DR. HOWELL: Are there questions of Marie, and of Brad, who is on the phone? Reed?

DR. TUCKSON: Again, just a terrific presentation. I particularly liked your analysis of some of the reasons why there is such variability state to state. In that, you mentioned that one of them is, and I think it really comes through, and what I'm trying to understand better is the clarity of the science behind this.

Do we have very clear science that says that all of the tasks that are available now should be performed? The 2000 AAP Task Force on Newborn Screening says that the standards and guidelines should be more uniformly applied. Who developed those guidelines? And are those guidelines pretty clear that tell everyone what to do?

And so therefore, at the end of the day, is the problem here one more of local politics, and uninformed people making decisions? Or is the problem at some level with competing views, and unclarity on science?

DR. MANN: I didn't mention it, and Dr. van Dyck is going to spend some time talking about it. But HRSA did contract, and you did, Dr. Howell also mentioned, contract with the American College of Medical Genetics to sort of address one of those action items from the AAP Task Force to look at the science and see if we would be able to develop some strategy or mechanism by which you could assess conditions to be added to screening panels based on the available scientific and clinical evidence

I think certainly Dr. van Dyck will speak a little bit to that, as well as Dr. Mike Watson, who will be making a presentation tomorrow, and will get into more detail. Unfortunately, that is one of the things we haven't done a good job of, is getting all that science there, but I think there is tremendous interest. In spite of, I think having necessarily have had the funding to make that research a priority, I think we must give credit to both the states and the federal state programs, that along the times, they have independently tried to improve and validate many of the technologies.

So even with limited resources, those who have been engaged in newborn screening have tried to improve on the science. We'll see some evidence of that when Dr. Watson presents.

DR. THERRELL: Can I make a comment?

DR. MANN: Yes, Brad.

DR. THERRELL: You mentioned also other guidelines. I can tell you that there are some guidelines, but they are not federally mandated, or necessarily recognized by anybody. These guidelines sort of arose over the years by us doing reviews of state programs.

In fact, we found out that many of the questions were the same, and that is why we actually went to the trouble in 1992 to write some guidelines for programs. These guidelines have sort of held up over the years, but they are guidelines that are interpreted differently by different programs.

What you will hear from Mike is a little bit better science to help re-write those guidelines, in a sense. We are kind of in a Catch-22 in some of the science, because in some cases, if you don't do the screening, you don't get the science, and we haven't done the screening because there weren't cures. There is always some sort of treatment available, but the real question is, is there a cure?

Another thing that hasn't helped over the years is that there hasn't been sort of a national mandate about accumulating data, especially with these rare conditions. So states have voluntarily submitted data over the years, and that data that you saw from Marie is data that has been generated from the voluntary responses of the states. But that is an issue that we need to deal with in terms of what data do we really need, and what data needs to be mandated? For instance, from programs, how we use it in the future to look at programs, and look at the evaluation of the programs.

DR. HOWELL: Jennifer? You had a question.

DR. HOWSE: Thank you for that excellent, decades-long overview of the slow but steady progress in newborn screening. One of the many interesting aspects of your presentation, I think, really was to bring out the patchwork quilt nature of newborn screening, which is completely different across the country, for a variety of reasons. But basically there is no federal mandate, so each state must make its own decisions as to newborn screening.

I wanted to focus on the data slot in your summary, on the number of newborn screening derived disorders from the voluntary reports of states. You showed a detection level of about 4,000 infants among the 4.1 million born each year, and then made a statement a little further down in the slide that you estimated about 1,000 conditions were undetected because the screen was not in place.

I just wonder, since the preponderance of states have still a smaller array of screens than the majority of states, how hard is that data, and what is the potential universe of detectable conditions, given a full array of screening in place? I suspect that it is more than 5,000 on a base of 4.1 million births. I think that is an interesting number for us to think about.

DR. MANN: Again, as Dr. Therrell mentioned, the reporting is voluntary. Brad, can you address that?

DR. THERRELL: Yes. The data is pretty good. We have gotten validation back from the states, and we'll be posting that soon with the ten-year data. We have done some calculations looking at incidents based on these data, and if you look at the babies as a whole, it is about one in 1,200 with the tests that we do right now, that come up with a diagnosed test.

If you added to that the diseases that are sort of traditional, but not yet done, it drops it down to about one in 800 would have some disorder detected. And then if you add to that hearing screening, then it comes down to about one in 250. So if you link the two programs together, there is a phenomenal number of babies that are being detected, and could be detected with these things.

DR. HOWELL: Piero, did you have a comment?

DR. RINALDO: Yes. I think there was an earlier question about how strong is the science. I think the science is there. I hope that one of the many things we hope to accomplish here is really to address the issue of how the science is implemented.

This is really not an issue about well, I just think of technology, and I start doing it. I think we are moving in a territory of a certain level of complexity where there are pre-analytical, analytical, and

post-analytical components, and you must achieve some acceptable level in all three. In other words, you might do a fantastic job pre-analytically, but then you really don't know how to interpret the data, and you lose most of the benefit that is potentially there.

DR. MANN: And I think that is an important point, is that when we are talking about science, it is not just that developmental phase, that once you implement that testing, is be able to follow and look at

that testing out to long term. It is no different than any other testing, or even with medications, it is sort of that post-phase where you post-implementation. We certainly need to devote more energies and resources to doing that.

DR. TUCKSON: So where is the guideline? That is where I was really trying to get at. I know we keep referencing back to Mike's presentation tomorrow, which will be terrifically anticipated. But who develops the guidelines now? Who has the responsibility?

DR. MANN: Well, one of the guidelines that Brad referenced was, and actually there were two sets of guidelines that were developed by CORN, or the Council of Regional Networks for Genetic Services, back in the 1990s, and again, they are not standards, they are guidelines that really provide guidance to programs as to how to implement newborn screening. These guidelines are available, and I would say they serve the frameworks for most programs.

DR. THERRELL: I think the bottom line, though, is that within each state, they develop their own guidelines that may or may not be based on these, but it is usually the responsibility of the advisory committee, if there is one.

DR. TUCKSON: Does the American Academy of Pediatrics, for example, and again, the American College says look, the smartest people in the country have looked at these issues, and it is unequivocal that states ought to — I mean, the March of Dimes recommendation is a very important one, they have very bright people.

Is there a place that we turn to in the United States for consensus of best science opinion on the guidelines for what states should do? Science is science, and the best analysis is the best analysis, and whether Utah does it, or New Hampshire doesn't, what is the best science?

DR. HOWELL: There are several comments. Let's start with Peter, and then Bill has come in.

DR. VAN DYCK: You're hearing the thorny issues that are going to come up, and this committee was formed to wrestle with these issues. The presentation tomorrow, we are anticipating it. It will try to analyze the science that we know, and translate it to practical and clinical recommendations to this committee. I think the Congress and the Department see this committee as wrestling, then, with this information, and this data, and making recommendations then to the Department, and to the Secretary, on what sets of guidelines he should consider implementing as a result of advice from this committee.

So this committee makes recommendations to the Department and the Secretary. It is not binding, but it is advisory. I think you're seeing a panel of experts here who are going to have to wrestle with this and make the best recommendations that they can.

DR. HOWELL: Bill, did you want to add to that at all? Or agree?

DR. BECKER: I agree, because it is a perfect lead-in to the question that I have. It comes out of Marie and Brad's presentation. There are several points in your discussion. You made the statement that there are no federal mandates.

So my question on the table is can this group recommend a federal mandate? And I'm sort of curious operationally as to what that might entail. I guess my subordinate question is are the states ready for a federal mandate, because you have seen the potpourri of approaches that the states take to addressing the standards that are already posted by a number of — well, maybe not a number, but a select few well-respected groups that have put together and taken the thoughtful time to put together some guidelines that are out there, as Brad mentioned, and could be followed, and to a certain extent are

probably attempted to be followed in good faith by the various advisory committees or councils across the states.

So my question is, can we recommend a federal mandate, are the states ready for a federal mandate, and what do we do, perhaps, to consider that?

I think, if I understand the presentation that we just heard, it sounds like that is maybe what the extreme need is in terms of moving newborn screening programs forward on a national basis. Individual programs obviously have individual needs, and they're going to be as varied as they are in the different states. But in terms of a standardized national newborn screening program, is the mandate the way to go? That's my question.

DR. VAN DYCK: And one of the things the committee will have to recognize, and you've heard several sets of words here, one mandates, one guidelines, one standards, there is a tremendous difference in those words. The committee is going to have to wrestle with whether there is a recommendation for guidelines, which are recommendations that states follow, or mandates, or standards which may have a requirement to follow, which has a lot of implications, given the fact that the states have the responsibility legislatively in their states for the program.

So these are all very difficult issues that the committee is going to have to deal with in their recommendations to the Secretary, and there is clearly more than one way to make those recommendations.

DR. HOWELL: We've referred several times to the report that Mike is going to give tomorrow. But to go back to Marie's question, is that certainly approximately 125 people over a period of two full years worked on the data that Mike is going to present. These are laboratory experts, clinical experts, and families.

In some areas, the principle information is expert opinion, and in other areas, there is some fairly good science. But it is at the current time probably the best information on what should be done. But again, I think the key thing this committee will have to wrestle with is to translate that into some action through the Secretary, which I hope we can really do.

DR. VAN DYCK: You may be wondering why that presentation is tomorrow, and we keep talking about it. We thought it was important to have the committee hear the background overview, what the different agencies are doing, what the existing programs are, how the structure works, what the states are doing, what the legal requirements are before we jump into this without the adequate background in having this uniform kind of being in the same place. So that is why that is early tomorrow.

DR. HOWELL: Steve?

DR. EDWARDS: Well, one more complication that I would throw into the hopper here, and that is that a lot of stuff is going on outside the recommendations of this group. There are commercial companies that are advertising over the radio about tests that have been available. There is a whole question about the use of the testing, and whether patients that are covered by public programs should have the same sort of testing as patients that are covered by private insurance, or patients who want to insure themselves separately.

So I think that all of these make this a much more complex situation than it otherwise would be. It is not just an intellectual exercise, it really impacts on lives, and especially the lives of children. So that I think that all of these things have to be considered in the deliberations of this group.

DR. HOWELL: I think that all this activity out there, both in the Congress and in the public and so forth, is just an ideal time to come up and make some sensible recommendation.

Ladies and gentlemen, it has been, I think, a very productive morning, but it is lunchtime. We have actually covered more than was on our agenda. So let's return here at 1:25. I have 12:25.

(Whereupon, at 12:25 p.m., the meeting was recessed for lunch, to reconvene at 1:25 p.m.)

AFTERNOON SESSION (1:29 p.m.)

DR. HOWELL: Welcome back from lunch. I trust that everybody had a wonderful lunch. Welcome back after, I think, a very productive morning. We are going to vary slightly from the agenda, with your indulgence. The purpose over the next couple of days is we'll move back and forth to accommodate all the people we need to hear from.

I'd like at this time to recognize Ms. Wendy West, who is from the Sickle Cell Disease Association of America. Ms. West is from Ohio, and she is going to provide some public comment on the work on sickle cell. Ms. West is unable to be with us tomorrow. That is the reason that we have moved her up to today, so let me be clear about that.

MS. BERRY-WEST: Well, good afternoon, Chairman and members of the committee. My name is Wendy Berry-West. I am the Executive Director of the Ohio Sickle Cell and Health Association, and also a member of the Sickle Cell Disease Association of America.

First of all, I want to thank you for allowing me the opportunity to testify before you today regarding newborn screening as it relates to the devastating illness of sickle cell disease. As you may know, sickle cell disease affects over 70,000 Americans. Each year, approximately 2,000 children are diagnosed with the disease. One in 400 African Americans are affected by the disease, and one in 10 have the trait.

Sickle cell disease is a genetic condition that does not just affect African Americans, it also affects persons of Hispanic, Asian, Indian, Greek and Mediterranean descent. Its devastating effects on the individual, as well as the family, are long term.

There are three areas in which I hope the advisory committee considers as it makes its recommendations to HHS Secretary Tommy Thompson. These three areas of concern for newborn screening should relate to expansion, standardization, and funding.

As far as expansion is concerned, newborn screening should be an expansion of the existing services which are culturally appropriate, comprehensive, and provide opportunities for universal health care that will encompass the etiology of medical homes for newborns and children affected, and at risk for sickle cell disease.

As far as standardization, counseling, education, and testing protocol should be standardized, so as to provide the most effective and enhanced services for the targeted population. This will assist health professionals to provide care which is sensitive, accessible, and appropriate for the disease itself.

Finally, funding. I believe that appropriations to support services and improve screening should supersede the existing funding levels, so that state-of-the-art testing is available universally. It allows for assistance to programs to provide direct, indirect, comprehensive, and competent services to individuals and families affected that are at risk. Also, to assure that in this country, we are advanced as other countries that provide newborn screening, as well as to allow for room for advancement of services.

I want to thank you for the opportunity to testify. I also represent an organization that has a program for services for sickle cell diseases. We receive federal dollars, and we provide education, testing, counseling, and support services to individuals and families that are affected. So I think it is very important that we consider all those pieces, as Dr. Mann had indicated, in these services for newborn screening.

DR. HOWELL: Thank you very much, Ms. West. Would you entertain questions from the group?

MS. BERRY-WEST: Yes.

DR. HOWELL: Are there questions of Ms. West?

DR. TUCKSON: Could you remind me of the the financing for testing in all of the states? Is all that paid for federally, or by the states? Or do you know of any states where that is billed back to the family?

MS. BERRY-WEST: Well, I only really can speak for Ohio. I'm sure it is different in every state, but in Ohio itself, the programs in which we are funded from the state perspective, is funded by the newborn screening fee. Out of those dollars, which are about $30 approximately, hopefully, $27, out of that, $3.50 go to sickle cell programs.

DR. TUCKSON: And also the database there in Ohio. Once you are diagnosed as positive, you are screened, and it indicates the presence of the disease. Does that automatically then cause something to happen? Is there a system, an infrastructure, that kicks in that then provides resources for that family?

MS. BERRY-WEST: Exactly. And also not just the disease itself, but trait, which is important as a follow-up. That is one of the primary roles that our organization takes care of is trait follow-up, so that we can reduce the severity of the disease.

DR. TUCKSON: And is it adequate? Does it work?

MS. BERRY-WEST: Is it adequate? I think it works in some respect. I think we are probably very successful in Ohio, and our relationship with the state lab, the state sickle cell coordinator, and then trickling down to the sickle cell programs across the State of Ohio that provide follow-up services for individuals and families affected. But that does not mean that we don't need additional dollars to help make it better.

(Laughter.)

DR. HOWELL: I think that if you said you did need additional dollars, Dr. Becker may get out of his seat.

MS. BERRY-WEST: I know he would.

DR. BECKER: That's exactly right. We have a fairly well structured system of notification of the regional sickle cell projects in Ohio, who by agreement, both with the state and with the practicing community, I have to say, are very aggressive about going and finding those affected infants, making sure that they get the proper care, prophylactic antibiotics are started in the proper time frame, and reporting the information back, importantly, for the public health purposes so that we can know that these infants have had the appropriate care and follow-up services. We are very proud of the sickle cell projects and the sickle cell program in Ohio.

MS. BERRY-WEST: And I think the federal dollars that have come to the organizations in different areas of the country to enhance the existing services are either at the state level, or whatever they were doing in each particular state, have helped to enhance the existing services.

There is just so much more that needs to be done for these families, and I don't want it to stop at this point, but there is just so much more pieces of the puzzle. I keep going to what Dr. Mann said, the need to be intertwined.

DR. HOWELL: Mrs. West, let me thank you very much for making yourself available today.

MS. BERRY-WEST: Thank you.

DR. HOWELL: I think that many of us are very much aware of the life saving efforts in newborn screening for sickle cell disease. At the same time, let me be sure that everybody in the room is aware of the fact that not all states in the United States currently screen for sickle cell disease. That is something that we will need to address aggressively, because some of us don't think that is the way to go.

MS. BERRY-WEST: Exactly. Thank you very much.

DR. HOWELL: Thank you very much.

We will go back now to the agenda, if we might. I'd like to ask Dr. Elizabeth Edgerton to begin our presentations. I think that they are at Tab 10, the material. Dr. Edgerton, as she said earlier, is from the U.S. Preventive Services Task Force for the Agency for Healthcare Research and Quality.

DR. EDGERTON: Thank you for having me here today. I'm wearing two hats. One is Denise Dougherty, who is our child health representative from the Agency for Healthcare Research and Quality, and I'm here as a new position in the sense of overseeing prevention at the Agency.

The Agency has ten portfolios which are kind of our focus areas of the Agency's mission that fall under quality care, safety, and improving health outcomes among Americans. The prevention portfolio at AHRQ oversees both the U.S. Preventive Task Force, and then also the dissemination of these findings at the patient and provider level.

What I hope to do this afternoon is give you a little bit of an overview of the methodology of the task force. I think it may resinate well after the discussion that occurred this morning in the sense of the framework in which some of these difficult issues of health outcomes and health decisions are made. I hope you use it just as a benchmark to kind of understand how one group approaches some of these questions.

Again, the U.S. Preventive Services Task Force was modeled after the Canadian Task Force, and was established in 1984, so it celebrates its 20th anniversary this year. It historically had been brought together to develop a book of recommendations around health care issues that are relative to the primary care physician. Currently it has a rotating board that comes for a term of three years.

The key about the U.S. Preventive Services Task Force is that it bases its recommendations on

evidence-based medicine, for preventative health services for the use in the primary care setting. I ask you to remember that as I present some of the recommendations that have been addressed, that it is primarily looking at what occurs in that primary care setting with the provider and the patient. It looks at health outcome issues that relate to screening tests, which is obviously pertinent to this advisory group, and also counseling, and chemoprevention.

To bring it home to what the advisory group here is looking at, these are some of the topics that the task force has looked at. Again, congenital hypothyroidism, Down's syndrome, sickle cell hemoglobinopathies, neural tube defects, PKU, and newborn hearing screening.

So the task force is a unique group, in that it is actually an independent panel of experts that are compiled of primary care physicians, whether family practitioners, internists, pediatricians, experts in behavioral science, and experts in methodology. Its goal is to provide impartial assessment of the existing evidence, and that is not the position of any federal agency, but it is supported by the Agency for Healthcare, Research and Quality in the sense that it underlies our mission to enhance the quality, appropriateness, and effectiveness of health care services.

Again, it has a panel, as I said, of diverse individuals with expertise in primary care. We also make use of evidence practice centers, or EPCs, which help us in the systematic review of the evidence. Again, we engage federal and private organizations as expert partners to review the recommendations.

There has been discussion brought up this morning regarding heritable diseases, how consensus or guidelines are established, whether they are by professional or federal organizations, and they kind of fall into two groups of what we call kind of formal consensus, or expert panels, and those that are

evidence-based. The task force is ceded in the sense of evidence-based approach, which can sometimes cause a little bit of concern, because often we'll come up and say there is not enough evidence present, and that presents a dilemma when a decision needs to be made. Again, I just want to remind people the difference in the sense of the U.S. Preventive Task Force is based on evidence-based methodology.

So how does this process work? Well, again, the task force, each time they convene, decide what number of topics they're going to address, and address that over the term of the task force. They start with defined questions, and those questions address some of the issues that were brought up this morning. Again, this screening is screening effective, but how does it improve health outcomes? Is there a benefit in long-term health status for the patients?

We come up with a question, we do a systematic review of the literature, we get a peer-reviewed evidence report in the sense of what is the summary of the literature, and then the task force comes up with its recommendation and rationale. They have developed a methodology which has been published of going through systematic evidence reviews, and then also engaging expert opinion on the results of these reviews.

Again, it is a comprehensive literature search, it is a critical appraisal of individual studies that have internal and external validity so that there is a grading process that I'll review with people. There is a synthesis of results, not only in narrative form, but in what we call outcomes tables which allow us to kind of conceptually understand, what does it mean. If we do this test, how many individuals have to be screened to find one individual with that disease process, or what is the impact if we do find someone on the overall health outcome of the population? And again, a grading of the evidence. How strongly can we stand behind the results we find?

Again, internal validity, and finding good quality studies. External validity, direct evidence, generalizable to the primary care setting, that there may be studies that have evidence, but we can't translate it to the setting in which we're making recommendations.

So again, this is kind of the table, or grid, that the task force uses. They published these approaches to how they grade the evidence. So if you look on the vertical column, there is a strength of the overall evidence of effectiveness, again, versus efficacy. So effectiveness, does it work in the real-world setting?

Again, good, fair and poor. It is kind of based off the Cochrane approach, randomized control trial usually is the gold standard. So we have few confounders that we really know how we're interpreting that evidence, and then we go down the scale.

As we go from left to right in the columns, it is a matter of the net benefit, and benefit could be described as health outcomes, cost, quality of life. That, again, is determined by the task force. So again, A or B, there is strong evidence, we feel that there is a benefit. If we go to the far right, D, there is a negative consequence of doing that activity. Then at the bottom, insufficient evidence.

Again, sometimes there is confusion when the task force comes out with recommendations that are called I recommendations of insufficient. People say, well, does that mean that we shouldn't do it? It just says the task force can't support or not support that activity because the evidence is insufficient.

I think sometimes it is helpful to understand that that may be an issue of research agenda, those areas where the gaps are. I think those questions came up earlier this morning in some of the presentations.

So again, there is a role of expert opinion in all practice guidelines. It is kind of a check on our work in the science and putting it back in the clinical perspective. Again, the wording of the recommendations. When the task force does come out with a recommendation, they give it a letter grade. Here is kind of the matrix we use, A, that they strongly recommend this activity. There is good evidence, and benefits substantially outweigh the harms.

B recommendation, there is at least fair evidence, and again, the clear benefits outweigh the harm. If we go down to the D recommendation, it is ineffective, meaning that our practice really provides no benefit. Or again, the harms outweigh potential benefits. Then I, again, is insufficient evidence.

What leads to an I recommendation, like I mentioned, is lack of evidence on clinical outcomes. Again, the task force sets out at the beginning of this process of what they use as outcomes, and those are usually long-term health outcomes. That is important, I think, to consider as this group moves forward of what your outcomes need to be. It is a matter of just identification? Is it a matter of improved quality of life? Is it a matter of morbidity/mortality?

There may be poor quality of existing studies, so studies may exist, but we can't really put a lot of confidence in what the findings are, and there may be good quality studies, but conflicting results, so we can't get a consensus about what the findings are.

So if we look at some of the recommendations we currently have, the top ones you see all received A recommendations. So in the sense there was a benefit of screening, there was some form of treatment that led to improved health outcomes for the individual, so the task force came along with A recommendation. At the bottom, you'll notice newborn hearing screen, which has been mentioned. The task force came out with a recommendation of an I. Again, insufficient evidence, which again, may be in contradiction to some other policies that have been presented this morning regarding screening.

So what happened? Well, there was good evidence to say screening does lead to earlier identification and treatment, so that's consistent with what other groups have found. What the task force did find was that there was inconclusive evidence that the results had important improvement, and again, their outcome was improved speech and language skills at three years or beyond, they were not present.

While there were some studies, the task force was concerned about the study design, or the quality of those studies. So again, it may not say that we should or shouldn't do universal newborn hearing screening, but what it says is that we cannot find evidence for what we consider outcome improved speech and language at three years of age.

Again, we found inconclusive evidence regarding the benefits, specifically that early identification and treatment improved the quality of life for families. The studies that they looked at found that there were quite a few false positives, anywhere from 25 to 50 false positives for every one child identified. Again, the follow-up rate for confirmatory tests, there was a failure of follow up 31 percent of the time. So again, the task force was looking at this from a global perspective, and saying, the current evidence we have, we're concerned that we couldn't show a direct benefit, again, with screening. It does not mean that we recommend or not recommend it, it is just pointing out the gaps in research.

Some of the issues that the task force deals with, and again, I think this advisory group will be facing this, is efficacy versus effectiveness. Again, the task force recommendations are supposed to consider real-world settings. Benefits often decrease as risk increases, and interventions are implemented in real-world versus the trial setting. Again, requiring effectiveness data may seem too limiting and inconsistent with medical practice. But again, this is the methodology and the standards of the U.S. Preventive Service Task Force.

There is the challenge in assessing the magnitude of the net benefit, and there is no explicit criteria for magnitude, how much is good enough. We use outcome tables to illustrate tradeoffs. Again, the example of the number needed to treat. That may seem an arbitrary point of view, but when we have limited resources, it allows us a matrix to understand the decisions we're making.

Substantial benefit, does it have an impact on high burden or major effect on uncommon outcome? The problems require evidence on harms, and a common metric for benefit and harms. Again, also when we look at the harms of screening with newborn screening, it is the number of false positives. What is the impact of someone having a false-positive screening? The increased anxiety, or increased medical tests, labeling, over treatment? Again, the magnitude and duration of harm is subjective, and sometimes it is hard to compare that with normal matrixes.

The challenges of pediatrics. Fewer studies in children, maintaining normal development versus morbidity/mortality. What are the health outcomes that we're using to mark the benefit of what we do? Our outcome is going to be biochemical, school performance, interaction with family and peers, and knowledge of the child's condition by parents.

Again, do we bundle screening? Do we look at newborn screening as a package? Or do we look at individual tests on how we look at things? Again, interacting with school and community based programs.

There is often sources of disagreement in prevention recommendations. What was presented this morning, and what the task force has found in their evidence review, and again, it may be based on the methodology used, whether it is a consensus panel of experts versus an evidence-based approach. Clinical versus intermediate outcomes is the outcome to identify individuals with a problem, or is the outcome to improve the overall health status.

Consideration of possible harms, whether that is the concern of cost, whether it is a concern of the quality of life, effectiveness versus efficacy, and primary care versus specialty perspective. I think someone raised the issue of taking the public health perspective versus the clinical medicine perspective. So again, it is deciding what those benchmarks and framework that you're working within are. And again, the approach to uncertainty, to do no harm.

So again, in summary, the U.S. Preventive Service Task Force is to provide evidence-based recommendations regarding preventative services in the primary care setting, and focusing on the areas of screening, counseling, and chemoprevention.

Thank you.

DR. HOWELL: Thank you very much, Dr. Edgerton.

One of the things I'd like to remind this committee of is that the committee is the advisory of the Secretary of HHS, who is responsible for the entire HHS, including the NIH. So you have mentioned several times a potential research agenda, and I would hope that we would keep that very much in mind. There will be a lot of things that come up that need fundamental research, and that will be the responsibility of some of the agencies in HHS that do research. We should be sure to outline those.

Reed?

DR. TUCKSON: Really, that's exactly what I wanted to ask about. Maybe there is an opportunity for recommendations from this committee to urge a look at some of those unanswered questions that are important. So the first of my two questions are, is there, or could we obtain if we asked the U.S. Preventive Services Task Force, for a list of the critical issues that was indeterminate, but were important questions, to assure that those issues were being attended to, or at least funded to be looked at in a timely fashion?

DR. EDGERTON: There are two approaches to your question, in the sense of when the task force takes on a topic. Those are usually when those gaps are identified. In the sense of I think there is always potential for collaboration of the topics that the task force are looking at. So again, if this advisory panel identifies certain areas and there are questions, that the task force methodology can be applied such that their recommendations or identifications of gaps can be determined.

DR. TUCKSON: But to be assured then, in other words, when the task force says that there is an issue that is important, but around which there is yet today insufficient information to make the kind of level of decisionmaking that they have to make, does it in there, or does that automatically trigger some action in HHS that says to AHRQ, CDC, NIH, extramural grant program, something that says, let's get the answer to this question?

DR. EDGERTON: That has to be kind of a domino effect in the sense that the task force remains as an independent panel. So they set out their recommendations and rationale, and then it is left at the audience, those federal agencies, or others, to take the ball.

DR. TUCKSON: Not to belabor it here. I wonder then, and again, I don't want to get ahead of ourselves in terms of recommendations, but one of the things maybe that would be good to do would be to ask formally for the U.S. Task Force to give us a list of those things that were indeterminate, to maybe just make sure.

The other question I had real quick was how was the agenda set for the committee's deliberations? I notice you didn't quite get into who sets the range of questions that they're going to look at, and what they are. You say peer-reviewed, but somebody has got to put it on the table. Is there any opportunity for the Secretary to request certain issues to be evaluated?

DR. EDGERTON: Yes, there is. Each time the task force convenes, and again, it is an evolving process. Before there was a task force where it would sit for three to five years, the first, second, and third task force, and now it is a rotating three-year position. But at the beginning of a session, the task force seeks nominations for topics, and it is a public announcement. Then again, the members of the task force put their priorities in an agenda, and vote on these topics that have been submitted.

Depending on resources, it is limiting of how many topics the task force can address. Primarily there have been a core set of topics that the task force continually re-addresses, but now again, with the advancing science, we are addressing issues that are new to the task force.

We have had federal partners who have come to the task force and said, these are important issues. Can we apply your methodology? Will you look at this topic? So that has been another approach that has been used in the past.

DR. TUCKSON: Has it ever been that the Secretary has ever said, I mean, this is really important to me, and I've got an advisory committee that is beating me in the head about this, and therefore, here is a couple of bucks, and we just want you to go out and get this done for us?

DR. EDGERTON: I think the potential may be there. I can't speak to the full history, I'm not aware of that in particular. Again, I apologize, I'm at the

four-week mark, so I don't have my full history yet on the 20 years of the task force activities. I know other federal partners have come to the table and asked, and the task force has voted on those issues, and felt that they were appropriate and pertinent to the primary care setting.

So in the sense if we were to take it one step regarding some of the discussion that might occur in this panel, I think there is the potential for future discussion.

DR. HOWELL: Piero?

DR. RINALDO: I have two questions. If I understand correctly, the role of the task force is to provide recommendations regarding preventive services in the primary care setting. I take this concept, and I look at the list of current recommendations, and I'm wondering if you can elaborate how Down's syndrome got in this process? What was actually the recommendation? The second question I have is how long does it take to close the circle and basically get a recommendation when something is recognized as a target?

DR. EDGERTON: It is an evolving process. It has become much more rapid over the last few years, because previously when the task force met, their goal was to publish a comprehensive book of recommendations regarding preventive services. We have moved away from that, so we're now addressing individual issues so that the time process is much more rapid. I would say between the 12 and 18 month mark in our current system. But again, that may be under change. I'm just using a benchmark from the last year to two years of how we have done that.

In the sense of how topics were addressed, that again is public notification regarding what topics, whether professional groups, individuals from the public, other federal agencies felt were important to primary care, and what the task force also felt was important. Then there is a process of voting, and then the top X number are chosen. So that is how some of those recommendations were looked at.

Regarding the full recommendations, I am going to defer you to the website, because they are quite lengthy. But in a sense of the A recommendation, it means that the task force strongly supports screening for those conditions.

DR. RINALDO: So screening for Down's syndrome at what stage?

DR. EDGERTON: I don't have the details with me. I apologize.

DR. HOWELL: Coleen?

DR. BOYLE: I was just going to respond to Reed's question earlier about how the recommendations or rulings from the task force are picked up by federal agencies when the I, insufficient evidence, came out for newborn hearing screening, we at CDC, and maybe Irene as well at HRSA, tried

to look at whether or not we could develop the science base to try to answer some of those questions in terms of long-term follow-up.

It became very difficult, because newborn screening was now being mandated at the state level. So there were a whole bunch of ethical-related issues in terms of trying to develop a clinical trial to actually further evaluate that. So in some ways, these two things are working in opposition to each other.

DR. TUCKSON: I just want to underscore, and I'm sure everybody does appreciate that the task force's recommendations are really, really important out there in the world, especially in the insurance reimbursement world. That is what most folk out there in the world take as their guide. So I would just underscore how important when they make a recommendation, it translates into real tangible action out there in the real world.

DR. HOWELL: Steve?

DR. EDWARDS: Going back to the current recommendations you listed in your slide, if I understood it correctly, and if I didn't, correct me. For example, the March of Dimes listed ten conditions. You list three of those as being A, and you list one of them as being I, and you don't mention the others.

Part of it could be what you have looked at for evidence-based. So what information can we have about what you have looked at for evidence-based information in making your recommendation?

DR. EDGERTON: The other areas that the March of Dimes have listed have not, as far as I'm aware, have not been looked at by the task force. Part of the rationale of the task force is the magnitude of burden, and again, whether that is the amount of mortality associated with something, or the prevalence in society. So again, each task force comes up with their own decision on the topics they look at. So again, those were the topics that were addressed and met those criteria for the task force at that time.

DR. HOWELL: Other questions or comments for Dr. Edgerton?

(No response.)

DR. HOWELL: Thank you very much. We'll move ahead now to Dr. Boyle from the CDC.

DR. BOYLE: Well, again, I wanted to express my pleasure both in terms of serving on this committee, and in recognition of all the work that Michele, Peter, and others have put in in terms of making this committee happen. I really look forward to my term on the committee, and hope we can wrestle with some of the really challenging issues that have been addressed so far this morning.

I just wanted to briefly clarify some of CDC's activities in newborn screening. Unlike some of my other federal representatives here, our activities are actually distributed across four groups at the Centers for Disease Control and Prevention. However, with our new reorganization and futures initiative, we may all be in the same place. But right now, we have the National Center on Birth Defects and Developmental Disabilities, and the Office of Genomics and Public Health that Muin Khoury heads up. We have a laboratory education group, and another center, and then we have our, as you heard earlier, Newborn Quality Assurance Screening Laboratory. So it is a fairly eclectic group.

CDC's activities really go back to something that Reed Tuckson talked about earlier this morning, and that is really trying to improve the science base for newborn screening. We work in a number of different areas, but primarily our activities, which is classic to CDC, encompass the areas of surveillance, long-term follow-up, and epidemiologic studies that are generally developed from our surveillance and monitoring programs. Then laboratory quality control, and standards.

In terms of surveillance and long-term follow- up in regard to newborn screening, what we're really talking about is the whole issue of clinical utility, and that really is to try to understand the impact long-term for the child, and for the family, in terms of newborn screening activities. I'm just going to highlight for you a few of these. Is Irene still in the room? There is Irene. We partner very closely with HRSA in the area of newborn hearing screening. I start with this, because I think it is an excellent example of really trying to develop the science-base as you're ruling out a public health prevention program.

At CDC, our mission really is to ensure that every state and territory has a complete early hearing detection and intervention, tracking, and surveillance program. The reason for developing that data system is really to ensure that children follow through from early identification through screening, through diagnostic, and through intervention to ensure that in fact they have achieved the appropriate communication and social skills commensurate with their cognitive abilities.

We have 32 states that we fund where we're working with them to develop surveillance and tracking programs. The ideal is that we will have individualized data from those 32 states, or all of the states, actually, that have mandated newborn hearing screening, so that we can basically answer a number of questions in relationship to clinical utility, but just looking at the implications of the program for various ethnic minority groups, or whatever other questions arise.

Built on top of the surveillance and tracking programs, and again, I'm trying to use the EHDI program to illustrate what we should be doing in the area of blood spot screening programs. We have a number of research programs built, addressing issues like cost analysis in Utah, and quality of life. We actually have a research program looking at the contribution of the cytomegalovirus to congenital hearing loss.

We are looking at family and psychological issues, genetic services issues in North Carolina,

long-term outcome in Hawaii, and family satisfaction in a collaborative project in Colorado and Massachusetts. Then we have a more detailed etiologic genetic study that is based in four locations in the U.S. I think that's it. A couple more, loss to follow-up, and quality of life.

We would really like to grow the same type of program in terms of long-term follow-up for blood spot or MS/MS screening. Right now we have a program, it is really a pilot program in two states collaboratively, Oregon and Idaho, and Iowa. They are funded to develop a medical records abstraction system for long-term follow-up of infants identified through MS/MS screening.

Hopefully, and I think we're working fairly rapidly towards this, what we develop in those states is a tracking system that could be easily adaptable to other state programs. Marie Mann mentioned this morning the idea of developing an integrated child health record. The idea that we don't want to do blood spot screening separate from newborn hearing screening, separate from the other types of child public health programs that are available.

Actually at the tail end of one project, and again, it is a pilot project funded in Colorado to investigate integrating newborn screening programs into one database. Here, they are linking hearing, metabolic screening, and screening for hemoglobinopathies.

This is just an example, and this is a little bit of an older project that was one of our initial projects that was funded. I use this as an illustration, again, to look at the power of data to follow up state programs for screening for hemoglobinopathies, and look at the impact on morbidity, as well as mortality. This is data from an MMWR that was published a couple of years back, looking at the impact of newborn screening from hemoglobinopathies. You can see the mortality rate for state programs relative to the mortality rates in prior years, showing at least a profound impact on newborn screening in terms of overall mortality.

Epidemiology. Again, it is hard to separate the surveillance and the epidemiology at times. We have done a number of different activities. Some of them are based on data that we have collected on state levels, and others of them are evaluations of the evidence. This is just a collection of recent MMWRs or journal publications, and I'm going to highlight a few of these.

We just heard about the systematic evidence review. We have done a number of scientific evidence reviews, not of this systematic type, but more of a quantitative evaluation. We had a recent meeting around the whole issue of screening for cystic fibrosis in early January, and have had an evaluation of the scientific evidence. Cystic fibrosis, for those of you who know a lot about this area, is probably the one condition that has the most data, scientific data accumulated on it, so it is really a nice example to sort of chart the course in this area.

One of the recommendations from the panel was that we take cystic fibrosis and do a systematic review, and see what the outcome from that would be. We have an MMWR that is coming out in September from that January meeting.

We also did a similar type of evaluation, and this is one where there isn't a lot of evidence for newborn screening, and that was with muscular dystrophy, and we did this one a couple of months ago, inviting scientists from different countries where they actually are looking into the issue of newborn screening, or are doing screening for muscular dystrophy.

As a result of that meeting, we have just issued an RFA to basically investigate parental and other related issues on screening, both in the newborn period, as well as in the infant period. We also did something in the area of maternal hypothyroidism, which is another issue in terms of developmental outcomes in children. So that's an example of essentially trying to evaluate the evidence, not as rigorous a fashion as the task force would do, but just looking quantitatively and qualitatively on the issue.

This is another example of the types of work that we have done. One of the hypotheses is that a number of children who die suddenly, either in infancy or early childhood, may in fact have an underlying, undiagnosed metabolic disorder.

This is a study that Piero helped us with, in looking at all children who are identified from the Virginia Medical Examiner's Office. From this study, we found that about 1 percent of children who died under the age of three actually had an undiagnosed fatty acid oxidation disorder, or organic acidemia.

Our Office of Genomics and Public Health is very intrigued and interested in the idea of using newborn dried blood spots for epidemiologic and other public health purposes. We have had a series of discussions over the last couple of years in terms of the use of stored newborn dried blood spot specimens. Obviously there is a lot of implications here, both in terms of their utility for newborn screening issues, assessing new technology, and looking at laboratory quality control issues.

They are obviously a gold mine in terms of looking at public health epidemiologic research, and there are other applications as well. These are the results from a study yet to be published. This was done in collaboration with APHL. This is looking at state response related to storage and use of residual dried blood spots. This was presented at the APHL meeting back in May.

Just to walk you through this quickly, what the survey found was that 40 percent of responding states stored spots for more than 12 months. More than 80 percent favored storage of identifiable spots at either a state or a regional level for one of those purposes that I stated earlier. But importantly, again from an epidemiologic standpoint, that 20 percent representing about 2 million annual births, would consider participating in an anonymous multi-state survey, whether it be looking at the prevalence of specific genetic markers, or other factors. So clearly there is a lot of utility and potential, at least from a research perspective, in trying to answer some of the questions that this committee will come up with from newborn dried blood spots.

This is just a very busy slide, but it just highlights one of the projects that our Office of Genomics and Public Health is doing. It is based on the NCHS NHANES III DNA databank, and it is basically looking at the prevalence of genes of public health significance. Actually looking at, if you can read the slide, over 87 variants of 57 genes are going to be examined in this study.

Another example here of epidemiologic variation. This is a study that was published not too long ago looking at the prevalence of C677T homozygotes genotype in relationship to which is associated with some cardiac defects. It shows you the varying prevalence by ethnic background. This is actually using our Georgia newborn screening blood spot program, as well as different programs in these varying countries that also had information on prevalence of various birth defects.

The laboratory issues, this is a really big area for CDC, and many of you know, Harry Hannon, who couldn't be here today, but hopefully will be at the next committee meeting, he has been working over the last 25 years and has developed an excellent Newborn Screening Quality Assurance Program specifically for dried blood spots. These are some of the attributes of that program, and I just want to highlight some.

They actually provide services for over 35 disorders, and that includes close to 400 laboratories in 35 countries that are now enrolled in newborn screening quality assurance and proficiency testing programs. So this really helps in terms of standardizing testing from both within the U.S., as well as outside the U.S.

The types of activities or services provided by this program include filter paper quality control, reference materials, proficiency testing, and obviously consultation. The major partner for this activity is the Association of Public Health Laboratories that Harry has worked with very closely over the years.

This gives you some more attributes of the quality assurance blood spot collection. Close monitoring for performance of new commercial lots, special evaluations of paper/trouble shooting, and other quality

control-related issues for filter paper collections. Bob and I came up on the 6:30 flight this morning, Bob is an immunologist who works with Harry. We were talking about sort of the revolution in the lab, and the fact that they are now moving into the whole area of R&D and research, which is really terrific.

This just gives you some of the areas that the laboratory is working with in terms of research and development, in looking at genotype proficiency testing for some of the newborn screening conditions on the horizon, including cystic fibrosis and MCAD. Looking at genetic markers, and Bob can tell you a lot about this issue, for Type 1 diabetes, we have a number of projects going on there, and there are some really exciting data looking at the impact of early identification and treatment in terms of long-term outcome for children.

I think we're going to hear tomorrow about SCID and its applicability to newborn screening. We are working in Denmark, as well as at CDC, in looking at a number of protein markers that in fact a couple of years down the line may in fact be ready for prime time in terms of newborn screening-related activities. So a lot on the horizon to think about in terms of newborn screening opportunities.

Just some other laboratory issues, and I think Marie actually mentioned some of these this morning, involved in laboratory testing. Communications, improving communications between laboratory and health care providers to ensure that genetic tests are used effectively. We are involved, our laboratory and training group, is involved in training courses for laboratory personnel for newborn screening, such as MS/MS, and that was the collaborative project that Marie mentioned, as well as quality assurance.

There was a recent conference that we collaborated with with NIH to explore approaches to assure available quality testing for rare diseases, and conditions in ways to assure that new gene findings are appropriately translated into clinical test issues. Those are my sort of summary of CDC's related activities. I'm hoping now that CDC is sort of reconfiguring itself, and we are all going to be hopefully located within the same cluster, although that is yet to be determined, that we internally actually can do some more coordination of our activities and really have a stronger force, both in terms of the surveillance epidemiology, and the complementary laboratory testing related issues. Any questions?

DR. HOWELL: Any questions of Dr. Boyle? Reed?

DR. TUCKSON: Sorry to keep asking these questions. I feel bad. Is there anybody at the level of the Secretary's office who looks at the integrational coordination of the recommendations around, or the information or knowledge, again, and the behavior around newborn screening activities?

We just heard a wonderful report from AHRQ. Now you have talked about another look at it. Someone outside of the agencies would get the impression that these various sectors of HHS are operating somewhat independently, although there are these collegial friendships between the two of you. But you don't get the sense of an overall strategic plan. I'm just wondering, does it exist? Or is it something that is needed?

DR. BOYLE: I'll speak for my own agency. We do work independently. However, I think over the years, both Michele and I in serving on some of the same committees, and obviously being impacted by the same types of forces, have tended to collaborate, or to move in the same areas. That is just because of friendly collaboration versus an overall guide to that process.

DR. TUCKSON: The other question is you didn't touch, or maybe you didn't imply it from the epidemiological presentation, on the large population-based studies. I think that Dr. Howell in his introductory comments talked a lot about the promise of knowing more about the individual genomics, and the environment. Is there a plan that you're aware of for funding for this large population-based research study?

DR. BOYLE: I'll let Jim maybe address some of that. From NIH's perspective, there has been discussion and planning around, and you may be familiar with this, the National Children's Study, which would be a large population-based study of about 100,000 pregnancies. Whether or not that would be helpful in this realm, I'm not sure, based on even though it sounds large, it is not large enough to answer some of the direct questions that are arising here.

There has been talk about a family genome study, or a family study from NIH as well. We have a number of population-based studies that include biological samples, but they are generally around specific diseases like birth defects, diabetes, cancer, or heart disease. So it doesn't necessarily encompass the conditions that we're talking about here.

DR. HOWELL: I think that many are aware of the fact that Congress has mandated the National Children's Study where 100,000 pregnancies would be followed, and the children, and so forth. Coleen had suggested maybe Dr. Hanson would like to comment about that. As far as I'm aware, in spite of the fact that has been mandated, and an extensive effort has gone into planning that and so forth, I do not believe that adequate funding is on the table for that at the current time. Is that correct?

DR. HANSON: (Inaudible.)

DR. HOWELL: And Judy, would you like to comment? Ms. Waylan from the Director's —

MS. WAYLAN: You covered it.

DR. HOWELL: I've covered it, okay. The bottom line is that I think that there is a great sense that it would be extraordinarily valuable to look at the pregnancy and outcome of this group of children, and also there are many questions in older adults that need to be looked at as far as genes and the environment. To do that requires a very large number, and there obviously at this particular juncture, is concern about the availability of the large sums of money it would take. But I think that those would be extremely valuable studies, and we'll hope that they will get moving along.

DR. BOYLE: Let me just respond to one other issue that would address that, too. I do feel like with the state newborn blood spots and the fact that they are a very important repository, if we would be able to set up some type of research setting which involved a number of different states, or segments of states, where they were able to look at follow-up and look at issues that related to natural history, a specific disease. We need huge numbers here to be able to address some of these issues. So it will be through something like that, I think, that we'll be able to answer some of these questions.

DR. HOWELL: Piero?

DR. RINALDO: One question. In one of your earlier slides, you said that the CDC's goal is to improve the science, and it makes perfect sense. But what I heard is a lot of sort of representation and suggestions for communication between government agencies and various bodies. But what about the professional societies? What about the clinical chemist? Pathologist? The geneticist? There is a wealth of other people out there that do this for a living.

I would like you to comment on what really has been done, or should be done, to sort of enhance the communication. Certainly what I have seen lately happening with the college is a good sign, but I think there is a lot of resources, intellectual resources, that are being completely untapped.

DR. BOYLE: Piero, I think that is an excellent point. I believe that we have just started to try to reach out to professional organizations, at least from my center's perspective in terms of taking advantage of that collective knowledge, and working through those organizations to actually do some of the science.

DR. HOWELL: Reed apologized for asking so many questions. But as usual, he asks questions that aim right for the heart of the subject. I think that it is my impression that the newborn screening community, be it the CDC, the NIH, or HRSA, has an extraordinarily large amount of interaction and interpersonal relationship. Most of the people who work in the area know each other, they call each other and communicate.

But I think that to have a centralized effort that might tie the research into the deficits of some of the quality assurance issues and the clinical study, would be substantially advantageous. Maybe no one else feels that would be, but I think that would be a neat thing. Are there other questions or comments?

DR. BECKER: Rodney, I would just add, as I was listening to the general conversation based on Reed's question, of course, HRSA, NIH, CDC, AHRQ, and then not to be forgotten in this whole equation if there is going to be some strategic sort of coordination or direct report to the Secretary is something not to be forgotten, is the people that pay the money on the other side, and that is CMS, Centers for Medicare and Medicaid.

DR. HOWELL: Absolutely.

DR. BECKER: Also involved in this, all under the auspices of HHS.

DR. HOWELL: Yes, yes.

Any further comments? Dr. Hanson? Dr. Hanson introduced himself earlier as a member of the staff of NICHD.

DR. HANSON: I was just going to say with regard to this last point, there is an existing model that could be used. That this the National Vaccine Program Office, which was used in the last President's childhood immunization initiative, which then included representatives from a variety of agencies. They were coordinated through that kind of approach.

I might point out that one of the positions in that office was to have a senior advisor for provider liaison. So having been in that position, I know that there was an effort to be sure that plenty of health professions organization's points of views were well represented.

DR. HOWELL: My associate to the right has a word to say.

DR. LLOYD-PURYEAR: This morning when I went over the committee structure and the relationship between the legislation and the charter, I emphasized that the charter was based on the legislation. The committee's membership is limited to 15 members, and again, the federal liaisons are here, plus the non-voting members are members, and they count towards that whole 15.

There are three entities missing from this table. One person's son was graduating, another person's father is dying, and the third just was unable to be here. So we're full.

However, the committee can add to the expertise. That is one issue we're talking about with CMS. The other agency that has come up is FDA. You can add to the committee's expertise what you feel is needed if you choose to by adding consultants to the committee. They are non-voting consultants, but you can add expertise in that way.

Then the structure that Jim was talking about, Dr. Hanson was talking about, is that the National Vaccine Advisory Committee was formed by specific legislation. That legislation, unlike this legislation, that legislation called for a national office, but also called for an interagency coordinating committee, and demanded and specified the federal agencies that needed to work together and coordinate. They met monthly, sometimes just face to face, but monthly either face to face or sometimes just by conference call. But that was a very successful model for overseeing and coordinating immunization-related activities between very desperate missions in the federal agencies.

DR. HOWELL: Thank you very much, Michele. It seems to be that there are several issues that have come up that we'll need to discuss to try to accomplish some of those goals.

I'd like to ask Dr. Jennifer Howse now to review some of the activities in the areas of newborn screening for the March of Dimes, of which she is President, and which organization has a very long history in this area. Dr. Howse?

DR. HOWSE: Thank you very much, Dr. Howell. I'm just going to keep my seat here. I have prepared and submitted beforehand essentially a legislative summary of the activities of the March of Dimes in this newborn screening arena. I wanted to come at this issue from maybe a bit of a different perspective, a real practical,

on-the-ground perspective with regard to newborn screening.

I think that with the work that various ones of us in this room have done to support the implementation and development of newborn screening, I think all of us are agreed that there is a wealth of opportunity here in this area, both from the standpoint of the emerging screening technologies, as well as from the standpoint of the emerging genome-based science.

I think all of us agree that in terms of the development of a preventive service or a predictive medicine dimension, this is an arena that is extraordinarily active. So the question for our organization, a consumer organization, really came to given all of the activity, given the opportunity, and given the complexity of just beginning to get consensus in the area of newborn screening, what could we do as an organization that would be the most useful, the most practical, just to at least take another slice through the Gordian knot of how to make sense of the opportunities in newborn screening.

So we want to take a focus that would be very, as I said, practical, very on-the-ground, a focus that would have the newborn, and the needs of the newborn front and center. We have been following these various reports through the years, and have been active in the area, but we are particularly taken with the quality of the AAP Task Force, the issuance of that report, and the principles contained in that report, the patchwork quilt of screening services on a state-by-state basis which was elucidated in that report.

Principle Number 4, which you heard described earlier, which was kind of an understatement, it said, Greater uniformity would improve the situation for family, professionals, and the public health community," which we took to be a rather significant understatement of the situation with newborn screening.

So collectively as an organization, what you can see from the legislative summary before you, the position that we took was to answer this question, what is the irreducible minimum of newborn screening tests that our organization, the March of Dimes, would recommend? We came to call these core tests. We really arrived at two rather straightforward criteria, which Bob Guthrie was talking about years and years ago, which are that the test is reliable, and that the condition identified is treatable.

Now, I realize we have dealt with a couple of different definitions of is treatable evidence-based treatable, or is treatable a consensus-based treatable? But we made a decision that from the March of Dimes standpoint, that treatable meant that early discovery of the condition would make a demonstrable difference in the health of the newborn, and the child.

Through those kinds of deliberations, and actually a number of you in this room directly or indirectly were involved in those deliberations, we essentially issued a policy which called for nine core tests, plus hearing screening, which means ten core tests. We said, these are the March of Dimes tests, and they are based on both reliability and treatability of the condition.

We prepared then a commentary, which was published in the Pediatrics, and made a statement which seems kind of simple, I guess, on its face, but I'll tell you, we got an awful lot of letters, and we stirred up a lot of discussion, which is what we intended, frankly, to do. The statement, I'll just read it in its simplicity. "We believe that a test, even for a rare disease, as long as its early discovery makes a difference to the child, must be conducted for every newborn."

That was in August of 2000 in Pediatrics. Having made that statement, and published it, we then set about on a state-by-state basis, because this is a

state-by-state issue right now, to put our bipartisan advocacy machinery into gear. We worked with Brad and the Center, and got an inventory of the newborn screening tests that were in place on a state-by-state basis.

At the time of that inventory in the year 2000, nine states did all of our ten tests. They were mandated, they were listed, they were funded, they were in practice. Then we set about in the old fashioned bipartisan advocacy way, to find parents who had been involved, to get advocates in the business community, and essentially to start working through the state legislatures to get additional laws on the books, and to get additional appropriations to bring all the states up to the nine core tests, plus hearing screening.

As of 2004 in the latest inventory, as you see from the statement that I sent down for you all, there are 25 states who have those laws on the books, have the tests listed, have the money available, and are carrying out those tests. Fourteen of the states had it in place as of a year ago, and 11 states just approved the dollars necessary for expansion, bringing it to 25, which is half of the states.

So I think from our standpoint, the March of Dimes standpoint, one of the recommendations, perhaps even a central recommendation from the work of this group that would be very important to our organization and our constituents, and we believe to the whole area of newborn screening, would be for this advisory committee to recommend a set of core newborn screening tests with whatever criteria this group deems appropriate, and then

by so doing, leave in place equity for every newborn in America. So regardless of what state that child is born in, that child will be guaranteed a minimum core set of newborn screening tests. The March of Dimes has proposed one set of criteria, but clearly other sets of criteria can be taken into consideration. But the principle remains that since this is currently a state-by-state decision, that one of the recommendations from this committee be the creation of a core set of newborn screening tests that will be put into place.

The other comment that I would make is that as an organization, we are certainly pleased and supportive when states add tests, which many of them have, beyond these ten March of Dimes recommended core tests, and I just call them systems benefits to be obtained from this. That is, states that are doing a core and doing it well, with all of the considerations that we've been discussing so far this morning of health systems capacity, reimbursability issues figured out, quality issues figured out, professional and consumer education issues figured out, treatment and follow along figured out. States that can do that for a core are in a position to do that for many, many other tests.

I think the other big message from our conversation so far this morning is that this is a field, perhaps an exploding field is too strong to say, but maybe that this not too strong a word. We feel it is essential and important to be prepared, and to have a strong foundation on a state-by-state basis, so as this field grows and matures, and the science comes to bear on so many different tests and conditions, we will be in a position to reap the benefits of that progress for our newborns. So I think I'll just pause here, and see if there are any questions or comments.

DR. HOWELL: Questions or comments for Dr. Howse?

(No response.)

DR. HOWELL: I think that the efforts of the March of Dimes have been truly legendary, and particularly I think that the grassroots, as well as the national legislative efforts, have obviously been extremely successful, and that will, I hope, continue to be a major responsibility that you assume.

Piero?

DR. RINALDO: I think that there is no doubt that the work done by March of Dimes has been absolutely critical to the evolution of the process. Yet, as you know, I do remember once a meeting where you joined in by conference call, an agreement about the addition of MCAD, and particularly giving proper consideration to this whole issue about the condition detectable by tandem mass spectrometry, which I think is still quite notably missing somewhere in all of the official documents, or statements made by the March of Dimes. So is that still sustainable? Or do you see a possible change sometime in the future?

DR. HOWSE: Well, you know, we added MCAD to the list of core tests, and did that on the basis of the discussions that had informed the other tests that had been added to the list, which is basically that there is a reliable test, and that it is a treatable condition.

You're right in certainly identifying that it brought the tandem mass spec issue to the fore, but our central concern was around a reliable test and treatment potential.

DR. HOWELL: That will probably come up again before we leave.

(Laughter.)

DR. HOWELL: Reed?

DR. BOYLE: You have to be impressed when Jennifer Howse says that after the March of Dimes has engaged in essentially state-by-state hand to hand combat, to try to get these things implemented, that she then says what we really need is to get a federal standard here. You just can't keep relying on the availability of those kinds of resources to be devoted to every little thing.

So I just would have to underscore that it is hard to ignore her recommendation after there is an organization that have committed those kinds of resources. I'm hopeful somehow, Mr. Chairman, that we will get some information later in our deliberations, we think it is important, on what is the actual prediction in the next five years of the number of tests that will meet some level of relevance of criteria? And then, what is the infrastructure necessary to be able to add on all those tests?

I think Jennifer makes an important point that at least under current scenarios, adding one, two, three more to the infrastructure in place now may be fairly

cost-effective, and that's encouraging. I think we really need to drill down on that, and try to learn more about what that really means. But then also move that a little bit towards five years from now, in terms of what are we really trying to plan for? And be able to escape to that puck, instead of where the puck is today. I hope that we can find a way to get some real analysis to us as we think about this.

DR. HOWELL: I think that, again, to fast forward a little bit to tomorrow, I think that tomorrow you're going to get a fairly good window on what that perception is. I think that that window will provide many in the room with great glee, and an equal number will get hives because of the concern about how do you deal with this?

(Laughter.)

DR. HOWELL: But I think that a national standard, I would think, to ever achieve adoption is going to require the regional hand to hand combat that you have done in order to make it percolate and get along. Are there other questions of Dr. Howse?

DR. HAWKINS: I just have a comment.

DR. HOWELL: Thank you.

Greg?

DR. HAWKINS: As we continue to talk about genetic testing, and you bring up this issue about how things are going to just explode, and we're getting into costs as we develop newer and newer tests, I think one thing that has come up when we talk about genetic testing, in the realm that we're talking about it, is we're still talking about looking at some metabolites. What do we detect in blood?

As we move on, when you talk about the real, real genetic testing, when you go down to the DNA level, you explode, you start doing some genetic tests. I look at it as something like a disease gene like BRCA1 that has over 200 mutations in it. If you ever find a gene like that where you want to do all that

testing, I just want to make a comment how this really does explode in a cost realm, and that is something to really consider as you make these type of recommendations.

DR. RINALDO: I have to strongly object to the characterization of biochemical testing is a known genetic. I really strongly disagree with that, that's incorrect.

DR. HAWKINS: Well, I'm not meaning that it is not a genetic test. When you talk about a person on the street, when you talk about genetics, they think DNA. I mean, from my perspective, that is what I think about, but that is just because of my training. That has no slight on the type of testing that is being done.

DR. RINALDO: Genetic testing is testing for genetic conditions.

DR. HAWKINS: Exactly.

DR. RINALDO: How you do it, there is more than one way.

DR. HAWKINS: Right, right. But I'm just saying that when you are at Wake Forest University and someone comes in and says, I want to do a genetic test, the first thing that goes through my mind is what base pair am I looking for? So that is something we have to differentiate as we go forward.

DR. HOWELL: This brings up a very interesting thing. That is that many people still don't have it in their heads that newborn screening is genetic testing. Actually, I have a slide that I usually start with that said, newborn screening is by far the most common type of genetic testing done in this country. Again, I think that for some reason, because PKU came up in one environment and so forth, it was "not thought of as genetic," but obviously it is.

One of the reasons that I actually talked about the glycogen disease is, one, I'm interested in it, which is always key. But the other thing is that it is a condition and the lysosomal diseases are rapidly becoming treatable.

Number two, the technology is different than what we've talked about. In other words, you're going to have to be measuring by some methodology, the presence of an enzyme or mutation. In other words, not the traditional soluble metabolite that we have looked for in other than the hemoglobinopathies. So it does introduce brand new technology to the table.

DR. TUCKSON: I really do hope that, and I really appreciate the dialogue that just went on. But I think that for those of us who are not as sophisticated as Piero is on this, that if we do decide to ask for this kind of analysis so we understand it, I think Greg's point is, we need to understand it.

Regardless of the terminology, I think what he is getting at is more of what you just underscored, it is the technology required. On the face of it, for those of us who are not as sophisticated, it would seem that there is a difference between the blood spot kind of work, and those kind of things being done, versus the genetic databases.

The cost of accumulating and analyzing those may have some differences. This is not a pejorative question, it is one for more definition of understanding the issue.

PARTICIPANT: Right.

DR. HOWELL: Greg?

DR. HAWKINS: A good issue, I mean, metabolize versus genetic, as you mentioned earlier this morning about looking at pharmacogenetics. There were a number of genes that we're looking at right now from a pharmacogenetic approach. We basically do a haplotype analysis where we have to do genotyping or cross the gene, and we have to look at as many as eight, ten, or twelve different genetic determinants across that gene and create a haplotype analysis to actually determine whether this person may be a responder or not a responder for a specific type drug.

You talk about moving to testing for pharmacogenetics. That is one of those type of realms we move into as far as doing the genetic analysis. That is just an example to delineate. Piero, I didn't mean to slight what you mean by genetic testing in any way, but I just think that especially if you were to tell my wife what a genetic test is, she only knows what I do, and I don't think my wife would even have a clue what real genetic testing really means. I think that is something that is an education issue, and I think it is something else to work on.

DR. VOGT: Bob Vogt, CDC. I have a question for the committee about this, and some of this is just a rose by any other name. But there are also important issues buried underneath here. To exemplify them, let me ask the following question.

There is one state that screens for toxoplasmosis as part of newborn screening. That, I guess, would clearly not be a genetic test, and I guess everyone would agree with that. Is that under the purvey of this committee?

DR. HOWELL: I don't know the answer to that. I had not thought about infectious disease in newborn screening, but maybe someone else had. I have been thinking of what would be traditionally called genetic testing in the broadest sense, metabolite, microchips, you name it.

DR. VOGT: So without answering that question maybe, then let me make it even fuzzier. One may get more information from an array of tests of expression, I have chosen to call them, in contrast to genetic tests. For instance, cytokine levels, or antibody levels, or things that are definitely not relatable to a single genetic allele or locus or defect.

Those may prove to be very useful as we sort out "proteomics" and "metabolomics" and what other "omics" may come. So then also philosophically I'm asking the committee, is that under the purvey of this committee? And then finally, to make it fuzziest of all, if one considers something like the haplotype risk for auto immune disease, which is very well established and very genetic, but not predictive, not terribly predictive.

So certainly having a DR3/4 is not a genetic defect, but it puts you at very high relative risk for Type 1 diabetes. That screening is ongoing in research centers now, and there is some movement towards generalizing that, certainly into higher risk families and so on. So that is genetic testing, but it is not the kind of genetic testing that is associated with a specific defect and a virtual certainty of a medical outcome.

Then of course you can throw in the well, what about the different CF mutations and you can go on and on. So this whole thing is just going to get fuzzier and fuzzier. The more we do, the fuzzier it is going to get, and it is not going to get better. I would just try to caution the committee to, and I don't like the term "genetic testing," because as a laboratory person, I do think of ATCG or wrinkled green peas or something like that. But I understand that it came from the inborn errors of metabolism that you showed so nicely to open the program here. There is more than just wordsmithing to that whole issue.

DR. HOWELL: Would anyone like to comment to Bob's commentary? We have a comment here.

MS. JOHNSON: I just have a separate comment. I'm Alissa Johnson with the National Conference of State Legislators. There are also legal issues, in that newborn screening is generally not covered under state genetics laws pertaining to privacy and discrimination, whereas DNA testing is.

So if you get into talking about developing a core of recommended tests, the legal implications if you start expanding to DNA testing, are quite different, and vary from state to state.

DR. HOWELL: Thank you very much for that comment. I think it is very clear that we will have in the recommendations of this group, certain testing that will be DNA-based without a question, even before we get there, because this already included, for example, the one that comes to my mind right now is CF testing at the current time, and sickle cell in many states is done that way. But CF testing is done with immunoreactive trypsinogen, and then a backup with DNA testing.

So I think that that is already here, and I think your point is very well made. But I would go back to I think that the complexities that Bob brings up about the genetic testing and so forth is indeed very complicated. That's why I think it makes this job challenging, but also interesting.

DR. TUCKSON: Yes. I would hope that for the record, that Bob would summarize his point and submit them for us. I think that, again, if we determine as a committee that this is worth looking at a little further, his challenges to us are thoughtful enough that may be incorporated in our turning to other experts to help us to think about it, if that is something we choose to do by the end of the meeting.

DR. HOWELL: His comments are recorded in perpetuity, and we'll ask him to see if that is what he thinks he said.

(Laughter.)

DR. HOWELL: Bill?

DR. BECKER: With respect to the comment about infectious diseases, while it is certainly true that you probably couldn't make the argument that they are either genetic or heritable, it is a fact that there are a couple of states that are doing screening as part of their four infectious diseases, as part of their newborn screening program.

The collection of the data is similar, the analyses, if you apply the March of Dimes criteria, is there a reliable test? And is the disorder treatable? You could make the case that infectious disease is being considered in newborn screening panels, because the model for prevention or intervention in this particular case, could be seen to be very similar. So it is probably something that the committee is going to have to acknowledge, even though it might not be explicitly written in our charter as it currently exists. As several of us around the table know, we will hear about the issue of infectious diseases in screening as part of a potential panel in Mike's report tomorrow as well.

DR. HOWELL: Yes. That, we will.

Coleen?

DR. BOYLE: I was just going to bring up the issue of hearing screening as well. That is obviously screening for a functional limitation in children. Some of that is due to a genetic basis, others it is not, and there are complexities on that.

DR. HOWELL: Right. Potential genetic conditions. Amy?

DR. BROWER: And I just wanted to go back to one point that Jennifer made that I'd like to underscore. The states that do this really well, that are doing the core today, doing it really well, and have it all figured out, have those logistics worked out, I think we need to understand those models so we can maybe do potentially some state-to-state mentioning or capitalize on those early wins.

DR. HOWELL: Any further comments on this immediate subject?

(No response.)

DR. HOWELL: If not, let's take a break. We're right on the moment. Let's be back at 3:15.

(Recess.)

DR. HOWELL: We're going to continue our discussions here, and hear from Dr. Steve Edwards, who is the immediate Past President of the American Academy of Pediatrics. He will summarize the activities of that group that have been considerable over a long period of time in the area of newborn screening.

DR. EDWARDS: Thank you, Rod. That comes from one of our members, and I'm sure that there are a lot of other members around the table, too. It is nice to be here with you.

One of the things that hasn't been said that I'm sure is implicit in everything that everybody has said is that we're not dealing with diseases, we're dealing with people. We're dealing with people who get sick, we're dealing with families, and we're dealing with them through their diseases. But I think we need to keep in mind that these are all individuals, and all individuals who need care.

The other thing that I'm going to point out from the Academy is you'll notice from the title of this talk, it is "Providing a Medical Home." I think that not only are these individuals who need our help, but also that the Academy feels strongly that this should be carried out. Dr. Boyle raised a question, and this question Dr. van Dyck answered, and I think this is a very important question for this committee. That is what is the spectrum of the work that we'll do?

I thought that the question was, are we just sort of focusing on the diseases, are we going to focus on the system that works through to handle these diseases, and make recommendations on it? I thought I heard that very clearly from Dr. van Dyck, and this is certainly the approach that the American Academy of Pediatrics would strongly endorse.

So I want to talk to you just a little about what we're doing. I think most of you are aware of the mission of the American Academy of Pediatrics, to obtain optimal physical, mental, social health and well-being for all infants, children, adolescents, and young adults. We have about 57,000 members at the present time.

As I talk to you about what we're doing, I think it would be helpful to you, and I don't want to try to explain to you, I don't even know after 30 some years whether I totally understand the way the American Academy of Pediatrics works.

(Laughter.)

DR. EDWARDS: But I do have a little better understanding than I did a few years ago. I'm going to talk to you about some of our components. This work is being done by different groups. There is a committee on genetics.

Now, our committees are six or eight people usually, chosen by a board of directors. Committee members are chosen on the basis of the expertise, and they are asked generally to write policy for the Academy over specific issues. We'll talk about some of the policies related to genetics in a few minutes.

Then we have in addition to committees, we have what are called sections, and a section is a little different. Sections define themselves, we have about 50 committees and about 50 sections. We have a committee on genetics, and a section on genetics. Sections have pretty level criteria for anybody to join in, so it is kind of like anybody in the organization that is interested in genetics.

Now, you do have to work in genetics or do something, but you don't have to have the same criteria that you would have to be a committee member. So this is a section, and we have about 250 people in the section, as compared to like six or eight people on the committee.

Then we have other committees and sections. For example, we are talking about genetics, but pulmonology, for example, would work with and make recommendations for cystic fibrosis, or there are lots of other examples of diseases where several different sections would be working to make recommendations for policy for the Academy.

Then we have our own organizations, a department. We have the Department of Community Pediatrics, and in that department is the Division of Children with Special Needs. We do have Sunnah Kim here representing that department today. Sunnah was not here when everybody was identifying themselves this morning, so I just wanted to thank her for coming. She came from Chicago today, for being here, and also for what the Department of Community Pediatrics does for the Academy.

The Committee on Genetics, this is a small group to make recommendations to the board. Its mission is to make recommendations to the Board of Directors on recent advances in genetics, and support the chapters on state legislative issues, such as they relate to genetics.

One of the things that maybe you don't understand is that in addition to our national organization, we have at least one chapter in every state, so we do have people on the ground pretty much in the same way that March of Dimes I think has the same organizational structure. But we do have people in every state in the union who are advancing particular legislative issues.

Now, the committee is appointed experts, and fulfills its mission primarily through development of policy statements, clinical reports, and technical reports. So they all come as recommendations to the Board of Directors, and all have to be approved by the Board. But essentially, the experts are the creators of policy of the American Academy of Pediatrics.

So what are some of the things that the Committee on Genetics is working on now? Now, I'll caution you, if you look at this, you're not going to see necessarily the most common things that were on the March of Dimes list of ten. For example, the committees on the Academy work on things that are not consensus in the literature. The committee doesn't work on things where if there is information and everybody pretty much agrees on it, that's not the kind of thing that the committee works on.

The current statements that are being worked on on Down's syndrome, and these are more like how do you treat them, and what should you do for the patients who have them, and so forth. Down's syndrome, Marfan, sickle cell disease, Turner's syndrome, and Williams syndrome. They are also working on the statement of folic acid for the prevention of neural tube defects, which has been highlighted recently.

Maternal phenylketonuria. As we've had patients with phenylketonuria grow up, there is a second problem that comes along, and that is what do you do with the mother who has herself phenylketonuria, what do you do when she gets pregnant? The newborn screening fact sheets. Now, these are mainly for our practitioners. They are a two to three page list of information, and I noticed in Jennifer's top ten, we

have fact sheets on all of the ten, plus two or three others. So these are fact sheets for our practitioners about how do you work with council and help the families whose children have one of these genetic difficulties?

Then still the Committee on Genetics is in the process of making some additional statements, in addition to what we discussed earlier. Prenatal screening and diagnosis for pediatricians, the evaluation of the newborn with developmental anomalies of external genitalia, health supervision for children with achondroplasia, Fragile X, neurofibromatosis, molecular genetic testing in pediatric practice, and newborn screening for congenital hypothyroidism.

Now, obviously that is an old subject, and I'm sure that we try to update statements every five years, so I'm sure that this is an update. Genetic aspects of evaluation of the child with development delay, and mental retardation.

Now, we talked about the separate group called the Section on Genetics and Birth Defects, and that is the Academy's home for fellows who are interested in genetics, and there are around 250 members of that section. Now, where the committees deal with developing policy, the sections deal more with educational activities.

They would work, for example, with articles for the literature, for educational meetings such as National Conference and Exhibition, which some call our annual meeting. We have a spring meeting next year. So they help in writing articles, and in developing the educational program.

Also advocacy, and one of the things that has not, I don't think, been discussed at the table today, and I don't want to put it at the top of the agenda, but if this committee comes up with ideas, Dr. Tuckson has mentioned this several times. If we come up with recommendations, there is going to have to be some sort of way of compensating people if they are doing additional work.

Program development. Young investigator recognition is one of the things that we try to work on in the Academy. Now, the Division of Children With Special Needs comes into the Department of Community Pediatrics, as we discussed. Some of the Maternal and Child Health Bureau-funded activities are the Newborn Screening Task Force Report, which has been referred to several times, serving the family from birth to the medical home. It is the article that is in the back of your agenda books that you got for the meeting today.

Our speaker earlier who was concerned about our work with sickle cell disease, newborn screening for sickle cell disease, we are working through our chapters, targeting states that did not offer universal screening for sickle cell disease, and trying to encourage them to work at this state level to accomplish this.

State-specific fact sheets and an online toolkit for sickle cell disease.

Then we've done a lot of work over the past three years, and I think that there has been a remarkable change, and I don't give us the credit for it, but we have been there working with early hearing detection and intervention. I think, Beth, if you go back, there may be more evidence coming along, but we have worked hard at the chapter level, and at the state level, to try to develop what are called chapter champions. This is basically promoting the hearing programs within the state.

Of course, one of the huge problems with the hearing programs when they first came out was lots of people were being identified, and then lost. That, to us, is a huge problem, as it is for any system. It is also one of the things that this group is going to have to look at, in our recommendations. Our recommendations need to go all the way. We can't just identify things, we've got to identify them and treat them.

That is the next point I want to work into, is what we call the medical home. I have been to Washington a number of times over the last 25 years, trying to explain the medical home. We have come a long way. I remember the first time that I tried to explain the medical home, thinking that I was doing a fairly decent deal. The first question that anybody asked was, well, where do they spend the night?

(Laughter.)

DR. EDWARDS: So we've come a long way since then. I think people realize that the medical home is where every patient and every family should have a place to turn for medical care. Their record should be kept there, they should know that there is somebody there 24 hours a day, 7 days a week to address their needs.

Now, the medical home does not have to deliver all that care, but the medical home has to be there as a nucleus for the place for patients to turn. It is an approach to providing health care services, high quality, comprehensive, and fortunately, it turns out also, Dr. Tuckson, to be very cost effective.

Provision of care to a primary care physician through partnership with other allied health care professionals in a family. Now, I have to say, it doesn't absolutely have to be a primary care physician. If somebody was a pulmonologist and wants to provide care for a child with cystic fibrosis and they are the best person to provide that care, or an oncologist wants to provide the care for somebody with leukemia, as long as they are willing to keep the records, have the patient call them 24 hours a day, 7 days a week, and actually serve as an entree for that patient, again, they don't have to provide all the services.

The patient has to know when they call that number, or when they seek help there, that they are going to either receive that help, or be directed to resources where they can receive the help, and then acts in Children and Youth With Special Care Need's best interest to achieve maximum family potential. The medical home is accessible, family-centered, continuous, coordinated, comprehensive, compassionate, and culturally effective.

So I think that what I would say that the Academy's position on the screening program is, the science is very important, we have to do that right. But we also have to keep in mind the system of care, just discovering a problem is just part of the reason that really the bottom line on this is seeing that that child gets the maximum care that can be delivered to that child, and that's the bottom line on this.

I would ask the committee, as we look at this question, to keep in mind this point. That the medical home needs to be there for the child, we need to think in terms of not just testing, but of also a medical system that will deliver good results to every child.

So thank you very much.

(Applause.)

DR. HOWELL: Thank you very much, Steve.

Are there questions of Dr. Edwards?

DR. TUCKSON: One short one. When you talk about the coordination of those resources, given that you know better than I would ever know, the full range of services that so many of these families will require, that some of them are medical, and quite a large number of them are non-medical, social, and community-based services.

Do you have a sense of today who is it that ought to be collecting that information, that data, the knowledge-base to be able to help, and to be able to facilitate that care management across clinical

settings, and across medical and non-medical settings? Do you really see that as being something that the pediatrician or the primary care provider's office will want to do? Or does that become the purview of some other entity?

DR. EDWARDS: Well, that's a great question, because that is at the heart of the medical home. I would like to say that the medical office will do this. Certainly the Academy would try to help with that. But I realize that medical homes will differ, relative to the persons who direct that care.

So I think it is going to have to be a collaboration, again, and coordination. I think that health insurance companies have done a really helpful job in many instances about pointing out the resources that are available for families. I think our academic institutions have been very helpful in pointing out to our practitioners the resources.

I think our public health facilities have been helpful, and in many cases, provide some of those resources. So it is really, the question to me is in the best sense of the word, we all need to be working together on that. My personal bias is though that the one to be held responsible for that is the medical home. I think we all work together on it, but I'd say that the entity to be held responsible for it is the medical home.

MS. REED: Question. Is it appropriate to as a question? I will be tomorrow for public comment, but I just wanted to ask a question. My name is Kathleen Reed, and I'm an anthropologist.

One of the issues that has come up in my mind about the medical home model has been both international, as well as interstate, and I'll have more to say about that tomorrow. But have you taken into consideration, while there is a primary home, that in many cases with the immigrant populations, people go back and forth, and they really are dual nationals now. So much so that they really feel comfortable living in two places, and also the interstate issue between children living in one place, but then going somewhere else as well.

DR. EDWARDS: Well, that's a tough question. If you ask have we looked at it, yes. Have we resolved it? No. Let me do the interstate part first, because I think that is really pertinent to the work of this group.

For example, right now for the newborn screening results, if you have a child who is born in North Carolina, my state, and they move to Virginia, it is practically impossible to get the data from the health care screening. Of course the reason has been the confidentiality question, and that is a tough nut to crack.

But we have got to, in my opinion, and I would ask this group to give strong consideration to this, is we want this done and the responsibility taken for it, we've got to make some recommendations that allow people, the health care professionals, to get this information about the children that they're taking care of. I don't know the legal ramifications of it, but I have to ask you, I think that's very important.

Now, the last part of your question about the international, we are working with it, but we have done a much poorer job on the international part of it than we'd like to, but we are trying. We are establishing relationships with almost every country in the world. Granted, we don't have relationships with every doctor, generally those who are pediatricians, but we have a significant number of pediatricians. We are putting some resources into that.

One of the major problems for us is that most of this is resource outgo. So where we have resource income, it is easy to deliver services, but we are living in a world that is getting smaller and smaller. I was in Japan in January talking about more cases of measles come to the United States from Japan than any other country in the world. You think of Japan as a very developed country. So we are

all truly getting interdependent, and I think we have to do a lot better job than we're doing. But let me say this, we are trying.

DR. HOWELL: Steve, one of the important agendas as we move forward is the research agenda that gives us more information about some of the conditions that we don't know a lot about, some of the rare fatty acid oxidation disorders that we don't know a lot about them, and we need to follow them up.

The primary care physician is going to be an important place where that research can take place. In other words, to be in contact. Now, having said that, that is going to be tough to do without electronic records, I think, so that you can readily transmit back and forth between a data collection center or something. What is the current state of electronic medical records in pediatrics, and where do you see that going?

DR. EDWARDS: Well, I think probably less than 10 percent of offices have electronic medical records. Sunnah, Marie, maybe you have got better information. But I can tell you that I have retired now, but the office that I practiced in is looking at getting electronic medical records in.

We weren't always the first ones to do everything. So I think that almost everybody is recognizing that at some point soon, and soon would be five years, that you're going to have to have medical records, not just for this reason, but for lots of reasons. So I think that if we set up the system, I think the electronic medical records will be there in time. But you're right, they're not there now.

DR. HOWELL: The other areas, I think, are some of the large population studies that have been discussed where you are looking at a genetic trait, or a genetic diagnosis, and looking at environmental changes. Again, those are going to have to be done, to some extent, in the primary medical home. I can't see how you can really manage those without electronic records back and forth.

DR. EDWARDS: Yes. Well, fortunately, there are other factors that are driving it. I don't think people would get electronic medical records just so that they could report genetic medical diseases.

DR. HOWELL: No, I'm quite sure.

DR. EDWARDS: But there are other forces that are driving the electronic medical records. I think if we got the transcription, the vocal determined transmission, that we would get them all in a hurry. We have been talking about that for five years now, and it is right on the horizon now.

But I think that there are so many other medical trends that are pushing towards electronic medical records, the safety as far as you know, prescriptions written electronically are a lot more accurate, they are printed out so that there is not the difficulty with the pharmacist misreading them with my terrible handwriting. I think there are a lot of forces pushing us towards the medical record.

I believe that this committee can assume that in a reasonable period of time, and I'm not talking about tomorrow, but five to ten years, that the electronic medical records will be almost universal.

DR. HOWELL: Piero?

DR. RINALDO: I'm reading here the components, and one says that the medical home is a continuum. That really brings up the issue of portability. Say a family with four children moves from North Carolina to Virginia, or for that matter, Washington state, what do they carry with them, assuming this is an average family with health insurance? Don't they bring a copy of the medical record with them?

DR. EDWARDS: Yes. Yes, but the records don't necessarily always have the newborn screening results in them. Some records are not really good. The other thing is, and one of the things that I hate,

and I don't know how Marie was in practice, but I really hated to get this thing about four inches thick. It is a medical record, it has got everything about the patient in writing that you can't read, and you don't know how it is organized. So it is really, really hard to ferret through that, especially for a patient with complex problems.

Now, I think that the printed record, and also access to the state information would be a big help, because if somebody has to thumb through 400 pages to try to find the results of the newborn screening, which may not even be there, should be there, but may not be there.

DR. RINALDO: Is it true, at least in my past practice, but really looking how things happen, the lack of information about the results of numerous screening implies a negative result?

DR. EDWARDS: Yes. But just look at the court records if you want to see that that is not true. In North Carolina, our incidence of PKU is 1 in 25,000. So we have like 100,000 deliveries a year, and four cases, and we have lost some of those four kids. So can you imagine what is going to happen when we've got, and I think it was said this morning, Brad Therrell I think said 1 in 250 kids is going to have something that is diagnosable.

That is my plea, that we work from the start to set up systems of communication where doctors need to be held responsible, I totally agree with that. But we also need as a group to make it as easy as possible for the information to be coordinated, for the care to be coordinated, and so I think that is our challenge. We have to recommend the system that has a strong likelihood that it is going to work.

DR. HOWELL: And you sound like you are beginning increasingly to testify about the advantages of the electronic medical record, which would be very helpful. This is aside, but several years ago when the NIH sponsored a consensus conference on phenylketonuria, one of the things that came to me as a tremendous surprise, there were a number of young adults who were identified at that meeting who had only recently discovered that they had PKU.

They had been diagnosed as infants and treated, and it was fashionable to discontinue the diet. So they knew they had some problem and they had a special diet, but they were young adolescents, and sometimes there were college students who had just found out they had PKU, which I still find remarkable. But they were there in life, speaking, so they were really true.

Any further comments to Steve?

(No response.)

DR. HOWELL: Thank you very much, Steve, for that very helpful discussion.

Dr. Collins was not able to be here today, but Dr. van Dyck is, I'm told, going to make some comments about the Secretary's Advisory Committee on Infant Mortality, with which he has direct oversight.

DR. VAN DYCK: Jimmy Collins wishes he were here. He's sorry he can't be here. He has become the Chair of the Secretary's Advisory Committee on Infant Mortality over the last year, and has been a member for a number of years.

The Secretary's Advisory Committee on Infant Mortality was formed about ten years ago in a committee like this to advise the Secretary of Health and Human Services, Secretary Tommy Thompson now, on the issues around infant mortality. The committee has 20 members that are a broad representation of academic, insurance, private, public sector, academics positions, nurses, and social workers who have an interest and expertise in infant mortality.

The purpose of the committee is to advise the Secretary basically on two issues. Those are issues that surround infant mortality, and how the Department can better decrease infant mortality in the United States. The second is to advise the Secretary and the Department on the Healthy Start Program.

The Healthy Start Program is a specific federally funded program with grants to about 100 communities around the United States who have the highest rates of infant mortality, particularly minority infant mortalities. So there is a project in the Bronx, there is a project in Harlem, there is a project in Cleveland, there is a project in Detroit, and there are also projects in other smaller communities, and in several rural areas, as well as some Native American populations.

The program's goal is specifically to reduce infant mortalities within prescribed geographic areas of high rates. So the purpose of the Secretary's Advisory Committee on Infant Mortality is to advise the Secretary on those two issues.

The committee has issued three reports in the last two years. One was a report on low birthweight, and it was an analysis of why low birthweight is increasing across the United States, and a recommendation to the Secretary on what might be done within the Department to begin to reverse that trend.

The committee was very concerned that there be an integrated, coordinated approach across all agencies within the Department on research related to low birthweight. And so the committee recommended to the Secretary in this report that he form an interagency coordinating council in the Department on low birthweight.

That committee was formed about nine months ago. Duane Alexander, who will be here tomorrow, who is the Director of NICHD, and myself, as Director of MCH, chair that committee. We will be issuing a report probably within the next two to three months on all research in the Department related to low birthweight, where every agency is thinking about going over the next five years in research, and how those efforts might be coordinated better. And then I guess the plus at the end of the road is how we can better translate those findings we do know are related to low birthweight, research related to low birthweight, into practice more readily by better coordination between agencies that do research, like NIH, and agencies that do service delivery, like HRSA.

A second report was on Healthy Start, and I'm not going to go into that. But it was ways to improve coordination and collaboration, and evaluation of the Healthy Start sites. The committee has been very involved in designing, or helping to design, advising on the design of an evaluation to determine whether these sets of Healthy Start grants have been successful.

The last was a report on early discharge. As you remember, several years ago, there was an intense congressional interest, as well as consumer interest, in early discharge. Discharge of mothers earlier and earlier and earlier down to less than 12 hours, actually. A committee was assigned by congressional legislation with coming up with a report on whether early discharge was helpful, harmful, or neutral, and what recommendations might be. I might add that newborn screening is an important component of early discharge, because the earlier the discharge, perhaps the less adequate the first tests may be. States are largely doing just one test.

So that was a report issued, and since the issuance of that report, actually the issue has quieted down a bit over the last three or four years. So those reports were the result of about three or four years of work by the committee. The committee is turning over now, a lot of the members are turning over. So in the last couple of meetings, and the next meeting, which is next month, we'll be looking at investigating or deciding on, or setting priorities for new issues. Kind of the same process this committee is in, and will be in, I think, for a couple of meetings.

So the issues that are on the table now, and what the committee does is raise issues, and then at the next meeting, have two or three experts come and discuss those specific issues, and then the committee deliberates and decides whether that fits into their priorities, how they want to address it, and how they want to deal with it. And the incidence of increasing low birthweight, carrying on while the first low birthweight report had a research focus, this would be more of a service focus, or antecedence, or causal components.

There was a jump in the infant mortality rate this last year preliminary from 6.8 to 7, the first jump since 1958. Whether that is going to hold or not, or whether it is going to start back down or not, is of great interest to this committee. So as you might imagine, that is of tremendous interest to the committee.

We have had discussions around increasing obesity, particularly increasing obesity in pregnancy, which does increase low birthweight, and infant mortality. Prenatal care, international comparisons of infant mortality, long-term morbidity resulting from low birthweight and different degrees of low birthweight, and investigating increased fertility and fertility assisted pregnancies as a cause of increasing low birthweight.

The effect of decreasing state budgets, and its effect on infant mortality and service delivery, related to both infant mortality and low birthweight. The standardization of data collection across states related to low birthweight, related to minority status on birth certificates, related to matching birth/death certificates, and the timing of birth/death matching.

New birth certificates are being introduced over the next year or so, and so states are gearing up for the introduction of new birth certificates. The electronic conversion in many states from hand-filled birth certificates to computer-filled birth certificates. So this all is related into a data package.

What did I write there? Something first year of life. I can't read that word. Now, see if I had had an electronic record, if I had done that on computer, I'd know.

(Laughter.)

DR. VAN DYCK: Oh, injuries. Injuries in the first year of life, and contribution of injuries to infant mortality and morbidity, sudden infant death syndrome, Back to Sleep campaign, the tremendous decrease in infant mortality due to Back to Sleep campaign, the reduction in SIDS that has occurred because of the Back to Sleep, but there is a long way to go in daycare centers, and in minority populations.

Last but not least, the contribution of newborn screening to infant mortality and morbidity in infant mortality in the first year of life. So that last is a set of current issues that the committee is looking at this last couple of meetings, and will continue this meeting, and probably the next in its process of determining the priorities to really hone in on over the next couple of years, and again, issue reports that go to the Secretary specifically.

So there is a natural, I think, relationship that can be formed between the Secretary's Advisory on Infant Mortality. I think there is some potential for synergism in the recommendations that come from a committee like this, and the committee that Reed is probably going to present on next, and this committee. Similar recommendations are recommendations that have interest to each committee, all going to the Secretary in a coordinated way, or at least independently, but recognizing each committee has some of the same interests, and perhaps some of the same solutions really carries extra weight. So I think it is important for these liaisons to exist, and for them to be active and good.

DR. HOWELL: Thank you very much, Peter.

Are there questions of Dr. van Dyck?

(No response.)

DR. HOWELL: In view of the tremendous interest in the Barker hypothesis, particularly with the dramatic increase instance in such things as diabetes and hypertension in infants who were born small, how long are the babies going to be followed in this study? The babies who were born small, how long are they going to be followed?

DR. VAN DYCK: Well, if we're talking about a study, the only one I mentioned was the Healthy Start Program, which is a grant program, and those babies are followed for two years.

DR. HOWELL: For two years?

DR. VAN DYCK: Yes.

DR. HOWELL: Okay. Maybe that will come out of the National Children's Study and so forth.

Any further questions of Peter?

(No response.)

DR. HOWELL: Excellent. Then maybe we can lead to — you had a question?

DR. RINALDO: One. The natural history of some metabolic disorders clearly show a tendency to sudden unexpected death after the first year of life. And so I'm wondering if, especially if you're looking at the impact that the newborn screening might have on infant mortality, if there is any specific intention to monitor a reduction of mortality after the first year of life?

DR. VAN DYCK: I don't think there is an intent by this committee to look at that, but that is certainly something that is monitored. Sudden death after the first year of life? Or just death after the first year of life?

DR. RINALDO: Sudden, unexpected death. This is one of the sore points in the epidemiology of sudden death. While there is enormous attention given to death in the first year of life, there seems to be like a vacuum after. This is something that is being painfully addressed by a number of particular support groups. But there are states where if your child dies at 11 months and 29 days, we receive all sorts of evaluation, and also psychological and social support.

If a baby died a week later after the first birthday, they are left alone. If you look at the statistics, there are actually quite large numbers of death after the first year of life that nobody seems to care. You really look at the emphasis and the research funding for SIDS, but when you really start looking at what has been done after the first year of life, this is directly relevant to what we do.

The chances are, our chances of reducing the infant mortality by greater application of newborn screening is probably not in the first year of life, it is later. These are the three, four, five-year-olds that die suddenly and unexpectedly and may have as a cause of death, pneumonia. These are the teenagers who decide to lose weight without medical supervision. That is really where you find a lot of cases, especially with MCAD.

So I just hope that somebody will keep in mind that really the greatest opportunity is not in the first year of life, especially when you are specifically monitoring the newborn screening, is well after.

DR. VAN DYCK: I think that is a wonderful suggestion to remain on the table for a future agenda topic for the committee, to bring somebody in to analyze just how many of those cases there are, and look at it more carefully.

DR. HOWELL: Any more comments at this point?

(No response.)

DR. HOWELL: Thank you very much, Peter.

We will now go to Dr. Tuckson, who is going to report on the Secretary's Advisory Committee on Genetics, Health, and Society.

DR. TUCKSON: I'm going to try to do this sitting down from here. As you can tell, I'm struggling with a case of the crud, which is a technical, medical term.

(Laughter.)

DR. TUCKSON: First, I think that Peter really set it up very well for what I'm talking about.

I'm pleased to be the liaison from the Secretary's Advisory Committee on Genetics, Health, and Society. This clearly has a direct relationship to what we're doing here, and so I'm going to zip through. By the way, there are some handouts of these slides at your places, I think, and I'm going to go fairly rapidly through some of this.

The committee's mandate was, first of all, we were empowered by the Secretary in September of 2002 to explore, analyze, and deliberate on the broad range of human health and societal issues raised by the development and use, but also very much guided by the concern of misuse, or the potential therein of genetic technologies, and then make recommendations to the Secretary and other entities as appropriate.

The scope of the committee deals with seven key things. Number one, assess the integration, and I have been sort of pushing on that a little bit here at this meeting, genetic technologies into health care, and relevantly to this committee, public health practice. To study the clinical, ethical, legal, and societal implications of these new applications, and emerging technology approaches to clinical testing.

Number three, to identify opportunities and gaps in research, and gaps in the data collection activities and efforts as well, very pertinent to what we've been talking about today. Number four, exploring the use of genetics and bioterrorism. Number five, examining the impact of patent policy and licensing practices on access to genetic technologies. Clearly a key and important issue, as we see the emergence of the private sector in so much of this work.

Number six, analyzing the uses of genetic information and education, employment, and insurance, including health, disability, long-term care, life law, family immigration, and forensics. Here again, very much concerned with that agenda I mentioned earlier around concerns around misuse of information as much as the appropriate use. And finally, serving as a public forum for the discussion of emerging scientific, ethical, legal, and social issues raised by these genetic technologies.

Just like here, again, the public comment sections are particularly important in receiving the guidance from professional societies, advocacy organizations, and the like, as a way of surfacing key issues and bringing them in front of the public for a reasoned public discourse.

Given all that I've talked about, the committee of course has to have quite a wide variety of expertise. This is just a summation of some of the kinds of bright people or bright talent that is available to the committee in a broad range of areas.

The committee's membership is as you see. Ed McCabe is the Chair. He has been mentioned previously in the meeting earlier. A notable stalwart in this field, as well as from the American Academy, is Dr. Edwards, as you know. Ed was also the Chairman of the previous committee to this, the Secretary's Advisory Committee on Genetic Testing, on which I also had an opportunity to participate. So there is a sequential nature to some of this work.

The committee also benefits from 19 ex officio people who serve in two capacities. First, as technical and policy experts in their areas representing their agency's domain. But also they serve as a steering committee to also help guide and shape the direction of the committee. We are very appreciative to each of these departments.

Our initial meeting was in June of 2003. In that meeting, we reviewed several things. The current status of genetic technologies and their current uses, this was an educational experience, trying to get the committee all on the same page. We looked at the emerging developments in research directions, we looked at health care financing of genetic technologies, we looked at current issues related to patent and licensing procedures, and we started to explore current understanding of the ethical, legal, and social implications of these technologies.

As a result of that meeting, we did two tangible things. Number one was to draft a letter to the Secretary supporting the legal protections of genetic discrimination in health insurance and employment. I will continue to come back to this issue in my presentation. But of all the things that the committee felt that needed to be addressed first and foremost was really getting behind support for antidiscrimination legislation. We sent a strongly-worded letter to the Secretary in support of the bill at that time.

Secondly, we asked the agencies to collect information, and also private sector activities, in addressing the education and training of the work force in genetic issues. A very key issue that we from the very first meeting became interested in, and quite frankly, concerned about.

Our second meeting then in October of 2003 dealt with this issue of oversight of genetic tests and laboratories, and the role of pharmacogenomics. This oversight issue was important as coming out of the original Secretary's Advisory Committee on Genetic Testing, where there was a great deal of interest on the role of the various federal agencies, and how well they were prepared to be able to oversee the world of genetic testing.

And without going through the painful detail here, know that this is a complex mosaic, different federal agencies supervising things from the laboratory itself, from the data collection of genetic tests,

post-genetic testing data and analytics, and FTC in terms of the oversight of direct-to-consumer advertising. There are a number of federal roles here, and we wanted to be assured that the various agencies were prepared to exercise their responsibility.

We also had a session on genetics education, training, and workforce issues. We also looked at how other industrialized countries were approaching these tasks, and we had an update on genetic discrimination legislation. As a result of that meeting, we appointed an inter-meeting task force to begin a systematic prioritization process of all of the various issues that had been brought to us, so we could start to think about how do we narrow these down for focus.

That is really a challenge that this committee will have as well. There are so many things to do, how do you begin then to make some prioritization in narrowing it down? Well, here are the list of issues presented in alphabetical order that were before us. We had to whittle these into some kind of order.

Clearly we dealt with many of them already in this meeting. Access to care, coverage and reimbursement, direct-to-consumer marketing, genetic discrimination, education and training.

This idea of genetic exceptionalism is increasingly important, and it is meant to convey the notion that as we move to knowing more and more about the molecular biological revolution, molecular biology is not something off to the side called genetics. It is, in fact, the core of much of medical and clinical practice. So we need to start to think, how long do we make genetics this thing off to the side, or when does it become so mainstream that there is really no special category to talk about it, but more to talk about it as it has become part of the very marrow of clinical and public health medicine.

We talked about the notion of large population studies. Again, oversign, patents and access, pharmacogenomics, public awareness, and then an idea of a vision statement that would sort of lay out what we thought was our rationale for deciding what is important. Out of all of that, we spent a lot of energy between meetings on the phone and came up with this priority setting process.

Basically it identified and classified high priority issues and developed a long-term work plan. Well, here is the classification that we came through with. First, high priority issues requiring in-depth study as a key first cut for us on those issues. And then we looked at the issues as high priority requiring

short-term action and monitoring, issues requiring

high-priority requiring monitoring alone, and then finally overarching issues that are so embedded in all the others as to be understood in the context of the other issues.

So this was the grid. So now, how did that laundry list and menu fall out in each of these four criteria? Essentially, they came out like this. Those requiring in-depth study were coverage and reimbursement of genetic technology and services. Secondly, large population studies. Third, pharmacogenomics, and fourth, direct-to-consumer marketing of genetic tests.

What we focused in on these four are number one and number four. Numbers two and three, we will be addressing in subsequent meetings. But where we are today is looking at number one and number four of this list. On coverage and reimbursement, we are preparing a report and recommendations on coverage and reimbursement of these technologies and services, which will be presented next week at our meeting. So that will be presented in some detail. Those are now in draft form, so you'll just have to stay tuned for that.

On the direct-to-consumer, we did prepare a resolution on direct-to-consumer marketing, and it will be presented at our June meeting. We will then defer further in-depth studies until other issues are addressed. However, we are interested in sending a recommendation to the Federal Trade Commission as they look at this issue. We actually do have something that will go to them at the conclusion of the June meeting, because we think that this issue, and it came up again earlier in our meeting today, how important it is to get at this notion of preparing the American people appropriately for the marketing of these tests.

Those items in the high priority requiring short-term action and monitoring were obviously genetic discrimination, education and work force training, and a vision statement. Under genetic discrimination, we sent a letter subsequent to the original letter to the Secretary, pressing for further action once we noticed that the Senate had passed the Genetic Testing Antidiscrimination Act, S1053, and are now urging that it be pushed through the House of Representatives.

We expect an update on that at our meeting next week. So I will, along with the rest of the committee, learn more about where this is. We think this is something that everyone should pay attention to.

In terms of genetic education and training of the work force, we are preparing a resolution on this issue, and again, we will have a roundtable on this at our June meeting. So our meeting next week will be significantly devoted to this topic.

Vision statement, we thought it would be useful to prepare a document that described the process that we did use in identifying and prioritizing these issues, and what the effect of our process was. We would be pleased, Mr. Chairman, to share that document with this committee, if you think it will be useful in our prioritizing the issues. We can at least share with you lessons learned, and lessons to avoid in such a process. It may help us all in moving forward.

For those issues requiring high priority requiring monitoring, patents and access are key. We are waiting to do a little more in this area, pending the work of the National Academy of Sciences, which has a patent and access effort undergoing right now, and we expect that work to be completed shortly, and then we will take benefit of that in our process.

Oversight, again, by the federal agencies we see as always important. And finally, on the overarching issues that are pertinent to everything which we will continue to keep an eye on, would be the access issues. That's why, again, on the reimbursement issue, it is so important to us. We see that as being key to access.

Public awareness always, and then this idea of genetic exceptionalism, which I have explained.

Finally, to conclude, these are the phone numbers for those that want to get closer in touch. But we also have here staff from the committee, and again, we look forward to sharing our work with you as we go forward. I will try to do my job as a liaison between the two committees.

Thank you very much, Mr. Chairman.

DR. HOWELL: Thank you very much, Reed, for that presentation.

Are there questions for Reed about his committee and the work they're doing?

DR. TUCKSON: Just because I asked a lot of questions doesn't mean you all have to.

(Laughter.)

DR. HOWELL: Jennifer?

DR. HOWSE: Not so fast, Dr. T. I am very impressed by the rigor of the thought process of the committee, and the classification of issues into priority and monitoring. How did you all go about doing that? Did you sit around a table like this and come to this level of rigor? Or did you commission consultants to come and make a case, if you will, for this long list of considerations in this area?

It strikes me there are certain aspects, both of the way that you all went about doing this, and also a similitude between the issues that we have already brought up this morning and this afternoon that we know we're going to have to sort through. I just have that kind of curiosity.

DR. TUCKSON: It was a combination of two approaches. First, certainly obviously we did have ample time for debate in a meeting such as this, but not a lot of time. And then we did a lot of surveying, and particularly made good use of our federal liaison partners, we really pushed them very hard to give us a sense of what does the world look like from their point of view. I must commend HHS staff across the agency for really taking these kind of matters to heart and putting in an awful lot of extra effort.

But then, Jennifer, in addition to that, and that sort of polling of our experts, it was an awful lot of conference calling. Painful, agonizing, difficult, laborious, tedious conference calling, and then very good leadership on the part of our chairperson and designated committee chairs for this activity who really took a leadership role and just pushed us through.

Over a series of conference calls with sort of strong leadership, we were able to get this down. And also setting very rigid deadlines, which again, were painful to me.

DR. HOWELL: Any further comments or questions?

(No response.)

DR. HOWELL: It is my assessment that we are through for the day, unless someone else would like to bring up something, that would mean that we're finishing early today. We have had a busy day, and I think very productive with a lot of good discussion. Unless I hear otherwise, I think we should go home so that we can have some R&R and be back fresh in the morning.

Thank you very much.

(Whereupon, at 4:20 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Tuesday, June 8, 2004.)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
ADVISORY COMMITTEE ON HERITABLE DISORDERS AND GENETIC DISEASES IN NEWBORNS AND CHILDREN

Tuesday, June 8, 2004

Horizon Ballroom
Ronald Reagan Building and International Trade Center
1300 Pennsylvania Avenue, N.W.
Washington, D.C.

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C O N T E N T S

P R O C E E D I N G S (8:43 a.m.)

DR. HOWELL: Ladies and gentlemen, let me welcome everyone to the second day of our Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. I think we had a lot of wonderful comments yesterday from the folks around the table, and hopefully we can continue in that line.

We will continue today with some important federal agency and liaison briefings, and the first of those will be from Dr. Duane Alexander, who is director of the National Institute of Child Health and Human Development.

Dr. Alexander?

DR. ALEXANDER: Thank you, Rod.

Good morning, everyone. I'm very happy to be a member of this committee representing NIH. I apologize for missing your meeting yesterday. Unfortunately, yesterday was the date chosen by Dr. Zerhouni for his annual budget retreat with institute directors to talk about the preparation and plans for the fiscal 2006 budget. So that was something I had to be present for. I'm sorry I missed yesterday, but I will try to catch up and fulfill my responsibilities as a full-fledged member of this committee.

I was asked to talk about genetic testing and screening from the perspective of the NIH. Let me give just a little bit of historical background, focusing on newborn screening, which is an obvious point for NICHD to focus on. This whole area began, of course, with screening for phenylketonuria, made useful because of the development of dietary intervention and the discovery of the genetic defect. The NIH really played little or no role in the development of this screening for PKU. This was done by Bob Guthrie and implemented with early support and testing from the Maternal and Child Health Bureau with his bacterial assay and actually preceded NICHD's establishment by Congress in 1962.

We came along in time to do some of the evaluations of this particular intervention that documented its usefulness in reducing the likelihood of mental retardation occurring if the intervention was carried out properly in response to the diagnosis in the newborn period. That evaluation, in fact, showed that the affected children, appropriately screened and with early treatment initiation, had IQs really not different from those of their unaffected siblings. So with that assurance, the program went on to expansion to all 50 states and became the standard, and prevents about 250 cases of mental retardation due to PKU each year.

The second test that's used in every state, screening for congenital hypothyroidism, had a more direct NICHD association. The methodology for that screening was developed in an NICHD-supported laboratory of Dell Fisher at the University of California. His microassay for T4 and TSH, from the same newborn filter paper blood spot as used for PKU screening, made possible this particular addition to newborn screening, with similar effectiveness. This, of course, prevents about 1,000 cases of mental retardation from congenital hypothyroidism a year and is the other test that's universally done in all states.

Other presentations you've heard or will hear talk about the issues in newborn screening for other conditions and disorders that have been developed in subsequent years, the wide variability in state programs for screening and follow-up and some of the problems that are associated with that, that will be a significant part of this committee's activities.

The NIH has, of course, been engaged in other activities, particularly gene discovery, supported by our research, which is an essential aid to screening and testing. One example is cystic fibrosis, where there is a study evaluating the effectiveness of newborn screening and early treatment and intervention for this condition.

Another program at the NIH that's of interest is the ELSI program, the Ethical, Legal and Social Issues program in the National Human Genome Research Institute. By law, Congress provided a set-aside of 3 percent of the budget of the Genome Institute for these types of studies, and there are a number of studies that have been done or are ongoing that relate to genetic testing and screening, including newborns.

There's another study that's being supported by the National Institute of Diabetes, Digestive and Kidney Disease that's of some interest. While we don't have a specific gene for Type 1 diabetes, and it's not a single-gene disorder, there are things that you can screen for that indicate an increased likelihood of developing Type 1 diabetes. The State of Washington, with support from NIDDK, has a program going on at the present time using these tests to identify people at higher risk for developing Type 1 diabetes, and then following them and looking for whether the development of this condition as well as whether the fact that knowing that they're at higher likelihood for developing it makes it possible to detect or intervene at an earlier point in time.

To date, the results suggest that these people, because they are identified at high risk, are more likely to be identified as having Type 1 diabetes before they present with ketoacidosis than if they were not.

There are also a number of new ventures in this area that are under way or under consideration. One of these is the National Children's Study. I understand there was a little bit of discussion here at the committee about that yesterday. Let me say just a couple of things about this.

This is a national longitudinal birth cohort study of environmental influences on children's health and development, which is why we call it the National Children's Study for short. The Congress mandated that this study be conducted as part of the Children's Health Act of 2000. Planning for it was already underway as a consequence of an administration task force on environmental health risks and safety risks for children. The concept of this study is that we would screen approximately -- or that we would incorporate in this study about 100,000 children and their families identified before or during pregnancy and follow them until 21 years of age. We would get information on environmental exposures from the parents, DNA from both parents and the child, follow that course of the pregnancy, labor and delivery with observations of the child in the newborn period, a couple of times in the first year of life, again at age 2, and then at intervals after that time.

We are looking at environmental exposures. So we will be sampling the environment: the air, the soil, the water, the community where the child grows up, as well as specific measures of toxin levels in the parents and the child. We will be looking for gene-environment interactions, but we are also looking at the environment from a much broader perspective than just the physical and chemical environment of the child. We're also looking at the social, behavioral and cultural environment that that child grows up in: the home, the community, the schools, and other exposures that the child has, and the interactions and interplay of these environmental factors on that child's health, as well as their growth and development.

There's a major opportunity here to gain information from this kind of a study beyond what you can get from observational studies that are short-term or that have small numbers. This allows you to make cause and effect relationship establishment, beyond what you can do from just observational studies or short-time studies. It also, because of the large number of variables and large N, allows you to look at the interaction of a variety of variables with each other. So instead of looking at just one environmental exposure, or two or three, you can look at hundreds and the interactions that these have.

So this is a study that is being planned, as directed by the Congress, with leadership from NICHD and three other agencies. The National Institute of Environmental Health Sciences at NIH, the Centers for Disease Control is highly active, and Environmental Protection Agency formed the Interagency Coordinating Committee that is leading the planning for this study.

But that's far from the whole story. In addition to those, there are about 40 departments and agencies of the government that are involved with this, because many other agencies have an interest in this kind of a study, and we have had 22 different working groups involving several hundred scientists from outside the federal government, and a couple of hundred from inside, all giving us advice on several different aspects of this study, how it should be organized, what the sampling methodology should be, what questions should be asked, what hypotheses should be tested, what data should be collected, when they should be collected, and how, and so forth.

We have made remarkable progress in putting this study together over the course of the four years of the planning. We have a small staff in place. We have gotten loaned staff from other agencies. We have funded a number of pilot studies and analyses looking at the best way to organize the sampling methodology for the study, the hypotheses that should be tested, and the testing that ought to be done.

We are starting to write the protocol based on the input that we have received from these 22 working groups and an advisory board that's chartered, just like this committee is, to provide advice on the conduct and organization of this study. We have spent about $20 million so far in the planning for this. We're spending another $12 million this year. There's $12 million requested in the budget before Congress at the present time.

The plans are, if we were able to achieve the necessary funding, to actually be in the field. We're starting a piloting of the protocol in 2005, and with recruitment of the actual subjects for the study by the end of 2006. But we don't have the funding for this. This is not a cheap undertaking when you have a sample size this large and you need to recruit that sample as quickly as we hope to do, which is a time period of about four years, and follow them as intensively with the kinds of measures that we need to do if you're going to get maximum benefit from a study like this.

The total cost of this study over 25 years is about $2.5 billion, around $100 million a year on average. But the hooker is that your biggest costs are in the recruiting times, which are the first four years of this study. The cost at that time starts at around $140 million for the first year and peaks at around $220 million in the third year, and then drops back to a maintenance cost of about $95 million a year for this study.

We believe that the gains from this study are well worth the cost. If you look at just a few of the outcomes that are being evaluated in this study, a decline of 5 percent in the incidence of conditions such as asthma or obesity or diabetes or several of the other conditions that we're looking at, learning disabilities, by applying information gained from this study would pay for this study several times over in one year's cost savings for the whole cost of the study over 25 years.

So we are hopefully going to get the funding for this study. There has probably never been a worse time to be looking for dollars of this magnitude from the federal government, as people who are advocating for this funding have found, but we are still pushing because of the enormous benefits that could be gained from this study, some of which are clearly of interest and benefit for the work of this committee.

There's a second activity that relates to newborn screening, and the prototype for this is a grant that we've just funded from the University of North Carolina, with Don Bailey as the principal investigator, on newborn screening for Fragile X syndrome. This is a study that will screen about 1 million newborns for Fragile X syndrome in selected states, designed to answer eight research questions.

First, what's the incidence rate of Fragile X in the United States? Does this rate vary as a function of ethnicity?

Second, how acceptable to the public is screening for Fragile X syndrome? What proportion of parents will voluntarily participate in screening? What characteristics differentiate patients who choose not to participate?

Third, what is the relative effectiveness and acceptability of different models of informing families about Fragile X status, and supporting them in gaining information about the disorder and their reproductive risk?

Fourth, does the bonding and attachment relationship between parents of children with Fragile X syndrome differ from that of parents of normally developing children or children with non-heritable disorders?

Fifth, how does knowledge of reproductive risk affect subsequent reproductive decisions of parents of children with Fragile X?

Sixth, what patterns of development characterize infants and toddlers with Fragile X syndrome? How do these patterns vary as a function of factors such as Fragile X mental retardation protein, physiologic variables, SES, gender, and autism?

Seven, what is the efficacy of contrasting models of early intervention for children with Fragile X and their families? Does treatment efficacy vary in accordance with severity and nature of disability?

Eight, what patterns of coping and adaptation characterize families of children with Fragile X syndrome during the early years? How do these patterns vary as a function of child, parent, family, and ecological variables?

I emphasize this a little more than I might otherwise because of its relevance to the work of this committee. This is a pilot study. This is a planning grant, an R21 grant, that has funding for three years to actually do the planning that's necessary to put a study like this in the field. It has great relevance to the next activity that I want to describe, which is an initiative on newborn screening applying new genetic techniques that would markedly enhance our ability to do newborn screening. It addresses many of the questions that we must address seriously as we pursue this initiative.

So we've just funded this grant. The work is under way, and we'll be working closely with Dr. Bailey and his team as they pursue this very important and significant study.

There's another thing about this that's of particular relevance to this initiative that I'm about to describe to you, and that is that this is a disorder that we don't have a clearly effective treatment for, like we have for PKU or congenital hypothyroidism. There are interventions that we believe will be helpful for these children, but they're interventions that we think are helpful for many children with developmental disorders and developmental delays. The question is whether these interventions will be successful for these children, what kind of a difference will they make, and how can we measure them.

But we don't have a therapeutic intervention directed specifically to the Fragile mental retardation protein that that's an effective treatment, like we have for the others. So this is a change in paradigm, a change in the dogma that says you only screen for things you can treat effectively. That's important because of the initiative that we are talking about with the CDC and with the Maternal and Child Health Bureau, with NICHD leadership, a program of expanded newborn screening.

What we would hope to do is apply some of the technologies that have come from the human genome initiative, particularly the microchip arrays that we can utilize to screen for many conditions at once. These microarrays are chips about the size of a microscope slide that can put almost the entire

genome on them at once. So you can put thousands, literally, of genes on these genes and look at many abnormalities or many genes at once from these chips.

What we would hope to do would be to develop a chip with selective genes on it, and their variants as necessary, to identify several hundred disorders. Anything that we have a gene for we can include and screen for. So there are several hundred mental retardation-associated syndromes or neurodevelopmental disorders that are potentially screenable for, the congenital immunodeficiency disorders, hemoglobinopathies, coagulopathies, the muscular dystrophies, cystic fibrosis, and possibly some of the deafness syndromes, essentially anything we have the gene for and it seems appropriate to include.

To do this, though, clearly most of these are going to be things we don't have effective treatments for. So we need to address changing the old standard dogma that you don't screen for anything you can't treat for. Part of that involves broadening the definition of what constitutes a treatment. Clearly, there are potential benefits other than just a specific intervention to cure or prevent a condition. Those benefits include the possibility of early interventions for a child with any kind of a developmental disorder such as is being tested in the Fragile X study that I just described. Also, the benefit of not having to shop for months or even years for a diagnosis once symptoms become apparent, as well as the potential benefit of having interventions available to test.

There also is the benefit for family planning. Too often, families have had another child, sometimes an affected child, before they had a diagnosis on the first child. So there is that benefit to be gained as well.

Equally important is the fact that early identification like this enables presymptomatic treatment interventions. For many of these conditions, the degeneration has progressed so far by the time the diagnosis is made that a preventive intervention is not even possible. We need, if we're going to have preventive interventions for many of these disorders, to be able to intervene as early as possible. We also need to have a population of patients for whom the intervention can be tested, because many of these conditions are so rare.

So a part of this screening program hopefully will be the establishment of a registry with all privacy protections included, and parents' approval, to include these children by disease on a registry so that with the parents' approval they could be contacted by investigators proposing to test interventions, and they could consider whether to involve their child in a particular clinical trial of a proposed intervention.

Stimulation to develop proposed interventions for these disorders at an early stage is essential, and we are presently preparing a program announcement from NICHD to go out to the scientific community, encouraging them to develop and test animal models to the extent possible, but prepare for human testing on a population of presymptomatic children that would be identified by such a program of these kinds of interventions.

So these are the kinds of things that we're talking about, and there are many components of such an initiative. Developing the technology, the chip, the microarray, and ancillary technologies that also may be extremely useful in this, is one part of it, as well as developing the laboratory mechanisms, the computerization, the robotics and so forth that are involved in this. We would be using presumably cord blood on this rather than heel stick blood so that we hopefully would miss absolutely no one.

We will need to pilot this in states. We will need some ancillary but essential components. We need to be able to have centers where we can refer patients who screen positive for a confirmatory diagnosis, for counseling, for initiation of treatment, for follow-up to the extent necessary. We need to prepare the physician community, the pediatric community in particular, and the Ob/Gyn community, and the family physician community as well for these types of interventions, particularly in the pilot states where we hope to test this.

We also need to prepare the parents. They need to know about this. We will need to have their consent because this will be introduced in a research context, and we need to be able to get that consent, including the ability to opt out if they don't want to know information about a condition for which there really is no effective treatment. I think we'll be looking at this from an ethical standpoint, but my guess is the conclusion is going to be that we will need to allow them to opt out if they don't want to receive that information.

We'll need to develop new interventional studies, thus the program announcement that I mentioned, and the registry if parents are willing to participate in it with families willing to be contacted by investigators proposing interventions. We are still in the early developmental phases of this. We have the good fortune of having Dr. Howell working with this to advise us on this, and we also I think have the good fortune of having this committee. Clearly, we need an advisory group at many levels to help us as we proceed with this, and this committee couldn't have come along at a better time, as I see it, not just for the full-fledged committee, but for the capability of appointing subcommittees or other working groups of this committee as well that we would hope would be able to advise and assist us as we proceed to develop this initiative.

So that's where we are from the NIH standpoint, and the NICHD in particular, and I hope that we'll be able to have lots of interaction with you as we proceed along these lines. Thank you very much.

DR. HOWELL: Thank you very much, Dr. Alexander.

I wonder if there are questions of Dr. Alexander before we move on to our next presentation.

Oh. I'm sorry, Peter.

DR. COGGINS: If I can just borrow the microphone, you mentioned a screening program for Type 1 diabetes, and you plan, if I understand correctly, a number of different gene markers to identify those individuals at risk. But having identified individuals at risk, what is the follow-up or the monitoring of those babies?

DR. ALEXANDER: Peter, I'm sorry. I can't give you the specifics on that. That's an NIDDK study, and I actually just heard about it yesterday. So I can't give you the specifics, but I can get those for you. I'm sorry.

DR. HOWELL: There may well be someone in the audience that knows that, and it seems that Bob from the CDC back there has his hand up.

DR. VOGT: The TEDDY study is perhaps the one that you all are referring to. There are a number of studies that use newborn screening to find recruits for natural history and intervention in Type 1 diabetes. The most recent that I'm aware of is the TEDDY, Triggers and Environmental Determinants of Diabetes in the Young, a multi-center study, three centers in the U.S., three centers in Europe.

The initial screening criteria are inclusive, higher risk haplotypes. The follow-up is to occur within three months to allow a sampling of the higher-risk infants early on to look for the influence of environmental samples. The surveillance is to look for the appearance of auto-antibodies. It's a very good time to bring this up because in this month's issue of Diabetes Care, there is an article by the group from Denver led by Marian Rewers, who has operated one of these, the DAISY study, for many years. In this article they show, I believe for the first time, that the screening program in DAISY resulted in a 12-fold decrease in hospitalizations in newly-diagnosed Type 1 diabetics. The rate went from 44 percent in community diagnosed Type 1 diabetes to 3.6 percent in the families that had been made aware through DAISY screening. The incidence of DKA was dramatically reduced.

They excluded from their study one two-year-old in the community group who was not in the Denver area who went into reversible DKA and died. We believe from the mortality tables that there are a handful, a dozen or so infants or very young children each year who go into irreversible DKA before they are diagnosed. So the first intervention is to inform the family of the higher risk. The surveillance is auto-antibodies, which are highly predictive. Then the goal, of course, is to find an intervention that prevents the autoimmune destruction of the islelets before the metabolic disease commences.

DR. COGGINS: Okay. Thank you.

DR. HOWELL: I think that Dr. Alexander has made one very important point relevant to this committee, and that is that the NIH is at the beginning of a program looking at newborn screening, particularly at technologies and so forth, and I think that there will be then the opportunity, if there needs to be examination or pilot studies about new technologies, and obviously microchips being one area, but proteomics expanded, mass spec and so forth, can all be on the table. But there will be the opportunity of having a mechanism to actually fund some studies and so forth, which should dramatically enhance the function of this committee, and we're delighted with Dr. Alexander's generosity in suggesting that.

Dr. Rinaldo?

DR. RINALDO: Dr. Alexander, I presume these 100,000 children will be from all over the country. Yesterday, Marie and Brad Therrell told us that if we look at just the current, perhaps advanced but current panel of disorders tested at birth without going into a futuristic mode, we are talking about a rate of detection of 1 to 150. So that means that there will be about 400 plus or minus cases in this cohort. I hope also to impress on this committee that there will be an attempt to make sure they will all receive the same screening panel, because that's very much the reason why we are here. We're dealing with the fragmentation and differences across the country.

So I presume that will happen or it has been discussed?

DR. ALEXANDER: We can't guarantee that that will happen. Basically, these people are going to be picked up and recruited where they are. Although it's not final yet, we are trying to obtain a representative sample of the U.S. population, and probably we'll have 50 to 60 sites around the country that are recruiting subjects that are identified by the National Center for Health Statistics, like they set up their health interview survey sample, to be a probability sample representative of the population. We will contract for people to recruit from these geographic areas.

So whatever the policy is for newborn screening in that area will be what that child gets screened for. It will not be uniform across the whole sample. This is an observational study, not an interventional study, and so we will take them with whatever information we get. Unfortunately, that means that some will be screened for two or three conditions and some will be screened for 50.

DR. HOWELL: Reed is in line. Do you want to follow up on that, Piero?

DR. RINALDO: No.

DR. HOWELL: Reed was next.

DR. TUCKSON: Given the amount of money for that study, this is very exciting. I mean, it's incredible. It's also interesting that it sounds like a lot of money has been spent or appropriated without giving you the final amount you need to actually do it, which is sort of an interesting budget process.

But is this the definitive government genetic population intersection study, or is there something else in addition to this that is contemplated that will give us the information we're looking for between genetic predisposition and environmental factors?

DR. ALEXANDER: Well, first let me say that no dollars have been specifically appropriated for even the planning for this. All the agencies have taken dollars from their regular appropriations and redirected them to this effort. So the $20 million so far has come from the eight budgets of those four agencies.

As far as the definitive genetic study, there is nothing in place for children, or even planned for children, that will come anywhere near this in terms of size and scope and ability to provide answers about gene-environment interactions and genetics and disease that this study will provide. Interestingly, this study has spurred international interest, and Canada is planning a similar study trying to model their protocols closely to ours. Japan, a number of European countries, Mexico, and other countries are also talking about doing a comparable kind of study, close to the same time frame, close to the same questions and analyses. So the sample could be potentially larger, and there could be some international comparisons of some of these outcomes.

There is under discussion at the present time, without any definitive resolution, about an adult component or counterpart to this coming from the National Human Genome Research Institute, taking a look at sample size perhaps on the order of 500,000, looking at genetic and environmental interactions in chronic diseases, multi-genic disorders such as hypertension, other heart disease, diabetes, obesity, and some of the other causes of death and chronic disease in adults. This would be again a sample probably like the children's study sample, recruited from 50 or 60 sites across the country, and followed for a comparable period of time, not followed quite as intensively but looked at for the development of these disorders, and then with the ability to look at genetic differences, SNPs, et cetera, in terms of their relationship to the disease that they develop.

We are discussing with them integration with the children's study to the extent possible, perhaps using the same geographic areas for sampling, perhaps using the parents of the children that we're going to be sampling anyway as part of the population that they would include, perhaps sharing some of the resources for the study like the contractors that are recruiting, like the repository for specimens and so forth.

But all that is under discussion at the present time, nothing definitive, and clearly no funding commitments for that study or the children's study.

DR. TUCKSON: That's actually the answer I was looking for. Some of us have heard rumors about this other kind of study, and it was a little confusing. I guess what would be helpful for this committee would be if you could -- again, if we could get it from the Secretary's office, or at least maybe from NIH, somewhere in the government, an idea of what you would be looking to do. I mean, these are big numbers.

DR. ALEXANDER: They sure are.

DR. TUCKSON: I mean, not only the population numbers but -- I mean, it's terrifying when you think about the kind of economics you're talking about, but also when you think about the importance of this. So I just wonder if there is an open commercial in some way that we could get some guidance as to what would be appropriate things for a committee like this, how can we be supportive in a responsible way that didn't have dueling, competing, and then ultimately unfundable initiatives at a fragile budget time. So however we could be helpful, it would be sure nice to know.

DR. ALEXANDER: Thank you. The numbers sound big, but they're not horrible. The size of the children's study in toto is about the same size of the federal investment in the genome project over 12

years, and ours would be over 25 years. So it's not quite that monstrous. It's big. This is big science. I'm not trying to belittle it at all. But when you spread that cost over that many years and compare it to other big science projects, it's not out of line.

DR. TUCKSON: That B number got me. I don't know about you, but that B thing scares me.

DR. ALEXANDER: It is scary.

DR. TUCKSON: I don't want to belabor it, but based on our chairman's -- you missed Dr. Howell's opening presentation, but it's real clear that these population-based studies -- I mean, this is really a big area going forward for all of us here. I just think that how we approach that is going to be very -- we need to be very mature, but I think very accurate, and I think we need guidance on that.

DR. HOWELL: We're going to have a comment from Coleen and then move along. We'll have a chance to come back. I think there are a number of things, but we've got some discussion time before lunch.

Coleen, do you have a final comment?

DR. BOYLE: Just quickly. I just wanted to congratulate you, Dr. Alexander, on some of your bold thinking, specifically the microchip array initiative, as well as the Fragile X study. I guess I would urge you to try to think of combining those activities somewhat. I mean, as we heard yesterday, part of the issue here in moving this field forward is a lack of science. I think some people would argue with that, but I think at least science on the population-based level. I think a combination of those two initiatives, thinking really boldly and broadly about screening a number of large populations, a million children, as is being considered for the Fragile X study, but moving beyond just Fragile X.

The idea of creating a registry I think is a fantastic idea in terms of what researchers could actually tap into, actually start to look at some of the efficacious issues of early intervention and whether it would be medical, educational or social interventions is just a really important initiative. So I congratulate you on that.

DR. ALEXANDER: Thank you.

DR. HOWELL: Dr. Alexander has already ensured that those efforts are combined already.

But let's move along. We're running a little behind. We started a little late. We'll now hear from Peter van Dyck, who is, as I think you already know, Associate Administrator of the Maternal and Child Health Bureau, and he's going to talk about the important activities of this group.

DR. VAN DYCK: Good morning. I finally have my chance to talk.

(Laughter.)

DR. VAN DYCK: I get to share with you this morning some of the programs that HRSA is funding and has funded and anticipated funding, and I'll try not to duplicate what other folks have talked about.

The mission of the Health Resources and Services Administration, or HRSA, is to work to assure quality health care to underserved families and individuals nationwide, and we have really a goal of moving towards 100 percent access to health care and zero disparities for all Americans. We have to understand that there are research institutions and surveillance, perhaps, agencies and service agencies within the Department, and HRSA is certainly one of those service agencies.

The vision is to assure the availability of quality health care to low income, uninsured, isolated, vulnerable, and special needs populations, and to meet their special, unique needs. Out of the bureaus and offices in HRSA, the Maternal and Child Health Bureau, the Bureau of Health Professions, the HIV/AIDS Bureau, the Bureau of Primary Care, and then a couple of offices, the primary genetic and newborn screening activities occur in the Maternal and Child Health Bureau and the Bureau of Health Professions.

I'm going to talk about the Bureau of Health Professions first quickly, and then talk about the programs in the Maternal and Child Health Bureau. The Bureau of Health Professions increases health care access by assuring a health professions workforce that meets the needs of the public. The BHPr projects generally do faculty development, curriculum development, continuing education, and graduate and undergraduate education. They develop the health professions workforce through research, analysis and planning, improve distribution and diversity of health professions, particularly in rural or urban underserved areas, improve the quality of health professions practice and education, and focus on key 21st Century health professions issues such as geriatrics, genetic translation, and diversity and distribution.

Clearly HRSA, in partnership with NIH and AHRQ and CDC, with states, private organizations, public organizations and universities, I think creates a facilitation of trying to increase health professions genetic knowledge, and to adapt and to adopt and to improve their ability to practice scientifically appropriate medicine now and in the future.

A few other examples of what BHPr projects do. The American Academy of Family Practice has a clinical focus in 2005 in genomics. These are funded through BHPr projects, genetics through the primary care lens at the University of Washington, Genetics in Primary Care: A Society for Teachers of Family Medicine. HRSA, AHRQ and NIH are collaborating on that. Faculty development for nurse practitioners, physicians assistants and certified nurse midwives; that's a grant with Duke. Predoctoral training in primary care, a program at Case Western. A residency training in primary care at Mayo. Genomics Education for Advanced Practice RNs at San Francisco. Genetics education program for RN faculty at the University of Cincinnati, and the genomics revolution in public health, an effort between the American Association of Public Health and HRSA.

So a lot of programs designed to improve workforce knowledge in genetics and translation.

The Maternal and Child Health Bureau now has a mission to provide national leadership to really assure the availability and use of medical homes, which we heard about yesterday from Stephen Edwards with the Academy of Pediatrics; build the knowledge and human resources in order to assure continued improvement in health safety and well-being of the MCH population, important words. The MCH populations is not just mothers and kids or pregnant mothers and kids. The MCH population really does include these days all America's mothers, infants, children, adolescents and their families. It includes individuals across the lifespan, women of reproductive age, fathers and children with special health care needs.

So the Maternal and Child Health Bureau is really positioned legislatively and with flexible legislation to address issues that occur in the entire population.

The mission of the genetics services program is to improve early identifications with or at risk for heritable disorders; the development of genetic services that are comprehensive, accessible, family centered; the understanding of the genetic contribution to health and disease upon which services are developed; and we have a set of program goals, to facilitate the development of public health and health care infrastructure to enhance and expand newborn screening programs, and to improve linkages among them and the state and community systems of care for children and youth with special health care needs.

The second, to examine emerging issues and evaluate emerging technologies in genetics, with a special emphasis on financial, ethical, legal and social implications.

Third, to improve the genetic literacy of the MCH population by enhancing its understanding of the benefits, risks, limitations, and implications of genetic testing.

Four, to provide leadership in defining the educational needs in genetics of health professionals working with the MCH population.

Five, support the hemophilia diagnostic and treatment centers, and thalassemia and sickle cell disease programs as models of comprehensive care for the delivery of genetic services, which include testing, counseling, education and coordinated systems of services.

Six, to build on the expertise gained from the genetics activities to provide national leadership on expanding and enhancing genetic services for the entire population.

A few programs, just very briefly. Public education grants with the March of Dimes, the Genetic Alliance. We have a program on developing a family history tool. We have a Bright Futures for Women project which is to improve access to care for women across the lifespan. There are training programs. GPC stands for general primary care to help train pediatricians, family practice and internists in genetic information. GENE tools is pilot testing curriculum for those family practice and pediatricians. Then newborn screening education tools is the development of materials for parents.

Capacity building, both in workforce and the development of regional collaboratives; and again, some of these, like the workforce analysis, is a combination or a group that includes BHPr, or Bureau of Health Professions, and NIH. We have some small research projects in Fragile X and in developing a nomogram for hyperbilirubinemia to better identify children or babies who may go on to develop kernicterus.

Now, newborn screening. We have some major issues in newborn screening as well, and our vision for newborn screening is a systems approach with defined public health roles at both the state and national level. A lot of these we've discussed in general terms in the last day or day and a half. Quality assurance clearly is important. We believe there needs to be a public/private partnership for assurance for the systems approach and a comprehensive, efficient care and management, and particularly equity for families, equity in access to testing, equity in access to follow-up, both financially and in service delivery.

We've funded a resource center, the National Newborn Screening and Genetics Resource Center. You have a brochure at your place this morning which discusses this center. It is in Texas. Brad Therrell is the director. You heard him on the phone yesterday and heard a little bit about the center. The website for the center is on the screen, and it serves as a focal point for national newborn screening and genetics activities and provides related resources to benefit customers or consumers, health professionals, public health community and government professionals.

Our program goals in newborn screening are to support a framework for effective partnerships between parents and professionals and among professions, agencies, and officials at all levels of government and the private sector; to promote the linkage of newborn screening programs to medical homes, family support networks -- they need to be based in the medical home -- strengthen the network of specialty/subspecialty health professions to provide an adequate system of follow-up, diagnosis, referral and management; to strengthen existing public health infrastructure and to facilitate the integration with the health care delivery system. This newborn screening system should not sit aside or be parallel.

To support state and territorial efforts to coordinate activities among different programs; to have information systems which provide tracking, assessment and evaluation across different programs; to assure information among the various groups; to assist states in their efforts to monitor and evaluate the programs; to support prescreening and screening education and training initiatives, and to support state implementation of technological innovations.

Goal 3, provide ongoing leadership and support for the development of newborn screening standards, guidelines and policies. I'm going to talk about some of these very briefly. To engage in a national process to develop nationally recognized standards and policies; support the development of model strategies and materials for implementation of effective newborn screening systems; and to support the hemophilia diagnostic and treatment centers and thalassemia and sickle cell programs as models of comprehensive care. They may be able to model these systems of testing, counseling, education in a coordinated system of care.

Just to say we do have a hemophilia program which is funded 12 to 13 hemophilia diagnostic centers across the United States. There is a special drug pricing program that's involved with that, and we have money going towards sickle cell centers as well across the United States.

Now, I want to talk about current activities for a minute, particularly in newborn screening. Again, all these current activities I think are fair game for elements that we may want to discuss at future meetings of this committee, and they're certainly elements that we need to bring to this committee periodically for advice and knowledge and sharing.

The expert panel was convened to review the available information on newborn screening based upon accumulation and analysis of best scientific evidence. This is the study you're going to hear about after I finish and sit down that you've been waiting to hear, talking about for the last day that Mike Watson is going to present for the American College of Medical Genetics. So this is an MCH-funded activity which has been in process for several years. The purpose of this expert panel that was convened was to address model policies and procedures and minimum standards for state newborn screening programs, to create a model decision matrix for changing newborn screening panels, what tests might be added or subtracted and what are the criteria, and to develop a uniform panel of conditions for screening which might be recommended universally or for the United States for potential adoption for state programs.

Then there are other programs that we have: analysis, state statutes, regulations, policies regarding consent for newborn screening, including recommendations for a state resource toolkit, and to look at state statutes, regulations and policies regarding storage and use of residual blood spots following newborn screening, including recommendations for a state resource toolkit. This is a project that's been funded at UCLA. It involves five states: New York, Utah, Louisiana, Texas, and Maryland.

They also will develop a sample newborn screening educational toolkit to analyze the content and suitability of one set of prime educational materials from 50 states, and to prepare a draft content for educational programs for parents on newborn screening. That's in process.

To develop educational materials for prenatal providers for educating parents. This is a partnership with the American Academy of Family Practice and with ACOG. Again, the target is health professionals with a primary responsibility for prenatal health care, labor and delivery, like OBs, family practice physicians, and nurse midwives. This is a grant to Louisiana State University.

Regional genetic services and newborn screening collaboratives. We have a new announcement. The grants have not been reviewed yet but are coming in as we speak for the development of regional collaboratives for newborn screening. The purpose is to enhance and support the genetics newborn screening capacity of states within defined regions, and these projects will undertake a regional approach towards addressing the maldistribution of genetic and newborn screening

resources. As it is set up, we are asking to develop seven regions across the United States which would include all states. All states are assigned to one of those regions.

Clearly, they have to be willing, the agency or center which applies, has to have a willingness to serve as a regional center. They have to be willing to promote a collaborative and regional approach towards facilitating access to the genetics expertise, services and technology needed to diagnose and manage, and they have to develop the infrastructure of public/private regional collaborative partnerships to provide genetic newborn screening and other relevant subspecialty services.

One of the difficulties, as we all know, as we continue to screen or advance our screening for a rare condition, is to have ready access to the array, small as it may be, of experts in each of those conditions. This regional approach we think is an easier way to set up equity in access where states are assigned a regional center and can develop a relationship with that regional center and can establish referral patterns and screening patterns across a regional area, and then with the seven regional centers working together to develop some national collaboration as well.

Other projects. There's a consumer-based family history tool to increase the public's awareness of genetics. This is a partnership between the Library of Congress, Genetic Alliance, and the American Society of Human Genetics. This is a project that's just been awarded. Translational genetic services and analysis of models of genetic service delivery, including economic and policy issues; discussion and dialogue and agenda setting to address the translation of genetic research into practice, and this is a cooperative agreement with Washington State.

There are two newborn screening projects, one to establish a quality assessment and evaluation scheme for newborn screening programs, which is at the National Newborn Screening and Genetic Resource Center, and also to support a newborn screening informatics practice network to develop best practices for newborn screening integration projects. Integration projects are those that -- and we funded almost half the states at some period in the last several years -- develop a unified tracking computerized information system across newborn hearing screening, newborn screening, perhaps high-risk registries for children who are in the intensive care unit, or some states are doing birth certificate high-risk screening to identify infants who may need more intensive follow-up. We feel there's a benefit to developing a common system in states to track those and develop those kinds of systems.

So there is some contact information, and I would like to say a small advance every day will eventually total much less than a big advance every day. So we need to make a big advance every day, and I think that's what we're doing, and we'd love to have the help of the committee to do that. I hope I've shared with you a few of the ideas and projects that we're working on, and we'd be happy to share further as the committee matures over the next year. Thanks.

DR. HOWELL: Thank you, Peter, very much for that presentation.

I think Jennifer is first in line here.

DR. HOWSE: Peter, thank you very much. That was a very encouraging presentation. Certainly there is a lot of very important support work that is going on in connection with driving this issue of how to improve newborn screening.

I'm just interested in your comments on how to connect some of this very important work with the products, the work products of this committee. To me, from the conversations we've had so far, the two big advances, to use your snail analogy, the two big advances that we need to consider are, first of all, finding the means to recommend a core of tests to the Secretary as the proposed federal standard for the floor, if you will, of tests that need to be available to every newborn in the country, with encouragement to states to add panels and to add tests as they can. So that's a big piece of work, and I would really urge

that we seek your guidance and your comments about how to connect up that task with the excellent groundwork that's already going on.

Then the second and related area has to do with this advice that we're to be giving about the Title 26 dollars, the purpose of Title 26 basically to be to give states increased capability to carry out these tests and all the other activities that need to go along. So I know it's not a B word, the funding, like Dr. Alexander used earlier, a B word in terms of the funding that is being sought for Title 26, but having your commentary about where the funding picture for Title 26 stands at the present time I think would help to align our thinking with what kind of advice we think we're going to be gearing up to give states. What is your vision? What is the big picture for this resource called Title 26, which is really intended we believe to connect every newborn with a basic set of tests and access to those tests and the follow-along services?

DR. VAN DYCK: A couple of good questions. First is the American College of Medical Genetics was awarded a cooperative agreement by us, or a contract -- which, Michele?

DR. LLOYD-PURYEAR: Contract.

DR. VAN DYCK: A contract, to specifically look at some of these issues, excluding Title 26, the first piece of your question, to come up with a minimum panel of tests, to come up with a recommendation for a minimum panel of tests which all states would benefit from screening for, which would form a floor from which they could add as they chose. That report is in its draft final phases, and that's what we're going to hear about in the next hour. So the formation of this committee, as Duane said, could not be more timely because it coincides with the production of this draft report, which has in it those elements which I described here, those three or four elements.

I don't want to preempt the next discussion, but it will be covered in the next discussion and will come to this committee. We certainly in the Maternal and Child Health Bureau are looking for guidance from this committee and from the report, and we hope that the committee can develop a consensus of some kind to help advise the Secretary and the Department on how we should then implement the findings of this report. So that's the first issue.

I think we've responded to the 2000 report from the Academy of Pediatrics, which we also sponsored, which is in the back of your notebook, which had a strong element of developing this core panel and how to opt in tests and what are the criteria for opting in tests, what are the criteria for doing screening in the first place. So that I think we've responded to, and you'll hear about it.

Title 26 is also in your booklet under Tab 3, maybe. It's in the front. It's not very long, and it's not very well funded. In fact, we have no money in Title 26 so far. So if you want to read Title 26, it does say that there should be the formation of a committee such as this. Even without funding, we felt it was so important to develop this committee that we're doing it out of other money, general MCH money. But there is no appropriation as such for Title 26 yet for the carrying out of those other activities which, as you suggest, are to help develop a system of newborn screening and to help states get equity and all the rest.

So I can't say this, but it's important for the committee to know that there's no funding and to make appropriate recommendations on how to improve newborn screening services across the United States. Does that help?

DR. HOWSE: Absolutely.

DR. HOWELL: Steve, you had a comment?

DR. EDWARDS: I commend you for the collaborative system that you've identified here, and I would suggest to the other committee members that they save this as a reference because I am going to be.

One of the things that I want to promote in this is a collaborative system, the involvement, the coordination, the seamlessness that you have kind of identified here. So if you want to really know what I'm going to be talking about, refer back to this because I think this has a good groundwork of exactly the kind of system that I would envision involving the medical home, close collaboration between that medical home and the specialist groups that will be delivering the services.

You don't mention strongly the families, but I think that it's implicit in all that you put in here, that we do have to be very conscious of the effect of the things that we're doing on families and try to make things as easy and informative as possible to the families. But I commend you for putting this together and I hope that we can use this as a reference for all the recommendations that we make.

DR. HOWELL: Peter, thank you very much.

I think that we're going to have an opportunity to have more discussion, but I think that we should move on.

As I look at the time for the agenda, I think that what we'll do is we'll have our next presentation, then we'll take our break, then we have a good bit of time to discuss because there's going to be a great deal of discussion about the next presentation, and it will go way beyond our break. So we probably won't have many burning questions until we return.

So at this point, I would like to introduce Dr. Michael Watson, who is executive director of the American College of Medical Genetics. There have been considerable comments about the work he's going to present over the past two days, but I think it's fair to say in the simplest summary that Mike, with a contract from Maternal and Child Health, has been overseeing one of the most careful and thorough looks at newborn screening that has been done to date that has involved a very large group of people of different expertise over the past couple of years.

Dr. Watson?

DR. WATSON: All right. Well, thank you.

Peter mentioned that this was a contract with the College, and early on a number of people commented as to whether we got a contract or whether a contract had actually been taken out on us, because this is one seriously large body of information that we had to deal with over what seemed like a long time at the start. But two years really flies when you're doing something of this magnitude.

I'm going to try to walk you through a number of aspects of our project, what I call it now rather than a contract, and that makes me feel a little better. Let me figure out the system here.

I think you all know this map quite well. It's been shown in various forms. This is the way things were in 2002 when our project began, a number of states doing four tests, a number doing five tests, a number of states doing six, additional states doing seven disorders, and as you saw yesterday, now we have states up in the mid-30s, others still down around 3. So there was a combination of public interest in why this disparity had developed. We have a very mobile population now. People move from one state to another and don't appreciate how things have changed in just their simple move, and there are other aspects of this that have actually become difficult across state borders when there's this amount of variation.

I come from Washington University in St. Louis. We saw lots of kids from Illinois. So it was always a question of which screening program was somebody participating in when we saw them. So it's a lot of those kinds of issues, I think, that's driven the interest in moving towards some uniformity.

As I said, I'm not going to be able to cover in any great detail anything that we did. I'm mostly going to have to show you sort of the endpoints, and we'll be delivering the written report over the next few weeks. I think I'll give it to you in draft form very soon because I'll finish the last section tonight when I finally get out of here. But we'll be adding on, because there's an enormous reference section for the number of conditions that we ultimately evaluated in our study.

There were seven basic goals of the project when we started, and our steering committee, our expert committee took those and turned them into a set of goals that were workable and prioritized. These turned out to be the two primary goals in the minds of the committee for the contract. The first was to develop that uniform panel of newborn screening conditions. The second is -- you can't do the first until you've done the second, actually, which is develop a decisionmaking tool to use in program expansion. What are the criteria by which we're going to evaluate all these conditions, both today to see where things sit and in the future as we begin to consider the enormous number of conditions that are in sort of the pipeline right now of eligibility for newborn screening?

They meet many of the criteria. They may not have a test today, but there's at least half a dozen for which the test is really in a translational stage right now and in clinical investigation. Treatments are in the pipeline for many of the metabolic diseases. So getting these criteria set were really the two primary goals of our contract.

But as we progressed through this, it became very clear that the likelihood was seeming high fairly early on that we would recommend a rather large number of conditions be evaluated, and I'll go into more the numbers game that goes on when one is counting conditions. But it was very clear that the potential was there, and we wanted to look very carefully at the system, because if we were to make a recommendation of a significant number of conditions and expansion of newborn screening, we wanted to be looking at the system in parallel to see that the capacity was there to deal with recommendations and that certain issues that allowed for that to be done well in the full spectrum of a newborn screening program was important.

So these were boiled down really into two secondary goals, enabling program evaluation to ensure that those expected outcomes, the reason that you put a condition into newborn screening in the first place, was this beneficial outcome that was expected; and in order to realize that, a number of standards need to be put in place. We looked at the full breadth, all the components of a newborn screening program, right from how many babies get screened in the birthing facilities, in midwifery types of delivery systems. We looked very broadly at the entire system, and I'll be able to share some of that with you, but not in much detail today because I'm mostly going to focus on the criteria and the conditions for the panel.

But we also looked carefully at whether there should be a national process for quality assurance and oversight.

So I'll try to overview the process for you first. We had a steering committee that was formed at the outset of the contract. A number of major organizations with interest and involvement in newborn screening were involved. The American Academy of Pediatrics, Steve Edwards, was on the steering committee; the March of Dimes with Jennifer Howse on the steering committee. I'm going to have to learn to manage my thumb here. The Genetic Alliance, representation from HRSA and CDC. We also formed an expert group of physicians, consumers, policy, legal, the full spectrum of interest groups in newborn screening.

But our interest was really on the scientific expertise because we were asked to do a scientific evaluation of the literature on the conditions that might be considered for newborn screening. So we actually avoided as much as possible going to an organization and saying we want you to give us somebody, because our goal was really to go for people who had the science backgrounds, and that was really our focus.

So I've alluded to the steering committee. I'm going to go through this. I think this may tell Reed Tuckson why he was asking so many questions yesterday, because I think you may see a lot of the names sitting around the table. They've been listening to me talk about this for a couple of years.

The expert group itself was chaired by Dr. Howell. A number of people representing public health laboratories, the newborn screening programs in the states, legal, as I said, a full spectrum of participants, and the list of names is in there, not to suggest that we couldn't have done this without them, but I don't want to use up too much time reading names.

So the next stage of the process was to really get some input about what were the issues that we had to be dealing with. We had invited speakers from various areas of medicine, various interest groups. We had participation from both the United States and from international groups who had dealt with a number of the issues that we're currently dealing with. The U.K., for instance, and Germany had gone through an exercise of evaluating tandem mass spectrometry and other new technologies for their applicability to newborn screening.

We had a number of opportunities to seek public comment to get as much input as we could in the process of working through this project. And then we made some very direct requests for information from organizations who we thought it important to hear from. And the dreaded literature review, which for some conditions is dreaded and for others is really fast. But we'll try to touch on some of that as we go through this.

The last stage of the process, we formed workgroups within our committee. One was a uniform panel and criteria workgroup that Dr. Rinaldo chaired. Another looked at the diagnosis and follow-up system that would be in place for newborn screening, and that was chaired by Harvey Levy. We also formed an external review group which commented on many of our early drafts of material and the process we had undertaken, and we're in the stage now of finalizing our recommendations.

How do you even start with a project like this? What is appropriate for newborn screening? The tack we took was to look very broadly and be as inclusive as we possibly could. We looked anywhere in the world that a condition was screened, automatically put it on our list, anywhere in the United States that it was already in a screening program, put it on our list. We also had individuals who contacted us directly and said you need to think about this condition, and that would put it on our list. And then at the time that we were collecting information, we left an open field for people to supply information on conditions that they thought we had not included. So we were as inclusive as possible.

You can see that we looked at endocrine disorders, infectious diseases, which I'm going to bail out on at the end because we got really insufficient input. They weren't well represented on our committee, and we chose not to make any decisions about newborn screening or recommendations about newborn screening for infectious disease.

Hemoglobinopathies, genetic conditions, inborn errors of metabolism that could be detected by tandem mass spectrometry broken out into the two groups of amino acids and acylcarnitine disorders, and then additional inborn errors that may or may not be detectable by tandem mass spectrometry, including galactosemia by transferase deficiency, a number of lysosomal storage diseases, and other conditions as well.

That brought us up to a total of 83 conditions that we evaluated in the project, plus whatever add-ins people might have thought we needed to hear about that were not in our original list.

The first stage of our process was really to develop our committee's sense of newborn screening, what we thought were really the overarching principles, those things that would help us decide where to draw lines in data and in literature information around priorities that our committee developed. So I'll walk you through these fairly quickly, because time is flying. These go through actually some order. They start from the broadest perspectives, and they narrow as they go.

So that is the general framework that we're talking about. The committee thought that universal newborn screening was an essential public health responsibility, critical to improve the health outcome of affected children. For us, that was primarily an access issue. As a mandated public health program, that was the only mechanism available currently to ensure that every baby in the United States was able to access newborn screening. So we thought that very important.

Newborn screening policy development should be primarily driven by what is in the best interest of the affected newborn, with consideration of the interest of unaffected newborns, families, health professionals, and the public. This evolved over time, and we've moved towards increasing emphasis on the benefit to the infant in our analyses, though we acknowledge throughout that there are other important interests that have to be taken into consideration when evaluating these conditions for newborn screening.

Newborn screening is more than just a test. It's a coordinated, comprehensive system which Marie and Brad overviewed for you very nicely yesterday. It's a coordinated, comprehensive system. It includes education, screening, follow-up, diagnosis, management, and program evaluation. All of those things have to be put into place for newborn screening to work effectively.

The medical home and the public and private components of the screening program should be in close communication to ensure confirmation and the appropriate follow-up care for the individuals who are identified. This is actually a variation on a theme that I think you've seen several times. I think Peter touched on it. But it's really a tripartite structure. There is a newborn screening program that is often at the state or territorial level. But there are also the specialists and the primary care providers, and it's getting this triangle linked together so that these various providers are hooked into the state program and into the goals of those programs in order to make the newborn screening programs as effective as possible.

Number five, the recommendation of conditions appropriate for newborn screening should be based on an evaluation of the scientific evidence and expert opinion, both now and in the future. I think you'll be coming back to this. As I said, there's an enormous pipeline of stuff coming through that will, to varying degrees, meet many of our criteria. Many of these are rare diseases occurring in one in 50,000, one in 100,000 in the population. There's a very limited number of patients in the country with the conditions. So finding these mechanisms by which we will not be replicating in every state and territory the scientific analysis, which is fairly straightforward -- I mean, the literature is what the literature is, and the limited number of experts and their opinions are what they are. So I think finding ways of dealing with really the scientific analysis is going to be important.

The states and territories and others delivering newborn screening programs will have other issues to deal with about where they draw lines based on resources available and other issues of not just financial resources but experts that can deal with diseases and other aspects of their systems.

Number six is that to be included in a newborn screening program, a condition should meet the following criteria. This is fairly classical stuff. Identifiable at a phase at which it would not ordinarily be recognized clinically; there's an available test with appropriate sensitivity and specificity; and that there are demonstrated benefits of early detection, timely intervention, and efficacious treatment.

The seventh principle was that the primary targets of newborn screening should be conditions that meet the criteria that are listed in number six above. The newborn screening program should also report any other clinically significant result, and we'll come back to that, but that was actually one of the early decisions that our committee made, that if information became available in the course of screening for a specific condition that informed you about another condition that may not have been on your target list, that you should at least find ways of making that information available to providers and the system.

There should be centralized data collection for longitudinal assessment of disease-specific screening programs. I must have 50 slides going back to 1995 that have that principle in them in one way or another. It was one of the major recommendations of the Task Force on Genetic Testing that I was involved with in the mid-1990s. The Secretary's Advisory Committee on Genetic Testing has booted this one around a long time. But we're in the days of big science, and in order to accomplish big science, it's going to take the kinds of investments that Dr. Alexander talked about to allow us to collect this kind of data and information. If it's to be at the population level, there is really only one mechanism into studies of that sort.

We're going backwards again.

Total quality management should be applied to newborn screening programs. Newborn screening specimens are valuable health resources. There's an enormous array of ways states deal with these. Some dispose of them three to four weeks after testing. Others keep them for six months or so. Others have kept them as a newborn screening resource, really for the long term, to use for future validation of tests and other applications, development of new tests as well, and we consider those to be very valuable health resources and that every program should have a policy to ensure their confidential storage and their appropriate use.

Then public awareness coupled with professional and public education and training are significant program responsibilities that have to be part of the newborn screening system.

Now we'll take a walk through the criteria. That was really the first stage, as I said, in moving towards an analysis of all conditions. It was establishing the criteria that we thought important in evaluating those conditions. This I think is probably the most difficult part of our task, was rather than doing what has historically been done, which is evaluate a condition to see if it meets criteria, rather to do it in a way that allows you to evaluate those conditions against specific criteria, and then have some way of ranking them against one another or comparing them against one another for how they might perform in a newborn screening system. That is actually quite difficult.

The interest groups and the differences of opinion amongst interest groups make that quite difficult, and I'll touch on some of those as we look at some of the criteria. But I'll take you for a walk through these now.

The first criteria, incidence of condition, a very common criteria, seen in Wilson and Jungner. The Australasians have a system for evaluating conditions, and that's obviously in it. It was also an important criteria in the U.K., in their system. Obviously, the more common the condition, the more important it is to get that into newborn screening if there are important treatments that are available.

So we looked at the incidence issue and broke it out from 1 in 5,000 being among the more common. Something like congenital hypothyroidism would be in that range, down to things that might occur 1 in 100,000, where we gave them no points, though some of those may get offset later as we talk about how technologies change your perspective of how incidence impacts on the decisionmaking.

The next criteria was that the signs and symptoms are clinically identifiable in the first 48 hours of life. If you can never tell that the baby is affected, it gets more points. It's more important to identify them as newborns if you can make a significant impact on their outcomes. If they're always found at the time of

birth, then there's no need to screen for them because they will be apparent to the physicians in the delivery service.

The next criteria was burden of disease. Having watched cystic fibrosis, for instance, evolve in newborn screening, and knowing that there are over 1,000 mutations now described in the CFTR gene itself, we wanted to really tease out this particular category, because while one might argue that it's important to screen for classical cystic fibrosis, there are other mutations in the CFTR gene that lead to sinusitis. If your ultimate decision in newborn screening is identification of the classical or severe forms of the disease that can be treated, then screening for sinusitis is not probably your goal. So we wanted to tease that issue out so that we were really going after serious, severe conditions.

The next one really is a criteria without which you can't really think about newborn screening in the first place, and that is is there a sensitive and specific screening test currently available? When we talk about is it currently available, we talk about it being available and validated in a large population setting. There's a lot of tests out there in the pipeline now of development that haven't gone through that stage of really general population validation, and I think it's similar to what Peter talked about for hyperbilirubinemia and the nomogram that HRSA is currently developing to allow for that kind of testing to take place if it's found to be still important. We'll come back to why I was so cryptic in that comment.

The test characteristics, though, were also important in our decisionmaking. The ability to do a test on a newborn screening dried blood spot obviously is a matrix that has already been integrated into the system. The whole flow back and forth of information related to blood card-based tests are all in place, and the ability to be able to add to what is already done on that particular sample type was considered an important criteria.

Is it high-throughput, the test itself? Meaning can you test large numbers of people at relatively low cost? Are multiple analytes that are relevant to one condition detected in the same rung? There's lots of history in newborn screening programs of that kind of thing occurring. Some of the tests for PKU, for instance, can inform about galactosemia. Others can't. There's a lot of flexibility and difference in the states as to which test they might choose for a particular condition, but many of the tests have the capability of detecting something that informs you about another condition that may not have been your primary target.

Are other conditions identified by the same analytes? You'll see some of this come up when we talk about MCAD, for instance, where an elevation of the C8 acylcarnitine is probably the single most characteristic lab finding, but it's also informative of a number of other conditions. I'll give you a lot more information about how we dealt with that sort of a situation.

Somebody should just wave at me if I'm going through slides while I'm up here waving my hands around. Go back another one? One more. This is what happens when you've said something so many times that you can just pick up on virtually any slide and go on.

Multiple conditions or the multiplex platform. We gave, obviously, a lot of weight to multiplex capabilities of testing, considering that really two things have driven -- really only two things have driven the evolution of newborn screening since the 1960s. One has been the consumers and the families with babies that have these conditions who have pushed legislatively for screening to occur. The other is technology development, and there's been significant evolution of technology over the course of the evolution of newborn screening programs.

Multiplex platforms are something, because of their capacity to test multiple things at one time on a single platform, have public health value in that sense. We considered that to be something of importance in newborn screening.

The availability of a treatment really a critical criteria, and this is the treatment for the affected newborn in this particular context. We broke that out as to whether or not treatment exists and is it widely available in most communities, treatment exists but is of limited availability, and this may be because the disease is very rare and there's limited expertise, it could be because the intervention is highly complex and therefore there may be limited expertise, or it could be something like what Dr. Rinaldo spoke of yesterday, biotinidase deficiency, or Dr. Howell, I forget who talked about it, but the treatment for it is quite straightforward. It's a vitamin. This is something that can be distributed out to the primary care level and to families to assume much more responsibility for the treatment phase.

Cost of treatment. Somebody talked about our cost-effectiveness study yesterday. I don't plan to talk about it much today, but we do consider it important. We were asked to look at the science, so that's what we focused on. We can't ignore costs, and I think it was about between 5 and 10 percent of all the points that are in our system are cost related, though you could find many others distributed throughout here that do have cost implications, I think.

Is the cost of treatment inexpensive or expensive? What is the potential efficacy of existing treatments? Can you prevent all negative consequences? Some of the treatments may target a specifically severe component of a disease but leave you with other components of the disease still expressed. Some treatments may deal very directly with the full spectrum of issues in a particular condition, as in PKU with the diet.

Benefits of early intervention to the individual. Is there clear scientific evidence that early intervention resulting from screening optimizes outcome? That got the most points, obviously, all the way down to that there's no evidence that intervention results in any change in outcome.

Benefits of early intervention to family and society. I think a number of people have commented that there are obviously benefits from newborn screening to others than just the infant, and that these may accrue to the family, most frequently probably to the family.

Am I going backwards? I should yell "next slide" or something.

I won't touch on these. I think we've already heard a fair bit about the types of things that might be considered here from Fragile X screening, where families had very much completed their childbearing by the time they have established the diagnosis of a condition like Fragile X, and have considered that reproductive decisionmaking might be an important aspect of newborn screening information. Obviously, people who have children with untreatable conditions in the classic term, very severe untreatable, may have information of value to the family that can accrue from newborn screening. Then does early diagnosis and treatment prevent mortality? Obviously, we favor survival.

Diagnostic confirmation part of the criteria. Providers of diagnostic confirmation are widely available. This is very much like the availability of treatment. This now looks at whether the providers and the simplicity of the treatment are going to be well distributed across the country or restricted to academic medical centers in large cities. Acute management of the condition. Are the providers widely available? A very similar kind of concept. And then the simplicity of the therapy. Is it something that can be managed at the primary care or family level? Or is it something that requires the routine, regular involvement of a specialist? We allotted points based on those sorts of criteria.

Do you have questions about those before I proceed on to what we learned from doing all of this?

(No response.)

DR. WATSON: Okay. Well, as I said, we took a number of tacks at developing the information by which we evaluated these criteria. The literature was a prominent source of information. Any time we had information that was scientifically strong in the literature, that's what we used to inform us about a

particular criteria for that particular condition. However, as I said, there also was interest in developing sort of the perspectives of different communities, and it's very interesting as we look at these -- and I'll show you some in a minute. For instance, in PKU, the physicians commonly said that this treatment is easy, it's a change in diet. The families said, well, that's not as easy as they think it is. They're dealing with this on a day to day basis at home, trying to maintain someone on a not very tasty and a difficult diet. The families had a different perspective on this criteria than the providers.

That's one of the things that makes the comparative part of this very hard, is those different perspectives that might be in place out there among consumers versus physicians and versus legislators. So we developed all of those criteria into a survey that went out very widely through a number of newborn screening listservs. You saw the prior list of people we directed it to. Then for all of these 83 conditions, we really went out and directly started targeting the acknowledged experts for those conditions to collect information.

In the end, we had nearly 300 people responding, and those 300 people provided individual scores of -- well, a total of almost 4,000 scores for individual conditions, meaning they looked at most or all, informed us on most or all criteria for a particular condition.

A wide array of respondents, people involved in testing, the follow-up system, administrative and newborn screening programs, policy development, primary care providers, consumers, specialty care providers, all provided us information for our surveys.

At least with regard to the survey component of this, it was considered important, since this was a rather novel approach to collecting information, it was important that we at least acknowledge that it was well balanced geographically, and it was, that it was balanced around how the population is distributed around the country, and the data was. Was it balanced among constituencies? As I said, we had a large array of people with different backgrounds providing us information, and in all areas except infectious disease, we felt like we had had adequate input into our decisionmaking. So I won't talk about infectious diseases much more. You may see them in future tables, but at the end of the day we're not making specific recommendations on them.

We wanted to make sure we had at least three acknowledged experts on each condition, because sometimes we had rapidly developing information. For instance, I think Coleen Boyle talked about a CF newborn screening meeting that occurred just back in November. Obviously, we can't go back and resurvey everybody, but we went back specifically to our experts, many of whom were involved in that meeting, to get additional input where we knew things were breaking around conditions over the course of our contract.

So this is just an overview of the way the data would lay out for a single condition. This is MCAD.

I don't see a pointer. Oh, there it is.

Each one of these columns is an individual who responded on a survey, and you can see that each of our criteria is on this side. Not everyone was as well informed on every criteria as every other person. So the option was available to say I just don't know about that particular criteria versus a zero saying that they think it's incredibly rare, for instance where we're talking about incidence here.

That made just summing up individual scores impossible if people were unable to give us information on a specific criteria. So we had to begin to look at this in other ways and basically decided to take the tack of looking at the sum of all people who responded on a particular criteria to develop the sum of the means and the sum of the medians. You can see for MCAD how those would fall out. I think we have leaned towards using the sum of the mean, largely because it tends to acknowledge dissent a bit more than does the sum of the median.

This would just be the total scores and how they laid out in a graph for MCAD deficiency, and you can see that most of the scores are aggregating up here in the 1,400 to 1,600 range. So now I have to move to aggregate data. I'll show you a little bit of individual data in a minute just to give you a sense of it, but this is really moving now into aggregate data. As I said, without a newborn screening sensitive and specific test, there really isn't a newborn screening decision to be made at this stage. We wanted to lay down every condition and our analysis of it regardless of whether we said there was a test or there was not a test, because that is what will drive a research agenda. It's finding those gaps for every single disease, and those are going to be ultimately included in our report, identifying all these gaps in the system, in individual diseases, or in our broad perspectives of groups of diseases so that everything was laid out and everybody would see the basis on which we decided whether something was amenable to screening or not.

This is the torture part where you probably can't read the bottom, the X axis here. It's basically every condition that we evaluated. MCAD scored the highest. Congenital hypothyroidism, PKU, biotinidase, sickle cell, congenital adrenal hyperplasia, isovaleric acidemia, very long-chain fatty acid defect, MSUD, galactosemia by way of the transferase deficiency.

I think there's one point I didn't make earlier that I need to make here, and that's the scorecard thing about how many conditions. You always see that people are marketing their program: "I do 50 conditions" or "I do 30" or whatever. We looked at this actually quite differently than programs tend to calculate the number of things they do. Galactosemia to us was three different diseases: epimerase deficiency, kinase deficiency, and that thing which is really the primary target of screening, the transferase deficiency. That occurs in an enormous number of conditions, so we had to break them down into their specific etiological type to be able to look at them as a unified group to see how they meet our criteria.

So when a state says they do galactosemia, they always do GALT, they may do kinase, they may do epimerase depending on the method they've chosen for their screening. So that background variability still lays out there regardless because of the enormous variability in technologies applied.

I think the other thing that came out of this particular view of just all conditions that we have evaluated is that MCAD, PKU, isovaleric acidemia, VLCAD, MSUD, are all conditions that can be detected by tandem mass spectrometry. In fact, for MCAD, that's the only way you get at it. So by virtue of it being first, we essentially are saying that we think it's important that programs are using tandem mass spectrometry in newborn screening.

I'll only briefly say at this point that among all these other conditions that are also detectable on acylcarnitine profiles in tandem mass spectrometry, they covered an enormous spectrum of the acylcarnitine profile, which led us to make some very specific recommendations about whether profiles might be preferred to selected reaction monitoring. I may touch on that a little bit. There are methods that allow you to basically only see certain analytes when you get your results back from a tandem mass spectrometer, and as I'll touch on later, we think that profiling may have advantages over those types of highly selective analyses.

All of these conditions had no test, and there's a lot of lysosomal storage diseases out here on this end, at least a half a dozen of which have those treatments and have those tests in the pipeline right now. So I wouldn't be surprised if about this time next year you're pondering what are you going to do about all the stuff that's happened since today and this time next year when you meet.

We chose for a couple of reasons to now break out the conditions into some groupings here. Hemoglobinopathies, a unique group because of the technologies used. Isoelectric focusing, HPLC, are capable of detecting every hemoglobin variant that exists. That's the nature of the test. You may be targeting sickle cell SS disease, SC disease, sickle beta thal, but you will get information from the test that will inform you of over 700 variants in the hemoglobin molecule, a number of which are clinically

important or clinically significant conditions, and that ties back to our earlier principle where we suggested that if clinically important information is acquired in a newborn screening test, it should be used in some way and disseminated. We'll touch on some of those options in a bit.

Tandem mass spectrometry brings a similar kind of situation to the table in that you are able to look at all metabolites across this range in the acylcarnitine profile or across the amino acid profile that one would run with tandem mass spectrometry, and may detect conditions that are not those you primarily went looking for, such as MCAD.

Out here you see conditions that are in that other group. Congenital hypothyroidism, again the highest scoring in this group and second overall. Biotinidase deficiency, CAH, galactosemia by transferase and by kinase deficiency, ranging all the way down here to Krabbe's disease.

So how do we draw lines in all this stuff and make some decisions around it? We used our overarching principles to help us make some of the decisions. We also had to really go at the individual evaluations of the conditions, weighting things toward the literature review where that literature information was what informed the criteria, but for rare diseases and for many conditions that are coming out of tandem mass spectrometry, some could be 1 in 50,000. There are not many patients available, so we had to use expert opinion to a fair degree.

Let me step back and say the weighting of the criteria was assessed throughout this process. We sent out independent surveys to people asking them to tell us whether they thought we weighted the different criteria appropriately against one another and made adjustments as we went along. These were not what we started with in this process but have adjusted to what seemed to be consensus about what was the most important criteria for newborn screening.

The next stage of decisionmaking was the new tests and technologies being something that are driving the system. I've talked a little bit about the multiplex capability being a benefit independently, and I've talked a little bit about that difference between looking at a profile on a tandem mass spectrometer, where you see all metabolites laid out, versus that selective reaction monitoring approach that just informs you about specific narrow ranges of mass units on a spectrometer. The issues that sort of helped us decide which was the preferred route to take, realizing that it is possible to combine these two concepts and perhaps get to a similar place.

The reasons that we leaned towards the profile were that the profile maximizes the use of the technology itself. Our high-scoring conditions I said were spread across the full spectrum of the profile, arguing that you would be developing these selective reaction monitorings across an enormous number of peaks, and that the profile offers a better quality control system because it allows you to see everything down on the baseline. If you've got contaminants, they're much more readily identified, and other spurious signals and things become much more apparent on a full profile.

Then the profile, because of its ability to help inform you about background and other analytes, gives you improved interpretation of your test result. So on those alone, we argued in favor of tandem mass spec profiling.

Then the next stage of decisionmaking was trying to rank things and figure out where to draw lines. I'll touch on it now because I've written it here and I have to, which is that we ultimately ended up with two groups of conditions, those that we considered to meet all of the -- they had very high scores, meaning that by virtue of those high scores, they met all of the really important criteria. But when we moved into the gray zones, we looked very carefully to make sure that a condition that we were saying should be in the core had a beneficial treatment and had a well understood natural history. That became something we independently overlaid on the scores at the end because, as you'll see, we're going to be informed about a large number of those conditions whether there may be a treatment or not, and I'll show you how that arises.

Within the system, though, we pondered what do you call this stuff. We went through periods of calling them our primary targets and our secondary targets. But ultimately as we looked at the system and the way it functioned, we came to calling them the core screening panel, and then a set of conditions that may not be treatable but are going to be informed by one of these multiplex tests, and within the system there is already a mechanism to deal with essentially a false positive done for anything that's in a core panel, meaning you do the test, you find people who screen positive, then you go establish your diagnostic confirmation. If you're not confirmed as having that condition, the newborn screening program says okay, fine, and you're off their list and they're not following you any longer.

With that mechanism in place, we thought that that might be a reasonable place to embed this group of conditions for which we're going to be informed by the test but which may not meet all the criteria well, and that we called report only. That report only is a minimum. I mean, a state may choose to follow those patients, collect the data about them and make decisions as though it were a pilot program for them. But we thought that it was important at a minimum that they be reported, and that's what we've called this particular category.

So we had these 83 conditions. I have to tell you, these slides have gone back and forth between me and my PowerPoint expert sitting over there next to Dr. Tuckson, so a few things have gotten modified in the formatting as they went back and forth between us, and this is one of them. It won't add up to 83, you'll see. But we'll try to deal with that as we go.

So among those 83 conditions, we end up with 30 conditions in this primary target category. That's really what we would call our core panel, and 22 more conditions in this report only category, which I'll come back to in a minute. Nine are excluded because they had no test. I'm sorry, 23 had no test. Nine, some of those are sort of in a deferred decisionmaking process right now. As I said, we went back out on cystic fibrosis and have rescored it around the criteria, and we have a couple of others for which this is still occurring, and I'll touch on those when we come to the lists themselves.

I mentioned there were 30 conditions on the core target list. These can be broken out into the acylcarnitines, which include organic acid disorders, fatty acid oxidation disorders. As I said, the acylcarnitine is a single run on a tandem mass spec. That's one of the reasons we separated it out here from the aminos. You can see, from highest scoring to lowest scoring, the conditions that scored highly and had the treatment in place and a sufficient enough knowledge of natural history for the group to consider it to be included in this core panel category.

Fatty acid oxidation disorders, MCAD, VLCAD, amino acid disorders, PKU. I've updated this I think since what went into your book was developed about a week and a half ago. So I think you can see here that hearing loss actually comes in and scores between GALT and GAL kinase. Cystic fibrosis and G6PD we're in the final stages of sorting out relative to our list.

This is an issue that I think is important to have a general sense of, because it underlies some of our decisions about this report only category and the core panel category itself. If you took all those things that had a score above 1,200, for instance, by our surveys, you'd have this group of disorders listed. However, this is where that language of primary targets and secondary targets really began to get difficult for us, so we moved to that report only category.

PKU, as I said, is a number of different conditions. Hyperphenylalanemia and two biopterin deficiencies will be conditions in which this compound will accumulate in someone's cells. So when you're screening for PKU, these guys are all in your differential diagnosis for that elevation that you've identified, and that occurs throughout this process. I'm not going to do isovaleric acidemia or I'll have to tell you what 2MBG is. I'll try to find an easier one. Well, I guess I'll do that one. Isovaleric acidemia, 2-methylbuteral glycinuria would be a part of that differential diagnosis. If you're doing MCAD testing, MSCHAD, MCKAT would all be included in that differential diagnosis. So whether or not you're actually

screening for the condition, because it's part of your differential for one of these other conditions, it's actually being screened for in reality.

However, there may not be that treatment or there may not be sufficient knowledge of natural history. So we didn't think it was always appropriate to impose on a state program the need to follow outcome, to understand how over time, either short- or long-term follow-up, how that patient ended up, because you don't have a treatment in place perhaps by which you'd expect there to be a significant change. That sort of underlies this report only category.

So here would be the report only category. Now we have conditions all scoring highly. They're almost all above 1,100, and a few above 1,200, but our committee did not feel that all of them had adequate knowledge of natural history. Some of these there may be only three to five patients identified in the world so far. So we've laid it out in the exact same format, and you can see -- I'm not going to go through all of these, but you can get a sense of it, and a copy is in your book.

No test available. We had a few conditions here in the acylcarnitines and amino acid disorders where we didn't think that the tandem mass spec test really was a very good test for those particular conditions, and we've called those no test available. Here you see actually an interesting condition. Hyperbilirubinemia was among the top three highest scoring conditions in our surveys. Our group did not believe that there was an adequate test available for hyperbilirubinemia as a risk factor for the development of kernicterus, so it ends up in this no test available category, yet it scored very highly.

There's always been, I think, a lot of discussion among practitioners as to whether or not hyperbilirubinemia and kernicterus risk is something that just should be routinely done in the nurseries, as opposed to being part of a newborn screening program, because if you're going to do newborn screening for hyperbilirubinemia, you've got to do it in the nursery. That's the only place you'll have adequate turnaround time to address the issues that are important for that particular condition. So that would give you a second condition now, similar to hearing loss, where you've essentially assigned the newborn screening responsibility to the nursery itself, and there are lots of mechanisms in place for that information to flow between health programs, public health programs and the institutions in which this information is developing.

Then you can see a ton of the lysosomal storage diseases down here that you'll be thinking about again in the near future.

Now, we also looked a lot at the infrastructure to make sure that a recommendation that included 30 core conditions was actually feasible, was the system really adequately developed to be able to provide something like that. As we've already talked about several times yesterday and today, there are several key components to these programs. Our infrastructure components working group that looked at diagnosis and follow-up broke each one of these down into its individual pieces. Education, for instance, is broken down into is there prenatal education available, and there are no states in which there is a formal prenatal education program supporting the newborn screening programs, but it's not uncommon that they have made some effort to make those available to OB offices and such. It's just not a formal part of the educational program yet, and there are grants out there to develop these kinds of programs, as you've already heard today.

So we did that in each one of these categories, and that will be part of the final report, looking at what each state does in each one of these categories, whether five states, ten states or fifteen states have something in place to deal with a specific component of delivering a newborn screening test in the context of the complete system.

Not surprisingly, we still have more work to do, and you have even more work to do. There's still a fair bit of data in review. One of the charges to our group that is going to take a little bit longer is tool development. How do you turn this into a tool that can be used prospectively by a state to say, okay, I've

got a new disease coming along. We now have, for instance, a test for Pompe disease, and there's a treatment in place. How do I evaluate Pompe disease? Ultimately, we will take our survey, all the information we've gotten will be the background standards against which people can compare a new condition in the system to see how it scores.

But nevertheless, I've learned this since I foolishly started thinking about developing a tool, that there are people who do tool development for a living, and it takes a long time not just to develop tools, but there's a long period at the end of tool development where one actually validates that it's doing what you want it to do. I think that's the stage we have to move to now, getting this down as a potential tool, and then seeing how it works. There's a number of state programs that have already begun to look at how to use it and integrate it into pilot testing already.

Then a lot of other issues came up throughout the course of our analyses. As I mentioned, a research agenda becomes very clear when you look at things in this level of detail. So we'll have recommendations that go all the way from the broad down to the very narrowest criteria for an individual condition that will be included in our report.

We're also going to find that there are conditions in our analysis where the test did not perform that well in 24 to 48 hours, and this is something that has been well understood. The U.K. screens much later, I think out to a week of life, and there's clear differences in the performances of the tests, of some of the tests when one screens at seven days as opposed to 48 hours. One of the things that became clear is that some of these tests actually performed quite well out at a month or two months. So things like familial hypercholesterolemia, Wilson's disease, congenital disorders of glycosolation were conditions where tests would perform very well at the first well-baby visit, for instance.

So if you acknowledge the general mantra in public health of sort of screening is not just done at a point in life, it's ongoing, it's lifelong, I think one of the things that you're going to have to begin to think about is that there may be other opportunities for screening for important conditions of infants and children that may not take place in that 24 to 48 hour interval but may be good at some time slightly thereafter.

It's an enormous system, lots of participants in the system, and because it's been a state mandated and directed program, parts of the system have not played as fairly as they might play, nor have been as participatory in the system as they might be. Obviously, all babies in newborn screening arise in hospitals, or most arise in hospitals. Yet there are no standards in place for hospital-based screening. They use some very interesting systems of getting specimens out of the hospital and to the state newborn screening labs or whoever the state works with, often leaving straight from the nursery. They don't go through the institutional laboratories, which allow tracking.

This is a very important issue when it comes to making sure you can find that baby who ultimately screens positive and for whom you may have a very short period of time to act, and we've begun to talk to JCAHO about how we might bring standards to this important area of the newborn screening system itself and have gotten some relatively positive feedback, and we'll incorporate that into our report to you to pick up and see where that might go to help close down some of the gaps in the system.

Cost effective analyses, there just aren't very many in newborn screening, and certainly not many in this generation of newborn screening. Many of them don't look broadly at genetic diseases per se. They may look at how that particular test performs for the individual without giving any acknowledgement to the value that that might bring to the family. So there's a lot of aspects that haven't been factored into cost analyses, and I think a lot of room for these to develop over time.

One of the things that was a major concern to us was this issue of how this field is evolving. In order to ensure access, we suggested in our very first principle that the public health-based screening program was the best approach to newborn screening. That leaves you with this state-mandated

program or a national approach, if that ultimately is what you think is appropriate. The concern, though, is if the states do not progress well and proactively in newborn screening, that we're beginning to see what will evolve as a standard of care in the practitioner community.

Pediatricians, I think, are getting a little bit nervous about the fact that there is this large number of conditions now for which we can test or screen and prevent negative outcomes for which they are beginning to wonder what their liability might be, and those are going to be important issues as we develop, to make sure that we're able to allow the programs and the systems to grow and to build this research piece in, because I think that is probably what has happened as technology has evolved, that there's been a leapfrog of the state programs as these new technologies evolve out in the private sector and get used in our hospitals. It's a little bit late in that development process that they're moving into the state programs, and figuring out how to integrate that better is going to be important.

Wow, I really went backwards.

Then I think as others have said, this collaborative management model is really going to be important to get the various players in the system to play well together. Our diagnosis and follow-up workgroup looked very hard at what happens in the interface between programs and the diagnosis and confirmation part of the system, recognizing that there's a combination of either primary care providers on the front end of that, or sometimes specialists are contracted by the states. But there has to be an interplay between them in the ongoing care of that particular patient.

So we've begun to look at developing the confirmatory algorithms and guidelines for the individual diseases and their confirmation and their management. Historically, I think what has happened in this area is that we make the recommendation that it should be done, and then the national organizations begin to come in and develop the fact sheets and the guidelines and such. We're trying to front load that a little bit more this time by developing a lot of this within our committees as we've gone through this process.

We've gone one step, sort of laying out a framework for what we call an ACT sheet, different than a fact sheet that goes out to the physicians saying that this is an autosomal recessive and occurs in this, that and the other number in the population, but have actually gone to an action sheet which basically says here's a result, it says you've got 2.0 micromol C8 on an acylcarnitine. What does that mean to a primary care physician?

Well, that means that you've probably got an MCAD. If you're between 1 and 2, it's not as likely it's an MCAD. If you're above 2, you've probably got one, and you need to move quickly to develop your referrals with metabolic physicians, or if it's within something you manage yourself, to really get moving on taking care of that patient. So we've begun to develop those, and there will be several of those included, probably about 20 or so as models in the report when it finally comes out.

Then the last stage. I've talked about screening after the neonatal period, that there are certainly conditions that look like they might be amenable to such a time, new things coming fast. Hyperbilirubinemia, as I said, has a test. It may have a nomogram in the near future. The question is will standard of practice change so that the problem of increasing kernicterus in the population is dealt with independently of it having to be screened, and that will be something you'll have to evaluate at the time a test is available.

Then disorders of mental disability. It's not uncommon for many of these conditions that -- I think historically, if you look at PKU, it's sort of the poster child. The difference between untreated and treated is enormous. But there are a significant number of conditions, a huge number of conditions where the improvements may be more incremental, and figuring out how to weigh an incremental improvement for one condition that's common against another condition that may be rare but for which the improvement is significant may be an interesting problem to sort out as you deliberate on newborn screening.

That's all I have from this, and I'll go home and start writing so I can get you the final report in the near future, hopefully.

DR. HOWELL: Mike, thank you very much.

What I think would be prudent -- I can't imagine that there's not lots of discussion, so you can't go home yet. But I would suggest that we take a break right now. If we could come back at five after 11:00, if you'd be good enough to come back and respond to the considerable number of questions that your presentation has raised.

Thank you very much.

(Recess.)

DR. HOWELL: I wonder if we could get Dr. Watson to come back up front, since I think that much of the discussion is going to focus here. While Mike is coming up front, the website address is -- this committee currently has a website, and the address of the website is on the screen if you have not noticed that.

I'd like to go back now, if we might, and focus on Mike's presentation and get comments and responses. I think that one of the things that Mike alluded to a couple of times in his presentation is that the deliberations of this committee certainly identified certain areas for the research agenda, because there were a number of conditions that seemed to fit the requirements for inclusion on the list that don't have yet a proven test. I would imagine that's going to be one of the areas that's going to have some of the greatest change in the coming weeks and days and so forth.

Who has a question for Mike about the presentation?

DR. TUCKSON: I'll just ask one quick one. You discussed this a little bit, Mike, but I don't think I understood it all. How did you all process the idea of the type of technology for testing? You talked about mass spec, and you were here, I think, and heard the discussion yesterday around as we start to have new diagnostic modalities that would augment or supplement mass spec. Did you all sort of look at the world as it is this moment, and that's where this study is going? Or is it anticipating a future two years from now with new and different things, with many more kinds of testing availability through different techniques and try to sort of look at what that's going to mean? Or were you looking at a slice of today?

DR. WATSON: I imagine we looked at it more from a today perspective than a tomorrow, although we always thought about tomorrow as we were doing this. From the outset of this we approached it the way most states have, which is by condition, and it became clear that as we began to move into new technologies, that you couldn't even always look from a condition perspective. You were often looking from an analyte perspective. I mentioned C8 as an analyte with MCAD and glutaric acidemia and other conditions.

I think the thing that we weren't able to do around technology that is obvious from tandem mass spectrometry are the number of permutations that you could use of tandem mass spectrometry to do an analysis. You could look at MCAD all by itself. You could look at these criteria around a half a dozen conditions diagnosable by that one test. You could look at it all the way out to the 40 conditions that are either acylcarnitine or amino acid based on a tandem mass spectrometer and look at really what do all of those in aggregate, from these two runs of the test, how does that lay out for all these criteria. That we haven't done. We really looked very much from a singleton kind of condition, but you can see by the way it laid out that some are report only, and there's some value in those.

We haven't taken that next step, though we have thought about DNA arrays, either genomic or expression arrays, and we've tried to use language around our criteria that allow for those things to come into place. So as a DNA array came in, it would have to deal with the same clinical sensitivity and specificity issues and as any other test. If the DNA-based diagnostic is not the one that is the most informative about what to expect from an individual but the expression is, then it will win.

So I think we've tried to develop the language so that new technologies can come along. The hard part has been that some of these you would almost look at as a bunch of things done by a technology, as opposed to trying to compare MCAD to CF or everything on an acylcarnitine profile to CF. Obviously, the more things you're getting out of the profile, then the differential between those two things begins to grow, and that we haven't done.

DR. HOWELL: Coleen?

DR. BOYLE: A couple of questions. I appreciate you actually presenting this to us again. It was very helpful, and I actually was very pleased looking at the overriding principles again. It kind of brought up some issues of the juxtaposition of those versus the criteria that are involved in the screening instrument.

But I first wanted to mention -- and I know you've heard this from me before, and that is really what we want to move towards is sort of an evidence-based paradigm that helps us with our decisionmaking, and you've rightly showed us that there isn't a lot of evidence base, although that didn't come through clear in your talk.

I asked you a question, and that is with many of these conditions that obviously present themselves based on the new technology available to identify them, it's going to be very difficult to develop an evidence base because they're very rare. Dr. Howell and I were talking about that during the break. So as a committee, one of the complexities and the quandaries that we're going to face is what do we do in that case? I know what you have done here is based on expert opinion. Is expert opinion appropriate for public health mandates? What do we do to grow the evidence base as we go forward with these public health mandates? Maybe just some thoughts you have on that one.

So that's one. The second question is --

DR. WATSON: Can I answer that one first?

DR. BOYLE: Sure, go for it.

DR. WATSON: I'll never remember it if you do another one. You almost have to refresh me on the start of that one.

DR. BOYLE: Just the fact that we don't have a sort of scientific evidence base for many of these conditions, and because of their rarity we may never have that.

DR. WATSON: I think there's two sides to that problem on the evidence base. One is that we can accumulate evidence, clearly, by developing data collection systems on people identified. But then there's the genetics of these things, which is that if you take cystic fibrosis as an example, probably 80 percent of the mutations in the CF gene that affect maybe 5 or 10 percent of all the patients are private or rare, meaning only one person, only one family in the world got there that way. So there ain't much of an evidence base, which sort of gets you to the technology side that can go through a ton of evidence development.

There's a clinical interpretation side I think that's evolving in newborn screening that's going to be a little different than it has been historically, and that's what happens I think with some of these new technologies, whether the interpretation of a genomic array will be quite different than the interpretation of the expression array. I think although life might have been easier on a genomic array had we had 100,000 genes, the fact that we got 30,000 genes and umpteen ways of splicing them into proteins says that the next generation of functional stuff is going to be even harder if it moves into proteomic arrays.

So the evidence base is going to have to accumulate around the diseases. There's a lot of programs that are evolving in the country to do those. The rare disease centers that have come out of the Office of Rare Diseases are places where one can develop natural history information. I suspect that the NICHD research study that's going to look at applying a new technology tool to newborn screening clearly will identify people, and I suspect that an important aspect of that identification will be understanding the evolution of the natural history of those, because that really is the only place where we understand ultimately the general population aspects of these things.

Without that, you're always sort of in a pilot mode until you get there in newborn screening.

DR. BOYLE: Just a follow up. We heard yesterday from the AHRQ and their judgments around newborn hearing screening, and I was discussing following that the complexities that have since prevailed in that area and trying to justify newborn hearing screening, because once it's mandated, it's difficult to study the efficacious aspect of treatment. You can do it from an observational standpoint because all children are mandated to be screened. The same thing will happen here.

It's not that I'm advocating not screening. I'm just trying to get people to realize that once we move forward with screening, once we mandate it, it's a difficult issue to say one of the principal issues of screening is that treatment is beneficial. As Dr. Alexander pointed out, maybe we just need to modify the criteria for screening someone and just say we're advancing age at diagnosis, we're advancing age at treatment. We also have to make sure we don't do any harm in that process.

DR. WATSON: I completely agree that this is going to be an interesting evolution.

DR. HOWELL: Interestingly enough, if you look at that list that was in the category of no test available, that's an extremely interesting list because it obviously is the foundation for research. It says this is where we need research. But the other thing is that embedded in that group is a considerable number of diseases that we know are lethal, the lysosomal storage diseases, of course, being classic, Krabbe, Pompe, et cetera, and SCID, for example, about which we know a great deal. If you have a reliable test for those, it's very easy to say, I think -- this is a personal opinion -- that those clearly should be done, and if you can demonstrate that they're life saving, that's an important advance. Obviously, if you can return nearer to normal, the better. But you can assess that later.

There are obviously some in that category that are not clear, and so forth. But certainly at least some of those that I would say are in the waiting room for reliable tests, and fortunately there are some very exciting tests that I'm personally aware of on the horizon that's going to move those into the scene and, again, make the newborn screening program more complicated than it already is.

Bill?

DR. BECKER: Yes, I think to add to that, and I think Mike alluded to this, is one of the major challenges and difficulties for the programs I think has been a reliance or in some cases an insistence on having scientific or evidence-based information backing them up, and I think a lot of times the single-disorder consideration to panels was based on those things.

Rodney, your comments are perfectly appropriate because I think we're already at that point where we're not going to have the rigorous scientific evidence, like I think a lot of us would like to see,

available to us to make the decisions. We already don't have them for the report that Mike just gave, and I don't think we're going to be able to wait for NICHD to do formal rigorous studies on the myriad of disorders that we're going to potentially or be considering adding to panels in the not too distant future.

So I think what we're left with, and this is what I think Coleen's point is, is what do we do when we don't have that good evidence-based foundation to stand upon? We talked about using science-based evidence versus clinical-based evidence, and I think we're moving very quickly -- the pendulum is moving, in fact probably already has moved over into that arena, and now we have to get the programs to accept that in lieu of this rigorous science that I think we all would like to have and like to see because it gives us that good feeling that we're doing the right thing, but I don't think it's going to be there for many of the things we're going to be considering.

DR. WATSON: The newborn screening programs have always had built into them a research component that they tried to fulfill themselves, and I think that the change that's about to happen is that we're going to have a research agenda driven by a different organization, with lots of research money to drive things with, and that we have to figure out how to bridge the public and private parts of the system because clearly, by tandem mass spec, we can already identify people who have peaks that we think might be significant, but we just don't know.

I would never say that we should screen for those, but I think from somebody who has been in academics most of his life, that those are the patients that you'd like to be able to say there's an opportunity to figure out what this really means for your child, and there's a rare disease center focused on those kinds of metabolites, whatever they might be, and ultimately try to build a system that actually integrates in a research perspective in the evolution of the newborn screening programs themselves, and it's difficult to bridge those public and private parts because of the privacy issues and everything else that arises that's different between them.

DR. HOWELL: Let's hear from Steve, if we might, and then Carol Greene is anxious to say something.

DR. EDWARDS: The advisory committee has obviously gone for inclusivity, because basically there were 30 tests that were recommended and another 23 that will be reported. It may be 22, slightly off. And then the one group where there is no test was 23. So essentially, the recommendation is going to be for almost all the tests that are available will be the recommendation that comes from your committee.

So my question is this: What power do these recommendations have as far as the states are concerned? This would, I assume, go as a recommendation from this group or another group. What control is there as far as states is concerned? Is there any sort of mandatory part of this, or is this optional for the states? We do know that the states have, at least up until now, for the past few years, have been under a severe budgetary constraint. Would there be financing available to the states who would be implementing this?

And then the other question I'd ask is how many states right now do tandem mass spectrometry? That seems to be the big change that might occur.

DR. WATSON: I wondered at the start of this whether I should have put a whole bunch more conditions on the list that I knew would never fulfill the criteria so that it wouldn't look like we were actually going to say everything we looked at should be. But that wasn't practical.

The work we did was a contract to HRSA, and we will provide the information in our report to HRSA, which is I think very much intended to inform you. So you'll get all of the data and all of the analysis of that data back. I have no power to make the states do anything. I think, though, that our recommendations will help them. I think it's an expert group who have developed the scientific literature

on which they can make decisions over the short term while you're pondering how to bring uniformity to the system. But I think it won't be an immediate turn-around, that they're going to sit back and say let's go do this.

My sense of tandem mass spec is -- I don't know how many states are doing it, but my sense was that we were right around the point where just over 50 percent of all newborns were being screened by tandem mass spec in the United States.

DR. RINALDO: Well, actually, that's not entirely correct. Thirty-four states currently are using tandem mass spectrometry. The problem is that they're clearly divided into two groups. There is one group that actually accounts for about 70 percent of all the babies born in the U.S. that are screened for seven or less conditions, and these are including some of the traditional ones. It really depends, like PKU and MSUD. So only 30 percent of the babies born in the U.S. now are screened for at least 14 conditions, up to 36. The 50 percent that Mike was referring to is actually specific for MCAD. MCAD right now is at that critical juncture where 49.7 percent of the babies born in the U.S. are screened for MCAD, and 50.3. That actually makes it an interesting situation, because you might argue -- and this actually was for a while above 50 percent because of a California pilot.

But as the California pilot ended, we sort of got back below the 50 percent mark. There are issues, I think, of the fact of creating a standard of care that might clearly affect the decision. But you're absolutely right, this in a sense is not even a recommendation. It's an evaluation of where things are now, and I think actually fits extremely nicely what Dr. Watson described before about trying to encourage, if not force, states to work in a regional collaborative manner, because that will be very conducive to really looking and trying to achieve some kind of uniformity.

DR. HOWELL: This report, as Mike says, is a report to HRSA. Maybe I could ask Peter to comment about what will happen with the report once it gets to you, the draft of the report that will be finalized and sent to you.

DR. VAN DYCK: The report does come to us, and we'll review it, study it, look at it and decide how to receive help in what eventual recommendations we would make as a Department related to the findings in that report. We will certainly use the committee to help us make those kinds of decisions. We will get input from this committee on how to make those decisions.

But I would think it would ultimately lead to a recommendation of a core panel of tests coming from Maternal and Child Health, but it's not something that's going to be done lightly and without thinking about the whole system and how the system works and incorporating into the new regional collaborative centers and assuring follow-up and equity and all the rest. So this is not something that next month suddenly there are going to be these recommendations for coming out and doing all these tests.

DR. HOWELL: I think the question embedded around the table is what is the most effective mechanism for this report and this committee in particular to make recommendations, et cetera, that can be put into play that will really affect newborn screening nationally? That's something that we will obviously need advice and counsel on, because that's really critical, because the potpourri around the country today is clearly leading to the death of children, and it shouldn't be that way.

It's very interesting. I like to point out on the map -- no one pointed it out, so I'll point it out. The map that was shown yesterday showing the states that have mandated screening, not optional screening, there was one state on the map that had mandated screening for 40 conditions, which is the highest number of mandated screenings in the country, and happens to be Mississippi, which we always expect to be following at the back of everything. It should embarrass everybody that Mississippi is now number one. I think Massachusetts is probably a little embarrassed.

Carol?

DR. GREENE: Thank you. I have one brief comment and then a question for Mike and other people who contributed to that incredible report we just heard.

The comment is that decisions have to be made with the limited evidence, and I really appreciate all of the important points that have been made about the limitations of the evidence available to make decisions that have to be made now. My comment is really beyond the scope of the committee, but it's about the term "evidence based." Everything we're talking about here is evidence based. We're talking about the nature of the evidence.

I for one am a little concerned, working out there in the real world, that when we say not evidence based, we here know that we mean it wasn't a randomized control study of a huge population. But what they hear in public health when we say not evidence based is we made it up out of whole cloth and they don't need to listen. I'm really concerned about the use of the term "not evidence based," because everything here is evidence based. It's only the nature of the evidence that's in question.

So that's my comment. I appreciate the chance to say that.

My question is in the consequences of the term "report only" -- and I really appreciate the thought that went into the distinction. I personally really liked the primary target and secondary target, and I'm sure that an enormous amount of discussion went into this, but I am concerned about how the states, given the current systems, might interpret "report only" when "report only" means report to the care provider and not necessarily report back.

I have two major concerns. One is for the accuracy of the data. I can conceive of a state, if something is report only, if the phenylalanine is 6 and the tyrosine is .4, and that's a positive screen for PKU, and the follow-up shows that the child has biopterin deficiency, that the report back, the follow-up data says it was a false positive because it wasn't positive for the primary target of screening, it wasn't positive for what the state is trying to screen for. That will really confuse the data and the accuracy of what we're developing in the future.

Another concern based on my knowledge of Colorado, the language of the provision for care -- and this may be secondary because there are other ways to provide care for children, as has been in the past -- is in Colorado, our clinic when I was in Colorado was funded by the state to provide care for children with diseases detected as part of the newborn screening program, and that means if you were a secondary or if you were a report only target, the care might not be covered.

So I only raise the question of whether you might revisit going back to primary and secondary target because of concern about the consequences of report only, or whether another term might be found. Thank you.

DR. WATSON: Well, the reason we ended up with this report only category I think was an acknowledgement that within newborn screening systems, there was already a point in time where they made a decision about long-term follow-up or not, when they make that decision about whether something is that dreaded term "false positive" or not, at least false screening positive.

So we embedded it in that term, and they are part of the differential diagnosis, so you are screening for them. We were trying to make the point that long-term follow-up that the state funds may not be appropriate for those conditions if there isn't a treatment. Whether you call it secondary or report only, I think we were only trying to be more specific. I think in the historical use of "secondary" there have been things that have been secondary that have not met all the criteria as well, and they were distinguished from things that met it very well. These are things that I think are a bit more in a gray zone, because they are picked up in the screening for the primary target, and there is a point in time when you can deal with that information.

Now, I would say on the evidence-based side of this that clearly, when looking at our data, we saw a wide range of quality of evidence, and I think if I was looking at it prospectively, I would look at something that's a common condition, like diabetes is now, as something for which the evidence base should be much stronger, and I would not lose as much sleep over the evidence base for a condition that occurred in 1 in 300,000, like homocystinuria. So homocystinuria you will pick up in the amino acid screen by tandem mass spec. You'll have evidence of the condition, but it's incredibly rare. Historically we've avoided screening for it just on its incidence alone, though many states do screen for it.

So I think you can expect different levels of evidence linked to how common something is, and the more common it is, I think the stronger the evidence base needs to be.

DR. HOWELL: Greg? Or did you have a question, Jennifer?

DR. HOWSE: Yes, I did. The report I think certainly is a commendable effort on every level. I think those of us who have been involved in various stages of it certainly appreciate all of the complexities and all of the number crunching and the work that you all have done to put it together.

I do think that since this report will most likely serve, at least in its final form, because I know you're still doing a few tweaks and refinements, but the report will likely serve as the formal basis upon which this committee considers and deliberates the development of a recommendation for a core of recommended screening tests for the states, that we may wish to really consider setting aside at our next meeting yet another run at going through this, really understanding it, having a chance to really probe all the aspects and implications of the report.

I mean, maybe you have some questions about the principles or the criteria or the scoring system or the weights that were established for certain categories, and I think it would be quite important to do that. But assuming at the end of the day, after we go through this process, we understand more about the validation that was used for the system, let's just assume hypothetically at the end of the day that we wind up with 30 tests to recommend to states which carry the weight of the recommendation of this group. Then I think it's quite important for us to think about a couple of things.

First of all, the system by which new tests would be considered. I mean, several of the slides and several of your comments dealt with the pipeline. We've got treatment in the pipeline. We've got reliable tests that are in the pipeline. So what is going to be the formal process by which new tests would be considered and then recommended to HRSA, recommended to the Secretary? So I think some time maybe needs to be spent on that.

Secondly, this question of the evidence that's associated with treatment for each of these screenable conditions, I think that question for all 30 -- again, the hypothetical 30. But that question with respect to all 30 of these conditions, it seems to me that that's information that should be assembled and digested, and we should have a chance to read it and understand it and discuss it at a future meeting so that we can say with some certainty and clarity, yes, these are the 30 hypothetical conditions that we're recommending, the test is reliable, this is why we know it is, the treatment is efficacious, and we have studied and are aware of the evidence upon which that is based, so that we've got a very strong footing upon which to make the recommendation.

Then the other piece with respect to this core panel of recommended tests, which I'm obviously very enthusiastic about coming to that point, would be how we want to connect up our advice to the Secretary with respect to the distribution of Title 26 funds, which we all have a big job to do to see that there are some funds available, and how we want to tie those to considerations of state grants. Do we say states get up to the 30 and then you're eligible to receive additional funds? Or do we say states, our recommendation is that to help you get from point A to point B of this recommended panel, these are the kinds of grants that we're interested in? So that's one set, and I'd be interested in your comments on that.

Then the other area just has to do with capacity. If, for example, we took this hypothetical 30, is there enough capacity out there right now? What's the gap? Someone needs to do a good technology analysis for us so that we can say here are the 30, the test is reliable, the clinical evidence is there, and P.S., there's 30 percent of the capacity to do it, or there's 80 percent of the capacity out there to do it, and this is what would be involved to bring the states up to this next level.

I don't know anything about that capacity issue. You all began to talk about the availability of tandem mass spec and so forth. But just from the relationship of the technology to the population, I think that would be an area where you could give us some remarkable insights.

DR. WATSON: You know, I think that the technology piece is going to be a tough one. This uniform panel, there are lots of ways in the system to get at standardization. You can make people do stuff through the flow of money, obviously. That's how you herd cats. You can bring it down through Title 26. There's also places in the system -- many of the programs commonly bill for the testing in the system. Many states have come to the AMA CPT panels asking for a CPT code for newborn screening, which they've always been denied because there was no consistency among the states around which they could develop a code. They've already told me that as soon as there's a national standard, that a code can follow almost immediately.

Now you've flipped the whole situation around. Now if you want to bill that code, you actually have to do everything that's in that standard or else you're in the Medicare fraud side of the game. So there are lots of places in the system where you can bring people along around a standard that you've recommended.

I'm trying to think of the other parts of your question.

DR. HOWSE: Capacity.

DR. WATSON: Capacity, yes. Capacity is an interesting question, and I think you'll have to deal with the state boundary issue and the national boundary issue in thinking about it. I think, Piero, you'll have to help me here because tandem mass spec is not what I do for a living. My sense is that 50,000 a year is approaching sort of a minimum number that you want to run through a machine to really have it well standardized, well understood, and many states don't even have that birth level. So regionalization can impact capacity but also can impact quality by concentrating a lot more testing in a single facility. Homocystinuria, if it's 1 in 300,000, there are states that have screened for it for the last five years that have yet to see a patient. So just from a quality assurance of your laboratory testing where you like to see a positive go by every now and then just so you get that warm and fuzzy feeling that your system is working just never happens for many of these.

So there's lots of aspects of whether states should be doing testing or should they be overseeing any part of the program, not just testing. Clearly, they need to oversee everything. It's their responsibility at the state level to do that. Whether they should do the testing, whether there will be contractual relationships for testing, there are an enormous range of options that would have implications for capacity. If we keep it all in the state screening laboratory programs, then we have to look not just at capacity but at sort of what are the new technologies coming down the pike looking like, and are those things going to be able to integrate into the classic model of the screening laboratory or not.

But I think a lot of states have already begun to look at the capacity issue and decided to build relationships with others. I think Wyoming does all of its testing through Colorado now and has a relationship for diagnosis and follow-up with Colorado. Oregon Health Sciences, I think we saw the other day, covers Hawaii, Idaho, and perhaps another state. So I think people look at these from their local perspective and develop their perspectives on how they deal with the capacity issue independently somewhat.

But I think once you break down some of the state barriers and think about this is national issues, then you start to think a little bit differently about how one develops capacity.

DR. HOWELL: Piero, do you want to comment about the capacity issue?

DR. RINALDO: Well, first I would like to offer clarification, because I've seen here on a few occasions and in a few comments "test" and "conditions" are kind of exchanged fairly liberally, and that I think is potentially an issue. The panel includes 30 conditions, not 30 tests. This is actually one of the major things, especially we heard from Dr. Alexander now we're beginning to talk about chips. So we'll go to a multiplex platform where one test can cover N conditions, and the N can be now 30, 40, 50, 60. It depends how you count. In the future, it can be heaven knows what.

So if you really want to know, this panel quickly counted would imply 11 tests for 30 conditions, and pretty much no addition if you are the secondary target, as Carol pointed out. So that's one point.

About the capacity, I think there is a reason we have seen now experiments of states putting their best effort to try to develop or add tandem mass spectrometry to their program, which is nice. I think it's certainly a valuable thing. I wonder if that is really the best use of resources. The fact is that you see states with less than 10,000 babies that try to have a lab around 20 samples a day cannot be efficient. It's really not a valuable use of resources, especially when the resources are finite.

So regionalization has been used, but it seems that lately there is a trend that is somewhat different, and I will call it consolidation. Consolidation means that it doesn't follow geographical boundaries. There was a very nice slide that Marie presented with arrows that fly in any possible direction, and for any possible distance for that matter.

I believe that it's really more than trying to create locally. Sometime you really might want to think about what it would take to have maybe 10, 15 centers that provided testing around the country. Would that be feasible? I don't know. There are clearly many obstacles. Would that be the most cost efficient and effective way of doing it? I think so. The question really is which way you go, and I think it's when you really have a goal of universality and uniformity now, I really think it's important to start paying attention to this kind of issue. Whether it can be done better and possibly cheaper in a certain situation, I really think it should be on the table.

DR. WATSON: I do want to expand on Piero's explanation of a test, because it was something that evolved over the course of our deliberations in this project, and that is that the test is a test algorithm, really. It's not just a test. When we screen for cystic fibrosis now, we screen by IRT on the front end, but then we follow it up with a direct DNA mutation test as a second-tier test, and the potential for second-tier tests -- I think they're already significant.

For MCAD, we can fall back on a single mutation that is fairly common in MCAD. We don't have that in all conditions, but when you overlay that with the comments yesterday that 1 in 250 babies are going to come out of newborn screening programs as screen positives, a significant proportion of whom will be false screen positives, building up the ability to do some of these second-tier tests to deal with that false positive situation on the front end -- I mean, it's what we did as congenital hypothyroidism evolved. Some people did T4, some did TSH. Now they all do both, ultimately, either together or one as a second tier to deal with that false positive and really impacting families and moving them out into the private sector system for evaluation.

We can actually reign some of that in in the newborn screening laboratories themselves to manage not sending as many people out who aren't true positives. So there's a tremendous potential for second-tier types of testing, a fair bit which is already done in newborn screening labs, but I suspect over time increasing sorts of capacity to deal with that to minimize sending the ones that aren't true positives out into the system.

DR. HOWELL: I think we have a comment in the back here, and then Carol Green has been very patient. Nancy Green, excuse me. Carol has been much less patient than you have been, Nancy.

(Laughter.)

MS. RASKIN: Hi. I'm Lauren Raskin from the Association of State and Territorial Health Officials. I recognize that right now we're talking about capacity for the testing, but I'd be remiss if I didn't bring up capacity for the whole system. You can give states technology, but they really need to have everything else in place to be able to do a good job with the newborn screening program, and that's following up the children, being able to collect the data, doing some long-term tracking, making sure everyone is educated about the system. So I just want to make sure that this is included as we talk about the capacity. Thank you.

DR. HOWELL: Thank you very much. I think everyone is extremely sensitive about the capability of following up the positive patients and so forth.

Nancy, please.

DR. GREEN: Thank you. I'm Nancy Green, March of Dimes. We're not related, although she does have a reputation for being less patient.

(Laughter.)

DR. GREEN: No. Sorry.

(Laughter.)

DR. GREEN: I wanted to follow up on Dr. Boyle's comment about the long-term treatment follow-up and evaluation if you're screening in particular for disorders for which the rarity necessitates lack of good treatments or good follow-up. I think, Dr. Howell, you'll appreciate, as a fellow oncologist, the example of neuroblastoma screening in the Japanese experience, screening for an unusual disorder through a urine test, not blood spot. After a number of years of collecting very rare patients, evaluating that, the early screening was in fact detrimental to the health of those children who were affected by neuroblastoma rather than effective.

So I'd just use that as an example to both remind the committee that newborn screening goes beyond metabolic disorders in its potential, and also in particular to address the issue of not only regional but probably the need for national databases and study groups akin to what happens with neuroblastoma treatment in the U.S. for really long-term outcomes and organization around treatment, because while that's certainly way beyond what the states' current capacity is, as this issue of newborn screening for disorders for which there's less and less data moves forward, I think that then increases the pressure on a national level to do collective treatment and follow-up for these affected children.

DR. HOWELL: Let me comment very briefly about that. I think that the whole ethical/legal/social issues surrounding newborn screening are very important, and Dr. Alexander mentioned that. But the other thing is that the Genome Institute has just finished a round of grants to set up special interest centers, centers of excellence in ELSI research, and they had a dramatic response to that, and they have just announced funding of a number of those, with anticipated co-funding from some of the other institutes. Some of those are focusing on newborn screening. We hope that they will be looking at the sort of thing you're talking about. It certainly is a great opportunity to do that.

Piero?

DR. RINALDO: I would like to go back for a second to comment about capacity. I think one important distinction here is really to understand that the analytical capacity ought to be considered differently from the follow-up capacity. I am, like Carol Green, I don't shine for patients, but last week somebody told me that nine women couldn't have a child in one month. It made me elaborate on the fact that there are certain things that cannot be accelerated, done sort of faster. But the testing, there is an efficiency intrinsic in consolidating the testing and supporting the best possible way the follow-up and all the other components of a screening program at the local level. But the testing is somewhat of a different entity. It can be seen differently.

DR. HOWELL: I've always been impressed with the extraordinary capacity of tandem mass spectroscopy as far as a given instrument and reliable results, which is very impressive.

Bill, and then Reed please.

DR. BECKER: A question for Mike. I believe one of the secondary goals of the project was something you didn't have a lot of time to elaborate during your formal presentation. It addresses the issue of quality, quality assurance, particularly as it revolves around the testing. Would you comment on how that's going to be in the report and some of the recommendations that come out about that? Because I think it addresses a little bit of the concern for analytical capacity that Dr. Rinaldo is mentioning.

DR. WATSON: That's a difficult one, and we spent a good bit of time looking at it, because the ways by which one manages quality varies across different parts of the program. Commonly, medical practice is regulated through laboratories. So there's a lot of capability of managing quality directly through the laboratory piece and regulatory components that are imposed on it.

Then we move to the diagnosis and follow-up side, where we're in the practice of medicine side of the equation where guidelines, standards, and those sorts of things tend to drive the quality of the system. So that inherently makes it difficult to sort out all of the quality issues.

If you look at what exists now, we have a program in place at the CDC, the NSQAP, that looks at that initial screening stage. After that, we don't have much in place for quality assurance. The CAP/ACMG proficiency testing programs that deal with the laboratories who do the confirmatory diagnosis in those patients, they have a program, but most of the conditions on my list of even the primary targets are not things that we specifically target in proficiency testing. We end up making sure somebody can do an organic acid analysis, for instance, or some other more general type of proficiency, and then use that to extrapolate that if they can do it for that condition, then they can do it for these conditions as well. It's hard to do that when something is as rare as some of these conditions are.

So I think we're looking at how one can drive quality across the full spectrum of the program, and it's going to be a mix that's specific to each of the components along the way.

DR. HOWELL: Reed, you had a comment.

DR. TUCKSON: Yes. A lot of the comments that are being made are starting to focus us towards some of the consensus building around how we want to proceed after this meeting. I think Jennifer's points were very good in that regard.

Piero's comments a few moments ago sort of really make me also want to understand, as we organize ourselves going forward, more about the actual efficiency. As we try to get at this idea of what is the standard set of measures that ought to be recommended, if we in fact do, and I'm sensing a momentum towards getting to a standardized set of universal measures that all the states would implement. If that is true, something about the cost efficiency of more is more efficient than fewer. If in fact that is true, to try to understand that better, because it seems logical.

But then the second point that comes from that is the ability of the states to be able to assemble that information and to do something with it in a rational way, as we heard from our ASTHO colleague a moment ago, and others. So I think one of the things we're going to have to get at is trying to understand what does it take to make sense of this in a meaningful, clinically relevant, family supportive way.

Then finally, I continue to come back to this question of -- and again, because I'm less sophisticated than others around the table about this at the technical level -- what is the relationship, then, between the new DNA chip or assay test and these tandem mass specs? Is there an inevitability around the technology in the next two or three years that sort of says let's don't get caught recommending things that are already not outdated but certainly not current going forward. I'd like to find a way in which the committee can learn a little bit more about that going forward.

Last and finally, because I may not be here for that part of your discussion -- I've got to step away, and I'll come back -- is the overall concern around how are we able to make recommendations, even through grant support to the states, that is rational and reasonable given the budget and other financing problems that states have and all the multiple competing public health, in addition to other health concerns? So this issue of the cost efficiency, the cost effectiveness of what we recommend, the practical implementation of these things is just -- I mean, I know it's on everybody's mind, but I think those are real important issues for the committee to at least take a real sober look at so we don't wind up appearing a little irrelevant if we make overly broad, sweeping recommendations.

DR. WATSON: I can tell you that one of the things that will be in our report will be a stunningly basic cost analysis, cost effectiveness analysis. But we felt like we needed to do it, and I think it's worth hearing about, because the issues that arise when you begin to think about cost effectiveness are actually kind of interesting and they're things you're going to have to factor into your decisionmaking. If we don't screen for something, there are likely costs to the system, and those people are going to have to get into a diagnosis and follow-up system of some kind, if they're lucky. If they're not lucky, then they'll be managed at some level of the system not knowing what they have, probably, and that is a very costly diagnostic odyssey that can't be ignored.

So that's an aspect of cost that's kind of hard to tease out of this, is how many would have a specific cost to the system if they had not been detected. Most of what we know about the cost stuff is very short term, as well, and they relate to the states' investment and the states' benefits, my sense has been with limited acknowledgement of sort of the long-term benefits in the system of having identified someone, and those may be benefits that accrue in the private sector and into the public that have not always been well acknowledged, I think, in the cost effectiveness analyses that I've seen.

But what amazed me about the stunningly basic cost effectiveness study we did was that for something like newborn screening, if you use quality adjusted life years as your measure of whether or not you should or should not do something, the bar is set pretty high, or low I guess. I think it's $50,000 per QALY is what we already acknowledge that we should do things about. Newborn screening tends to have a much better cost effectiveness analysis attached to it because you're doing something that impacts a child as a newborn, and therefore you accrue so many life years of quality that it tends to win in those analyses in the end, just because you've started so early, and what we are screening for are things that are treatable, where we have a clear difference in outcome and benefit to society in productivity.

DR. HOWELL: We have a considerable flurry of interest. All that buzzing you hear is Brad Therrell has been with us all morning on the phone, and he is very excited out in Austin, Texas, to tell us something.

(Laughter.)

DR. HOWELL: Brad?

DR. THERRELL: It's raining here. But actually, I've been very interested in the discussion.

A couple of points. One is that Piero's comment about regionalization of the laboratory I didn't quite understand, because there are plenty of examples around of the regionalization of the follow-up as well. So I think that eventually you're going to need to look at the examples that are out there and analyze those, as Reed was mentioning a minute ago.

Also, you shouldn't lose sight of the fact that there are some state laws that actually mandate that testing must be done in a certain laboratory in a certain way, even to the point of prescribing the technique that's used.

And then finally, this issue about data is an interesting one that one that's going to be very difficult to solve in some cases because we're talking about public and private data that we need to get, and it's always been an issue how do we get the private data. An example of the difficulty right now is, for instance, with G6PD, Marie mentioned that G6PD screening is mandated in the District of Columbia and Mississippi, and yet in neither case do we have any data about the follow-up, whether the test is sensitive or not, and what we're finding from that disorder. So as the disorders are picked up by the states, there needs to be some guidance as to how that data is collected and what's done with it.

Thanks.

DR. HOWELL: Dr. Alexander has been patient.

DR. ALEXANDER: A question for Mike. One of the criteria that you listed was frequency of disorder, and this I assume is based on a cost effectiveness decision. Most of us have had experiences talking with moms whose child has been damaged and had a condition that was not screened for because it was too rare to be cost effective. This has always bothered me. In fact, this is one of the motivations for trying to pursue this microarray approach, to be able to screen for many, many, many disorders and conditions with one test.

I'm just wondering if, in fact, the add-on cost of these rare conditions is essentially zero because you're using the same test to screen for it, whether that would modify your use of that criterion to either eliminate it or diminish its significance.

DR. WATSON: We thought about that. I mean, we have this array of conditions to look at when some were really evaluated on an individual condition basis. Cystic fibrosis you look at as an individual condition because the screening test is very unique, coupled to a DNA test.

In our system what we did was build in at that multiplex level more points than you could get from incidence alone. So even if homocystinuria, because it's 1 in 300,000, gets no points for incidence, because it is a freebie in the multiplex tandem mass spec system, it picks up 200 points and offsets what it lost for incidence just because it is still cost effective to get it because it's part of the information already available in the test. So we tried to look at it from that perspective and kept it in for that reason, because not everything could recover points in another part of our system.

DR. HOWELL: And we have a Alissa at the microphone here.

MS. JOHNSON: Yes, hi. Alissa Johnson, NCSL. I just wanted to respond to one of Dr. Tuckson's comments about practical considerations. I alluded to yesterday that genetic statutes may be one practical consideration in states trying to implement core standards, and there are certainly some other issues such as whether new conditions or new tests are added in our statutes or regulations. NCSL would certainly be willing to help develop perhaps a set of questions once you have core standards that

states might need to ask before they move forward, and the answers to those questions are going to be different in every state.

I have done some work with this in NCSL with Brad Therrell. He would be a great resource also. But we'd certainly be willing to help at that stage in any way we can.

DR. HOWELL: Thank you.

DR. WATSON: I'll add on to that to really encourage you to follow up on that, because we began looking at some of these state policies early on, and some states say you're screening for metabolic diseases. Their legislation doesn't let them add CF. Some screen for genetic diseases, and their legislation doesn't let them do something else. Some do specify what conditions are screened. Some do specify where that screening will be done. So there is this enormous array of policy and legislation and the way all that crap is interpreted that you're going to have to try to sort through.

(Laughter.)

DR. HOWELL: Alissa's help will be greatly appreciated.

Piero has been waiting, and then Reed.

DR. RINALDO: I think the question Dr. Alexander asked is actually proof to me that something is right in those criteria, because those criteria really are trying to address something that hasn't really been done before, and that is trying to compare apples and oranges put together in a comparable, similar, or unified scoring system conditions that have historically never have been linked together.

So that's why the only endpoint at this point -- I think it's proper to say that if there is no test, and at this time there is no test, end of story. But for all the others, you might actually have a very low incidence and get no points, and yet because of the weight of the other factors, be competitive. So the fact is, if you remember, this has to start somewhere, and we started from the Wilson and Jungner, where the criteria had to be common, there had to be a treatment, and also that the test had to be simple. So I think of those criteria as important, of historical significance, begin to show their age.

That's why, I think, we have to do two things. One is really put in a way that nothing or scoring poorly in one particular criterion is not a final blow. It's just allowed to put things in perspective. The second one that I think is very important -- again, Alissa, your point -- is putting the emphasis that now the primary, the main stakeholder, is the affected newborn, the child with the disease, and the rarity of the condition the child has is I wouldn't say (inaudible), but it's certainly weighted or mitigated by many other factors.

I just want to make one more comment. Brad Therrell is absolutely right, sometimes we're dealing with real rigid language in state laws, but perhaps it's time to have another Boston Tea Party. Those laws need to be repealed somehow, because they were really ill advised.

DR. HOWELL: We have a helper who has volunteered to help on that subject.

DR. RINALDO: The other point is that I think nobody for a moment thought that when we put the emphasis on education, that excludes legislators. We really have to educate the legislators. Some states I think have done the right thing. Some states I know have language that says that the extent of the panel will be really decided by the state advisory committee, and that is perhaps a much better approach to things. I think that Mike is right, having states with all the conditions but then don't let you do other things, that's the wrong approach.

DR. HOWELL: Now, Reed, you be your eloquent self, because you're the last person before we leave for lunch.

DR. TUCKSON: Everyone is going to throw things at me now.

As part of the Boston Tea Party movement here, one of the things that I don't think I've thought about as much before, but maybe we might benefit from understanding better around the grants process or public -- what is it, 1090?

DR. LLOYD-PURYEAR: 1109.

DR. TUCKSON: 1109. The point being that if you think about things like -- I don't know whether there are lessons to be learned from things like highway grants, seat belts, where people don't want to change, or the speed limit or whatever it is. They don't want to change, but because of the federal money that comes down the pike, that gets the state legislators' attention for that. So I just want to make sure if we know that there's any role that the Secretary can play and that we might be able to support in terms of our advice to the Secretary around this notion of the way in which the grant funds are used to try to get folks to be on the same page we want them to be on. Just something I want us to look at.

DR. HOWELL: We have one brief comment, apparently.

PARTICIPANT: And it will be a brief comment. I just wanted you to have a comment from a user group. I have a hereditary disease, multiple hereditary exostosis, and because we have a very, very strong support group, we now have a genetic test for this. This test is very rare. But I want you to know that I receive a lot of emails from people who haven't been able to have this test. There's an email from a man who has a son who is two years old that has these bone growths all over. But my son, because he's had this testing, he and his wife will be able to take part of this preimplantation genetic testing in Chicago, and hopefully within one generation we'll wipe out a disease, and I think that's just terrific.

So I wanted you to hear something from a user.

DR. HOWELL: Thank you very much.

I think that we have had a wonderful and very fertile discussion of this very important report, to which we're looking forward.

But let's return at 1:15, and let's be prompt. We have a number of distinguished persons who are joining us after lunch to present in specific areas. So we'll be back at 1 o'clock, 1:15, and we'll start off with Tony McKinney.

(Whereupon, at 12:15 p.m., the meeting was recessed for lunch, to reconvene at 1:15 p.m.)

AFTERNOON SESSION (1:20 p.m.)

DR. HOWELL: Ladies and gentlemen, we're very pleased to have a considerable number of folks making comments this afternoon. I think one of the things is that although each of the people speaking has a lot of important information, we're going to ask everybody, as we had in writing, to stick closely to five minutes. I even have signs over here that have evil words on them should you get a little bit too long-winded, because it's important that we have a chance to hear from everybody, and I know that many people have very tight schedules this afternoon. So we do want to stick with that.

The first person on our agenda today is Anthony A. McKinney from LysoPlex.

Tony?

MR. McKINNEY: Thank you very much for this opportunity to speak to this committee. Also, thank you for your work on behalf of the kids and the families with these inborn errors.

My name is Anthony McKinney. I'm the president and CEO of a start-up company called LysoPlex, LLC. We are dedicated to developing technology that was discovered in Australia by Professor John Hopwood for screening newborns with the lysosomal storage diseases, the other category that we've heard about all day today.

I come to this newborn screening world from the perspective of the pharmaceutical and the biotech industry, where I've been involved with the development of treatments for these kids via both enzyme replacement therapy as well as gene therapy. As you know, LSDs are a group of approximately 50 inborn errors of metabolism resulting from mutations in enzymes comprising the normal degradation pathway of normal cellular biomaterials. As a group, the LSDs are among the most frequently observed genetic diseases, with a combined incidence of around 1 in 5,000, actually quite common.

Put into perspective, this group has an incidence of approximately half that of CF, but certainly several times larger than many of the diseases that are already currently screened. The difference with LSDs from the classically screened diseases is that simple measures such as changes in diet, prophylactic penicillin, or avoidance or fasting, cannot improve these patients' outcomes. Therapeutic action must be taken, and in many cases be taken very rapidly before severe damage has taken place. Children with LSDs often experience severe mental retardation in many diseases, or organ failure in others.

For example, children with the infantile form of Pompe disease generally die of heart and lung failure within the first year or two of life. So the action here involves replacement of the deficient enzyme through bone marrow transplant or exogenous replacement of the deficient enzyme -- in other words, enzyme replacement therapy. The FDA has recently approved substrate inhibition therapy that is helpful in certain situations.

These measures are not inexpensive, nor in the case of BMT innocuous. In spite of the drawbacks, however, these therapies are the only option for these kids, and in time, though, my hope is that gene therapy and/or stem cell replacement therapy will be a cure for these kids rather than these symptomatic treatments now.

In every case, determining that the child has a treatable LSD is the trigger that initiates therapy. If treatment is sought after the beginning of symptoms, it may be too late. In some cases, therapy must be initiated within days or weeks following diagnosis, whereas in other situations it may be okay to just simply monitor the patient and wait until the patient needs therapy. Regardless of when therapy is initiated, we believe that providing a diagnosis to the parents will enable them to plan for the future not only in establishing the diagnosis for their children but also in planning for future pregnancies.

One of the tragedies we hope to avoid is the subsequent birth of affected kids while the parents are still trying to gain a diagnosis for the first child. This happens all too frequently, and in my work I've seen this occur dozens of times.

So what is it that LysoPlex is asking of you? First, continued advocacy for universal access to newborn screening. We acknowledge that states have primacy when it comes to newborn screening. However, all kids born in the U.S. should be protected through universal and equal access to testing regardless of where they're born. The current system is complex and unwieldy, particularly when it comes to the financing of newborn screening. Concentration of expertise in regional centers with substantial federal support could potentially be a route to universal testing. Regionalization, as we know,

is already occurring. We believe that this trend, combined with the resources of the federal government, could be a solution to the fractured current structure of newborn screening.

Second, continued support for the development of new technology which enables testing for inborn errors beyond the current group of screened diseases. We are taking forward a novel multiplex technology which enables simultaneous measurement of multiple lysosomal proteins. As a small, flat organization, biotechnology companies like ours can often translate discoveries into approved procedures faster than other organizations, especially when combined with ready access to the federal government's resources and expertise. The ability to rapidly mobilize these federal resources could be extremely beneficial to a start-up that must often bootstrap themselves up from a very modest base prior to real professional investment.

That's all I have today.

DR. HOWELL: Thank you very much, Tony, for that informative presentation.

The list I have I think was comprised from the people in the order that they wrote Michele and so forth, rather than any other mysterious listing.

The next person on the list is Ms. Jill Fisch, who is a parent that would like to address the group.

MS. FISCH: Should I sit there?

DR. HOWELL: I'd prefer -- I think you'd be more comfortable here, and if you would be good enough to push the little green button on the microphone so that we can hear you, Ms. Fisch.

MS. FISCH: I promise I'll be brief so you don't have to hold up your sign. Thank you for giving me the time to share today. My name is Jill Fisch. I live in Scarsdale, New York, with my three children: Zachary, who is 12; Sarah, 8; and Matthew, 3; and my husband Peter, a partner in the international law firm of Paul Weiss. I am the New York State monitor for Save Babies Through Screening. I am also a parent representative on the Newborn Screening Task Force in Albany and the president of Matthew's Mission. I have also recently started working with the Hunter's Hope group regarding newborn screening issues.

My son Matthew suffers from short-chain acyl-CoA-dehydrogenase deficiency, SCAD. SCAD, as you all know, is a disorder in which the cellular enzyme responsible for processing short-chain fatty acids is missing from the cells or working at a diminished capacity. This disorder can cause failure to thrive, developmental delays, hypotonia, or even death. We started Matthew's Mission to promote newborn screening awareness as well as raise money for SCAD research.

I became very involved with newborn screening when I realized that after spending two years trying to get Matthew diagnosed, this was something that could have been screened for at birth. Matthew now has a feeding tube, significant hypotonia, and various other issues. After finding out he was carnitine deficient, he was started on Carnitor and gained a tremendous amount of weight. If we had known from birth and he had started on the regimen he's on today, it's quite possible he could have had a different outcome. We will never know what Matthew's full potential could have been because he suffered so many setbacks while we were looking for a diagnosis.

Finding out about Matthew caused us to find out that I, too, have SCAD. Matthew probably saved my life. New York has the equipment to test for 60 disorders but currently only screens for 11. One answer to this problem would be for the states to use resources in the private sector to provide the supplemental screening. Most parents do not realize that screening occurs or that options for more

comprehensive screening are currently available through private labs. Unfortunately, we were one of those families.

New Jersey has enacted legislation mandating that parents be informed of additional tests available but not offered by their state program. This should be true of every state. Parental notification of supplemental screening must be made mandatory. Babies are being born every day, and many are suffering adverse consequences from lack of screening. Comprehensive screening ensures that newborns are getting the best chance of starting a healthy life. I wish that Matthew had had that chance. Congress should require states to inform parents in writing regarding outside screening through private labs. States that do not screen for all disorders should contract with an outside source to provide the comprehensive screening until the states are capable of doing the testing themselves.

Mississippi screens for all disorders through a private lab, with fantastic results. Don't all our babies deserve the same chance? We feel our rights as parents were taken away since we were never informed of supplemental screening. This is something that can be changed and is being changed in different states as we speak. We want to see every family give their baby the healthy start that it deserves. That is the goal of Matthew's Mission. Thank you for giving me the opportunity to share it with you today.

DR. HOWELL: Thank you very much, Mrs. Fisch. We appreciate your coming and appreciate your kind words. Thank you.

The next person on our list is representing the Hunter's Hope Foundation. Mr. Jim Kelly has come down from Buffalo.

MR. KELLY: Is this on? I'm colorblind.

DR. HOWELL: No. There we go. A red light and a green button is a bad combination for you.

MR. KELLY: That's right, that's for sure. But I saw her hold up the two-minute thing. I'm used to two-minute drills. I might have to call a few time-outs, though, because I'm losing my voice. But thank you very much.

First of all, I just want to thank you very much for all your hard work. For me, this personally hits home. During my football career, just real briefly -- I know this is not in the statement, but I spent a lot of time this past weekend with some of my friends who have special needs children, and just by talking to them and some of the things we're working on, and just really getting into a heart to heart with these guys, when I told them I was coming here, they said their special acknowledgements, too. So again, from everybody at Hunter's Help and all my friends throughout the NFL, there are nine quarterbacks through the last few years that have special needs children, and this hits home for all of us.

First of all, I just want to thank you for the opportunity to testify today. I became involved in this support concept of early detection as a result of my son Hunter and him having the disease called Krabbe leukodystrophy. Krabbe disease is an inherited neurodegenerative lysosomal enzyme disease affecting the peripheral and central nervous system. Without early detection, children like my son Hunter suffer through the rapid progression of this disease. My son Hunter is currently on oxygen 24 hours a day, cannot move or speak, is fed through a JG tube, receives treatment every four hours and around the clock, testing with a vest, and of course CPT. He takes multiple medications.

In contrast, children born with Krabbe disease with early detection have access to effective treatment with -- and this is going to be a tough one -- hematopoietic stem cells using umbilical cord transplant. This cord transplant prevents neurological damage, halts or alters the disease process, reverses the manifestations of the disease in the central and peripheral nervous system, saves lives and preserves quality of life.

It is because of the need for early identification that I am now involved with improving newborn screening. If Hunter had received early identification, he would have had access to the effective treatment, the stem cell transplant using umbilical cord blood. Children born with Krabbe disease who are identified presymptomatically, currently only possible in case-index families, have had their lives saved and are now growing up and are expected to live productive adult lives.

Our foundation, the Hunter's Hope Foundation, which my wife Jill and I started in 1997 to increase awareness and accelerate the pace of research with Krabbe and other related leukodystrophies, has already awarded over $3.8 million in grants. Last weekend our 7th annual scientific and family symposium was attended by more than 30 families, and a number of distinguished basic and clinical researchers were there. During the symposium, I had the opportunity to spend time with many children with Krabbe disease, including the children who were treated presymptomatically. It is because of the dramatic difference between children like my son Hunter, who did not receive early identification, and those who did that I am speaking here today.

With newborn screening tests for four leukodystrophies due to become available within the next few years, I am here to share with you our commitment to ensuring that all the children in all our states receive all existing newborn screening tests possible.

Today in the United States, thousands of children are suffering and dying needlessly. I have heard appallingly large numbers, that thousands of infants in the United States with treatable diseases go untreated each year and die due to inequities in the current newborn screening system. The current NBS system is legislated by state, as we all know. The range in number of diseases tested is Alabama, screening for four diseases, up to Mississippi, at the top of our list. Twenty-nine states currently test for 10 diseases or less. New York is one of the ones that tests for 11, just one over.

Children are suffering and dying needlessly because they are born in the wrong state at the wrong time. A child's chance for life should not depend on where he or she is born. No child should be denied the right to a healthy life, nor should parents' rights be denied to know that their children are at risk due to the inequities from state to state newborn screening. It isn't possible to fully express the devastation that these illnesses bring to the entire family.

There is a cost for freedom from disease, but the cost for the alternative is much, much greater. It extends far beyond our comprehension. I can't help but think that if we had received terrorist threats for thousands of our infants and they were going to be killed at the end of 2004, I think our nation would use all the money and the power that they had to stop it, and they would stop it. We have a worse threat right here today in our midst that is silently killing our children. It is within the very system, newborn screening, that we established to help our children.

Why are the state public health departments not using all the valuable resources, including private sector resources, to screen infants at birth? I do not understand how this can be in the best interest of the public health. I know that once our legislators understand the importance and the need for important action on this issue, we are confident they will help us.

We recommend that this committee encourage Congress to require states to inform parents in writing of the potential for their children to receive additional newborn screening tests that may not be required under state law. We must start by mandating that hospitals educate parents of the availability of supplemental NBS tests. This parental notification must be meaningful in informed and required consent. We must immediately put a plan into place for adding all testable and treatable diseases to every state on the nation's mandatory NBS list.

The solution seems so simple. Screening tests, technology and treatments are all available today. We just need to use them. We need to fix our current NBS system so that currently available resources are used to give every child the right to a healthy life.

Again, thank you all very much. I know at times this was lengthy, but I just want to make sure that I got my point across because I see what happens with my son, and I know back then that if he was treated early enough, he could have the quality of life that I see with some of these kids that go through the screening tests. I can see them walking, talking, and smiling now. Thank you.

DR. HOWELL: Jim, thank you very much. I think that this committee appreciates your devotion, and I think we're going to need the help of you and all the other people that have and will be speaking to try to get some consistent first-rate program with equal access across the country, because we certainly agree with those sentiments.

MR. KELLY: I appreciate it. Thank you very much. Thank you.

DR. HOWELL: My best to Jill and to Hunter.

Next on my list is Mrs. Jana Monaco. Mrs. Monaco is representing the Organic Acidemia Association and the National Coalition for PKU and Allied Disorders.

MS. MONACO: Good afternoon. It's an honor to be here on behalf of the Organic Acidemia Association and the National Coalition for PKU and Allied Disorders. Most importantly, I am here for my six-year-old son, Stephen, the third of four children, and to tell you about the harsh reality of undetected inborn errors of metabolism.

Three years ago today, I was sitting in Stephen's ICU room trying to determine when to discontinue life support. Ten days earlier, Stephen had contracted a typical stomach virus. However, I found him the next morning in an unresponsive state that no mother should ever have to endure. He was transported from one hospital to another. His tests indicated severe acidosis, leading them to suspect a metabolic disorder. The initial tests eliminated certain ones, but others had to be sent out. Twenty-four hours later, Stephen was diagnosed with isovaleric acidemia, a very treatable disorder found through reliable testing.

Unfortunately, Stephen's diagnosis came too late. He had slipped into a coma. While preparing for an MRI, Stephen went into seizures. Within minutes of returning to his room, he had crashed before our eyes. After a great deal of intervention, Stephen was clinging to life on a respirator. The MRIs revealed swelling around the brain stem and extensive damage throughout his brain. As you can imagine, we were devastated at the thought of losing our son. How could such a happy, healthy, energetic, normal child come so close to death in such a short time?

While we were trying to come to terms with his prognosis, we discovered that Stephen was a walking time bomb waiting to ignite and that this whole situation was preventable had he benefitted from comprehensive newborn screening at birth. We had also linked a similar episode at 18 months with the disorder, but the doctors failed to recognize the signs and symptoms. They had acted within the standards of care for a small community hospital, standards which we now know had a direct impact on his future. Hindsight is brutal.

Stephen started to show signs of progress, and after three and a half weeks he received a gastrostomy tube and was removed from the respirator. He was then transferred to Kluge Children's Rehab Center in Charlottesville, Virginia for six long weeks. Since then, Stephen has made progress. However, he is far from the little boy that we once knew. He requires total care, continuing to be fed via G-tube. He cannot walk, talk, sit up, nor hold his head up without support. He is also legally blind. Stephen takes four anticonvulsant medications, yet still has three to four seizures per day. Due to his neurological state, hiccups last four to five hours and usually result in a hospital stay because of GI bleeding. He recently had surgery called an orchiopexy to bring his testicles down that retracted due to spasticity.

Our days are filled with therapies and numerous doctors' appointments. I spend many phone hours settling insurance disputes. His medical costs have exceeded the million dollar mark and continue to climb. Stephen is now under the school system with an IEP and has been assessed at the functional level of a two-month-old. We are waiting for his second wheelchair, at a cost of about $5,000. I ask you, is this cost effective?

Gone are Stephen's opportunities for a normal life because our government and health system continue to debate the cost-effectiveness of universal newborn screening. Stephen's fate was already determined because he was born in Virginia, where only eight disorders are screened for. Had he been born in North Carolina, where the list includes 36, Stephen would be in a normal kindergarten class this year instead of occupying a special education slot.

It is a travesty that Stephen is a statistic at the hands of bureaucracy and lack of knowledge within the medical community. While the debate continues, more babies and children are going to die or share Stephen's fate. Yet the equipment and knowledge to avoid this already exists. The life of my Stephen and the thousands like him born each year should not be so devalued. These disorders can be debilitating and deadly if not caught.

A testimony to the significance of early detection is our 20-month-old daughter, Caroline. With the knowledge we gained with Stephen, Caroline was diagnosed with the same disorder through prenatal testing. Early diagnosis enabled the doctors, one being Dr. Carol Greene, to establish a protocol of care prior to her birth. With a restricted protein diet and medications, Caroline is doing very well and developing normally. She is a typical happy, healthy toddler, thanks to early detection. Unlike Stephen, she will have a normal childhood, and she will have dreams.

Although Stephen has suffered severe brain damage and dreams have been lost, we know that his life has a purpose, and we will see to it that it is fulfilled. Thank you to the advisory committee for your attention and dedication towards expanded newborn screening.

DR. HOWELL: Thank you very much, Mrs. Monaco, for coming and sharing your story of Stephen's illness with us.

The next person on my docket is Dr. Philip Vaughn from Pediatrix Screening.

DR. VAUGHN: Mr. Chairman, members of the committee, my name is Philip Vaughn. I'm a neonatologist currently serving as vice president of Pediatrix Screening, one of the private sector labs that's been referred to earlier. By way of introduction, I would like to mention a few brief words about Pediatrix' medical group, which is the parent company of Pediatrix Screening, in order that the committee can better understand how newborn screening complements and acts as an adjunct to our focus in newborn care.

Pediatrix Screening is currently the largest provider of newborn both maternal/fetal medicine and neonatology specialty care in the United States. We care for over 3,000 infants a day, and importantly we aggregate the information about those infants we care for into a clinical database through a unique information system we developed, in order to create an opportunity to learn and to more rapidly bring innovation and new practice concepts to the bedside. We have evolved a system of best demonstrated practice, as well as participating in clinical research trials, multicenter clinical research trials in order to generate the type of evidence-based information to appropriately modulate our clinical practice.

Our interest as a medical group in newborn screening started over a decade ago with newborn hearing screening. We evolved a newborn hearing screening program that focused on a high-quality program and made that available on a universal basis to a number of hospitals nationwide and are very proud of our history of acting in a position of advocacy for newborn hearing screening and seeing that program evolve.

We're now also proud to have in our company a metabolic screening laboratory that provides a very broad-based, comprehensive group of services in newborn screening that makes available a spectrum of testing that encompasses multiple different technologies -- biochemical, tandem mass spectrometry, as well as DNA-based technologies -- in order to provide the most useful clinical information to the bedside in a rapid time frame, which we all know is vitally important in the treatment of metabolic illness.

Rapid turnaround time is an important quality metric for programs and one that we mustn't forget as we move forward in programs. Equally important is the concept of positive predictive value, making sure that the information that gets to the bedside leads quickly and accurately to an appropriate diagnosis without encumbering the system of newborn screening with unnecessary costs that are caused by false positives.

We recognize that the committee has a very unenviable task of trying to generate public policy with regard to the evolution of newborn screening, and that's a difficult task on many different levels, obviously a complex one. We would like to thank you. We would like to submit that we represent an entity that can act in partnership with states to bring a spectrum of testing in multiple different ways that can be tailored to meet the needs of a newborn screening system with any state. We're happy to be a part of that solution in Nebraska, in Mississippi, Maryland, the District of Columbia, and soon once again in the State of Pennsylvania.

In addition to that, we work with hospitals as another avenue to provide expanded comprehensive screening to newborns in multiple different states, again advocating for universal screening programs to ensure that all infants get access to a comprehensive panel of testing.

The disparity that currently exists is broad, as has been mentioned, and we feel very strongly compelled to restate what has already been stated, that being that parents should be advised of the opportunity to have additional testing performed in states where a comprehensive panel of testing is not available. We feel that's important. Obviously, parents' groups and parents who live with the consequences of disabled children would say had we only known about our opportunity to get more testing, and given that the capacity for that testing currently exists, the capabilities exist, the opportunity to utilize those capabilities to improve the health and welfare for a lifelong benefit to infants is very important.

In closing, we'd like to add that if there's any way in which pediatric screening can act as a resource to the committee as they move forward in the evaluation, please feel free to give us a call. Thank you very much.

DR. HOWELL: Thank you very much, Dr. Vaughn, for joining us and bringing us up to date on the Pediatrix program.

Mrs. Micki Gartzke, who is director of education and awareness for the Hunter's Hope Foundation, is next on the docket.

MS. GARTZKE: Hi. I'm here speaking as a mom today, although I am the director of education and awareness for the Hunter's Hope Foundation. I'd like to say right up front, before I get any two-minute warnings or I'm told to stop, because I'm a little nervous I might go over. So thank you very much right up front for all of your work. This is a very important time for all of us, and I think what you all are doing is going to save a lot of children's lives in the future.

I really appreciate the opportunity to share comments with you. We're here to improve newborn screening, which has not kept pace with the current needs of public health, and I want to let you know that I'm here to help you help all of the children to receive equitably distributed newborn screening and

their right to a healthy start in life. We all know babies are dying unnecessarily because of lack of early identification and access to treatment.

My daughter LeA died because she did not receive early identification. There is treatment for her disease. It's the same disease Hunter Kelly has. But it needs to be started within the first 60 days of life. My daughter did not get diagnosed until she was 10 months old, a full six months after we started looking for a diagnosis. Consequently, treatment was well out of the range of possibilities by the time she was diagnosed.

I know a little boy who was born with the same disease as my daughter. He was born 10 days before my daughter. He was identified at birth. My daughter was identified when she was 10 months old. Today he's in first grade, and my daughter has been buried in her grave for five and a half years. The reason he received early identification was he came from a case-index family. So I have a very clear example of what newborn screening will do for children with diseases similar to my daughter's.

My daughter's medical bills in her short two years were about a quarter of a million dollars, so it was not inexpensive to maintain her until her death. Her death is one example for the native universal newborn screening, and this committee can greatly help many families in the United States by making recommendations to Congress about how to improve newborn screening.

I would like to share a few of the details of our lives, my husband's, my daughter's, and mine, so you can see inside of a family who has lost a child due to a lack of early identification and all that that means -- loss of love, loss of companionship, loss of hopes, loss of dreams, loss of potential, loss of productivity, just to mention a few.

My daughter was born October 14th, 1996. She did everything just like a new baby was supposed to. At her four-month check-up, our pediatrician examined her and declared that she was doing wonderfully. After the doctor was done with his duties at that appointment, I said so what's up with these thumbs? They used to be out, and I showed him what I meant, and then I showed him that they were just doing this tucked-in thing, and he had not seen that in the four-month appointment. So when I looked up from my daughter's hands, I saw my pediatrician's face turn white, and in the next split-second he said to me that thumb thing you described is called cortical thumbs, and it's generally indicative of a neurological problem; we'll have to get you over to see some specialists to find out what's going on.

So for the first four months, she was apparently a very normal baby, and there was this little clue that even my pediatrician did not recognize. Our lives changed just like that. Shortly thereafter, the uncontrollable, around-the-clock, unsoothable crying started, and it changed in one day -- again, just like that. From a happy, smiling and laughing child, LeA went straight to a crying baby with a rigid, stiff body, not able to eat, and she was inconsolable, and it was devastating.

We spent the next six months chasing all the clinical specialties around at the hospital from one misdiagnosis to the next. We orbited the hospital. We heard reflux, colic, cerebral palsy, we heard all the umbrella terms. We never got a diagnosis. We still kept looking. Finally, her second MRI showed us what the first MRI did not. The first MRI was inconclusive. The second MRI showed us that it was a white matter problem, probably a leukodystrophy. They confirmed it with an enzyme diagnosis, and it was globoid cell leukodystrophy. By then we had learned about the disease through our own reading, knowing that this problem was crucial to forming myelin development.

At that time, when the doctor told me about the disease, he said it's fatal, there's nothing you can do, take her home and make her comfortable. That was the end of what I think of was Stage 2, and it happened to be my birthday, so it was not a nice birthday gift to just be treated so callously.

We went home after the diagnosis and we had an NG tube, and then we got started with the G-tube, and then hospice became a big part of our lives, along with feeding pumps, suction machines,

specialty formulas, daily sessions with OTPT, nurses living at our house. My daughter remained stable, if you can call stable anything having to do with feeding tubes and oxygen.

The remaining ten months of my daughter's life continued with feeding tubes, formulas, but then I learned about deep suctioning. I can do deep suctioning, and I don't think a mother should know how to deep suction her child.

We had pneumonias, 36 doses of medicine a day, DNRs. Learning how to fill out a DNR on your 13-month-old child is not something a parent should do.

With the great help of many hours of private duty nurses and a great set of family and friends, we were able to spend quality time with our children. My daughter was robbed of her life on November 2nd, 1998. Her story is but one that provides testimony to the significance of early detection.

Please help save other families from having to share stories with you like this. The Children's Health Act of 2000 had promised to help fund state expanded newborn screening but has yet to follow through with the money. Perhaps as a bridge to the future, we need to consider the value to the newborns' lives, that the innovation of a public/private partnership will help to improve the quality and scope of newborn screening programs.

At this point, there are three items I'd like to ask this committee. Please encourage Congress to require states to inform parents -- you've heard this before -- about potential for their children to receive additional newborn screening tests that may not be required under state law. Please start by asking them to require hospitals to educate parents on the availability of supplemental newborn screening tests. New Jersey recently enacted this type of legislation. The solution is simple. It's all available today. We just need to use the existing resources.

Thank you.

DR. HOWELL: Thank you very much, Mrs. Gartzke. Again, we will need you and all your colleagues' help in seeing that those things get done.

The next person on my list is Dr. Mendel Tuchman, who I don't see in the hall.

Carol, are you going to speak?

This is not Mendel Tuchman but his sidekick, Dr. Carol Greene.

DR. GREENE: No lovely Israeli accent to charm you with. Dr. Tuchman could not be here today. He sends his regrets. He is president of the Society for Inherited Metabolic Disorders.

I'm Carol Greene, speaking as a member of the board, and we thank you for the opportunity to share comments. The SIMD -- and I'll tell you in a moment what the SIMD is -- looks very much forward to the work of this committee and stands ready to assist this committee in any way that we can. As you'll hear in a moment, the SIMD membership is well positioned to provide expert input on some points that might be of use to this committee.

At this the inaugural meeting of your committee, the SIMD would like to present our just-approved statement, and copies of this I think were passed out to the members of the committee, and I brought enough copies for the audience. The statement is on newborn screening and treatment of individuals with inborn errors of metabolism detected by newborn screening. As you have a copy, I will read mostly the highlights of this for the record.

I think it's been well established by discussion here today that newborn screening is a well established strategy to reduce death and disability, and we're very aware that as a result of many forces, including advances in technology and changes in the public health system, newborn screening and the systems of care for children who are identified by newborn screening are undergoing intense examination and change.

The Society for Inherited Metabolic Disorders is dedicated to -- and this is straight out of our mission and by-laws -- improving scientific and public understanding about inborn errors of metabolism to promoting advances in identification and care of those affected by inborn errors of metabolism. Our members are professionals who are actively involved either in clinical or basic research or inpatient care or research that is directly related to the inherited metabolic disorders. Our members are scientists, physicians, nutritionists, nurses, genetic counselors, and any other health care provider that is involved in either clinical care or research in inborn errors of metabolism. We work in the laboratory, in the clinic, in public health, in private medical systems, and in the biotechnology industry, in academia, and in the private sector.

The SIMD membership includes world leaders in newborn screening and in the care of patients with inborn errors of metabolism. Members of the SIMD serve on advisory committees and task forces at the local, state, and national level, and include people who participated in some of the reports you heard about today. We have in the past suggested that states examine and expand newborn screening, and over the past year conducted a survey of our membership, which survey led to this statement. A full report of the survey should be, as of today or shortly, available on our website, which is listed in the statement.

The statement is based on some key points which are summarized in the statement here, but I'll go straight to the recommendations. The membership of the SIMD recommends that screening of newborns for inherited metabolic disorders should be expanded in the United States to include MCAD deficiency and other inborn errors of amino acid, organic acid, and fatty acid metabolism detected by tandem mass spec. Our membership supports the notion that all infants in each state should be tested for the same panel of diseases. However, on the survey the members did point out that there are times when exceptions need to be made to that rule, and flexibility should be permitted when there are compelling reasons for variability in newborn screening testing between populations.

We also suggest that newborn screening should continue as a mandated state public health process, with ultimate responsibility for a successful program resting with the state public health department. But innovation through regional newborn screening networks and contracted public/private partnerships is likely to improve the quality and scope of newborn screening programs.

The fourth recommendation is that the diagnosis of the biochemical genetic disease in an infant detected through newborn screening should be confirmed in a laboratory where the director or the medical director is board certified in biochemical genetics or has equivalent qualifications.

The last recommendation is that state public health departments should develop mechanisms to adequately fund newborn screening and also to adequately fund the treatment of those inborn errors of metabolism identified by newborn screening, including the testing, the reporting of results, the confirmation of abnormal screening results, diagnosis, and comprehensive long-term treatment and evaluation.

We look very much forward to the results of your committee's work, and we're happy to assist in any way that our organization can.

DR. HOWELL: Thank you very much, Dr. Greene, for that presentation.

The next person on the list is Ms. Kathleen Rand Reed, from the Rand Reed Group.

MS. REED: Good afternoon, and thank you for allowing me to have the opportunity to bring forth some additional issues. Also, a special thank you to Michele Puryear for always allowing me and letting me know when these things occur.

I am an applied biocultural anthropologist, and also an ethnomarketer, and I always have the shorthand of saying that what that translates into is that if you give me a zip code, I can pretty much tell you what you've got in it. So that's a little bit about ethnomarketing.

There were some concerns that I had and just wanted to place on the record. One of the concerns -- I also serve on an institutional review board at the NIH for the Heart, Lung and Blood Institute, and one of the issues that always comes up when we're looking at clinical trials is the issue about vulnerable populations and the assents, especially from the miners. One of the concerns that I had, probably already being looked at but just want to make sure, is the idea that we are now reaching the point where, with the newborn screening, a number of these tests -- I've been very sensitive to and heard many of the parents, and one of the things I'm hearing is we want more tests.

However, I would ask that in developing this process of tests, if you will, that there be included a sunset or a moment of pause already put in the process. For instance, the idea of a teenage young lady that wants to know her breast cancer status, and she may be emancipated, she may not. But the idea is that she may want to know, and she has the right in certain other areas to know certain things, but her mom may not want to know, and you've got certain conflicts.

So that as this timeline develops from infant to childhood to adolescent, that this timeline be interrupted for these periodic moments of taking a look at the ethical implications of the vulnerable populations as they move on, because they do have, I'm sure as everyone knows, the implications for downstream, and now I really understand why we need the legislation in place in terms of the anti-discrimination legislation for genetics.

The second concern, and I want to bring this up clearly, is to take a look at the upstream social forces that lead to changes in heritable disorders and genetic diseases. I just completed some work on looking at what was happening in African American communities, where you have hyper-segregation in terms of 95 percent African American, incarceration rates of African American young men, changing the ratio of men to women, multiple matings, and what might happen with autosomal recessive disorders. There are some social forces that are going on in highly controversial areas where they need to be looked at as well so that as these issues are being developed, that they're developed with what's happening on the ground. For those issues that pertain to racial matters or are controversial, we just need to work with bridges and people so that we're not hampered by what's PC and we really get the real picture of what can happen.

One minute?

DR. HOWELL: Thirty seconds. I'll compromise. How's that?

MS. REED: Okay, that's it.

The last recommendation would be to develop a migration exposure and cultural grid. This is apropos to what we said yesterday about the interstate issues. There are children that are exposed when they, say, leave from Chicago and go to Mississippi to visit their grandma or what-have-you, that that 25 percent, that three months that they're in the south or they're exposed to toxins, carcinogens, et cetera, or pregnant women, where that's not included in their exposure and carcinogenic exposure rates.

Thank you very much.

DR. HOWELL: Thank you very much.

MS. REED: And the last line is anything I can do to help, please feel free.

DR. HOWELL: Thank you very much, Ms. Reed.

Actually, the final person on the agenda this afternoon, speaking on behalf of the Immune Deficiency Foundation, is Dr. Rebecca Buckley. Some may accuse me of putting Dr. Buckley last since she and I trained together at Duke, but that's not true. So we're delighted to have her here representing this foundation.

DR. BUCKLEY: I'd like to thank the advisory committee very much for allowing me to speak. I'm here speaking on behalf of the Immune Deficiency Foundation, which is a private non-profit layperson organization that is comprised of families of patients or patients who have these genetic defects in the immune system.

I'm here wearing another hat, and that is I'm a physician who is taking care of patients with these diseases for more than half of my life, and having seen the consequences of failure of early diagnosis.

Just to put this in perspective, when I was a sophomore in college, when someone became infected, most people thought it was because of some unusual organism in the community. None of these diseases were even known at that time, and you can imagine what spectacular advances have been made in the understanding of these diseases now. I think there are 120 different genetic diseases of the immune system that are currently known, and most of this has occurred just within the past 10 years as a consequence of the Genome Project. So we now know the molecular basis of most of these diseases.

One other comment about this particular slide is that the Immune Deficiency Foundation surveyed its membership and asked them how long from the time of the first infection until they were diagnosed. The average time was nine and a half years. Many of these patients have been hospitalized up to 20 times, and no one thought of the diagnosis. So clearly, this is a set of diseases where screening would be very helpful.

Just to again say that there is currently no screening for any of these defects at birth, during childhood, during adulthood, anywhere in the world. In countries where they give a live vaccine called BCG to prevent tuberculosis, in Third World countries, this means death for people who have these defects because they die from generalized infections from these vaccine organisms.

I'm not going to talk about 120 diseases, but I am going to talk about one condition that we used to think was one disease but we now know is at least nine different diseases, and this is called bubble boy disease or SCID. This is a fatal syndrome that's characterized by absence of T cells, and that's the main point I want to get across. There are other deficiencies as well, but the absence of T cells forms the basis of newborn screening for this condition.

This is just to point out that SCID is really nine different diseases, and these are all the genes that we know that when mutated can cause SCID. They would fit on your microchip, Dr. Alexander, but I think that there's a simpler way of doing this rather than trying to look for mutations in all of these nine genes. I'll comment on that as we go along.

This is just to give you an idea about the relative frequency of these. The blue pie there is the X-linked type, and you can see that all the other nine different types are around the pie. But there are still about 30 children there that we don't know the molecular basis of their defect. So there may be other genes as yet to be discovered.

So what's the incidence of this? Well, the prevalence has to be low because it's uniformly fatal, and the incidence is really unknown because no one screens for it. I suspect that most of these babies die before they get to a pediatrician, let alone getting to an immunologist. It's estimated that the frequency is around 1 in 100,000, but I suspect it's much more common than that.

Another point to make for your committee is that there is a treatment for this. Unfortunately, the average age at presentation of these babies at our institution is six and a half months. By that time, they've already acquired an infection for which there's no effective antibiotic. The other development that has occurred is that there is now a treatment that allows you to use a mother or father as a donor for stem cells that can cure this condition. This slide just points out that only 16 of the babies that we've treated over the last 22 years had a matched donor. But even if you don't have a matched donor, there's still a way to treat the condition.

This is what they died of. They died of viruses for which there's no effective antibiotic. So if you can make the diagnosis before they get infected, then there's a very high probability of success. We've been fortunate enough to be able to transplant 27 of these babies in the newborn period, and we've only lost one, and this was from a cytomegalovirus infection that was incurred at the time of delivery in a mother who had had no prenatal care. But you can see that all of the rest of these are living out to 22 years.

So this is a pediatric emergency, and the potential exists to diagnose the condition routinely at birth. If you can give a stem cell transplant in the first three and a half months of life, there's a greater than 97 percent probability you'll have success.

Is there an existing test? Yes, there's a test that's been available since before I went to medical school, and that's a white count and a manual differential. However, that's not routinely done for a variety of reasons that we can talk about. It's a screening test, and the process is not centralized because it's not usually performed because the HMOs don't want to pay for it.

This is just to show you what would have happened if the screening test had been employed. Over on the left side, you can see the lymphocyte count is very different between the SCIDs that are in the black dots as opposed to the normal control infants. There's a little bit of overlap right here in the early 2,000 range, but if one set the cutoff point as 2,500 and then did follow-up testing for anything under that, you could pick up all of the SCIDs.

DR. HOWELL: Becky, unfortunately we're going to have to wrap up.

DR. BUCKLEY: Okay. Then the other part of the slide here shows that if you tested for T cells, there is no question that you would not find any T cells there.

The other thing that I was going to comment on but that I won't really say that much about is that tests are being developed right now to measure T cells on the Guthrie spot. So this is something that I think should be done. There are preliminary data showing that this is a very effective way of diagnosing this condition. I would urge the advisory committee to look into this, and I'll be glad to answer any questions if there are any.

DR. HOWELL: Thank you very much for that impressive survival curve of the kids who have been transplanted early and so forth.

That actually is the conclusion of our group, and I congratulate everybody. It would have been nice to have multiples of the five minutes to hear from you, and hopefully during the course of events we'll have a chance to hear everybody.

I might point out that all the material that has been presented today will become a part of our report and will be posted on the website as that gets put together and so forth.

Does anybody have any additional comments about the wrap-up of presentations from the panel? Anybody, any questions or comments?

(No response.)

DR. HOWELL: All right. We're coming into the home stretch here. There are many, many people today that I'm aware have very tight schedules, and we're scheduled to conclude our business very soon. So we will move to that and so forth.

I might point out that we now are going to be dealing with committee business, but it's an open meeting. So anybody please stay and listen to what the committee has to say.

I think there are a series of things, and, Michele, you can remind me of things that we need to do at this point in time. One of the points of discussion is our future meetings, because the document that established the committee established a minimum number of committee meetings, which is twice a year I believe, and it's widely felt that that would not be adequate for the committee to keep its work moving along.

But could we have some comments about what the committee thinks about frequency of meetings and so forth?

Silence.

DR. RINALDO: Can we first define what the agenda is from now on? That might give us an idea how often we might need to meet.

DR. HOWELL: Perfectly fine. I think that the key thing is what strikes me is that there's a vast array of things out there, and I think if we tackle a vast array we're unlikely to come up with a product that would be worthy of this committee's work. So it seems to me that we should focus, at least up front, on a few areas that are considerably important, and also to be pragmatic on areas where there can be significant impact in the relatively short term.

What would you like to discuss and so forth? What would you like to have on the agenda? It's your committee.

Coleen?

DR. BOYLE: I guess the one issue that we've spent most of the day talking about is recommendations for a uniform panel. I guess I see that as being our primary concern, and then there are a lot of issues that would come off of that issue.

DR. RINALDO: I second that. I also think, especially in light of some of the comments we just heard, we always said that our analysis of the vast number of conditions really was needing to -- the condition of the condition now sort of ready for prime time or ready in place. So going after a uniform panel. But I really think we need to talk about the research agenda. I think we already recognize, at least I recognize the discrepancy that we have reached a conclusion based on expert opinion of a number of conditions, where at least in the eyes of the expert there is no test. But I think we have to take a hard look. We heard about SCID, Krabbe disease -- there are a number of things that we really might want to take another specific look about things that apparently there is no agreement or no consensus about what has a test available and what doesn't, and see what can be done.

DR. HOWELL: What specifically would you have in mind as far as approaching that particular issue, the question of is there a test available?

DR. RINALDO: Well, again, I think that we have now a smaller, more manageable number of conditions, and I believe, again as we just heard, that a number of them, we might find very qualified people to tell us that our conclusion that apparently there is no validated test might not be completely true. So the question is this has always been an issue not of passing or failing something but more of to identify where they are in the process toward implementation in a screening panel. So really take a hard look at what the issues are and what is missing.

DR. HOWELL: But what I hear you saying is that you would advocate that early in the game we have specific people come and talk about test development in some of the areas that we consider are ready for prime time that don't have tests. Is that what you're suggesting?

DR. RINALDO: I'm suggesting to continue along the work of the expert panel and try to move forward the implementation of a core or uniform panel, whatever you want to call it, but at the same time don't leave in limber all the other conditions where there seems to be scientific evidence that the apparent conclusion of the survey might not be entirely accurate.

DR. HOWELL: I think that many of us -- and again, I'll speak personally, but many of us are aware of tests for certain of these conditions that are quite far along, and I think it would be advantageous to have the people who are leading those areas to come and talk about what they're doing and the technology they're using and so forth. Becky alluded to the test that I think Jennifer Puck and her group is working on, and others, for the recent immigrant T cells, et cetera. Certainly there's an enormous amount of new information in the area of lysosomal storage diseases that we've not heard about that is moving along.

Steve apparently, to my right here -

DR. EDWARDS: Never sit to the Chairman's right.

(Laughter.)

DR. EDWARDS: They can never see you. And the same thing was true when I was chair of different organizations.

DR. HOWELL: But I have this person to the right who bumps me.

(Laughter.)

DR. EDWARDS: What I wanted to say is that I think we've heard enough, at least from the work that Michael Watson and his group has done, so that we can go ahead and make some recommendations. I'm concerned that if we wait until we have the final evolving package, that that's going to be a moving target. I think that there are certain things that we can go ahead and recommend. I do think that it would be irresponsible if we didn't pay any attention to the cost of this. We've not had any discussion about that, and I think if we're going to be credible, that we have to have some discussion of the cost and the way that this will be done.

As far as the mechanism is concerned about the states, I'm comfortable from the presentation this morning, the package is there, the system is working. I think that I would want to be sure that we are very firm in recommending a coordinated system and a system that's available to all. But I think those components are there.

What would concern me is not moving ahead with some of the things that we know we're going to recommend, waiting for a final package. It doesn't bother me to wait a little, but I think that for us to try to think in terms of what the final package is going to be, I think that's going to be evolving almost as we speak, and that if we wait for the perfect, that we're going to let a lot of good go by while we're doing that.

This Michael Watson has been working on this package for two years now. I think we've got some material that we can move ahead with, and I'd like to see us start doing that. I do think that the committee can continue to work on refining the package, but I think that we can move ahead with some recommendations.

DR. HOWELL: I personally share your impatience and so forth.

(Applause.)

DR. HOWELL: Bill?

And the audience shares your impatience even more. Was that impatient Carol Greene leading the way?

(Laughter.)

DR. BECKER: I certainly agree with Steve's comment that I think we need to move ahead with making some recommendations. I guess I am also reminded that Reed did request this morning a little more detail on the ACMG project itself. I think it probably would benefit the folks who weren't on the task force or the expert panel maybe to understand that in a little more detail. However, it may be that we don't have to wait until the next meeting in order to provide the information that would be beneficial.

So maybe I could make the request that a draft of the ACMG report be distributed to this committee's membership so that we can all start reviewing it. Some of us already have, obviously, seen it in various draft forms, but so that everybody can get a sense of what was going on out of that task force, maybe before waiting until the next meeting. Then at that point I think we could potentially -- I'll throw this out -- be ready at the next meeting to make those recommendations, which I think is what Steve is talking about.

One of the things that I'd like to see, Rodney, on the agenda for the next meeting, or perhaps it could be shared with the committee via conference call or some other methods, is a summary of the recommendations, or request maybe is a better word, of all of the people who testified today, what they've requested of us, and I think there are several common themes that are going to come through.

For example, the idea of universal access and equitable access to newborn screening. I think we heard that from a number of people, not only from the open comments but also from the association presentations in the last day and a half.

DR. HOWELL: The comments from the group today will be duly recorded and distributed.

I think one of the questions about the draft report, the report that Mike has presented today is a report to HRSA, and I'm not aware that that can be shared until it goes to HRSA and HRSA signs off on that. But obviously, Dr. van Dyck can comment about that properly.

DR. VAN DYCK: Well, that's true.

(Laughter.)

DR. VAN DYCK: As soon as we get the report and we have a few minutes to look at it, then we would be happy to share it. Perhaps we can share a summary or perhaps we can share pertinent parts. But I agree that I think at the next meeting it would be a good time to have some presentation worked out about elements that we think are important, as has already been suggested. But that doesn't mean we have to wait to make recommendations. I think it just further elucidates what's going on.

I'd like to make one other comment, too, and that is one of the other things we heard today often was the notification somehow that states should make to parents that there are other tests available or that other tests may be available to them, and I'd like the committee to take that up as a recommendation, perhaps at the next meeting, to see if that's something the committee would recommend to the Department.

DR. HOWELL: I would think it would be advantageous perhaps next time to -- some of us have been through this report tediously for a couple of years. But on the other hand, it seems to me it would be prudent to have a much more -- Mike presented a wonderful summary in an hour, but this is a two-plus-year project of 100 people, and it would be helpful I think to go through it much more analytically, and not to reinvent the wheel but to see what's in that report.

But I would agree that we should start. This committee is going to do something, I can assure you, rather than sit and talk forever, but we need to get some background. But maybe we can ask Mike if he would be able to come and go through the report in some detail and so forth. But we can indeed start some really, as far as I'm concerned, things that we can start sending upstream fairly soon.

DR. BECKER: Okay. I have two other suggestions for either the next meeting or perhaps information that can be provided to us in the interim time.

The first is a -- and maybe it can best come from Harry down at CDC. There were several questions that were around what is the current state of MS/MS testing, and I think rather than kind of guess what's going on, how many states are using MS/MS right now, how much training has occurred, and how much more is planned. I think we need to do an assessment, basically from basic public health. We need to assess what the current state of the environment is in order to understand how it's going to improve or go forward from here. So I think we need some report that summarizes that.

Then my second or my last suggestion is something that I think came out of yesterday's conversations that seemed to have some consensus around it, although we really didn't discuss it, was this idea that there is no one federal agency providing strategic oversight to newborn screening, yet we all recognize that within HHS there are at least four or five different agencies that have some input into newborn screening or some studies or research or something that has impact on it.

There was this suggestion that there's this National Vaccine Advisory Committee that does offer some strategic oversight. I guess I would request that if that's an idea that seems acceptable to us, that maybe we start to consider what a strategic oversight group might look like for newborn screening, if that's a direction that the committee would like to go to, and I'd like to start that conversation.

DR. HOWELL: Well, some of the folks who are expert in government affairs, there is a mechanism for having interagency coordinating committees or councils and so forth, and I think that's what you're suggesting. Is that something this committee could suggest or should suggest?

DR. RINALDO: What kind of authority do you envision from this committee?

DR. BECKER: Well, I think that's what we need to discuss. Is that kind of model what could work for newborn screening? It seems like there was some suggestion by several people yesterday that it may be that -- you know, we talked about the idea that there's no federal mandate or there's no federal oversight or there's lack of things at the federal level. It may be that that type of organizational structure

is useful, but I'd like to understand what model that would suggest. I'd like to understand a little bit more about it.

DR. HOWELL: Have these committees in the past worked well? Are they effective? I mean, I don't have any experience.

DR. LLOYD-PURYEAR: There are different models. We could have somebody come from one of those committees. What comes to mind is NVAC and the ICC that they have there. Dixie Snyder, actually, from NVAC, from CDC, could come and talk about the pros and cons. They've had a 12-year, if not 14-year, experience with that committee.

DR. HOWELL: Would you like to hear about that? I see some yeses, so maybe we could get someone to do that.

DR. LLOYD-PURYEAR: I would also, in terms of the role of a standards-making committee, either look at or hear from somebody who has coordinated ACIP, the Advisory Committee on Immunization Practices. I don't know how much Dixie is involved with that still. He used to be.

DR. HOWELL: Amy?

DR. BROWER: Thank you. I would request that the committee at our next meeting or the following meeting follow up in detail on Dr. Mike Watson's work as far as criteria for the new tests and new pipeline as far as how are we going to validate the next list of 30 or 40 or 50, and along with that the new technologies for the detection of those tests as well.

DR. HOWELL: What's the feeling about having a presentation on new technologies next time? I didn't get a sense of that. I would personally be interested in that, but --

DR. BROWER: Yes, I think that would be helpful.

DR. HOWELL: We know, obviously, certain new technologies. But if a member of the committee has a particular technology that you're particularly interested in and you know a great deal about it, please let Michele know and we'll try to find a group or a time that people can come.

DR. RINALDO: A request I would like to make is to try to target things that seem to be the closest to prime time, rather than talking about things that seem to be in the distant future. But I really would like to put emphasis on some practical aspects of what different technologies are there that could be implemented in the short term with adequate supports.

DR. HOWELL: You're talking about some of the technologies for lysosomal storage diseases, for SCID, and things of that nature, as opposed to the future of nanotechnology.

DR. RINALDO: Well, we may eventually want to cover various aspects, but --

DR. HOWELL: Okay. We'll come up with some new technologies and so forth for the next meeting.

DR. BOYLE: I was just going to make a suggestion that some of these issues could be taken up by subcommittees and we could explore some of these concepts, because I guess I feel a pressing need to address what we currently know now and to react to that, and then to take up some of these issues, the next wave of tests that we need to consider, the newer technologies that are on the front line maybe by subcommittee. That could be deferred a little bit.

DR. HOWELL: Okay. Any reaction to that? What's the sense of the committee? The committee is not very large, so one of the questions that comes up is what's your sense of subcommittees of this group?

Duane, do you have any wisdom on that?

DR. ALEXANDER: Yes, I think that we are clearly going to need to have some subcommittees established. The legislation authorizing us in our charter clearly allows the establishment of subcommittees headed by members of this committee, but with outside non-committee membership as well. I think we're going to need some of those, and I was actually going to suggest that we might want to authorize the chair to propose, in the interim between meetings even, a subcommittee structure to us even by mail for us to comment on and possibly even approve.

DR. HOWELL: I'd be pleased to do that. I think that I also, however, would appreciate if you could funnel things through Michele, if we can have some suggestions on subcommittees. I would hate to get large numbers of subcommittees, but one subcommittee on technology is a natural because that's certainly something on the horizon.

DR. BOYLE: Another one on coordination among federal agencies. That's another one as well.

DR. HOWELL: Right, et cetera.

Any other comments about that?

(No response.)

DR. HOWELL: I don't want to completely end this discussion, but we're going to leave at 3 o'clock. In the event that the witching hour strikes us, I want to be sure that everyone has seen and is aware of the bill that was introduced in the House of Representatives on June the 2nd, introduced by Ms. Roybal-Allard, U.S. representative from California, with a series of co-sponsors. The bill is House Bill 4493, and the title of the thing is Newborn Screening Saves Lives Act of 2004. The bill has a number of comments about areas that we've discussed today, but obviously it's a very timely piece of legislation to come along as we're moving along and so forth, et cetera.

To change the subject fairly abruptly from this bill, when would you like to talk about research? Would you like to put that off until a later meeting perhaps? What's your sense about that?

DR. RINALDO: I thought that the survey, the college survey, was supposed to point in the direction of where additional research is needed. So perhaps we can actually see what exactly those recommendations are.

DR. HOWELL: Okay. So your sense is as we go through the document in greater detail with Mike, when we get to that category, that will point out the areas and so forth.

DR. BOYLE: I also feel that just in deliberating, and I wanted to follow up on some of Jennifer Howse's recommendations earlier, which I thought were actually excellent, the need to feel comfortable with the evidence and the report by ACMG. But I think a lot of research-related activities will come out of just deliberating on those conditions. I mean, to me, much of what perhaps we'll recommend or propose, there will be a research component to that. There will be an aspect with that that we don't have the evidence, that we're asking that we collect the evidence as we implement. So I see them as going hand in hand, really.

DR. HOWELL: Okay. Are we at a point where we could think now about how often we should meet, or do you want to talk more about the agenda?

DR. RINALDO: Next week, same place?

(Laughter.)

DR. HOWELL: Well, Friday is a holiday, so we'll have to wait until next week and so forth. But it seems to me, and this is a personal opinion, that twice a year clearly is not enough to move the thing along. I think that we would clearly forget what we'd done the time before, if we'd done anything. So that's not it.

What's your sense about how often we should try to get together physically? And then we'll develop a variety of other communications in the meantime and so forth.

DR. COGGINS: I would have thought every three months at least, to get started. If we're making progress, then maybe cut it back a bit after that. But I would have thought we'll need to meet more frequently rather than less frequently.

DR. HOWELL: My sense has been about four times a year also, so that's strikes me. Is that sensible to think about? And then I guess the next thing, is there any way we can work on the calendar today, or is that a lost cause?

DR. LLOYD-PURYEAR: It's a lost cause.

DR. HOWELL: It seems to be a lost cause.

DR. EDWARDS: Probably we can do it by email.

DR. RINALDO: I would suggest that the Chair request a tight deadline for providing information. We should say within a week or two at most we should try to identify times that fit our schedules without waiting for months.

DR. HOWELL: I think it would be advantageous to do the year, if we can, to do four meetings, or three meetings. Obviously, it's important to get as many people as possible. There had been some conversation about the possibility of would it be advantageous to try to meet at other places other than in the District, and the answer to that is probably no, although it would be very nice to have an opportunity to hear from persons that are in more distant places. The practical matter of the facilities here, the federal facilities, along with the staff and the recording people are such that it's probably not practical to have scheduled meetings, although if there's something that somebody needs to go see or to meet with or something, that can be a separate issue. But it seems to me that they will all be here.

My own sense is that this meeting facility I think has served us well. Would you like to continue to try to meet here? It certainly seems to have worked well and so forth. So we'll try to meet here, we'll try to have four meetings a year.

We've got a fair number of things for the next meeting, particularly if we spend a fair amount of time with the report per se and spending time on it and so forth. You're going to let Michele have some information about subcommittees, and we'll be thinking about those and working on those.

Anything else that we need to do here?

DR. EDWARDS: I think we should have somebody from the state public health office, especially from a state that does not have a full package of screening, so that we can have some dialogue about how we can help them facilitate the kind of work that we think is going to need to be done.

DR. HOWELL: Of course, Bill is the state person from Ohio.

DR. EDWARDS: Yes, but he probably already has it.

DR. HOWELL: But they are very far advanced, so we're looking for someone who is behind the pack.

DR. RINALDO: Don't you think that what we'll probably hear is lack of funds and lack of in-state expertise? So I wonder if we are somewhat beating a dead horse. We know the roots of the problem. Maybe when I get sort of a personal --

DR. EDWARDS: I think, Piero, that that's probably what we're going to hear, but I think that we should go beyond that and try to explore areas in which we could be facilitators and where we could help make these things happen. I think if we let them sit in one corner and us sit in another corner and the two of us never get together to talk about ways that we could help them and maybe they could help us, I think we will hear that, but I think that there's a second level of discussion that could be productive.

DR. RINALDO: Well, I then have a question for Michele. It's about should we wait to see if a regional or collaborative project has any impact in improving that situation?

DR. HOWELL: We won't know that. Bill lives among these folks. What wisdom do you have?

DR. BECKER: Well, I think we've got two possible forums that we could invite to hear conversations. One is from the global perspective, which I think, Steve, you might be asking about, and that might be an invitation to the state health officials group to basically appoint a person to come and speak to the programmatic issues and the challenges to the programmatic issues that state newborn screening programs are facing right now. I think that's one very important discussion that the committee would find useful, I think.

The second level is one, because we always kind of drop down to the testing level, and that's the organizational aspects of the program oftentimes revolves around the laboratories, and while we have to acknowledge that the program is much bigger than just testing, we all know that, the reality is the testing really drives the programs to a large degree, and we could certainly invite, on behalf of the Association of Public Health Laboratories, or if you would like for me to speak to the state of the states from the laboratories perspective, I'll be glad to do that.

So I think you can have the global perspective from the state health officials, and I would strongly recommend we hear that conversation. Then if it's of some value to the committee, then perhaps the laboratory perspective as well.

DR. HOWELL: Lisa has had some words on the front row here. Why don't you go to a microphone?

DR. FEUCHTBAUM: Hello. I'm Lisa Feuchtbaum with the Genetic Disease Branch of the California Department of Health Services. I just wanted to let the committee know that we're just compiling the results of a national survey that we've done, and Bill Becker should be familiar with it. I think you completed one of our surveys to identify the barriers to expanding newborn screening. The survey specifically focused on tandem mass spec, but this is really what we're talking about at this point, I believe, and we didn't look at other technologies.

But I've received responses from at least one person from almost all the states at this point. I could go after the few stragglers, and I've yet to compile the data. It's true, though; by looking at what's come in, finances, finances, finances. That seems to be a key issues. But there are a lot of issues, and I asked people to prioritize those issues, and I can't give you the results today, but it is one of the projects that we're moving ahead with really as soon as I get back to California. That's one of our projects, so I hope that can be helpful.

DR. HOWELL: Maybe we'll have a chance to hear from that once you're able to do it.

Greg has a comment, and then we'll go back to Lauren.

DR. HAWKINS: Well, this is just kind of bouncing off a little bit what you said and what Piero said a little bit earlier. But you were talking about bringing someone in from a state that doesn't have a lot of testing. Well, something I think that we should put on the agenda, you're going to talk about the 30 tests or so that we should try to implement in all these states, but what is the cost? I'd like to know what each one of these tests costs to run so that when we discuss it next time, we would have some sort of idea what the states are going to be up against. The first thing the states are going to ask is how much is it going to cost? How much training? Who are we going to need?

I think it's one thing to tell them these are the tests you want to do, but we also have to have some sort of guidelines to tell them how are they going to do it. I think someone like Piero who probably knows a lot about this would be a good resource to kind of lay down some of this information as some of the others have spoken here today, because I'll be honest, I don't know what some of these tests cost.

DR. HOWELL: That's good. We'll come back to that in just a minute, Piero.

Let's go back to Lauren at the back.

MS. RASKIN: I'm just here as a representative for ASTHO. I just really want to offer that we'd be happy to help in any way to get whatever perspectives from any state that you need. An invitation funneled through us would be quite easy to do, and we're happy to provide that assistance.

DR. HOWELL: Thank you very much.

Now, California, does your report have some cost data in it?

DR. FEUCHTBAUM: Yes, that's another area that we're looking at, and we've come up with some preliminary cost estimates for screening in California given the California model. Another area that would be perhaps useful for the committee is we're looking at the cost of follow-up specifically. We've come up with a mechanism to collect data on follow-up services, and we're planning to cost out those services so that we start to get a picture of what follow-up actually costs. That may be, again, something that may be useful to the committee.

DR. HOWELL: Thank you very much.

Piero?

DR. RINALDO: I only wanted to say that we always focus on cost. I really wish that we could really target two specific aspects: one, who bears the cost of testing; and the other one that seems to be neglected at times, who writes the cost savings of doing screening. Because we often talk about cost, but believe me, there are major cost savings. Some of these catastrophic events, as you heard before in testimony, are just the tip of the iceberg, because that's really the other side. So it's a balance thing.

I hope that we will always try to ask the question about the two. It's not just the cost of testing as the end of it, because the testing will eventually result in some substantial cost savings. Those don't seem to be taken into adequate consideration, in my opinion.

DR. HOWELL: Any comments about that? I think that today in the public testimony we heard some extraordinary medical costs, which I don't think are atypical of children who have profound continuing illness and not uncommonly with a very bad result, frequently resulting in death or profound disability. Again, I think your point is those costs are ordinarily borne by the family and/or the insurance company, and even if the family is well insured, there are tremendous expenses that the family always has to pick up. So you have that very great and, at times, multi-million-dollar cost balancing, and some of those costs would come close to funding a state screening program that year. These are really, really enormous costs.

It's very interesting. Mike alluded to it briefly, but the College had a really substantive effort on cost/benefit analysis, and it's a worthwhile document done by very thoughtful people, but it doesn't shed as much light as you might like to have. That's candid, but Mike may disagree.

DR. VOGT: Rodney, if I may make just one comment from here, because it's always intrigued me. This is not my field at all, cost effectiveness, but my impression is there are two completely different travel streams for the money. The money that is saved through early recognition doesn't get back to the state newborn screening system, so it's as if it didn't exist from that standpoint, and perhaps that's one thing this committee could look at, an integration of the cost and the cost savings, because I suspect your discussion is quite correct. I suspect it is self-supporting, but that's not actually what happens.

DR. HAWKINS: In that respect, maybe the way we should be targeting this is even going towards insurance companies, saying if the testing is definitely -- if the insurance company is pushing for the testing, what are your cost savings, and get them on board to support this. I don't know how much slack the insurance companies give testing. Are some of the insurance companies not for it, some are for it? I don't have a clue.

MS. FISCH: Can I just say something about that?

DR. HOWELL: Please. Come to the microphone.

MS. FISCH: When I attended the newborn screening task force meeting in Albany and I asked them about the difference in costs, since we already have the equipment to do the testing in a state like New York, and they're not testing for all the disorders, the monetary difference is minor, versus what the costs are with early detection. I mean, in the case of Matthew, with it taking us two years to get a diagnosis, with the traveling and hospital care, medical costs -- I mean, to this day my insurance company does not pay for his feeding pump, his formula. I have therapists coming in and around my house five days a week at a cost of $1,000 a week that comes out of my own pocket that I can't get paid for.

Maybe these things would have been different for us had we detected his disorder earlier and he had received treatment earlier. So the cost of the tests versus the costs on the families, you can't even compare the two. You can't, especially when the equipment is already in place. From what I was told, it's just an incremental difference running 10 tests versus 50 tests, and that's what I would appeal to you, please, to really look at all this and how it affects us as families monetarily, physically, psychologically, and everything else, because it is something that's very simple to do and would really help a lot of families down the road.

Thank you.

DR. HOWELL: Thank you very much.

Any other comments of this group?

MS. MONACO: I do have one. In regard to the cost, I think as a parent I look at it as a Catch-22. We do incur a great deal of our own personal costs, and fortunately we do have good insurance coverage that is covering most of Stephen's care. Our daughter Caroline is minimal because all she is getting is her routine appointments with the metabolic specialist and her formulas.

However, looking at Stephen, insurance does pay out, and at some point that's going to be exhausted. But now as a child in the school system, it is our state that is funding his education and all his needs and therapies that he needs up until whatever age, into his 20s if it goes that long. After that, if we choose to exhaust our own insurance, then it's Medicare/Medicaid. Then the government is going to be paying throughout. So in one way or another, somebody does have to pay, with or without the screening.

That's my comment.

DR. HOWELL: Dr. Hanson?

PARTICIPANT: Sorry, Rod. Can I make a follow-up point to that? Please tell me if I'm confused, but my understanding is that currently hospitals that are told by the state that a test is mandated will conduct the assay and then bill a fund that the hospital has that they basically set money aside and eventually get paid back by an increase in their DRG two years later. So the hospital foots the bill for several years, but eventually the federal government does play a role in it via the DRG. Am I confused?

DR. HOWELL: Someone else can comment. Certainly, there are certain states that bill each patient who is being tested. They simply send a bill. You send 1,000 patient samples, they send you a bill for whatever they're charging times that, and these programs are self-supporting essentially. Many labs feel they're more than self-supporting. It goes through the general revenue once it goes over the top. There are other states that have different financing pathways, but certainly that's one system.

Jim?

DR. HANSON: Three points just for the committee's consideration. Let me first say that I personally would urge that one not hang one's hat on saving money long term as the justification for doing the right thing. I think that the committee, as you explore that, will find out that it perhaps really does cost more, but it does good, and that's just a thought and a suggestion that you not prematurely hitch your wagon to that star.

The second thing is I haven't heard much about consideration of provider behavior, provider knowledge and so forth. At some point, I'm sure that Dr. Edwards is going to be telling the committee that some of his constituents need help or think they need help. At a recent CDC conference on muscular dystrophy screening, we heard from other countries that the biggest barrier to implementation of some of these programs was from the pediatricians themselves. We are certainly aware of efforts by the American Academy of Family Physicians and AAP to try to address some of these needs, and I hope the committee will be cognizant of those and research questions that may relate to those.

Finally, I think the issue of what kind of research and service infrastructure for the nation will really be needed in an ongoing way, including the supporting public policy issues, some of which have been mentioned here, in my view will need attention.

DR. HOWELL: Duane, it's my impression that the NIH roadmap has as one of its pillars enhancing the infrastructure in this country for clinical research, and perhaps some of those infrastructure efforts that will be a part of the NIH could play into the support of the newborn screening programs as far as the scientific basis, because that's on the roadmap as I understand it.

DR. ALEXANDER: Yes, that part of the roadmap is largely trying to recruit community-based health care providers into a network for clinical trials and clinical evaluations. There's also some education and multidisciplinary training efforts for infrastructure, but we'd have to explore whether there's some of that that could be transferred and applied into this area.

DR. HOWELL: I have one minute to 3:00, and I think that in order that we stay right on time, unless there's some compelling reason to stay, let's go home.

Thank you very much.

(Applause.)

(Whereupon, at 3:00 p.m., the meeting was adjourned.)