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

Second Meeting

Wednesday, September 22, 2004

Burlington Rooms A/B
Jurys Washington Hotel
1500 New Hampshire Avenue, N.W.
Washington, D.C.

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C O N T E N T S

C O N T E N T S

P R O C E E D I N G S (9:06 a.m.)

DR. HOWELL: Ladies and gentlemen, let me welcome you to the second Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

I'd like to turn the podium over at this time to Dr. Dennis Williams from HRSA, who will welcome you and get us pointed in the right direction.

Dennis?

DR. WILLIAMS: Good morning. Thank you. First let me begin by welcoming the members of the Advisory Committee on Heritable Disorders and Genetics Diseases in Newborns and Children. I'm happy to see you again so soon after we all met in our first meeting of this committee last June.

Dr. Rodney Howell, the University of Miami School of Medicine, thank you again for serving as chair of this committee. Dr. Peter van Dyck, HRSA's Associate Administrator for Maternal and Child Health, is HRSA's representative to this committee. Thank you, Peter, for your leadership on these issues and your counsel to HRSA Administrator Betty Duke and to me. Most of HRSA's genetics programs, of course, reside in Peter's bureau.

The federal government's maternal and child health experts have been involved with newborn screening issues since the days of the Children's Bureau, long before there was a HRSA, long before there was a U.S. Department of Health and Human Services. In 1962, after Dr. Robert Guthrie devised a practical system for collection and transportation of blood samples, federal child and maternal health experts supported the field trial for the PKU test. The field test eventually involved 400,000 infants in 29 states. Soon thereafter, state laws mandating newborn screening became the foundation for HRSA's current genetics program.

Our concern now is that recent advances in technology have left a patchwork of screening standards in states across America. States, of course, are responsible for their own newborn screening programs. The federal government cannot impose standards on them. But we can issue guidelines, which as members of the advisory committee you are here to help us do. Your work is to advise us on steps states can take to assure that all American children receive a top-rate standard of care. A child born in one state deserves the same basic standard of care as a child born on the other side of the state border. Currently, differences in screening among states result in great inequity for parents.

We know that improving testing is an issue of paramount importance to parents. To make sure their voices are represented, we've set aside a period for public comments tomorrow. Parents who are unable to testify can send in letters that will become part of the official testimony of the committee.

The issue of equity for parents and their children is not confined just to the screening tests themselves. Equity also must include the service infrastructure that is a necessary part of the entire newborn screening system. We also ask committee members to weigh in on other crucial issues. Among the most important of these is cost. Testing incurs its own expense, and after-test costs to track patients and consult experts add to that expense. We urge you to find a balance between cost and the need to do comprehensive testing. These are difficult lines to draw and we welcome your advice.

We also ask your advice on issues of privacy and ethics. Newborn screening presents many ethical dilemmas, and more will come as technology evolves. Ethics and privacy issues need to be considered strongly in this debate. Very shortly you'll be briefed by Michael Watson from the American College of Medical Genetics on the draft report that was commissioned by HRSA. The report assembles

the available information on newborn screening, reviews the best scientific evidence, and presents options for model policies and procedures. We ask you to analyze it and give us your advice. Your work will inform and encourage a dialogue with MCH state directors and others.

Once that process concludes, HRSA will make recommendations to Secretary Thompson on the guidelines we feel states should follow to improve their newborn screening programs. This is an important topic and a high priority for HRSA. We plan to move quickly on it. However, please note that the report itself is considered an internal document until the full process is concluded. Discussion in this meeting about its contents becomes part of the public debate, but the report will not be made public until the Department prints and distributes it.

I don't really need to emphasize the importance of the committee's work to help us improve newborn screening services. Your recommendations will literally have life or death implications for children and their families across America. Newborn screening also is the focus of increasing interest from the press and the public at large. We are very confident that your knowledge and expertise will help us recommend guidelines to Secretary Thompson that will greatly benefit children and their families across the United States, and we thank you for your participation.

Thank you, and we look forward to your advice.

DR. HOWELL: Thank you very much, Dr. Williams. That certainly outlines the charge to this committee in a very clear way, and much work needs to be done.

The first item of business that the committee has is to approve the minutes of the first meeting, which was June 7th and 8th of this year, and the members of this committee have received those prior to this meeting by email, and they're appended in your agenda book under Tab 4.

Can we have a comment about the minutes?

We have a move to accept from Dr. Becker, a second from Dr. Rinaldo.

Can we see a vote on that? We need to vote to approve them.

(Show of hands.)

DR. HOWELL: And it appears to be unanimous at this point.

We're expecting three members of the committee here who were not here last time, and Derek Robertson is expected to be here but is not yet here. I think that we have three people that were not here before that I would like to have introduce themselves and tell a little bit about them, and then I'm going to ask everybody to go around the table and introduce yourselves because you weren't here, so you don't know who everybody is, and vice versa.

So can we start with Dr. Collins?

DR. COLLINS: Good morning. I'm James Collins from Chicago. I'm medical director of the neonatal intensive care unit at Children's Memorial Hospital. I'm also an associate professor of pediatrics at Northwest University Medical School. My research interest is looking at infant mortality, particularly as it applies to racial disparity and low birth weight prematurity. I'm a member of this committee because I'm chairman of the Secretary's Advisory Committee on Infant Mortality. As part of that committee, we're obviously wanting to work together with you to address newborn screening and how it applies to infant mortality in general.

Thank you.

DR. HOWELL: Thank you very much.

Dr. Dougherty?

DR. DOUGHERTY: Hi. I'm Denise Dougherty. I'm with the Agency for Healthcare Research and Quality, which is part of the U.S. Department of Health and Human Services, a sister agency to CDC and HRSA. I am the senior advisor for child health at the agency.

DR. HOWELL: Thank you very much.

Mr. Robertson is local and I'm sure is caught in the legendary Washington traffic, since he lives out in the Maryland neck of the woods.

Piero, can we start with you and just run around with your name and address?

DR. RINALDO: I'm Piero Rinaldo. I'm a pediatrician by training and a biochemical geneticist by trade. I work at the Mayo Clinic in Rochester, Minnesota, where I'm chair of the Division of Laboratory Genetics and the director of the Biochemical Genetics Laboratory.

DR. HAWKINS: I'm Greg Hawkins. I'm assistant professor, Wake Forest University School of Medicine. I'm also a member of the Center for Human Genomics. I'm a biochemist by training, but I'm also a molecular geneticist, and I'm involved in mapping complex diseases.

DR. COGGINS: Good morning. My name is Peter Coggins. I'm president of the Life and Analytical Sciences Division of PerkinElmer.

DR. BROWER: Hi. I'm Amy Brower, and I have a Ph.D. in medical genetics, and I work for Third Wave Technologies, whose goal is to develop molecular diagnostics, and my focus right now is medical genetics and medical informatics.

DR. BOYLE: Hi. I'm Coleen Boyle. I am currently the associate director for science at the National Center on Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention. I'm trained as an epidemiologist, have worked for years in the area of prevention of birth defects and developmental disabilities.

DR. BECKER: Hi. I'm Bill Becker, and I'm a pathologist by training. I'm the medical director for the Ohio Department of Health Laboratory in Columbus, and I'm also an associate professor in pathology in the Ohio State University Medical Center.

DR. HOWELL: We will also remind people to try to speak in the mike. Can you hear back there? I see some plus or minuses back there, and there's a good bit of humming. Maybe we can cure that.

I'm Rod Howell, professor of pediatrics, University of Miami School of Medicine. I'm a pediatrician trained in biochemical genetics. I've been interested and involved in newborn screening for longer than most people are alive in this room, having been involved with the State of Maryland in the institution of PKU screening when I was in charge of the metabolic group at Johns Hopkins. I was very young at the time.

(Laughter.)

DR. LLOYD-PURYEAR: Michele Puryear, executive secretary for the committee.

DR. VAN DYCK: Good morning. Peter van Dyck. I'm a pediatrician, director of the Maternal and Child Health Bureau in the Department of Health and Human Services and formerly professor of pediatrics at the University of Utah Medical School.

DR. HOWELL: Thank you very much. We're off to a great start because we're ahead of schedule.

One of the charges to this committee that Dr. Williams outlined very clearly was assisting and making recommendations to the Secretary about newborn screening, and one of the key aspects of that entire project is trying to have some logical mechanism to decide what conditions one should screen for, what are the data that would support adding that to a panel in the states. One of the most troublesome problems as we move around the country today, for those of us who have taken care of children with rare metabolic diseases, is the vast differences that exist from state to state, that a child will live in one state or be born in one state and fail to have a test, and the parents move or the child moves and this tremendous variation is a major problem.

HRSA has had a contract with the American College of Medical Genetics that Mike Watson is going to talk about to look at this problem of how do you define a standard panel and some other ancillary things. We're going to spend a lot of time on this today, and the plan is to have Dr. Watson present this in some detail about how the project worked, the large number of people that were involved with it and so forth, and some of the thoughts that have come out of that. Then we'll have an opportunity to discuss that, as you can see, between a break and lunch. Then we're going to come back and have a variety of other things from states and other experts about newborn screening and what they're doing with their states and so forth.

So I think with that we'll start with Dr. Watson, who will tell us about the work that he's been involved in over the past two-plus years.

DR. WATSON: Thank you. I appreciate the opportunity to present what has been a tremendous amount of work. I actually had that funny feeling last night that it was like the "Groundhog Day" movie when I read the Wall Street Journal and wondered if I was going to wake up every morning and give this talk again. It almost sounded like I had done it yesterday when I read the article last evening.

I also looked at the way this table is laid out, and I've asked a tremendous number of people to do work and to help us in this project, and they keep a safe distance from me now I think.

(Laughter.)

DR. WATSON: I expect them to be back after I'm done.

So let's jump into this, because we have a tremendous amount of information to cover.

I'm going to focus mostly today on one of the major aspects of our project, which was sort of a decisionmaking process to decide what should be in a uniform screening panel and core panels and that sort of thing. It's been an interesting process over the two-plus years of this project. This is how things actually looked at the time this project began. You can see sort of the distribution across the states of the number of conditions that are screening in those states. There's been a lot of change over the last two years and actually what's occurring in the states.

So the first question we asked is, is this project still important? Because there's been so much evolution within the programs. I think this slide will give you the impression that, yes, it still is important. This is a different look at that same slide we looked at, and I'm going to talk mostly rather than about states and programs -- Brad Therrell is going to give you the state of the states later. When we took on this project, it was at the national level. So much of what we discuss and recommend is based on looking at the United States as a whole, as opposed to local issues, state issues. We wanted to bring the science to the table, so that was really one of our focuses.

That's why I've laid it out here as percentage of U.S. births or babies born as to what's going on with newborn screening. You can see these are the mandated conditions at the time we started this project. There were about 30 percent of the births in the United States that were screened for five or fewer conditions. There were 5 percent that did more than 20 conditions at that time.

Now in 2004 -- and all this is data that we've extracted from the National Newborn Screening and Genetics Resource Center's website that is phenomenally frequently updated. So every time I thought I was done with this slide, somebody changed what they were doing and we had to update them yet again. But I think you can see here that now we have more states shifting to the right. We have a lot of variation, even more variation perhaps in what services babies in the country are accessing.

This is a pie version of that same slide.

Now, as we begin to look at what's mandated, you can see that an issue that I'm going to talk a bit about later is how do you even count how many conditions are being screened in a particular program? That's actually a very difficult question, and I'm going to address it in some detail later. But I think this to some extent demonstrates the issue, because on the far right of this slide, where you see one state that's doing 39 conditions and others doing 40, and another says it does 43 conditions, that's Iowa, Mississippi, and North Dakota. To a large extent, those differ by what you say you're screening for. If somebody says they're screening for fatty acid disorders and it looks like one condition, and somebody takes all of those and says here's a list of 12 to 15 conditions, you get very different numbers of conditions that appear to have been screened for.

Now, this is a little different. This is not mandated. This is where testing occurs, and it's not always under a mandate. The main difference you see at the right side of this particular slide is we've added in Pennsylvania, where by virtue of contractual relationships 99 percent of the babies are getting screened for a very large number of conditions, but not in a mandated program sense.

I'm going to go through these very quickly. There are a number of slides that are in your package which I put there largely for information. There are things I may have spoken about at the June meeting. I don't want to go into them in great detail again today, but they're really there for the record. So here you see where mandated and active tandem mass spectrometry is integrated into programs in orange. A subset of those states in a sort of brownish-tan color are doing MCAD only with their tandem mass spectrometers. But at this point in time, about 41 percent of the babies being born are accessing tandem mass spectrometry-based screening.

Here you can see the mandated conditions where a legislature has mandated that these be screened but it has not been yet implemented in the particular states highlighted. There are a number of locales around the country where selected population screening is done, trying to target what are perceived to be the high-risk groups, which is an inherently somewhat difficult process in genetics at least. About 10 percent of the babies in the United States are getting screened where the screening is targeted in a very selective way.

These are the states that have not changed their mandated conditions since we began the project. Actually, California has recently begun to make the move back to tandem mass spectrometry, and I think it will have that implemented perhaps in a year. But at this point in time, just

three states in this group account for 27 percent of the babies born in the United States. So these three states become very important in getting the universal uniformity that we're looking for in a newborn screening program for the United States.

Here it is all amalgamated together. This is where actually as a geneticist I have to make my apologies to the 7 percent of the males sitting behind me who are color blind and haven't got a clue really what this is showing.

(Laughter.)

DR. WATSON: So the state of newborn screening today. Newborn screening in the United States is not universal. There are only three conditions which are screened universally in the United States: PKU, congenital hypothyroidism, and galactosemia, and conditions that may be related to these by being variants of them. It's also not fair in that there are selected populations receiving screening in some areas, and I said they're very difficult to define quite often, and there are limited pilot programs around the country, and that's about 10 percent of the births, as I said, are in that category.

To a large extent, newborn screening is being left to consumer initiative in that I think many programs received this letter from Dr. van Dyck. Clearly, I think it's a recommendation that people clearly be made aware of the availability of newborn screening and supplemental screening. This is an action that can be taken very quickly, but it does pass the responsibility to the consumer to get access to the system, and there are lots of issues that impact their access. That's why we're moving into now talking about standardization across the country to get our programs aligned and uniform in their screening.

So as I said, it's not uniform right now, and that lack of uniformity is quite pervasive across the United States. It has implications and affects a number of aspects of the evidence base for newborn screening. It certainly has an impact on -- there's enormous variability on how decisions are made about what should be screening, what evidence is evaluated in making those decisions. This variability has tremendous implications for analytical quality. There are a number of platforms available for some tests, and they can be quite variable in the performance characteristics of that particular platform for the screening process. That has direct implications, then, on the interpretation of the results, because it determines exactly what either a single result or a range of results a technology is going to provide you.

It has implications for the outcome data. That's actually not such a problem with not being uniform in that there's very little of it occurring. We really need to be collecting much more information about individuals identified in newborn screening programs to be able to inform ourselves about how to evolve the programs and what's working and what's not, and this is going to be an ongoing process. Things have changed just in our own eyes over the course of the two years of this project.

So the project was done under a contract from the Maternal and Child Health Bureau of HRSA. I was the project director. Michele Puryear and Marie Mann have been our project officers. The contract itself or the project focused on two really primary goals, the first of which was to develop a uniform panel of conditions. The second was to develop a decisionmaking tool for use in newborn Add space screening program expansion or contraction. Part of that was really developing the criteria by which one would assess individual conditions to determine their appropriateness for newborn screening.

There were also some related goals in our contract. Clearly, if we're going to be screening, we wanted to make sure that we were screening well, that we understood how effectively the programs were functioning. So we looked at a couple of aspects of the programs themselves because we wanted to assure that if something was being screened, there was an expected outcome for that condition, which is why it got into the screening program from the outset. In order to know how well your

program is working, you need to have a sense of those outcomes that were expected and how the program is measuring up, and that actually broke down into a couple of areas.

We looked at some minimum standards and related policies and procedures for newborn screening that would allow for that information to aggregate to tell us how well the programs were functioning, and the ability to identify appropriate health outcomes that might be incorporated into those evaluation protocols, what were those outcome endpoints that one would use to determine whether or not you found the baby in time, put the intervention in place in time, and those sorts of aspects of the programs.

Then the last is looking at the value of a national process for quality assurance and oversight of newborn screening programs. All of these areas are largely dealt with in the written report that at some point in time will be made public by the committee. However, I'm going to focus largely on those first two primary goals today.

So I'm actually going to go pretty quickly through this next set of slides because there are things I did back in June when I presented to the committee, but I don't want to ignore those people and those organizations that provided data, put in a tremendous investment in labor and work in helping us put this project together. So I wanted them at least in the public record. But you can see that some organizations have been directly involved through a steering committee. Our expert group was very broadly representative of the interest groups involved in newborn screening. A large array of individuals well known in the newborn screening world have been involved directly with us.

Right from the outset it became clear that getting input and information was going to be the name of the game for figuring this project out. We sought input as broadly as we possibly could. We had invited speakers from around the world and from the United States, from programs, from consumers. We've had opportunities for public comment. We made direct overtures to some organizations for information that we knew they might have contained within their own internal records, and we've done extensive reviews of the literature.

We've organized two work groups under the contract. One looked at the uniform panel and criteria that would determine the appropriateness of that condition for screening, and another committee that is still active that has been dealing with diagnosis and follow-up issues of those newborns identified in the screening programs. We've had external review groups review materials as they've come out of the project, and we've delivered a written report to HRSA in the last several weeks.

So the specific goals of the contract. One of the first was to get our own gestalt of what was important about newborn screening to the physician community, to the consumers, to the state programs, to the whole array of interest groups that we've talked about, and to get that general sense we developed a set of overarching principles that would guide our thinking about how this project evolved and its recommendations evolved.

These are not really in order of importance, but they sort of go from more global issues down to more narrow issues. But this is certainly not a prioritized list that's ranked in any way.

Newborn screening is an essential public health responsibility critical to improve the health outcome of affected children. Newborn screening policy development should be driven by what is in the best interest of the affected newborn, and that's an important concept even though we don't disregard the value to society and the value to families, which is significant. One of the primary focuses and weighting that we gave was of it being in the best interest of the affected newborn.

We acknowledged that newborn screening is much more than testing. It's a coordinated, comprehensive system consisting of education, screening, follow-up, diagnosis, management, and program evaluation. The medical home and the public and private components of the

screening program have to be in very close communication for this to work. None of us can work completely independently of the other groups that have interest in this area in order for it to be functioning at its maximum capability.

The evaluation and recommendations of conditions that are appropriate for screening should be based on the best scientific evidence available and expert opinion. The science is critical, but it's clear in our criteria, as you'll see later, that not all criteria by which one evaluates the value of a newborn screening program can be quantified in scientific evidence. Objective criteria, such as the incidence of the disease, certainly can be boiled down to the science, but there are aspects of treating patients that are much more subjective. We know that physicians have a different view of how easy a PKU diet is than the family that's at home delivering that PKU diet to an infant. So there are very different perspectives that are often somewhat more subjective, and both become very important. So when I use the words "expert opinion," I'm not talking about the clinicians all the time and the scientists all the time. Those experts cover the full range of interest groups involved in newborn screening.

The next one deals with the testing itself, that a condition needs to meet certain criteria, and these are really sort of the key criteria. It has to be identifiable at a phase in which it wouldn't normally be recognized in the newborn. This basically says that you're not going to be able to appreciate that the baby is affected by their being in the hospital and their appearance.

There has to be an available test that is appropriately sensitive and specific for that condition to be screened, and there have to be demonstrated benefits of early intervention and timely identification of infants in the newborn period.

The next one says that the primary targets of newborn screening should be conditions that meet those three key criteria, and that the program should also report any other clinically significant result. We'll come back to that in that many of our platforms for testing provide more information than just on that one condition that is your target for screening. The nature of these multiplex technologies is that they can often tell you that there is clearly another clinically significant condition that may not have been in your core list, and we'll talk later about how we sort of separated those two kinds of information that might come out of a screening program.

There should be centralized data collection for the longitudinal assessment of disease-specific screening programs, and this is going to be, I think -- this is actually something that I think every advisory committee that's ever been involved in genetics has recommended. When I co-chaired the Task Force on Genetic Testing in 1997, this was one of our major recommendations. The Secretary's Advisory Committee on Genetic Testing, this was one of their major recommendations. They all appreciated, being from the genetics world, that we have thousands of rare diseases, and there are not for many of them very many patients affected. Unless we figure out how to collect them, understand where they are and what they are and aggregate that information, we'll never be able to do the kinds of statistically significant assessments of clinical trials and therapeutics that are going to be needed.

So it's been an obvious need for a very long time, and we're only now beginning, I think, to really start to look at how to deal with this information collection issue. I'll talk a little bit later about some aspects of our panels that really will need this and, actually having identified patients, will provide a population in which this kind of data collection can take place.

Total quality management needs to be applied to newborn screening programs. Newborn screening program specimens are valuable health resources. Every program needs to have a policy to ensure their confidential storage and their appropriate use, but they are very valuable health resources.

There needs to be public awareness that is coupled with professional and family education and training. These are very important aspects of newborn screening programs.

So our next specific goal was to sort of decide what are we going to evaluate. If we used any of a number of genetics resources, there are thousands, five thousand genetic diseases listed in these. So we were a little bit biased, I have to say, in what we chose to evaluate. Clearly, if something just blatantly didn't have a good understanding of the etiology of the condition or there was no test, we didn't go through a long exercise of evaluating it. But there were a large number of conditions that people suggested to us should be evaluated, and even if they thought that there might not be an appropriate test, we still chose to evaluate those conditions.

So how are we going to count these things? I alluded to that as being an administrative problem that often distinguished what one state said it did from another, but if you really look carefully, it was a much tighter packing of what they claim to be doing. It's a problem for several reasons, because you can count the number of conditions you're screening from a number of different perspectives. You can use the phenotype of the condition as a way by which one might count. So, for instance, hearing loss is a phenotype. But there are 400 genetic syndromes that involve hearing loss. So that becomes a difficult decision to make as to how you're going to count that particular condition.

You could look at established groups of conditions, like fatty acid oxidation disorders or organic acidurias. You could look at primary markers, and if there's a particular analyte like elevated phenylalanine, one could look at that and it relates to four different conditions that might have an elevated hyperphenylalaninemia.

One could look at this from the test platform itself and say that we're going to do tandem mass spectrometry for anything it finds and call that a single test. Or we could divide it into the 42 conditions that might fall out of a tandem mass spectrometer. The response to treatment might be one of the parameters that one used to sort of count the number of conditions, and the number of genetic loci or genes that cause these syndromes or diseases might be a point of counting.

So here's a couple of examples that sort of highlight how complex this can be. LCHAD deficiency and trifunctional protein deficiency, two tightly-related disorders. Twenty-two states say they screen for LCHAD. Eleven states say they screen for trifunctional protein. In reality, the biochemical phenotype for those two disorders is identical. You can't screen for one without screening for the other, so it's interesting that there's that two-fold difference in what is claimed to be screened for.

If you move on to hearing loss as an interesting example of a functional test for a phenotype of a large number of conditions, as I said 400 genetic syndromes that have hearing loss as part of the phenotype, for hearing loss, when one tests by audiometry and identifies severe forms of hearing loss, there are 77 genetic loci or genes for the non-syndromic forms of hearing loss, and there are 31 loci for the syndromal forms, plus some environmental forms that are also testable by the same genetic technologies. Whether or not the CMV genome is present can be done by the same kind of a DNA-based test. There are others that have been considered environmental, some of the mitochondrial susceptibility genes which only when one is exposed to aminoglycosides does one then express the hearing loss through this mitochondrial mutation.

Sickle cell anemia is a really interesting example. Most states target for primary conditions. SS, SC, S-beta-thal, and variant hemoglobinopathies is what they screen for. However, when one does a test like isoelectric focusing or HPLC, this test identifies over 700 variants in the hemoglobin molecule, of which about 25 are clinically significant. But there's enormous variability in whether states report out those other 25 and which of those 25 they choose to report out.

Hyperphenylalaninemias is another example. It's sort of the original newborn screening condition, started by tests that were able to identify elevated phenylalanine. It was found then to be associated with the primary target condition, PKU, but there were also patients with a benign hyperphenylalaninemia, a lower level of increase in phenylalanine that was a benign condition, and now we know that there are two additional defects of biopterin, one of biopterin biosynthesis and one of

regeneration, each of which has more than one gene involved in those disorders. So it becomes a very interesting conundrum that I think this committee is going to have to give some consideration to.

There are things that complicate the counting process. Clinical, biochemical and molecular complexity that I've already alluded to in going through some of those examples. Progress that's constantly made in our understanding of the natural history and etiology of the disorders. Implementation of these multiplex platforms now that allow one to see a lot more information than might have occurred had a singleton test for a singleton condition, and that there are significant gaps in the level of clinical knowledge and other types of knowledge, frankly, among the different interest groups. Some people are much stronger in certain types of information than others, and vice versa.

So our working group had to make a decision early on. Actually, we hadn't even thought through this condition counting thing to the extent that I've laid it out for you today. We clearly made some compromises in determining what our newborn screening list of conditions was going to be, those that we were going to evaluate for their appropriateness. We tried to strike these compromises around a number of parameters, establish practices. It certainly was a significant component of our consideration. Expert opinions about what should be divided or not divided, and the scientific evidence and the way it is collected and laid out had implications for how we chose to define the individual conditions.

In the end, we selected 84 conditions that we were going to evaluate. This is the list, a rough list at least, of those conditions. Endocrine disorders, infectious diseases. I'll say right off the top that we opted out on infectious diseases. We had neither the expertise within our group nor the input from the outside community that allowed us to feel comfortable in addressing this area, so it is one that still needs to be addressed, and I think it's something that will come back to this committee to decide how that will occur.

Hematologic disorders, a number of sort of unrelated other conditions, inborn errors of metabolism that could be detected by tandem mass spectrometry, aminoacidopathies, acylcarnitine disorders among those, and then we looked at other inborn errors of metabolism which may or may not be identifiable by tandem mass spectrometry, including some of the carbohydrate disorders, lysosomal storage diseases, and other disorders that might be tested by either method.

So these are the 84 conditions that we chose, and here you can get a sense of the percent of the U.S. newborns that are screened for those 84 conditions. You can't tell which they are, but you can see there's 10 that almost all newborns are screened for. That comes back to the counting issue. If you're screening for PKU, you're screening really for those four different conditions. So that 10 is really a count based on the way I laid it out in that list of 84.

But you can see that there are 18 conditions that are screened in more than 50 percent of the babies born in the United States. Most of them are in the list of 50 percent category. The 28 you see end up largely being those that we identified as not having a test available, so no one obviously is screening for them. But we'll look at these in more detail.

So the condition score cards. It's an interesting phenomena that we've watched develop really over the last six to eight months that's really gotten a lot of visibility and is not a particularly useful marketing tool at this point in time, but it is being used as a marketing tool, and I think that is one of the reasons why seeking some level of standardization will be good. Stepping back from it as a marketing tool, I actually kind of like the idea that it generates competition and brings people up to speed with one another and brings uniformity through competition. But as a marketing tool and an unstandardized measure, it's awful.

Quantity is an important issue, how many things are you screening for, but as a marketing tool, the entire concept of quality of screening is lost, and that is at least as important as is how many things are being screened. So yes, I think it does need to be standardized in some way.

What are the possible approaches one could take to standardization and uniformity? Assessment of the literature evidence, looking at the incidence of the conditions, natural history of conditions, screening tests, diagnosis, quality of testing and treatment. I'll talk a little bit about each of those because each one has some interesting issues attached to both how one assesses the evidence and what the quality of that evidence is.

Incidence. The best incidence we have on conditions is the incidence information we get from newborn screening programs. When you look at some of our fact sheets, you'll see that, for instance, PKU has been screened for several decades now. We have incidence data for the United States that's sort of at a level of granularity that's something like 1 in 3,924 babies based on -- I forget the number -- something like 29 million babies having been screened in the United States. That's very powerful data on incidence, and we get it largely because we're screening.

These are rare diseases, so the standard errors around this incidence information is enormous until you move into general populations, and many of the conditions have multiple genetic etiologies, as I said. Depending on how you define the condition, you can now begin to break those incidences out into the individual etiologies of the conditions, and that makes it a complex issue.

Onset of condition. As I said, it's important. You want to identify conditions that are not going to be apparent in the newborn but for which you can intervene and make a difference. When one considers that as just a criteria, it's limited in that it doesn't capture what we call in genetics non-penetrant cases or those cases which have the biochemical phenotype or a genotype that suggests they should have the condition but for some reason they don't experience the condition. It could be because they didn't get exposed to the stress factor that would allow the condition to be expressed. It may be that there's a modifier of some sort that impacts the expression of the gene. But you don't appreciate that until you look broadly at a general population.

The burden of the condition was an important criteria. We wanted to be looking, obviously, at conditions that were severe for which one could intervene and make a significant difference. Genetics is rife with bias in that we start with the most severe presentations of disorders. Those are the people that come to the doctor, they get the attention of the doctor, and they get defined. It's not until we then look at their whole family that we see, oh, this is a lot more variable than we thought, and it's not until we look at a much broader population that we can really appreciate that full range of variability of the condition.

The screening test itself can raise issues. The gold standards by which one establishes a diagnosis have evolved rapidly. Prior to the Human Genome Project, almost, I would bet, 90 percent of the conditions we're talking about would have been diagnosed by a clinical phenotype. We had no tests. We had no genes. Now, as we have both the metabolites and the genes in hand, we have evolving gold standards, and it's not clear at all times which is the best gold standard for the particular intended use. I mean, from my own view, functional tests are very good for newborn screening because they tell you that somebody has the condition is expressing it, as opposed to a genotype that may tell you they have a risk factor that could be a much broader sort of phenotype for that disorder. But they both have value, and you have to perceive them differently depending on what you want to get back out of the screening information.

We've evolved from singleton screening tests by bacterial inhibition assays for PKU to screening algorithms. You see it in congenital hypothyroidism, where most states were screening for T4, which was relatively inexpensive and straightforward, not a great test. TSH is actually probably a better screening test but more difficult, more expensive. So the algorithm has evolved of doing one and then

going right to the other as a second-tier test to tease out really how likely is it that this baby is truly hypothyroid and needs to get out into the system and raise the awareness of both the family and anxiety of the family, as well as the attention of the physician.

In the diagnostic area, issues arise. We have increasing complexity now with permutations. I mean, we in genetics have dealt for a long time with the fact that one gene could have many, many different alleles or mutations in it that can lead to the same disease and variations of severity of that disease. However, now we're getting something relatively novel, which is synergistic heterozygotes. We're seeing patients who have an LCHAD mutation in one gene, one of two genes, and an MCAD mutation in one of two genes. Those two in that individual are synergistic as heterozygotes. They're carriers for each, but when you get them both as a carrier, you end up with a condition.

So it's getting very interesting around how we define these individual conditions, and that will be a rare circumstance. But some of these mutations are not all that rare, and we will see these sort of combinations of things appearing.

Treatment raises some issues. There are a lot of conditions that require similar treatment. So when we look at a condition -- for instance, MSCHAD, a stunningly rare disorder; there's half a dozen patients that have been reported -- when we think about the treatment of some of these conditions, though, they have something in common among a lot of the fatty acid disorders, including MCAD and MCKAT, to which they're related in their biochemical phenotype. They may express hypoketotic hypoglycemia, and it's not always necessary that we appreciate how to treat hypoketotic hypoglycemia in MSCHAD itself in those five patients but can extend our view to a much broader group of patients with biochemically related diseases for which the treatment is quite similar.

So how one develops evidence around these areas where one can be much broader in collecting data or much narrower are things that we've been tortured with most of this summer.

The quality of the evidence is an interesting problem. Natural history studies are getting increasingly difficult as a result of ongoing intervention. There has not been a natural history study of phenylketonuria done since the 1970s. Most evidence-based studies go back and look at recent data. To do a natural history study of the disease PKU is probably impossible now, I hope, given that the screening has been universal for that condition. There is a very limited national, organized data collection effort that would allow us to collect the kind of information we need to really evaluate these kinds of criteria.

So the quality of that data is limited, and some data collection is now proprietary and very difficult to get at. Some of the best incidence data that's available is often proprietary and hard to get at but is out there. We'll have to work to find ways of accessing it to improve our understanding and knowledge base so that we actually have the best data on which to make these decisions.

Additionally, the problem of quality is one that's arisen for the FDA, and it largely was driven, I think, by the rareness of these conditions that we're dealing with in genetics and newborn screening. Treatment data, for instance, is increasingly subject to a reduced level of premarket approval by the FDA. I think when Fabrizine came to the FDA about a year and a half ago for their approval, they did something that was quite different from the way they have traditionally evaluated the clinical validity of this particular product. I think there were 50 patients in the clinical trials of Fabrizine, and ultimately they said, okay, we have enough data to approve the product, but we want more data, and engaged in a Phase IV surveillance process to collect data on an ongoing basis for all patients being treated, and I think that's a model that you might begin to think about for how we're going to collect data on patients.

We're going to be identifying them, and some of them will be relatively rare. Finding that opportunity and the system through which we can understand which ones got disease, which ones didn't, how severe it was, will inform us and help us understand how to develop the programs over time.

The evidence base. There's a lot of variable quality of evidence, as I've already said, but one can go through the exercise of collecting it. We've done that relatively extensively. I've given you about a half a dozen fact sheets which give you a sense of the magnitude of the literature, or lack of magnitude for some of these conditions. One can evaluate very systematically the literature, the clinical evidence that's available in the literature. One can look at cost and economic evidence and begin to try to model some of those finance issues. One can go into search systems. We routinely search Medline and PubMed. We've reviewed textbooks, major textbooks that discuss these conditions. We've reviewed health technology assessments from the U.K. that have been done for these conditions. We've looked on the Internet, at support group websites for information. We've looked for professional guidelines that might apply to the conditions.

Another aspect is the epidemiologic studies which involve issues of the design of the study, which reflects on the quality of the information that came out of it; the subjects involved, whether they were properly selected or not; what is the outcome in those individuals, and what was the effectiveness of treatment, all of which are best done through an epi sort of approach.

There's not a lot of that to be found, either cost information or epidemiologic data around these conditions because, for the most part, they haven't been involved in newborn screening, where we aggregate that high quality information.

So the Health Technology Reports we used a fair bit. These were developed by the National Screening Committee in the U.K., which has done some extensive evidence reviews of the literature and the science behind a large number of conditions that have largely been those already involved in newborn screening programs. We acknowledge readily the importance of this evidence base. However, there are caveats that have to be made clear about the evidence, and a lot of these were expressed by Rodney Pollitt. He was the chair of the first health technology assessment of newborn screening that was reported, I think, in 1997, an extensive literature review and analysis of the conditions.

The kinds of caveats he laid out when he spoke to us were that -- and these aren't obvious when one reads the health technology assessment reports. These are things that happened in the bureaucratic gaps between the assessment groups and the National Newborn Screening Committee. The committee, which included nobody with expertise in the metabolic diseases, for instance, made unwarranted assumptions about some of the conditions. They made the assumption, for instance, that if a phenotype is apparent, meaning that perhaps you had metabolic decompensation or some expression of a hypoglycemic event, that the diagnosis was going to be made.

Well, that's ludicrous. These patients languish, and the diagnostic odyssey is long and expensive, and making that assumption is something that's a caveat in the health technology assessment reports.

There was another problem that he expressed which he referred to as the self-evident evidence paradox, and that basically says that if an intervention is truly effective, nobody is going to study it. I think the example he gave is that arterial bleeding is an example. Find literature that says that stopping arterial bleeding is a good thing for an individual. Well, nobody studies it. It was one of those self-evident things.

So what kind of approaches can we now take to standardization and uniformity? Certainly, the evidence in the literature is very important. However, there are other interest groups that bring equally valid information to the table. As I said, there's often differences in perception of

how complex or difficult a treatment might be. So we sought to really collect information not just from the literature but from the stakeholders.

So we've asked questions about all of our criteria, not presuming that somebody was going to be more informed about one than the other and only restricting them to those, but let everybody answer all kinds of criteria that we established. We went to the providers of the laboratory services and the screening services. We've gone to the providers of clinical services, both at the primary care level and at the specialty level, and we've gone to consumers for their perspectives.

So defining the criteria and the scores by which we're going to assess the evidence and these expert opinions. This was the work of one of our work groups. Dr. Rinaldo, who is now on the committee, chaired this particular work group. As I said, we're eternally grateful to the people who participated, but I'm not going to go through the time to read their names off.

These are the fundamental criteria by which we evaluated conditions. What was the incidence of the condition, with the idea that the more common the condition was, the more important it was to screen for. Is it identifiable at birth? If there was major dysmorphology associated with the condition, they were going to be identified by the physicians in the nursery. They didn't need necessarily to be screened.

We looked at the burden of the disease. If one was thinking about cystic fibrosis, that gene has over a thousand mutations now identified in it, some of which cause classical cystic fibrosis, others cause sinusitis. The burden of the disease becomes important when one has the technological capability of testing, because now you have to start to step back from what you might test for because you don't want to identify things that may be -- I shouldn't say trivial importance, but certainly not of the magnitude of importance as identifying classical CF might be.

There has to be a test available, a sensitive and specific test available. Then we looked at a number of characteristics of a test. Is it a multiplex test or not? A number of aspects that we'll come to.

The cost of treatment and the availability of the treatment. Is the treatment something that a family can provide at home? Is it something that only a specialist can provide? For the primary immunodeficiency syndromes, bone marrow transplantation is the intervention. It's relatively easy to access, but there are centers and it's less available than is controlling a diet at home or avoiding fasting in particular kinds of patients.

Is there an early intervention available? What is the benefit of early intervention? What is the benefit of early identification of a patient? Does one prevent mortality? How complex is the diagnostic component of the program after one has screened? What are the acute management issues? Because there are certainly conditions we evaluated which may -- some percentage of patients may present before the newborn screening result comes back. So it's important to understand the acute management aspect, because some patients even having been identified may have that stress that causes them to decompensate. So it was a parameter that we thought important.

The simplicity of the therapy I've already alluded to.

So next we hit the issues of the data collection tool that we used as sort of our first cut at putting conditions into different categories. We developed the criteria very early on in the process of this work group, but on an ongoing basis we made modifications and adjustments. I'll talk a little bit about the nature of the response we got to these surveys. We had over 290 people internationally, mostly in the United States, but they were from around the world who responded. Those 292 people provided full information on 585 conditions. One person may have just done PKU, but another may have done five

different conditions. But we had 500 different profiles of individuals who analyzed a total of almost 4,000 conditions were individually profiled by this group of 292 people.

Was this a representative group that responded? There were gaps. Clearly, we had no responses from those states you see in black on the left-hand corner. Of those 295 respondents, you can see that they're spread around the United States. Of those profiles, some people were specialists, some people defined themselves as parents, others defined themselves as both a newborn screening program person and a specialist in endocrinology. So they may have been dually identified. So we had 585 of those sorts of profiles, and they were somewhat well distributed, and then those 4,000 individual disease profiles were reasonably distributed.

Then we moved into this process of revision because we didn't just ask people to tell us how they would rate something on a particular criteria. We also asked them whether or not we appropriately weighted that criteria against others in assigning scores. So there were changes made to the definitions of the criteria, to the language we used so that they were less ambiguous when that was found to be a problem. Fortunately, most of that happened in the early stage of the project when we were using an Excel spreadsheet that nobody could manage. So we only had about 12 or 13 responses back, and we pondered why, and from those we got a tremendous amount of information about these modifications when we moved to a much more simplified system of getting back information.

Here's where we were when we started, and you can see a set of criteria that defined the condition. Here are our criteria that defined the condition, a set of criteria that defined the test, and a set that defined the treatment.

Oops, I went too fast.

So you can see the scores here were lower in some areas. The distribution was uneven between the three general areas. As it evolved based on recommendations from people who participated and from the expert group committee that was involved in the project, and the work groups, we made modifications. We seriously elevated the importance to the infant in its score. Aspects of the test were increased because it was felt that multiplex capabilities, for instance, of a test had inherently a public health value in their ability to identify many conditions in one single test. So many modifications were made to these survey criteria as we progressed.

How did we sort out these conditions into a uniform panel? Well, the surveys were sort of the first cut, and we've talked about this before. These are the ratings of the conditions as they scored in the surveys. MCAD scored very highly. Hypothyroidism scored highly. Phenylketonuria scored highly. All these are conditions that were accepted to have a newborn screening highly sensitive specific test, and when we said test, we didn't mean a test was feasible or a test was being done in a diagnostic setting. We meant the test was validated in the general population, and on that basis, something that scored high like hyperbilirubinemia, our ultimate decision was that that test was not adequately validated at the point at which we ceased to take in data, which was late last year, really around the first of the year. So that is in a no-test category.

This is the same thing broken out a little differently. Here are conditions that can be found in multiplex platforms: hemoglobinopathies, conditions identifiable by tandem mass spec, and conditions identifiable by other methods, mostly singleton assays. We would never argue that there is a statistical difference across this range of conditions in here. Frankly, the numbers aren't big enough. We would never try to say that this is a ranking that is of value through this area, but I'm going to come back to that later and try to show you that there is actually some useful information to be gleaned.

So we came to the uniform panel through this process, at least our first cut at what was going to be a uniform panel, and this is going to be a little schizophrenic here because we have a uniform panel, so I'm talking about things that I haven't really completely explained to you how it is in the uniform

panel because at the outset, not everything that is listed as 30 would have been in the panel if we had just gone with surveys.

So here is what is our uniform panel now, which I'll justify as we move forward. You can see that there are nine organic acidurias, five fatty acid oxidation disorders, six aminoacidurias, four conditions from the hematology world, and six defined as other. That is the core uniform panel.

You can look at this a little differently here and see that we have two endocrine conditions totaling our 30, and here you see what are those conditions that we will refer to in time as report-only. What this really means is that when -- and I alluded to it when I talked about counting conditions. When one is doing HPLC or isoelectric focusing for the hemoglobinopathies, you're looking primarily for four key conditions, but the variant hemoglobinopathies are also identified. We called that one thing, but as I said, there may be as many as 25 clinically significant variant hemoglobinopathies.

If you look at amino acid disorders, we have six in the core panel, another eight here. The asterisk is there because one of the things that's included in that total is benign hyperphenylalaninemia, not a condition per se. That's in the list and I wanted to draw it to your attention as perhaps not a condition but certainly something that programs can get informed about and families often deal with.

So this is a category that we came to call report-only. It was information that was made available by the nature of the test, a multiplex test generally, screening for one of those conditions in our core panel. For instance, if I'm screening for MCAD, and that's fairly widely screened for now in at least about 50 percent of babies being screened, C8 is one of the primary markers on an acylcarnitine profile of MCAD. However, there are two other conditions that it may very well be with a similar biochemical type of view, MSCHAD and MCKAT. They're part of the differential diagnosis of an elevation of C8.

So when they go out into the physicians who are going to sort these out, they're going to find out that a patient may not have that core condition, MCAD, but they're going to find out that they have a variant condition that's related. However, that condition may not be treatable. It may not be a condition for which we have much natural history knowledge because it's so rare. So what we call report-only means that specialist or laboratory or whoever is establishing what that diagnosis is is going to come back to the state and say it's not MCAD.

MCAD is the thing that that state wants to track, and understand that they're reaching the outcomes that were expected, that they've made the intervention difference that was expected. We may not have an expectation of a difference in the other two conditions, or we may not know what is the expected outcome. So we suggest that those may not be things that the state would invest in or the program would invest in long-term tracking of because we don't know what that information is going to mean. However, it's valuable in that they know it, because if they were screening for MCAD and they got this result, it's not necessarily a false -- it's a false-positive for MCAD, but it's not a false-positive for a clinically significant condition associated with elevated C8.

So it's important information to feed back, and by having it in the specialist area, it's information that is provided to families in their diagnostic workup and gets them immediately into the system as well.

So that's how this breaks out. You can see the conditions laid out the same that are part of differential diagnoses of one of those other conditions in the core panel.

This is how this counting thing now evolves. As I said, we started with 84 conditions. We ended up with 30 conditions in our uniform panel, 25 report-onlys, for a total of 55 conditions that we have listed here. However, we could take any one of those aspects of a condition that we talked about earlier and count how many conditions there are. Had we used clinical phenotype, you

can see in the uniform panel we would have had 28 conditions instead of 30. If we had used the established group, like established acidurias, we'd have only had 10 conditions. If we had used primary markers, meaning the analytes, we would have 23 conditions; test platforms like tandem mass spec, 9. Had we used the number of loci or genes involved, individual genes in the condition, 143 conditions, and that's the way it's defined in OMIM, the catalog of genetic disorders.

Same thing for the report-only category. It's a very similar kind of perspective of the variation that you'll get when you try to count this stuff up. If we take it all together, if we were working at the level of the genes that caused these disorders, these 55 conditions are 178 individual conditions as defined by their fundamental etiology, an enormous difference, and obviously a dangerous marketing tool at the present time.

All right. I want to give you a little bit more on this aspect. I talked about the differential diagnosis and the fact that we utilized that.

What time do I turn to a pumpkin? I turn into a pumpkin at eleven? Okay. I got a long way to go here.

So that differential diagnosis area. As I said, we established at the first cut a score for individual conditions. These are conditions that scored very highly in our system. We also had conditions that sort of fell above what looked like a reasonable threshold for saying what should be in the core panel, but some of those are actually in the differential. If one is doing isoelectric focusing and looking for sickle cell, you're going to see hemoglobin S beta thal. You're also going to see the various hemoglobinopathies that may be report-only kinds of conditions.

So that evolves this way. You can see that there are conditions that are in the core panel that have relationships to other conditions that scored higher in the panel. You can see that there are conditions in the report-only category that have differential diagnostic relationships to conditions that scored very highly, and you can see that there's additional ones that had relationships to others that were in that differential category.

This is important, I think, because it keeps recurring as we talk about the treatment. I mean, it's this biochemical similarity among these conditions that makes us be able to look at treatment data more broadly now than we might have to for an individual condition that's very rare, and that's an ongoing effort to be able to start to look at things this broadly where one has limited data for the individual condition itself.

This is that same graph we saw earlier, sort of breaking out the total scores of the conditions, but now it's sort of separating things out into our categories. Here in the diamonds you see what we call our core panel, the 30 conditions all scoring high up here. The secondary targets are all here. Tests that we said were excluded. As I said, we didn't evaluate the infectious diseases. There were other conditions that we said had no test.

But if you take out the conditions that you're going to get because they're part of the differential for another condition, you end up with an interesting pattern within these graphs. I mean, you have this outlier here, which is hyperbilirubinemia leading to kernicterus, which scored very highly, and I've already explained why that is in this category for not being tested. You see at the two ends of this range that SCID is the next highest scoring here for which it's been generally accepted, certainly by the two experts that have reviewed our fact sheets that are in your materials -- Rebecca Buckley and Jennifer Puck both acknowledged experts in SCID acknowledged that there was not a test as we defined it, available and validated in a general population at this time, at the point in time when we ceased data collection.

At the low end of those that are in our panel is cystic fibrosis. We have a very significant gap between those two areas that made this appear to be an obvious cut point in drawing a line between the categories. It accounts for about 10 percent of the highest score.

Here's the list of conditions now for which we determined there not to be a test available at this time. This is the ultimate moving target, though. You see a large number of conditions down here from the lysosomal storage diseases. Some we looked at generally, some we looked at very specifically -- Pompe, Krabbe disease. All of these are on the verge of treatments going to FDA that are coming out of clinical trials. They're all on the verge of having tests that will be applicable in a newborn screening environment but are still going to have to move through that general population validation process.

So at the end of the day we end up with our 30 primary targets, our 25 report-only targets, six that are not included where we beat that hasty retreat, infectious diseases, benign hyperphe which is not a condition, those sorts of things that I've alluded to already, and 23 that we determined not to have a test available at this time.

Excuse me one moment. This has been a marathon. I've been told I have an FM radio voice and that I'd be perfect late at night when people need to get some sleep.

(Laughter.)

DR. WATSON: I think medical students would tell you that's probably the case. I can tell from sitting in front that that was likely the possibility.

So, our outcome. What you see here is this is our original 84. I showed this as the first graph that showed you what percentage of babies were getting screened, our uniform panel being in red, the 84 we selected being in yellow, report-only conditions in blue, and not included in black. You can see there's one condition nobody says they screen for, carnitine uptake deficiency that is evidenced on a tandem mass spectrometer if one analyzes by acylcarnitine profiles.

You can see up here at this end that of those conditions for which more than 50 percent of the babies in the United States are being screened from our panel, we have 12 conditions.

So back to our specific goals now. We've talked just now about the uniform panel and how we began to sort conditions out. Now I'm going to bring you into the evaluation flow chart we developed in order to make sure through our literature reviews that what our surveys said was consistent. This becomes the place where we begin to really apply the evidence base from the literature.

So the flow chart itself I'll just walk you through briefly. It takes you from the condition through a question about the test being available, those first cuts from the survey scores that placed it in one of two columns for us, and then we begin to apply questions, the answers to which derive from the literature evidence.

Is there a treatment available? Do we understand the natural history? These things get us to the core panel. Then are most patients clinically affected? That gets us into the newborn screening program. There are things like carriers that may be revealed that may be in this report-only category. So I'm going to walk through these individually and take you through some examples to give you a sense.

This would be our report-only category pathway, and this is the pathway for determining that we are not ready for newborn screening for that particular condition at this time.

We started with these 84 conditions that were evaluated. We sorted them on the basis of those survey responses, and we looked at test availability. We looked at the survey scores. The next level was is there a treatment? Is it part of the differential diagnosis of a condition that would shift it, perhaps? Is it done by a multiplex profile? Do we have adequate knowledge of the natural history of the condition? And do we understand the phenotype of the condition?

At that first level, is there a test available, we sorted this area based on consensus of the survey responses. You got 200 points from an individual if they said yes, there is a test, and you got no points if they said no, there wasn't a test. So we established 100 as the mean, because certainly some of our interest groups were not as well informed about the performance characteristics of a screening test, so obviously the information they may have provided would not be the best information one could get, and one would need to come back to the experts and the literature about the screening test itself.

But at the first cut, was the mean score above 100, which told us that most people said there was a test. The same thing down here for there is not a test.

So we'll take you through lysosomal storage diseases as an example. You can see the scores that we got about the availability of a test. It was generally acknowledged that these were all below 50 percent, and it was acknowledged that there was not a test by the vast majority of those who participated, and certainly by the experts and by the literature.

So through the pathway at the first step, is there a test available, no; then down to this area of not to do newborn screening. You can see what the total scores were around the aspect of the test.

There is not a multiplex platform available. Given the way this whole area of lysosomal storage diseases is evolving, it's likely that we're not going to be looking at these individually as we might have expected if the test had developed around each condition. It appears that what's likely to appear is a multiplex test for which one is going to be thinking broadly about lysosomal storage diseases as a group identified by a multiplex technology, much the way we had to think about tandem mass spec for fatty acid oxidation disorders.

It stopped responding. Sorry.

The survey score at this level of this particular algorithm. Sorting is now based on those survey scores at this first cut, and we basically said those that scored above 1,200, and I showed you that CF was at the bottom of that group in our core, it scored at 1,200. We had an intermediate group that are 1,000 to 1,200. Those are mostly conditions that are in that differential diagnosis group. Then those scoring less than 1,000, almost all had in common the fact that they had neither a treatment nor a test available, but we'll apply those criteria as we move through the algorithm.

So as we take our 84 conditions and sort them over this algorithm, if we just use the surveys as our information collection and evidence, we'd have said that of our 84, 35 should be in the core, 21 should be in this intermediate group, and 19 in the no test available group. Obviously, our numbers are different from that, so I'll show you how we applied these decision nodes where we have superimposed the evidence from the literature and from individual experts to adjust our decisions.

So is a treatment available and necessary is what happens at this node. It comes off of those that have been placed into this core category at the top. Down here we have is the natural history well understood. If it is, yes, it should go into the core panel presuming it's met these other criteria. If not, it moves over here to this report-only category. We may not know what to expect in an outcome. It may not be treatable. But it is clinically significant, and the information is available on the profile and we think it needs to be made available.

Down here, once we've decided it should be in the core panel, the last cut is are all detected patients affected. This was largely to discriminate the fact that if we're doing IRT followed by DNA, for instance, for CF, or if we're doing hemoglobinopathies, we're going to detect carriers. Carriers may not necessarily have to be the responsibility of a newborn screening program to deal with, but it's useful information for physicians to have to make available to patients as appropriate.

So through that side of the algorithm, is there a test, yes, that high score, treatment available, no natural history, goes to the core panel, and this is the list you end up with. However, once you move through some of the decision nodes, we end up with some conditions that move into report-only categories, and those are largely here in the carrier area.

So how do we correlate these survey scores and compare them with the existing literature evidence? We did this through individual condition fact sheets, only a subset of which I've given you today. I think I suggested that you would get a lot more today. However, when I found out just a couple of days ago that anything I said, delivered, or otherwise was part of the formal record, I chose to only give you those fact sheets which have gone through our full process of validation, and those are the ones in your packet there, and you'll see how they're laid out.

They have both the fact sheets and a third page which lists the individual experts who have validated the facts in the fact sheets, validated the reference literature, and have also gone one step beyond to apply an evidence level to the literature that was applied to that particular condition. We chose to use the American Academy of Pediatrics for levels of evidence as they define them, since that was one of our major target populations of physicians who would be reading this report and dealing with information.

So I'll give you a sense of these fact sheets. This is what they call a really awful slide. However, I'm not going to make you try to read it. We tried to keep this to a two-pager, so it has its constraints, but I'll take you through pieces of it. The first page shows you the facts, and the facts are of two varieties, as I've suggested. Up here you see information about the condition, the name of the condition, the enzyme disorder or whatever it happens to be; the type of disorder, aminoacidopathy, organic aciduria, whatever it might be; is there variation in ethnicity of individuals affected with the condition or variants of the condition; what kind of screening method is used; and what is its newborn screening status in the United States. This was drawn again from the NNSGRC website and tells us what percentage of births are being screened in the United States for the particular condition.

Here you have at least an indication of the magnitude of the literature for the condition. It shows you the number of PubMed references as of August of '04, the gene that's involved or genes that are involved, depending upon how you count these things, the locus or loci involved, and the online Macusic catalog number for the condition, or multiple numbers.

On the left side of each fact sheet are the survey score information. That's presented in terms of a percent of maximum scores for all individuals who responded on a particular criteria. It shows the responses, the conditions, the tests, and the treatments.

On the right side are the literature facts. The literature facts, as I said, come from the scientific references and systems of searching I showed you before, Web-based evidence, and applied to the condition, the test and the treatment, and the diagnosis itself sort of overlaps a few of these categories.

So on the second page of each fact sheet is a couple of different kinds of information. Here you see an area where we chose to show you the criteria for which we had the least consensus from the surveys. This is MCAD, and you can see here that there was differences as to cost, and I think that was determined by the nature of the people responding. Consumers often don't understand -- frankly, most people, unless you're sitting in a screening lab, you probably don't know the

real cost of that particular condition, and that is a highly variable number, because if you're using tandem mass spec for just MCAD, your cost is higher than if you use tandem mass spec for that whole range of conditions identifiable on a profile. So what you call cost per test is a quite variable number depending upon what you're screening for.

Here we have the inclusion criteria. The inclusion criteria were is there a test available, those decision nodes we went through, the type of test, secondary targets or parts of the differential diagnosis. It shows you the final score. It shows you its rank in centiles and the observed discrepancies between the literature facts and the information in the surveys. So if there was a significant difference between the two, we acknowledged it here, and it's generally commented on here in this comment box.

This is the reference side where we put down the reference that supports the fact that we've stated above. We confined ourselves to 20 references. We did not feel obligated to list every case report that had ever been reported, every bad study that had ever been done. We generally took those studies that were determined to be useful evidence as determined largely by the experts in those diseases, arbitrated to an extent by the work group, and if there was a clear difference of opinion in the literature, then we provide the best references that support that difference of opinion.

So were the fact sheets peer reviewed and scored by recognized experts? Yes. I mentioned the fact that there's a large number still out for comment. One thing I began to appreciate from my 20 years in academics is that we're really hard to find in August. We go away and we don't acknowledge the fact that we're even in our offices most of the time, except to do that which has to be done. So getting at our experts in August was slow torture, and we're still pursuing some of them because we hit a major inborn error of metabolism meeting during September that made finalizing all of our validation stuff possible.

All the fact sheets that we have in hand for all 84 conditions have gone through the fact checking part. We decided at a later point that we would then ask these experts to do one additional step, which was to apply an evidence level to the facts that they had checked for us, and that is the piece that is ongoing and we hope to be able to provide to you in the next couple of weeks.

So as I said, we used the AAP's evidence guidelines. I think if anyone has read their report on hyperbilirubinemia, they're all well discussed and referenced in that particular guideline. I'm not going to go through them in individual detail because time is rolling too quickly, but they do attempt to apply a level of evidence based on the quality of the studies and the nature of the studies that were done to develop that evidence.

So here's a cystic fibrosis fact sheet, for instance. Right at the very top I want you to understand that there's a typo in your fact sheets that we did not find until this morning. We developed the scores in two different ways. Because those things in the core had to have a test, there was a point in time when we said, well, we just won't add the test score in because it won't add much information. As I said, CF scored 1,200. We decided ultimately we'd have that test score information in. So this 1,200 is not the number you see on your fact sheet. The fact sheet number was taken -- the wrong question was asked of the database to stick the number in. That would have been a score without including the test score itself. So I will clarify those for you.

DR. LLOYD-PURYEAR: We don't have it.

DR. WATSON: Yes, you don't have CF, but the other ones have similar problems in that score category.

So CF, as I said, scored at the lowest end of our core panel, and I think it's apparent from those two criteria for which there was the least consensus among individuals and in the literature. That is, the availability of the treatment where you see a lot of variation in what people thought

of the availability of the treatment, and the benefits of the early identification. Does one realize that benefit in growth, or is it a nutritional benefit that one realizes that improves one's attendance in school and ultimately educational outcomes? Those have been evolving over the past year. Some of that information has not yet been published in the peer reviewed literature. We have some of it from a CDC conference that was done last November where we saw the information that was presented prior to its publication but are awaiting its presentation in peer reviewed literature.

The comment acknowledges that the screening is controversial, the nutritional benefits have been shown by improved growth were less pronounced after five years than they were in the first two years of those follow-up studies. However, recent evidence that has been more recently collected suggests that the nutritional benefits have a positive influence on cognitive abilities, though the data hasn't yet been published. CF may be reevaluated after the evidence presented at a recent CDC meeting is published. The message there is that this is never done. You guys get to figure out how to maintain this sort of analysis of both what's in and what's out on an ongoing basis.

So this path to report only. No treatment available or necessary is the node here. So if something was scored highly but we didn't have the treatment available, it dumped over to the report only category. But at this stage at least our thinking was that it had to be part of the differential diagnosis of a core condition. We did not make the leap of saying that we should identify all conditions in newborn screening for which there may not be a treatment, because we are focusing on the individual infant and the importance to that individual and felt that, at least at this stage of the development of this process, we would start from that point, and information gained in trying to achieve that would be acknowledged and reported at least.

Also in the path to report only were some conditions where there was no treatment available or necessary, the condition was not part of the differential diagnosis of a core condition, but it was still detectable in that multiplex profile. So, for instance, a condition like SCAD may not be related to one of the analytes that is related to a condition in the core panel. However, it is clinically significant information available in the profile, and on that basis it came back into the report only category.

This is a very important node in the decisionmaking process, and this one is for your benefit. It basically says that this has to be reconsidered on an ongoing basis based on new screening methods which are in various stages of development, new treatments which are in various stages of clinical trials now, and our evolving knowledge of the natural history of these conditions. Hopefully, data that we will be collecting from patients in this category, so we can ultimately understand these parameters to know if that's really where they ought to be or if they should be in the core.

So back to our specific goals. The evaluation tool for program expansion was the last sort of target goal. What we did was take our survey tool now and began to generalize it to be used by any of a number of entities. If one thought this was appropriate for each state to do -- I shouldn't say state, I should say individual programs -- then they might choose to apply this tool to collect some of the information, and the tool does have value, as I said, because not all of the evidence is fact based. There is evidence that has subjectivity to it as to the availability of a treatment or the impact on those delivering the treatment. Those are not clearly defined in the evidence of scientific literature.

However, there are certainly aspects of the science that are not necessary to be re-done by all 50 individual -- however many programs there are out there. For many of these, there are only so many patients, and to have 50, 20, however many programs trying to evaluate those same 50 patients to come to a decision about what the science says may not be the most useful application of the expertise that we need, because everybody ends up bringing all those same experts to the table to talk about them, to help them understand the diseases. So this is an aspect that might very well be done centrally.

There are a lot of things that the programs still have to make decisions on, but the science may be one thing that we can do centrally, provide to the programs for them to now overlay their other decisionmaking aspects to decide what to do to place things in various categories for screening or not.

This tool has a number of informational aspects to it. It tells people how to use it instructionally, it gets a sense of what kind of a background the person has, lays out the criteria, the scores that we applied or weight for those criteria, worksheet listings of other conditions we've already evaluated as reference points. That you see here. We can lay these out in any range of things that we think are useful, and I don't know that we've completed defined this yet. We can give people reference information for every criteria. We can give them the reference information for how the total score fell out for MCAD in our hands. We'd leave it blank at this point thinking that they'd see our score. They can score it individually and see how it comes out.

We can give them these. We can give them the entire set of conditions we evaluated as a reference point. They can then take any condition -- I mean, if a particular support group, for instance, was interested in how their condition might score in a system like this, they can go through the exercise of evaluating it and see how it compares to other things that have been evaluated. It could be used by any of a number of individuals across a range of expertise or involvement in newborn screening.

Clearly, these are conditions that are right on the cusp of having to go through this process. It's just an example of the ongoing nature of this process.

So overviewing that process, collecting the survey data from both the providers and the consumers, developing those first-cut scores, applying the evaluation flow chart, using the literature evidence to move off of the various nodes in the flow chart, and then making recommendations to state advisory committees as to what this analysis tells you.

Our expert group recommendations ended up being that one should mandate screening for all those core panel conditions. They met the key criteria for their appropriateness for newborn screening, and it was our sense, at least as an expert group, that that defined a group that should be mandated. Reporting of clinically significant conditions identified while screening for core conditions should be reported. We should yet maximize the use of multiplex technologies and second-tier tests. This is going to, I think, be an increasingly important component of newborn screening programs.

Brad Therrell, who will speak later, has done a somewhat rough calculation of what happens if one screens for those 30 conditions and follows them up in the way that we suggested. About 1 in every 250 newborns in the United States would come up screen positive. It was obvious this was a problem with congenital hypothyroidism early on. The programs themselves made the decision to go to a second-tier test and look at TSH to get rid of the false positives. IRT is also a test that lacks that kind of performance characteristic of the test. There's a lot of false positives. They go to a DNA-based test looking for the most common mutations to determine which patients get out into the specialist world.

That potential is there for a large number of conditions in our core panel, and we'll begin to have to look at how these second-tier tests evolve, because if those are done in the newborn screening laboratory, we'll be able to reduce those patients who get out into the system who didn't ultimately have to be referred out. That decision can be made before the families are notified and the physicians are notified.

It's important to recognize that the range of benefits from newborn screening go beyond the infant's mortality and morbidity. Families derive value from knowing that an infant has an identifiable condition. They can avoid the diagnostic odyssey, which can cost -- for instance, for SCID, a bone marrow transplant of a SCID patient costs about $40,000, and it's only that cost if you get them before they're symptomatic. If they appear in the hospital symptomatic, we're in the neighborhood of $1.1 million

to both manage the infections, do the bone marrow transplant, and get a less beneficial outcome than we would have gotten had we applied the $40,000 at identification of that individual. As I said, that doesn't have the test yet. It has the treatment.

Recognize the whole spectrum of benefits to families and societies that might be derived from early identification. There are conditions, for instance, like the Fragile X syndrome where mental retardation is the primary phenotype of the disorder. One can involve those individuals in early intervention programs and perhaps improve their ultimate outcome. They don't have the magnitude of improvement that one sees between a PKU-treated and untreated. However, most Fragile X families aren't identified, at least the first affected individual, until about the age of three and a half. Families have commonly completed their family planning and developed their family by then, and it's only now that they learn that they have a child with a genetic disorder that had they known in that early stage of life, they might have made their family planning decisions differently.

So there are values and benefits that can be derived from others than just the infant, though we placed maximum value on the infant.

We advocate strongly for outcome and effectiveness data collection. I think that's the way we're going to inform this, and I'll capture the rest of that thought in this last slide which looks at next steps. There's a number of ongoing projects that are going to help our ability to deliver these newborn screening programs effectively. We have a grant, for instance, to develop confirmatory algorithms that will walk through that confirmation and diagnostic step when one is identified as screen positive. We've also developed what we call act sheets or action sheets, which are for the primary care providers. They're one-pagers that basically tell them here's a C8 result that says it's 2.0 micromolar or more. It tells them this is very likely an MCAD. Here is the kind of response that might be appropriate in identifying the help you need and the timing in which you might need that help. It provides them with the referral resources they might need locally, and all that has to be developed at a local level, or at least identify the experts where they may be.

So those are actually ongoing, and some of them are examples in the report itself. HRSA has recently funded the regional collaboratives for newborn screening and genetics. This is an attempt to try to move from what has been an organized national effort to shifting things to the local community level, where the individuals who are affected live. So the regional collaboratives now aggregate states in a particular region, and they shift things from this very national focus of analysis to the local community. Those have recently been funded. There's a national coordinating center activity that will be providing to the regional collaboratives.

Ongoing evidence review is going to be critical to improving our knowledge of both the conditions themselves and the outcomes from treatment, and how do we pay for this? I think we've acknowledged that there are important value things here that can't always be quantified by the evidence in the literature. I think Rodney Pollitt captured it when he said at the end of the day, a lot of these analyses boil down to moral value judgments about whether to screen or not, because the evidence isn't the only thing that one has to fold into that decisionmaking process.

So once we get to that step, in order to deliver this, we actually have to figure out how are we going to have to finance the programs' capabilities to deliver the kinds of technologies and tests that allow it to happen. It's clear that this can't happen tomorrow. I'm not arguing that this is the standard of care next week to do all these tests. However, we have to look at how we can move towards being able to deliver it and finance the capabilities for doing that.

Thank you.

DR. HOWELL: Thank you very much, Dr. Watson, for that excellent report.

(Applause.)

DR. HOWELL: A tremendous amount of data. Again, the committee has your draft report, and of course, although you covered a tremendous amount of material, the report itself is considerably more dense than that.

Let me make a couple of comments. Mr. Derek Robertson has arrived as a member of the committee.

Derek, do you want to introduce yourself ever so briefly?

MR. ROBERTSON: Good morning. My name is Derek Robertson. I'm a consumer. I have three sons, two of whom have sickle beta thalassemia. I'm an attorney working in the area of hemophilia-related genetic disorders, and I'm happy to be here. Thank you.

DR. HOWELL: Thank you very much.

We're going to spend, after our break, an hour, roughly, discussing this document. I think the discussion will, of necessity, focus on the committee members, but if time permits we might also permit some questions from the audience. I think that will just depend on what the situation is.

I think that in view of the fact that we have a few minutes before the break. I don't want to get into the discussion before the break because we'll never get on the break, but there are two members of the committee that have been very active on this committee and who, unfortunately, were not able to attend. Since the committee has letters from these people and the audience does not, I think it appropriate that I read those letters.

The first letter that was addressed to the committee comes from Dr. Steve Edwards, who, at the time this committee started working, was president of the American Academy of Pediatrics and is a liaison member of this committee representing the American Academy of Pediatrics. Dr. Edwards' letter says, "I regret that I will be unable to attend the meeting of the Advisory Committee on Heritable Disorders and Genetics Diseases in Newborns and Children on September the 22nd and 23rd, 2004. Because the agenda today is so important and timely, I would like to offer comments on the recommendations and report from the American College of Medical Genetics' expert group.

"The possibilities for screening newborns have greatly expanded. During this expansion, the differences between the numbers of conditions screened among the states have accelerated. This report from the ACMG is an important step in the right direction. They have evaluated diagnosis and treatment in a scientific manner, with a priority being given toward treatable conditions, considered cost-effectiveness, and as an important criteria come up with concrete recommendations as a guideline for every state.

"I believe the recommendations in this report are an important first step. In adopting them, we have to keep in mind that this will continue to be an evolving field as diagnosis for additional conditions have become more practical and more accurate. We must act quickly to provide sound scientific advice to the states in hope of developing more uniform programs. Before us today, we have a tremendous opportunity to make a positive impact on the lives of children in this country. It is essential that newborn screening programs be based on the best scientific evidence and available expert opinion. Moreover, it is critical that a single, consistent advisory source determine the number and type of test recommended for each state to perform in its newborn screening program. This determination should be framed with the intent to enhance current state screening services and not to inhibit programs that may exceed these recommendations.

"But we must always keep before us the realization that our ultimate goal is not just diagnosis of these rare disorders but rather a coordinated system of care that provides the help that these children and their families need to lead improved lives.

"I encourage the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children to propose adoption of the ACMG recommendations. Partnering with families, pediatricians, and other child health providers, as well as state health official, we can work together for a coordinated system that is available for all who need them."

And it's signed E. Stephen Edwards, M.D., Immediate Past President of the American Academy of Pediatrics.

The second letter that we have is from Dr. Jennifer Howse, president of the March of Dimes, who also sits as an advisory member of this committee.

"As you know, I am unable to attend the September the 22nd meeting of the Secretary's Advisory Committee due to a previously scheduled trip to China. However, I do want to provide a written statement on the recommendations and report of the American College of Medical Genetics Expert Group from the perspective of the March of Dimes.

"The March of Dimes has carefully reviewed and discussed the preliminary report from the American College of Medical Genetics dated July 27th, 2004. We strongly commend the excellent contribution it makes to advance the field of newborn screening, defining a uniform panel for newborn screening, and providing a policy network for the states. We note that the report is due to be acted upon at the Secretary's Advisory Committee on September the 22nd, and to be published in a special supplement of Pediatrics, where it is submitted later this year.

"The March of Dimes supports the findings and recommendations of this report and urges its swift and positive consideration by Secretary of Health and Human Services. As a matter of record, the March of Dimes supports comprehensive newborn screening based on the principles of the best interest of the newborn and equity for every baby in this country, regardless of their place of birth. Our present policy is to support screening for specific conditions when three criteria are met: there is a documented benefit to the child, there is a reliable test, and where early detection is possibly from the newborn blood spot.

"We support parents' right to be fully informed about their baby's screening results, and we support the need for provider education programs. March of Dimes state chapters and their partners continue to work closely with governors, state legislators, and health departments to expand and improve state newborn screening programs.

"Based on our review and support of the preliminary ACMG report on newborn screening, the March of Dimes will expand its current policy on newborn screening in the following areas. Firstly, we will urge every state to screen every baby for at least 30 disorders as listed in the ACMG report. We note that these disorders meet the three inclusion criteria and include the nine core metabolic tests, as well as hearing screening contained in our present policy. We will revise our periodic measurement of performance of these by each state to include at least these 30.

"Second, we will urge states to act on the 25 reportable conditions named in the ACMG report for which there is a reliable test. We will revise our periodic measurement of state performance to include at least 25 reportable conditions.

"Third, we will urge states to inform parents prospectively about the potential benefits and the availability of comprehensive newborn screening.

"Fourth, we will urge professional groups such as the American Academy of Pediatrics, as well as government policymakers, to develop better systems for educating health professionals about newborn screening.

"Fifth, we will urge expanded efforts by public and private entities to develop new opportunities to improve the health of our nation's children through newborn screening. Such activities include the responsible development and validation of new technologies and clinical applications for those 29 additional disorders identified by the ACMG report as not yet conforming to the inclusion criteria stated above. We will also call for prospective evaluation of the impact of screening programs on the health of children identified through these programs, especially as the scope of newborn screening expands.

"Newborn screening is a rapidly changing field. We know that expert opinion on newborn screening will continue to evolve with scientific review, and accordingly we stand ready to appropriately update our recommendations to the state and to the public. Likewise, we urge that the ACMG report be periodically updated to accommodate new data and capabilities.

"In addition, there needs to be a timely review of infectious and other disorders in newborns for possible inclusion in universal newborn screening using the ACMG as a model for these deliberations.

"The March of Dimes has been working for 40 years to build newborn screening programs and assure their wide availability to all newborns as a matter of equity. In 2000, we stepped forward by calling for a state minimum of nine metabolic tests, as well as hearing screening, and advocating for national standards for the development of comprehensive newborn screening. Despite our best efforts and those of concerned parents and advocacy groups, based on the March of Dimes survey of June 2004, 68 percent of children are born in states which do not screen for even these core metabolic disorders.

"March of Dimes called for and supported the expert report on newborn screening by the American College of Medical Genetics, and I served as a member of the steering committee. We will actively support the report's implementation. Moreover, we commend the leadership of HRSA in commissioning the report.

"March of Dimes will continue to work at both the state and federal levels for comprehensive programs and equity in newborn screening for every baby born in this country each year. Accordingly, we urge all groups and concerned individuals to work even more closely together to achieve this common goal. Together we can move forward to that day when all newborn disorders are both detectable and treatable.

"In closing, we again urge that the ACMG report and its recommendations be commended to the Secretary of Health and Human Services for swift and positive consideration.

"Sincerely, Jennifer Howse, President, March of Dimes."

Having read those two comments from the committee members, the time is now for a break. Let's return, and then we can continue discussion from the committee and, if time permits, the audience.

Thank you very much. We'll return at 11:15.

(Recess.)

DR. HOWELL: Ladies and gentlemen, we're going to now begin the discussion of Dr. Watson's masterful presentation. Again, we will focus the discussion out of the committee.

Let me make a couple of comments. I would like, if we could, to have this period as one of discussion, and as far as what the committee will recommend doing with this report, we will have in our session tomorrow afternoon, in the area under the committee recommendations, about what we're going to do. But if we could start with members of the committee with questions or comments for Dr. Watson about his report.

Total silence? No, no, I didn't think that would happen.

Dr. Dougherty?

DR. DOUGHERTY: I have a number of questions. I guess I can ask them one at a time.

Is that on?

DR. HOWELL: I think it is.

Can you hear Dr. Dougherty?

I think it's coming up.

DR. DOUGHERTY: Okay. Some of the questions are around the survey method that you used. You presented the number of respondents, but how many people did you ask to respond, and how did you select the respondents? And could you give a sense of what categories there are in the respondents? How many disease-specific advocacy groups, what kinds of people? I don't get a sense of that from the report.

DR. WATSON: I presented a lot of that in June, so I didn't show that granularity on the response side this time. That's not my laptop, so I can't find it on it. At the first level, I can't tell you how many people we went to because of the mechanisms we used to go out. We went out through listservs to which people interested in newborn screening participate. So, for instance, Brad Therrell has a listserv of people interested in newborn screening through the NNSGRC. We sent out through it. We went out through HRSA's listserv of people involved. We went directly to individuals known to be experts in individual conditions.

We were wide open about trying to get people to participate, because we knew that that range of input was going to be necessary to discriminate some of those subjective aspects.

DR. DOUGHERTY: So these were people that you knew from the College and people that HRSA knew and people that your expert committee knew?

DR. WATSON: Not necessarily that I knew. I knew of because they were acknowledged experts in the world in particular conditions. They don't even answer the phone when I call anymore.

(Laughter.)

DR. DOUGHERTY: Okay. I guess the other question is about this chart, this one.

DR. WATSON: Flow chart?

DR. DOUGHERTY: The flow chart, yes. You do say that people are often uncertain about whether a test -- they may know more whether a test is available but don't necessarily know about its reliability and validity. It was unclear to me where the literature review findings are inserted into the process of coming up with the full core set.

DR. WATSON: I think most of that was done at the level of the work group early on because of the limited number of technologies that were being applied. The area of biggest change is tandem mass spectrometry, and certainly we had long discussions of the sensitivity/specificity issues of tandem mass spec when one tests for PKU, as opposed to doing a BIA or other methods. So a lot of it was sort of comparative and in proving gold standards of how testing is done, acknowledging the improved sensitivity and specificity of the particular technologies.

DR. DOUGHERTY: I noticed from some of your fact sheets that the sensitivity and specificity of the test is actually not in the fact sheet, and that would be useful information.

DR. WATSON: I think Brad Therrell and Harry Hannon would completely agree that that would be really useful information, and we would really like to be able to get it. But boy, is it hard. The best data is going out to those screening programs and saying what did you find? The problem there is that there is so much lack of uniformity and standardization in where they set their cutoffs across the country. Some states set the cutoff pretty high, with the intent of coming back and doing another test in their screening lab. Others set it at a lower threshold to try to catch that break point between those patients who really have it and those who really don't, and don't do a second test.

So there's inconsistency in the language that the programs use to define the performance characteristics of the test that makes it very hard to aggregate that information together. We can get analytical validity data pretty easily. It's available on these technologies. But clinical sensitivity and performance characteristics is a lot more difficult when one has that variability in how you define the performance characteristics themselves and the cutoffs and things.

DR. DOUGHERTY: So for most of these, we don't really know what the sensitivity and specificity is?

DR. WATSON: We have included in the standards -- I talked about that we had some other areas that we looked at. When we laid out what we think are appropriate standards that programs might use to measure their performance, we sought to standardize the language by which they use in their program to define a repeat or a second specimen. It is all across the board the way these things are defined, and it has implications for having a consistent case definition across the country. We don't even have that because of the differences in cutoffs and approaches to screening that are out there in the various states or in the various programs.

DR. DOUGHERTY: Okay, that's all for now. I'll give somebody else a chance to ask questions.

DR. HOWELL: Dr. Boyle?

DR. BOYLE: I appreciate your walking us through this, Mike, one more time. Each time you go through it, I actually feel like I learn more about the process even though I participated in the process.

I'm still very unclear, and I was just going to follow up on Denise's question about the actual flow diagram. I was pleased to see the fact sheets and the evolution of the fact sheets. Having

been on the committee, I felt like we needed to start with the evidence base and to augment that with expert opinion in the absence of evidence base. So it's good to see that these are evolving.

But I'm still unclear based on the report that I read, as well as your presentation, as to how that information is taken in to evaluate a condition. It continues to feel like we've done it sort of backwards. We set the basis based on clinical expert or other opinion, and then we've augmented that with the science base.

And just to follow up on what Denise just said in terms of actually looking at the clinical validity of a test, if we don't know that information, then clearly as we move forward in this process, we want to gain that knowledge, and we can gain that knowledge, as you just said, through newborn screening programs. So identifying the gaps is essential in terms of trying to advance the science here.

DR. WATSON: Yes. You may have to go back and enumerate those individual questions because I probably lost the first two or three as we got to the end.

It is hard to do. I mean, if we did that for homocystinuria, for instance, I could probably go to three state programs and ask for that kind of information, and those three probably have never found a patient. It makes it difficult when it's 1 in 300,000 to get at that kind of information.

One of the reasons I think we have as much expert opinion in influencing the outcome is a recognition of the rarity of the diseases and that the evidence itself is often not powerful. I mean, you don't have the large populations around which one can draw the same kind of evidence conclusion that you can draw about a much more common condition. I think we probably looked at this a lot like the FDA ends up looking at ultra-rare conditions. Do we have enough information available to go forward, and I think we do for the things that we said we should go forward on.

What we don't have in place is a way of monitoring that over the long term and surveillance to make sure that what we thought was very much the case was truly correct over the long term. A lot of times it's refining the performance characteristics. The literature just isn't there on some of these questions.

DR. BOYLE: And I appreciate that, and I appreciate the fact that some of these are very, very rare conditions and we wouldn't have information on it. But I think identifying that as a problem and really stating where we have information and where we don't have information -- and I think your fact sheets are headed in that direction, but they're not complete. Even limiting them to 20 references kind of undermines the integrity of the fact sheets.

DR. WATSON: Well, I think, though, that probably for 50 to 60 percent, certainly if you move out of tandem mass spec, you could probably take 10 to 12 conditions that are done by tandem mass spec and go straight to the -- I mean, if you accept the health technology assessment reports as having adequately collected all of the existing references up through 1997 --

DR. BOYLE: Well, the new one is 2004.

DR. WATSON: The Pandor.

DR. BOYLE: Yes.

DR. WATSON: Yes, yes. But I don't think we necessarily needed to go back and recreate what is acknowledged as a very good evidence collection that was done through those reports. We were really augmenting and trying to pull out studies that were done well that defined the answer around a criterion.

DR. BOYLE: I don't want to monopolize the conversation, so this will be my last comment. But I think maybe the richness of the U.K. reports is that they actually have a very standardized methodology that is replicable. Again, it may be that your system is. It's just that as described in the report so far, it's not there yet.

DR. WATSON: Yes, I must admit the report has been an evolving document, as you know, and every time it goes out, the next tier of comment and criticism comes back. We have most of that information that we've evaluated. We haven't necessarily laid it out. As I said, the validation aspect of the facts is something that we initiated very recently. What is the evidence that the person assigning the evidence level -- I mean, everywhere you go you hit another place. So you get experts to say that this is the level of evidence, and then perhaps the experts are biased in assigning the level. If they're experts, perhaps they were involved in the work and have some of the patients.

The flip side is what happened with the national screening committee. It was one of the things I took home from Rodney Pollitt's presentation to our group, that they did a very extensive review. They made very specific recommendations, and at the end of the day they had the exact same problem we had. A politician said I have a son or somebody with this, so we're screening this. So that came into play. There were aspects that were ignored by the committee that they thought very important. These things aren't reflected in the health technology assessment reports themselves. If the national screening committee chose to blow off something, you don't see it. You see all the evidence and all the stuff that they did, but you don't see some of the decisionmaking that was done behind the scenes about how things were presented and recommended.

Somewhere in between expert opinion and totally independent groups of people with perhaps no experts involved is the right place to make the decisions about these things. The expert opinion was actually very entertaining to get back. I remember Rebecca Buckley, for instance, sent me back her response to our SCID fact sheet. We said no test. No, no. On incidence, we said incidence unknown, estimated at 1 in 100,000. She writes back and she says wrong, the incidence is unknown. We won't know until we do newborn screening. She sent me back a two-pager and I sat there and said, oh my god, everything we did here is wrong. But when I read it, she actually was agreeing with us, that what we said was correct. She was putting a different spin on it, and that's the danger of experts, I suppose, that they advocate on behalf of a disease, and she was in her responses to me.

But for things like that, we got on the telephone and said, okay, I realize that the test is feasible for SCID. We can look for lymphopenia. However, it hasn't been validated in a general population. It might be done locally, but we don't have that which makes it a newborn screening test in hand yet. Once we agreed on what the language of that was, we were in agreement.

DR. DOUGHERTY: Another question. As long as we're on the survey and the evidence review, this is about the treatment. This is becoming clearer. For example, on SCID, to take one example, the consensus column says clear evidence for benefit of early intervention, and then under the literature and web-based evidence it says survival and better immune restoration and transplant costs will be such and such.

We're not talking about costs now, but when those four citations are included under the literature review, can we be confident given these levels of evidence that those are RCTs or a consistent set of observational studies? I assume they have to be RCTs because there are only three of them. So interpreting the literature here is a bit difficult.

DR. WATSON: It is, and SCID is very rare. So what we have is a collection of nine different genetic diseases. I mean, when one talks about SCID, we're talking 85 percent of adenosine diaminase-deficient patients present with a severe SCID phenotype, 15 percent are milder. So we aggregate around bone marrow transplantation and primary immunodeficiency. One can take that whole constellation and look at them as a group and look at the therapeutic response to bone marrow

transplant. There is so much similarity in the phenotype that there is similarity in the outcome to the treatment despite the mechanism or pathway through which they develop the disease.

So it's not always on a disease by disease basis that that statement is being made. It's often a more general statement that is driven by the phenotype itself that may be common because of the biochemical nature of the condition itself.

DR. DOUGHERTY: Just one more thing. I just wanted to bring your attention to a new American Academy of Pediatrics statement about their guidelines, which is that the recommendations in their guidelines reflect what the level of evidence is, and there's a very nice paper on how to do that. So I think that's sort of a middle ground. Well, it's not really a middle ground, because they used to say strong recommendation, fair evidence, something like that.

DR. WATSON: Yes, they have two tiers by which they assess things.

DR. DOUGHERTY: Right. Now they're actually recommending that you can't make a strong recommendation at the AAP unless you have strong evidence. So that's just something to keep in mind about the way this is going. I realize that there is no evidence for a lot of this stuff, so that's a big issue.

DR. WATSON: Two-year projects are interesting time periods over which to do --

DR. HOWELL: Let me make one brief comment. Dr. Dougherty was unavailable for our first meeting, but Dr. Buckley did speak on SCID at the first meeting, and the evidence that she presented as far as the early identification and transplantation was really quite remarkable. I don't have the data before me, but if they're not identified very early in life, before infections, they have a much more complicated and a very expensive course.

DR. DOUGHERTY: My question was a more generic one about how to interpret the fact sheet and whether those levels of evidence -- if something is cited, does that mean it meets the level of evidence.

DR. HOWELL: And I think that that's what you're trying to do with the four levels that you've listed here and so forth.

Do you have more questions, Coleen?

DR. BOYLE: Oh, yes.

DR. HOWELL: That's the reason I turned to you, because I knew you had questions.

DR. BOYLE: I really don't want to monopolize if other people have questions. Again, Mike, you just said something, that this is a two-year contract, and it is. It's very, very ambitious, and I was just thinking as Denise was talking about the fact sheets. If we are going to consider this as a committee as a prototype in terms of the ongoing assessment of conditions, you just talked about the complexities with SCID. Each of these conditions are very, very complex, and each of them warrants an in-depth review and acknowledgement of those complexities, and the acknowledgements of the scientific literature associated with that. So this is more maybe talking to the committee.

I guess one recommendation I did have for the fact sheets, because that's sort of where I'm focusing my attention to try to improve those -- I noticed you have one reviewer per fact sheet.

DR. WATSON: No. There are at least two per fact sheet, and if they differ -- I didn't bring any fact sheet to you that hadn't gotten validated by at least one reviewer. The second reviewer on the ones that you have with only one person has verbally responded and things are aligned with the first reviewer.

DR. BOYLE: Well, I make the plea, being an epidemiologist, that we have an epidemiologist look at some of them. I'm not going to point out the errors in the ones I have seen so far, but I feel like there needs to be another look from a different perspective on this since we are evaluating public health literature here.

DR. WATSON: There's room for improvement across the board. This was really sort of is there enough to go forward, and I think we'll learn some of the best things we can learn from ongoing surveillance. But when we talked about building a tool by which we would try to move conditions and decide where to put them, when you start looking at the tool world, there are people whose life is spent validating tools over two years. For any tool like this, that is not an uncommon thing, that you go through a long validation process.

Clearly, we can't do that. We can do whatever we can do up to a point, having developed things and brought us and the experts who we worked with up to a point of comfort that we can move forward. But there's room for improvement in all of the information on which these recommendations are made.

DR. BOYLE: I just want the committee to recognize some of the limitations. I had suggested you put a limitations section in your report sort of identifying what those limitations are.

DR. HOWELL: Let me make a comment to the committee, and that is that the charge to the committee is very broad in the sphere of newborn screening, and if we were to try to get a comprehensive look, it will be many, many years. I think one of the things it's important to have forward motion is to do things in logical segments, but there are all sorts of things that we're going to have to continue to address. I have a whole list of things here that we will need to do that are literally going to take years.

I guess that one of the things I think is before us is the prospect of developing an instrument, a tool for identifying what we would recommend for a uniform panel, and the thing is I would hope we could get that started a way and then see what falls out of that, because there are many things in the educational and ongoing assessment, and one of the things that's been mentioned repeatedly is the FDA thing.

For example, let's take SCAD deficiency, a very rare condition. We know that untreated in the newborn period, it can have serious consequences. We're not ever going to have many children who are diagnosed, we hope, that are not monitored and treated. So we're going to need to set up a mechanism to follow all the children that are diagnosed to learn about it down the pike. So ongoing, like the postmarketing approval, except considerably better.

DR. WATSON: I shouldn't say un-nice things about federal agencies, but they often don't play well together. I mean, NIH has --

DR. HOWELL: What?

(Laughter.)

DR. WATSON: They often have their own individual area that they attack. It's a lot better than it was 20 years ago, I'll say that for sure. But NIH is developing rare disease centers around

the country. These may be places where one can begin to aggregate information about different patient types. There's an epigenetics rare disease center down at Baylor. There's different kinds of these evolving. But the nature of this is the ultimate multidisciplinary area, and the ultimate multiagency kinds of problems. No one agency, I don't think, can get at all the things that we're having to deal with in thinking about newborn screening and the development of the programs.

DR. HOWELL: Dr. van Dyck has a comment.

DR. VAN DYCK: Well, I'm sensing perhaps a couple of different kinds of recommendations that can be made. One set of recommendations are things that would improve the quality of the report, improving the literature search, the quality of associating it better with levels and all the rest.

The other is perhaps the more public face of the report, the number of conditions and the panels and what's opted in and what's opted out, and how do we include those in. I guess my question to those of you who are raising the issues about the literature and the evidence and the scientific evidence is are you concerned enough about that that the recommendations of conditions or those reported, do you have trouble making those recommendations, while at the same time the panel coming up with a list of recommendations that would improve the overall report over time? To me, that's an important separation that we have to discuss.

DR. DOUGHERTY: That is important, Peter, and the other question I was going to ask is what's the nature of the recommendation that the committee would be setting forth to the Secretary? Would it just be on the top 30? Would it be on some of these other financing things?

But on yours, I'm not an expert in these areas, but sort of comparing this to how the trend of evidence reviews is going, the problem with the report is that you really can't tell to what extent this is an evidence-based review and which conditions and tests have more evidence than the other. So for somebody who is not familiar with -- doesn't have an expert opinion themselves about a particular condition, it would be very hard to judge the extent to which -- if you're a state, you might not want to do all 30. You might say, well, I want to pick the top 15, but which ones would you choose? You wouldn't have an evidence review laid out before you to help you make that decision.

So I can't really answer that question right now of whether there's enough evidence that may not be reflected in the report because I don't know, and I'm afraid that others will be in the same situation.

The other concern is -- well, there are two concerns. One is about the diagnostic tests, the screening tests rather. If there's so much variation across the country, shouldn't we be concerned about parents in different places? It's a different kind of unfairness, getting false positives or false negatives, since there's so much variation. What do you tell parents in that case? It's hard enough to tell them your child may have a condition, but what if you've missed it and people are getting told different things based on different results?

But the other thing is I'm afraid if I were a state and got this report as written, I would kind of challenge the conclusions of the report without a fairer -- and I think all Coleen and I are saying is that we need a more rigorous standardized presentation of what the evidence is. I mean, the people around this table and the people who are here probably know enough from their expert consensus to say yes, those are the 30 conditions, and we really need to study infectious diseases and a couple of others really soon, to make a recommendation on those. But I don't know that, so it's hard for me to say without a report that really lays out the evidence, and not just the expert opinion.

Does that help?

DR. VAN DYCK: This discussion came up a little bit in June, too, and I think it's an area that we need to try to resolve in some way, and it's going to clearly feed into our set of recommendations.

DR. HOWELL: Dr. Rinaldo, who happens to be a member of the committee but is also one of the leading experts on the laboratory side of things, might have some comments about some of the laboratory variations.

DR. RINALDO: Yes. The comment I would like to make is while I appreciate all the angles, the concern about the ultimate validity of the data in the context of what we're going to do, I really would like to make a couple of comments.

First, at least from my perspective, and I like to think of myself as an expert, at least for some of these conditions, I really believe there is a fundamental difference here between the experts as the ones who generate the evidence. There are those who write the evidence or write the papers, and those who read it. I think it's what this effort here has been, going after the people who have written the evidence and the literature. I believe that for a large number of the conditions that we have included in this study, you will see that virtually the Who's Who of every condition is included.

So I wouldn't want to say -- I don't know if the evidence, if the analysis, secondary and tertiary analysis of the evidence will really lead you to any better place. In fact, if you think of it, we have these wonderful reports in England. There was the '97 reports, the 2004 reports. It's a really impressive document. Yet, the U.K. is doing nothing. Do we want to go down the same path?

That's where people like myself, and probably several sitting behind us in the room, may feel that we've not fully appreciated the fact that while here we go through -- there is a colleague of mine at Mayo who said the "analysis paralysis," but children die out there. So we can go on through cycle after cycle of analysis and review. As Mike said, we review the facts. Then we ask the experts. We even review the experts themselves. To get where?

Children are dying. If you look collectively at these conditions, the numbers are 1 in 2,000, 1 in 3,000, 1 in 4,000. When you put it in the context of 4 million plus babies born in the United States, as you deliberate on these analyses that will be perhaps scientifically impeccable, or epidemiologically impeccable, children will continue to die. Can you sleep at night knowing that you, far removed from the trenches, far removed from where these things are happening, far removed from the practitioners who see the children who are brain dead, can continue to have all the time you want in the world to deliberate when the children continue to die?

DR. DOUGHERTY: May I respond to that?

DR. HOWELL: Dr. Dougherty?

DR. DOUGHERTY: I think you're right. Evidence makes some decisions possible, but evidence is not the only reason that people make decisions, important policy decisions. I think what Coleen and I are saying is one word, the transparency of the evidence. This committee can make a conclusion, but you can make a different conclusion than what's in here, or the same conclusion, but I think it's important to give the people out there who are going to incur the costs here -- you don't have to base your decision on the evidence or the transparency of the evidence, but just to let them know what was actually done.

I guess what Coleen and I are saying is that from the report as written, it's hard to tell what was actually done here, and maybe that won't be important.

You're from a state. Maybe you can speak to that.

We just want transparency of what was done and how the conclusions were reached. That's all. And that's not the only basis for the decision.

DR. HOWELL: We'll hear from Dr. Becker next, and then we'll go back to Dr. Rinaldo.

DR. BECKER: Thank you. I'd like to offer some comments in support of what Piero said, although certainly my comments won't be stated as eloquently as his.

From the state perspective, I think what we have seen for newborn screening programs is a very tight adherence to a certain set of criteria when we consider whether a disorder was included in a panel or not. Knowing incidence, is there a test available, a reliable test? You'll find that that's a common theme that's still with us today. And was there an efficacious treatment? Those, generally speaking, were the criteria, in some cases codified into state legislative law that states used as a consideration for including a disorder.

We have, I think, seen over time that there's this transition occurring over the last several years to now whether we don't have this tight adherence to knowing an incidence because, as has been described in other examples, maybe we don't know. But is a disorder identifiable at a time before its phenotypic expression is recognizable? That's different than incidence, and it suggests a slight lessening of the rigorousness of understanding the evidence.

Is there a reliable test? That's still consistent.

Now, there was a question brought up about some variability, and this is screening testing now, where the comment was made a few moments ago. I can use an analogy, as I was sitting here thinking about my response. PSA testing. I think we all understand the importance of screening for prostate cancer, but as a pathologist I understand the methodologies that are used across the country, and there's at least 10 or 12 that I can think of. I can guarantee you that a sample of blood drawn from me taken to two different hospitals will give you two probably different answers, which may lead on the one hand to a biopsy, which I wouldn't necessarily like or enjoy, and one where I'm told to watch it for another six months.

But in the main, in newborn screening, we look at the proficiency testing data that is available to us for the states that are currently doing MS/MS testing. While there is a range of results of the screening test for dry blood spots, we as a group of states or a group of laboratories are able to correctly classify potential positive disorders or potential positive samples from those that are not potentially positive.

There are always going to be some exceptions to the rule, but there's always going to be variability in the answers, and there's always going to be variability in how the states define their cutoffs. I don't think that's ever going to change, and that's just the nature of the laboratory business.

DR. DOUGHERTY: Okay, that's a good point. I didn't hear that before.

DR. BECKER: So that's the reliable test.

We've also gone from having this rigorousness of having an efficacious treatment to the concept that there are benefits to early intervention, a classic public health dynamic. Where we may not have long-term benefits, analysis, because we don't have enough cases to know long-term benefits, we just don't have enough cases, to the modalities of treatments themselves are so evolving that what might be true, what we might start in a treatment now two years from now may be totally different.

So we're not so rigorous, then, in our insistence on knowing that it must be treatable before we ever start. Does the best clinical evidence say that we can avoid mortality? That would be a very important thing, as Dr. Piero mentioned. Or do we think by our expert opinion that we can ameliorate some of the worst outcomes of a disorder without being so rigorous about knowing that it must be five years, ten years, twenty years. It forms the basis of great prospective studies but shouldn't limit us from not including a disorder in the panel. That's a big difference from what we used as our criteria from the state perspective.

Finally, and I think this is what the parents have been wanting for a long, long period of time, is that in our programs we have to say here's our core panel, here are things that are in the differential that we'd like to report to you to further evaluate, and if you either have a family history or if you're so compelled, there are other disorders that you could be screened for if you wanted that opportunity, like the lysosomals or the Wilsons or some of these other disorders which may eventually be rolled up into our programs.

So I guess my long-winded explanation here is we're in this transition period, from this rigorous criteria that we use to select disorders to a best evidence. Maybe it's not perfect, but it's the best evidence we have, and in looking at these criteria for inclusion of these disorders in a slightly different way than we had to up until now.

DR. HOWELL: Thanks, Bill.

Piero, you were next.

DR. RINALDO: I completely agree with Bill. The point I really would like to make is if we look back at the proceedings of the expert group and the magnitude of the people involved, at the steering committee, at the very panel, the people invited, the people who were being actively pursued to provide feedback, I don't know when a group is good enough, but it really is the best evidence that you can gather because it was a very deliberate and aggressive effort to go after anybody that knows something about these conditions. I think that still carries some weight.

I agree with you. You want to have sort of a fresh, perhaps a detached evaluation, and so I agree that perhaps an epidemiologist should come in. But I really think you want to keep separate the assessment of the methodology and the assessment of the evidence. What I mean by evidence is the conclusions. You have hundreds of the most qualified people in the world who have participated in this process. That must carry some weight to a point where you say okay. It's like an issue of incremental benefits. If a process reaches a point where we are 95 percent close to the absolute truth, is it worth it to wait a year, or another two or whatever, to get another increment of 1 or 2 percent? Personally, I don't think so. Professionally, I think it's unethical.

DR. WATSON: The evidence base is going to bring another problem to this. I mean, supplemental screening is increasing. In fact, we're recommending supplemental screening in sort of a standard of practice perspective.

DR. VAN DYCK: Please say what you mean by supplemental screening.

DR. WATSON: Supplemental screening means that somebody goes out and buys from whoever sells a screening test the ability to have their newborn screened for a much wider range of things that are mandated. So they can buy supplemental screening, and the population of people which we have to evaluate the condition, the burden, is going to vanish. People will be treated and may not present with disease, and that's the problem we dealt with already, that the data and the evidence around some of the parameters is vanishing.

DR. HOWELL: Dr. Hawkins?

DR. HAWKINS: I'm going to take a step back and take a little bit different perspective here. I'm not an expert on children's diseases, but I do work with more adult diseases, and one thing that I see that's happening with the community as a whole is that parents are wanting answers to their questions. Now, I have three daughters. One was born in Wisconsin, one was born in Maryland, and one was born in Nebraska. I came to this panel not being an expert in childhood diseases. I had no concept that there was the idea that the states were so unbalanced in their genetic testing.

Personally, I'm from North Carolina. I grew up there, and I'm proud to see my state doing so many genetic tests, and I wish all my kids were born there. But my kids didn't have that benefit. So stepping back and looking at it as a parent, we're looking for the experts to come up with something that we can actually do the testing, somebody can do the testing for us and give us these answers, because what's going to happen is if somebody doesn't do something now, it's going to start happening what's happening with adult diseases. There are companies popping up that are willing to do genetic testing for adults that are not necessarily giving them accurate results, and they're promising the world as far as saying we'll screen you for risk for this disease.

If we don't come up with a panel now and get the states doing this type of testing, when we see those types of industries rise up that are promising to do the testing but not doing it right, and maybe not doing the right type of test, I think that's what parents will turn to if we don't do some sort of mandating as far as coming up with a specific set of tests. I think this is where I step back and I don't look at this from the expert point of view, but I think the report has done a really good job for me as a consumer, as a parent looking at this and going you have really defined something that for me as a parent I would love to grasp hold of and make sure that every child is tested so that it's equitable.

Now, is it perfect? It's not going to be perfect right now, but there may be five more tests you can add next year, and maybe two more tests the next year. But eventually we'll get it to a point where we are covering all our bases, and we'll do it quite well. As a parent, I wouldn't be very comfortable with what's happening to my child.

DR. HOWELL: Dr. Brower?

DR. BROWER: I would agree with that and just follow up with what Greg said. I think what this report has done is really show us, in gathering the information, the gap analysis, and for future tests, as we want to add to the 30 or the 50 or the 70, what are the pieces of information that we can start gathering prospectively so that we're ready to add the next 5, 10, 15 tests in a seamless manner. I think speaking as a consumer and as a parent, I thought the report was very well written. It helped me understand what the committee went through. Having a group of experts versus having evidence and literature is much more valuable, and I think parents of children with rare disorders do go to experts for treatment, for opinion, and that's a real value I saw in this report.

DR. HOWELL: Further comments from the panel?

Denise?

DR. DOUGHERTY: No. My argument is not whether this is a set of tests. It's really about how the information is presented to be transparent. You can say this is the evidence we had and this is how we actually looked at it.

DR. HOWELL: So in thinking about the document and its potential handling by this committee, how would you make suggestions to Mike that would make your comfort level improve?

DR. DOUGHERTY: Well, I don't think it's about my comfort level.

DR. HOWELL: As a professional.

DR. DOUGHERTY: Well, if the committee as a whole is going forward to the Secretary, and then to the states, and saying this is an evidence-based review of where we are, and our conclusion is that these should be done, then I think as a committee we really need to be clear that we are saying this is an evidence-based review and giving people a little more guidance on how to figure out what the evidence is, and maybe all these fact sheets will help. So that's how I would feel as a committee member.

I think we would have to sit down and think through what could be done to sort of re-format, re-work the report a little bit. It shouldn't take two years. It's not like going out and looking for more data, it doesn't seem. It's just sort of re-formatting it to make it clear what was actually done, and that shouldn't take that long.

DR. HOWELL: Having seen the workings of this committee, there is an enormous amount of data, some of which is surfacing in the fact sheets. Are they more in line with some of the things you think would be helpful, or not?

DR. DOUGHERTY: I think it's more the presentation of what's in the data that could be clearer in the writeup, not so much what's in the data right now.

DR. HOWELL: So some amplification of what's in the writeup about how the materials evolved would be very helpful for you.

DR. DOUGHERTY: And I'd ask Coleen for her opinion, too.

DR. BOYLE: I just wanted to comment on Bill's comments. Bill, I guess I was not arguing at all about the criteria themselves. I realize the criteria for evaluating newborn screening are shifting, and I feel like that's very appropriate, and they're still evolving. To me, it's what Denise is saying. I was actually a little taken back when Mike was presenting all the evidence base that was gathered. It doesn't come through for me in the report. It doesn't have the methods session that it needs. So when I evaluate it, I'm not there with Piero. I'm hesitant that this is not a good basis for us moving forward or a good basis for us to continue using. I want to be there with Piero, but I'm not there right now.

So I felt like in your presentation that there was actually a lot more that was done that's not reflected here in the report. We could be specific about it. I just feel like that needs to be done.

DR. HOWELL: But it seems to me that those concerns, I believe, could be addressed rather readily, frankly. I guess the pediatrician and the geneticist coming out in me thinks that we do need to move the project ahead. Only at the same time, we need to be sure that it's as scientifically as sound as possible. There's absolutely no question that all the experts who work in this area are in this report. That's one thing we can be very confident about. Having been in newborn screening, as I pointed out earlier, before most of the people in the audience were born, there's never been a discussion of newborn screening that has involved so many people.

But the way that the expert referencing and so forth has been done could be amplified, and the methodology, without a big deal.

DR. DOUGHERTY: And I guess the other part of it is what happens when and if states start to do this panel? What is the nature of the recommendation to the Secretary? Will it be just about screening for these conditions, or will it have some of the other issues that have come up repeatedly

about financing, about guidance to parents, about resources availability and keeping a storage system so that you can follow up people?

DR. HOWELL: One of the reasons that I've asked the committee to delay the recommendations until tomorrow is that we're going to have some very expert input from some of our leading people in the states who are going to be discussing how their states finance it, how their states work and things of that nature, which I think will add some perspective about what we might expect from the states.

Piero?

DR. RINALDO: I realize that seeing this presentation like you, Dr. Dougherty, have done today for the first time, it's very different for some of the people, including you, Coleen. You have been through the expert panel from the beginning, and you and Bill and Derek and many others. We have seen this from the early stages. Perhaps there could be room to go back to the minutes of all the meetings, not just the expert panel and the working groups, to really compile the progress reports, because many of the questions you're asking I think have been addressed at some point. Perhaps now we take for granted that they are.

In fact, the first question you asked, I just opened up my laptop and saw that here it is. Remember that we went through an entire session discussing how to quantify a response to our request for inquiries. I believe it was Dr. Cunningham who was very vocal about this is a very small proportion of the potential people out there. But in fact, we elaborated and we came up, I think, in a convincing way with a conclusion that, again, is not perfect, is not 100 percent an achievable goal, but it's darn close, because we got involved an unprecedented number of experts.

Again, I don't want to imply anything with it. To me, the expert is the one who writes the literature, not necessarily the one who reads it.

DR. HOWELL: Any additional comments?

(No response.)

DR. HOWELL: We have a minute. Tomorrow we're going to have public comment on the document and public comment on the situation of newborn screening. But if there's someone in the audience that would like to specifically comment on the document, we will hear from them now.

Dr. Cunningham was the first to raise his hand, and then Dr. Hannon, and there's a hand in the back that I can't see.

George, if you could come up, please.

Dr. Cunningham is director of the programs in California, as many of you know.

DR. CUNNINGHAM: I was a member of the committee and I was intimately involved in all of these efforts. I'd like to first of all say that in addition to picking the tests, they addressed the issues of quality assurance and efficiency and effectiveness of the operation of the program, and they made the point that it is a public health program that involves education, that involves tracking, that involves follow-up, that involves treatment, that involves data collection, and that part of the report is excellent. They begin to grapple with the idea of how to compare apples to apples, a comparison of the effectiveness of the state programs, and that should not be lost.

Secondly, I think with regard to the critics of the data, this is a very complicated field. I believe the committee made their very best effort to collect all the available evidence. The issue as a policymaker is when do you have enough evidence to make action? We believe that the committee has put together enough evidence to support action at this point in time.

The problem I think with the report is an attempt to become too objective in an area that is subjective. Those scores have confidence intervals that are sometimes very wide, and the scoring system is debateable. The validity of the sample is debateable. So I think what they've done an excellent job of is identifying all the factors that have to be considered and weighted in making a decision and providing a protocol that can be used by states to do their own individual assessment. But I think some flexibilities have to be provided and some shifting of conditions will occur, but that should not prevent the feds from making a recommendation to the states as a starting point for their programs.

Now, the question of what constitutes mandate is a different issue. Are you recommending that the states mandate this or add this to their mandated program, or are we talking about a federal mandate on the states, unfunded, to raise a program? What is mandate? That will need to be clarified in your discussions.

DR. HOWELL: Dr. Cunningham will be addressing the group tomorrow about the newborn screening program and some of the cost analyses in his State of California.

Dr. Harry Hannon, whose duties at the CDC have for many years overseen the newborn screening laboratory efforts.

DR. HANNON: Overall, I think the report has moved a long way and is very good now. But when you list the 30 disorders, Mike, I have some questions about a couple of disorders. As you read the text, you have 30 disorders, but things like glucose 6 phosphate dehydrogenase deficiency shows up as an absolute on the table 30. But as you go over in the text, there's some questions about whether it should be on there and done or not, and CF is another one. So there are about two or three disorders that show up as an absolute, and if you talking about mandating the 30, you've got some questions in the text that say some of these might not be in the 30.

So there's a little discrepancy in how those are examined, and I have the fear that as you look at this table of core disorders, the way it's done and written, the reader and the viewer doesn't get the fact that there are some that have questions, although they're listed in the core.

DR. HOWELL: Mike, do you want to comment about that?

DR. WATSON: I can't disagree. I mean, that's why we wrote those separate paragraphs on conditions for which we perceive some difference of opinion. I mean, certainly G6PD has different implications in various parts of the world. In the United States, there's only one state, maybe two, that screen for G6PD at this point in time, and they have never published a paper to give us a sense of what is happening with their G6PD screening.

So we ended up with sort of two steps in this. One was we had to be as objective as possible, build a tool that could be used, and we had to work through the process we built. I couldn't at this stage throw things out because I personally didn't like them, and that's why we opted to have experts write paragraphs that address those areas of contention. I agree that there are about three conditions where that becomes an issue, and a state may choose to approach it differently than another.

DR. HANNON: What I'd like to see done is to key those -- we write our table, the table is supposed to be a stand-alone so that all information in the table is really included. You read the text for a little explanation, but the table is a stand-alone. So what I'd like to see done is that those disorders that fall into this category, that they're identified by some star, some different coloration or something, which

then sends the reader to the explanation, so they don't appear as a stand-alone, as an absolute, in case somebody looks at this and says, okay, we're going to mandate these 30 disorders. Well, when you get over there, there's some question about whether they should be there. So I think the viewer should be triggered to go read the other part before they accept that as an absolute.

DR. HOWELL: Thank you very much, Harry.

We have time for one more comment.

Could you please introduce yourself when you get there?

MS. VOGEL: Michelle Vogel from the Immune Deficiency Foundation. It's nice to see you again.

DR. HOWELL: Of course. It's good to see you, Michelle.

MS. VOGEL: I just wanted to make a few comments dealing with severe combined immune deficiency. Mike, we spoke a while ago about it. Dr. Vogt will be coming in from a meeting with Dr. Buckley.

DR. HOWELL: He's here.

MS. VOGEL: Oh, he is here.

DR. HOWELL: He's not only; he's here.

MS. VOGEL: He's here. Okay, that's wonderful.

But, I mean, there are a few things that concern me. When you're developing these tests that are recommended in these core diseases, I think there are a few things that you have to take into consideration. One thing that is somewhat, I think, misinformation is that there is a test developed to screen for SCID. Yes, it hasn't been piloted yet, and I think that if you're doing these mandates for states to pick up these certain disease groups, maybe there is a way to encourage states to do pilots with SCID, especially since -- I don't know how you're going to set up standards with rare disease groups. You may only pick up a few kids that have SCID when you're doing the pilots.

Those few are tremendous. If you pick it up at birth and do the transplant, you have a 98 percent chance of curing the child, whereas if you don't, the child is not going to live past a year. So I think those things are really important to take into consideration when you're making these recommendations.

DR. HOWELL: Thank you, Michelle.

Let me make a comment to that, and that is that many of us are very much aware of the TREC assay, which is a test that looks like it has been extremely useful that has not been piloted yet. There are other conditions that are in the same boat that are on that list, and I would alluded to two, and that's Krabbe's and Pompe's disease. Again, I'm aware and have seen the data. There are some excellent laboratory tests for these that, again, have not been piloted, and they're also not on the list. So I think if you read the report as it's written, once a test is there, these conditions will fall right into line. But the test has to be piloted. In other words, you could not introduce screening today as a standard for SCID.

But the point is that the way the report is written, it will accommodate conditions that have well-defined treatments and so forth once a test is available and it's piloted and is shown to be reliable and so forth.

MS. VOGEL: And in terms of the pilots, how extensive are you looking at the pilots to be done?

DR. HOWELL: I think the pilot is a separate issue. That would come under the area of a research protocol. I think that some of these pilots and research protocols, I would hope that one of the things that this committee might recommend is that agencies work together -- CDC, HRSA, the NIH -- to look at research issues in newborn screening that would again do pilot studies and pilot tests and develop tests and so forth.

But I would hope that that would happen. When you're looking at pilot tests like these, you need large numbers of samples.

MS. VOGEL: I just wanted to inform the committee also that in the Labor/HHS, both the House and Senate, there's both language encouraging pilot studies to be done on SCID, but also money included in the Senate for that. So hopefully it will make it through the process and will get there.

DR. HOWELL: That always speeds things up.

MS. VOGEL: Yes. So hopefully we will see that going on.

DR. HOWELL: On the happy note that we hear that there's money in the Senate for some research in newborn screening, I would like to suggest that we go to lunch.

(Laughter.)

DR. HOWELL: Let me thank Dr. Watson and the panel for a wonderful presentation and an excellent discussion and some very strong suggestions that will improve the quality of this document.

We will return here at 1:30.

(Whereupon, at 12:32 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)

AFTERNOON SESSION (1:35 p.m.)

DR. HOWELL: I think our group is largely reconstituted from lunch, and so let's begin our busy afternoon session. We will start off with a presentation on the use of tandem mass spectroscopy by state newborn screening programs, and the state of the states, barriers to incorporation of expanded screening with MS/MS by Dr. Brad Therrell, who, as noted in the program, is director of the National Newborn Screening and Genetics Resource Center. It was from his group that many of the data you saw this morning were derived.

Brad?

DR. THERRELL: Thank you very much.

What I'm going to do is first give you a little review from the last meeting about where the states are, and then talk a little bit about why those states have not implemented some of the traditional screening disorders that we have, and then what are the barriers to those states that are looking at MS/MS testing.

Just as a review, the question about who decides on newborn screening in the states. Ultimately, it's the state legislators because they control the purse strings, and every state has a law which they point to as giving them the authority to do newborn screening. Sometimes it mandates it, sometimes it just gives them the authority to do things for the good of the public or the good of the mother and child.

Also, a lot of legislatures pass on responsibilities for making decisions about newborn screening to state health officers, who in turn pass them on to state boards of health, who in turn sometimes pass them on to advisory committees. So any one or all of these people might be involved in the decision about newborn screening.

The how in terms of how states go about this process is kind of interesting. Lots of times it has to do with public interest; not always. If you think back to the way PKU got going, it was because of public interest. That still drives programs today. Also, professional interest. So lots of times professional interest groups will push certain disorders. And political interests, as was mentioned sometime today. Sometimes a politician's friend who has a kid gets that disorder on the list.

Often, programs are asked to look at cost savings, do the benefits outweigh the costs, which is, as Mike indicated, not so easy to get sometimes, nor is the scientific evidence, which is the last thing I've got listed here, often available. Often, it's the last thing the programs look at. So as we go through, you'll see some of this.

Just some miscellaneous information for you. There are eight programs that mandate two tests, and I've listed the eight for you: Arizona, Colorado, Delaware, Nevada, New Mexico, Oregon, Texas, and Utah. There are at least three others -- Alabama, Maryland and Washington -- that strongly recommend two tests, to the point that they get better than 80 percent compliance. So any of these decisions for those states are especially big because they have to think in terms of double their population.

All programs except two report having an advisory committee, and those two are California and Idaho, although many of those states that have standing advisory committees freely admit that they don't meet very often.

Fees exist in all but five programs, and if you actually look in Tab 7, I believe it is, there's a listing of the fees. This will be talked about in the next presentation, but you may want to refer to that as we go through what the states are screening for so you can kind of get an idea of what their fee is. You'll see, if you look at that list, that they range anywhere from free to $10 to $139. You can't make the supposition by looking at those fees that they necessarily cover everything in the program or that they cover the same things in the programs, because different programs do things differently, different states finance things differently. So often they'll have a fee which is supplemented from Title 5 dollars or Medicaid dollars or whatever. But just so you have an idea of what the fees are, we have put that table in.

Now, just to show you some of the models of laboratory services that the different states have, there are some consortiums or regional labs, if you want to call them that, and sometimes those have an effect over what the states in that region actually offer in terms of testing. So, for instance, this is the Northwest Region, which is run out of Portland, Oregon, and this year they got sort of tired of doing customized panels for everybody, and so they said to all the states in their region that beginning on

such and such a date, you either have to take the whole panel or find another laboratory. So that sort of drove some of these programs to increase their screening panel.

So this is Oregon laboratory, which does five states, as you see, including Hawaii and Alaska. This is Colorado, which does Wyoming, and they used to do Arizona and New Mexico, but Arizona and New Mexico pulled out over the years because they wanted more control over their samples and what was done with those babies.

Iowa does North Dakota's specimens, and then Massachusetts does all of New England, and also has a contract with Pennsylvania, and I'll talk more about that in a minute. For instance, Connecticut was in that region, but Connecticut withdrew. Another state in that area, Delaware, used to send their samples to Maryland, and then they sent them over to Oregon. Now they're doing them all themselves. So there are some other models that have happened over the years.

Then I've listed here Montana, which sends some of their work to Wisconsin. They do the traditional tests that were mandated by the state, but in order to do some of the supplemental testing, they entered into a contract with the Wisconsin laboratory.

Now, those were all public laboratories. If you now start looking at the public/private partnerships, California has a partnership with eight contracted laboratories which are overseen by the state laboratory in Berkeley. In South Dakota, they have a private pathology laboratory, and also they offer supplemental testing, and they send the supplemental testing down to a laboratory in Dallas. So that's why I have the arrow drawn like that.

The medical center in Indiana does the testing for them, and then the private laboratory, Pediatrix, in Pennsylvania has contracts with Nebraska, Mississippi, and the District of Columbia, and also they have a contract with Pennsylvania. So I've got Pennsylvania cross-hatched because Pennsylvania has two contracts, one with Pediatrix and one with Massachusetts. So the hospitals have a choice as to which one they want to use there.

Then there are a couple of states that actually allow other laboratories to do testing, and that's Louisiana and Maryland, and in both those states I think Pediatrix has several customers.

Then, Piero has gotten into an interesting situation in Minnesota, which may be a nice model for some states, and that is that there's a private partnership there with the state laboratory. The state laboratory does some of the testing and then sends some of it over to Mayo to do the supplemental testing.

In terms of mass spec screening, all of the states in the dark colors have mass specs of some sort. Some of them are doing the mandated testing and some of them are doing pilots or optional testing, and I've drawn arrows to show you that there are plenty of states that are sending their samples to other places to get them run for the mass spec if they don't have a large enough population to justify the cost or whatever.

Feel free to ask questions as I go along here, because these pictures may be more confusing than my talking.

Now, if you look at the numbers of disorders, I know you've seen the maps that Mike had. I'm going to sort of go through it one, two, three, four, five. This is the lowest number of mandated tests, and I'm going to talk only about mandated disorders. That doesn't mean that they don't maybe offer something else.

So in the case of South Dakota, they do allow the option of doing some other testing, but they mandate only three disorders at this point. Six other states mandate four disorders at this point. Three states mandate five disorders, including Texas and Florida at this point. Six disorders are mandated in four states. Seven disorders in another four states. Eight disorders are mandated in two states, and then everybody else does more than eight. So there are 31 states now that do more than eight disorders.

As Mike had mentioned earlier, counting is an issue here because my eight may not be the same as your eight. So if you look at March of Dimes, for instance, when they had their scorecard of nine disorders, some people got upset because their state actually offered 30. But in that 30 weren't necessarily the nine that were being judged by March of Dimes.

Here is actually the number of disorders and we stopped counting at 30. So if you do more than 30, we just indicate more than 30 because it gets pretty hazy at that point as to how you're counting.

Now, Mississippi has 40 mandated, and I've listed them as 40 rather than greater than 30 because they actually name out 40 disorders in their rules, okay? So some states name disorders in their rules and some say everything that's detectable by mass spec or whatever.

Here's another way of looking at the same data. If you look at the disorders by numbers of programs, then you see that the first three bars on the left are PKU, hypothyroidism, and galactosemia. Those are done in all programs. Hemoglobinopathies are actually available in all programs, although they're not mandated still in two states, and those two states are South Dakota and New Hampshire. Interestingly, in New Hampshire, if you order the testing, it's covered in the fee already; but in South Dakota if you order the testing, you have to pay additional for it.

Then you see maple syrup urine disease, congenital adrenal hyperplasia, there are 40 programs, one of which is still in the pilot phase. Maple syrup urine disease, there are 36, 4 of which are still piloting. Biotinidase, there are 34, 2 of which are piloting. Homocystinuria, 35, 5 of which are piloting. Cystic fibrosis, there are now eight states which either have piloting or available, four of which are optional. Toxoplasmosis, there are two states. G6PD deficiency, it's only mandated in one program, and that's the District of Columbia, although most babies in Pennsylvania get it because most hospitals in Pennsylvania have a contract with Pediatrix and they're offered in that panel. Missouri has it mandated, although Missouri is not doing it. When you call Missouri and ask, it's hard to find out why it was mandated. Nobody in the state seems to know, but it was in the law, so it's there.

That law actually lists a number of disorders, and this you'll find common in some states in political circles. It lists the disorders, it mandates them, and it says in little bitty print somewhere "subject to available funding." So because there's not available funding, these things don't get done.

You can see that there are two states that mandate HIV, although in reality it's one. New York mandates it. Connecticut also mandates it if the mother wasn't tested during the pregnancy. But if you call and ask the program do you monitor this, do you test for it, the answer is no. But the law actually says that it is mandated.

Thirty-four programs currently do MCAD, but four of those are still in the testing phase.

I put this in just to show you again the incidence. Mike alluded to it this morning. We've gone back and looked at 10 years worth of data as the states have reported it. Now, this is an issue because the states don't have to report anything. This is all voluntary reporting. Lucky for us at this point, states have been pretty good at volunteering to give us the data, although we tend to run two or three years behind. So right now we're working on the 2001 data, but we're putting a system online January 1 where states will be able to put that data in as they detect cases.

But at this point we've gone back and looked at 10 years worth of data, and if you do that, you find out the incidence of hypothyroidism, looking at 40 million babies screened, is 1 in 3,000. Sickle cell disease is 1 in 3,700 looking at 28 million. So as Mike mentioned, you get some big numbers when you look at 10 years worth of data. And so on down the list. Now, if you put together sickle cell disease and SC disease and S-beta thalassemia, they actually come out to be higher incidence than anything else we screen for at this point. I'm excluding hearing, but of the biochemical testing. Incidence is something like 1 in 2,500.

If you go down and look at toxoplasmosis and you look at the numbers screened, this reflects the fact that only two states screen for it. So over 10 years, there have been 989,000, versus 40 million for the other disorders.

Classical PKU actually is about 1 in 19,000, and it's at the top of this column. If you look at clinically significant PKU variants and you combine the two, then you get an overall incidence of clinically significant hyperphenylalaninemia of about 1 in 14,000, again looking at 40 million babies. You can see it drops off. Biotinidase, 1 in 60,000; MSUD, 1 in 230; homocystinuria, 1 340. Now, we don't have good data yet on those things screened by mass spec, but we hope that if states will start reporting the data a little quicker, we'll be able to put that data together.

So in terms of what the barriers are, we were asked to go out and take a look at this. We wanted to look at, first, what are the barriers to the traditional tests that could have been being done for 40 years and aren't being done yet. So we did a telephone survey. We called those states that still aren't doing those disorders and we asked them sort of open-ended questions: What's the problem? What are the barriers? What do you see going on? What do you think would help? So I'm going to show you what we found from that.

We found that overall, here were their concerns, mostly financial concerns. They gave the reason that there's not very good cost effectiveness to get beyond the tests that they're doing right now. So when you start into these lower incidence disorders, cost effectiveness becomes important to some states. Managing the data became an issue. So some states said, well, if we expand, then we've got to worry about fixing our computer systems, and that's a big expense, so right now we're just not going to do that, and we haven't done it for the last 40 years.

Authority to increase the fees. Some said, well, we'd like to do it, but we don't really have an easy way of increasing the fee. We have to go to the board of health, the board of health has to have open hearings, everybody is fiscally conservative in our state, so it's not likely that we're going to get this. We'll try a little bit, but it's not likely it's going to happen.

Authority to utilize the funds from the fees, another issue. Once we get the fee, do we get the money back into the program? In lots of states, they don't. So those are the main financial concerns.

In terms of personnel concerns, a lot of states said, well, we're always under a hiring freeze, and so you can't expand the program when you're under a hiring freeze. How do you do that? Well, some states have actually contracted those services out. But anyway, this was a concern in lots of states. Another concern was getting qualified personnel given that state health departments don't often give competitive salaries.

Follow-up issues were a concern in some states. They felt like they would get too many false positives with certain disorders. So rather than implement a test with a lot of false positives, they just didn't implement it at all yet. It's always we want to, but we've got a lot of things to overcome, and one of them is cutoff determinations. Another one is lack of subspecialists. There aren't enough clinical geneticists around, biochemical geneticists around in some of the states to help out. Again,

hopefully some of these means that HRSA is going about in terms of consolidations and collaborations within regions will help get around this problem.

Advocacy confusion is another issue. That is to say that internally in the department of health, they couldn't decide which was the next disorder. So a lot of states are looking to the guidance coming from this committee and from the ACMG report to help out with which disease should be next on our list, because there's so much internal politicking for certain diseases that it gets confusing, and rather than start anything, they just don't.

The same thing in terms of external pressures. There are a lot of different external pressure groups, parent advocacy groups who are well meaning, but the state takes a look at it and says I've got this group, this group, this group, I don't know which group to take next, so they don't take any.

Then last I've listed privatization. There are various issues here. One of the biggest that keeps coming up is, well, if we start talking about this, then people are going to start looking at the program, and there's a lot of pressure from outside groups that offer these tests that they can do it better, cheaper, whatever, and we might face this issue of privatization, and rather than get into that argument, we'll just stay status quo.

So let's look at disease by disease what the major factors were. This is sickle cell, and I've already mentioned that there are two states, both of which have it available. Now, you'll remember that there was a consensus conference in 1987 by NIH, the results of which said states should universally screen their populations for sickle cell disease. So that's 30 years ago, 25 years ago, and we still don't have universal screening for sickle cell.

In the case of this disorder, the major thing was cost effectiveness of low-incidence screening. So these states say, well, show me that it's cost effective in my state given that we only have a limited population of African Americans, totally forgetting that it's not only a disease of African Americans, and totally forgetting that they do other disorders which are lower incidence, if you remember our other chart. Even in their population it's lower incidence, but politically it wasn't decided to do sickle cell. Also, lack of subspecialists has been noted as a concern, although it's not a major concern. And advocacy again. Internally, people have said there are other diseases that are more important than sickle cell.

If you look at CAH, 38 states mandate it. Two of those that have it mandated are not yet screening, but they will be within the next year, one of which is California. There are 10 states which still don't screen for CAH, and there's one that has it as an option. That's Montana. Now, those 10 states that are not doing it, they listed mostly the fact that they were worried about excessive false positives, and also that there were other things that were more important on their agenda. In other words, there was internal and external confusion over what's the next test we should take on.

In terms of biotinidase, 32 states mandate it, two of which are still working on getting it up. Fifteen are not screening, and two have it optional or pilot. The 15 not screening, most of it had to do with, again, cost effectiveness, because the incidence is 1 in 60,000. I have cost effectiveness here kind of cross-hatched because this is the break point. Below 60,000 didn't seem to be as big a problem as the ones less than 1 in 60,000, as you'll see in the next slide. This was a concern, but it wasn't a major concern. But it definitely was a concern. Again, advocacy confusion, because people had come and said, well, there are other things you should be doing.

If you look at MSUD, 11 states are still not screening; 33 are; 4 have pilots. Here, cost effectiveness was a bigger issue because it was 1 in 230,000. So most of these states said, well, we don't have the problem in our state that would make it cost effective. Also, advocacy confusion, and you see that on all of them.

Homocystinuria, 30 states have it mandated, 13 are not screening at all, and this is a test, for those of you who aren't aware, that can be done on a mass spec, but it doesn't have to be done on a mass spec. So for the last 20 years people haven't been doing it on mass spec, and we said why haven't you been doing it for 20 years? Well, basically because it's such a low incidence in our state that we don't think it's cost effective.

I've got two more here. One is cystic fibrosis, and the other if G6PD. I didn't even list that table that shows you the reasons because it's multiple reasons here. You see that for most of the states, it's not on the radar. Now, CDC has had a conference recently. The Cystic Fibrosis Foundation has also had a conference, and the results of both of those will come out soon, and it probably will drive more states to start looking at this disorder. But right now, there are 39 states where it's just not on the radar screen.

If you look at G6PD, it's not on anybody's radar screen, essentially. If you look at the D.C. program and the Pennsylvania program for data, there are no data coming from those programs about G6PD. We're hoping that that will change. I've talked to the lab that does the testing. This is a joint issue between the lab and follow-up. The lab reports out the data, and there has to be some follow-up to get the data back to find out what you're doing, and that's not happening in these two states right now. So hopefully it will. I also mentioned that Missouri has it mandated but it's not on the radar screen to do.

Then in terms of MCAD, we're going to switch gears here and go to the mass spec test. You see there are 31 states that have screening mandated. I've got 12.5 that aren't doing it. The reason I've got a half is because in Colorado, there is a mass spec available at the university, but the state and the university aren't talking the same language right now. So it's available, but there's not a lot of interest in it from the state's perspective at this point.

Now, these data come from California. California has done a survey of the states as part of finishing up their mass spec project to find out from the states what were their barriers to starting the testing and what are the barriers if you're doing it, what are the barriers if you're not doing it. I've gotten these slides from Lisa Feuchtbaum in California, and I'm not going to go into a lot of detail except to show you that the reasons are quite similar, in fact, to the other slides that I've shown you.

I've got listed at the top a question on the left, and then those states that currently have mass spec available, do you have it available? No, yes, and then a combination of everybody who filled out a questionnaire. They sent questionnaires to all 50 states. They chose two people in each state from a list that we have available on the website that shows you the laboratory and the follow-up contact person. They got responses back from all 50 states, and nine states they got double responses from. The reason I can't talk about the Ns is because I wasn't able to determine from the data that I had which ones were duplicate and which ones weren't. This is going to be published later on by them. I just wanted to show you to give you a global picture of what's going on there rather than go into too much detail about this, and maybe George will comment later on when he's talking about the California program.

But basically what I've done is to list in priority order for the states that aren't doing MS/MS, one, two, three, four. California asked the question, and they gave them answers and asked them to rate them one, two, three and four. So the states that don't have MS/MS currently available, most of them said it's because -- if you asked them the question what are the main criteria your states uses to determine when new disorders are added to your program, most of them said the benefits of early intervention to the newborn. In fact, that was the same across all categories.

By the way, in Tab sheet 6, the handout material, you have another version of this same material where they've gone through and weight-adjusted the answers of the full 59 respondees,

and you may want to look at that to see how the questions broke out and what the answers were. But I've just listed them here to give you an idea.

The number one criteria were benefits of early intervention to the newborn. Number two was --

DR. VAN DYCK: Brad, excuse me. So the states said they doubt whether there were benefits to the newborn?

DR. THERRELL: This was just a question to ask them what are the main criteria your state uses. When you asked that question, they said the main criteria was does it benefit the newborn. The second most important criteria was the testing sensitivity and specificity, and this also turned out to be a tie for number four on some sheets. The third was a tie between knowledge about the burden of disease, cost of screening and diagnosis, and cost of follow-up. Then fourth was the incidence of disorder in your state population. But those are the top four. There's more than four there because of the way they got their answers in. I've sort of darkened out the answers from the ones that have mass spec because it was more important to me to get the ones that don't have mass spec, what do they see the criteria as and what are they going to see the barriers. This really isn't a barrier; it's more of a definition.

However, this one is a barrier. What are the issues that impacted your ability to expand newborn screening in your state to include MS/MS? Those not testing right now said the biggest issue was funding limitations. It was number one and number two. Number three was acquiring support within the organization, and number four was support from outside the organization. You can see over to the side the ones that already have mass spec, they didn't quite see it the same way. They also added in that they needed to get advisory board recommendations, and that was a difficult issue.

If you asked the question which criteria, if any, have been especially challenging to address in the context of MS/MS screening, number one was cost of screening and diagnosis in terms of short-term costs. So again, financing turns out to be a major issue here. Knowledge about the burden of disease if untreated was an issue. They didn't know enough about the disease. This gets back to the science-based information that's available. Number three was access to diagnostic services. In other words, do we have enough access in our state to take care of these babies who are going to have to be followed up? Number four was the cost of long-term follow-up.

The people who already have screening added to that access to treatment, clinical management, services and diagnosis. Again, that's pretty much the same as access to diagnostic services.

The laboratory issues that presented issues for your staff or caused delays in implementation. Number one, for those states who don't have it yet, is the high cost of equipment and supplies. This was also number one for the states that have it. Number two was the availability of trained laboratory staff. Numbers three and four was developed cutoff values, and tied for number four was validation of the cutoffs with known diagnosed cases. The ones who have it added to that delays in obtaining availability of equipment and supplies, unacceptable equipment downtime, and determination of presumptive positives for referral.

The follow-up issues that presented particular difficulties. For those states that don't currently have it was an accepted protocol or guideline for a diagnostic workup. They see that as a major barrier right now. They don't have it. They don't have people on the staff who know what they're doing who can write it. Tied for that, number two, was availability and access to appropriate follow-up centers and specialists. Number three, resources and staff for adequate long-term tracking, lack of a systematic approach to data collection, and then the availability of adequate educational materials describing the disorder. So all of the things that we've been talking about this morning, they all saw those as problems.

Again, there's a much more detailed survey writeup that's coming from California, and they allowed me to use these slides today just to show you what they've seen in a global sense. So I can't really answer too many questions about this, and I'll defer those to George later on.

Just to mention infectious diseases, because that was on the panel, right now here are the states that have infectious diseases on their panels. New York, and I mentioned Connecticut for HIV, and Massachusetts and New Hampshire for toxoplasmosis. The issue there in the other New England states, since they all use the same laboratory, the issue seems to be the viability of the treatment protocol. In other words, they're not sure that it works. So they're sort of still looking at the data and thinking about it. New Hampshire, on the other hand, doesn't do sickle cell, but they do toxo because of an historical thing there.

Michele asked me to mention just a little bit about research, and it will be a very little bit. Basically, state laboratories are not research oriented laboratories. They're service oriented. So any research that gets done is sort of done because somebody really wants to do it or because they're associated with a medical school or because they're a large state and they have a lot of samples and they have availability of these things. So it's larger programs, the programs with medical schools. So if you look around at the research being done in newborn screening, it's usually the Californias, the Iowas, Massachusetts, New York, North Carolina, Wisconsin, sometimes Ohio. I'll put that in for Bill. But it's a limited number is the point. It takes money to do research, and not everybody is interested in doing research because public health is service oriented.

That's it. I'm willing to answer questions if I can about what's going on today.

DR. HOWELL: Questions for Dr. Therrell?

Peter?

DR. VAN DYCK: Is there enough capacity in the states if you look at the number of mass spec machines that are in those laboratories? It looked like there were 30, perhaps, or 35?

DR. THERRELL: Thirty-five, yes.

DR. VAN DYCK: Do they represent a capacity that would be enough to handle all the states' screenings?

DR. THERRELL: I don't think so. It would be close, but I don't think so because states like Texas, because they do two, they have 600,000 babies they have to do a year, 700,000 babies. Florida has 170,000 births or something like that. So there's a little, but the machines are available. I mean, it's not a question of can the manufacturer supply the machines.

DR. VAN DYCK: No, that's not my question.

DR. THERRELL: Yes. It's a question of are they in place right now, and the answer is I don't think there's quite enough capacity. We have a lot of capacity, especially because in some of the small states they have machines, but I don't think there's enough capacity to do the whole country. That's my personal opinion.

DR. HOWELL: Piero, and then Bill.

DR. RINALDO: To follow up on that question, the issue of capacity is actually one that we spent a lot of time on. Do you have any idea about what is the definition of capacity utilization of an

instrument? Because that's where I believe there might be some major misconceptions. So what is your definition of an instrument utilized to capacity?

DR. THERRELL: Well, I don't do mass spec. Mass spec came along after I left the health department. But my understanding from talking with the manufacturers and the people who do it is roughly 100,000 samples per year per machine, and you have to have some backup capacity. So in a state like Texas, they're looking at perhaps eight machines to do 600,000 babies, maybe nine machines. You would know better than I because you have the capacity.

DR. VAN DYCK: I would think it would be higher than 100,000.

DR. RINALDO: Well, for one thing, you can actually do it in reverse. First you define the analytical time that is required for one analysis, and then you define the variable in a given laboratory in terms of what's the operation of that laboratory. Do you work seven days a week? Do you work 24 hours a day? Then I think you can actually come up with a very accurate estimate of what really would be required.

We combine newborn screening and a lot of different clinical assays by mass spectrometry, and not just in our lab but in toxicology, in endocrinology. We believe that if an instrument is entirely dedicated to a particular assay, we believe that it's wise and safe to define the operation of that instrument. We usually say 18 hours a day, six days a week as a minimum, but it can be more. You can start from there, and you say that the traditional analysis in a mass spec is, say, two or three minutes, and you can easily do the math.

However, there are constant technological improvements that come up. For example, now there are commercially available systems where instead of having one, you have two. So you have two HPLCs, so you can actually cut in half the analytical time, because instead of waiting for the peak to come up, you can actually sort of shift forward. Now, doing MS/MS for newborn screening is a slightly different story because there is no chromatographic separation. It's done by infusion.

But I think first you want to define what is capacity and then build it. On the other hand, I don't think the equipment, the hardware, is the limiting thing. I see sometimes really wild figures about the cost of equipment. I've seen figures of $300,000, $500,000. The reality is that the same model that PerkinElmer uses you can actually buy directly from Sykes for $80,000, $100,000 at the most.

So I think that's not the problem. It's more the issue about the next level, who is going to operate them, and even more serious is a concern about who is going to interpret the data, because that's really where the bottleneck is. It's not in the hardware, in my opinion. It's not in crunching up enough specimens, but really the post-analytical phase, what you do with it after the data have been generated.

DR. THERRELL: I think that you shouldn't lose track of the thing here that mass spec is not the only thing we're talking about. There are plenty of other disorders that you don't have to do by mass spec that still aren't being done, and those numbers about mass spec I'm sure that Peter can probably give you the numbers they use for their sales and that sort of thing.

DR. HOWELL: Bill?

DR. BECKER: Yes, I agree with Piero's comments. I was going to mention the need for backup because there's always anticipated -- you can calculate, as Piero said, what your throughput ought to be, but in my state's example our throughput says we ought to have about 1.5 mass specs for our daily volume. We have three mass specs because we have downtime, we have instrument training time, we have method validation time, we have a lot of the other things that go into doing this testing than just the raw instrument itself.

I suspect Brad's answer is the correct one, that there probably aren't enough boxes physically in place at this moment in time to handle the entire country. But I also agree with Piero that that probably shouldn't be the rate-limiting step in this analysis. Much like we're thinking about newborn screening as a system, the laboratory testing is the entire package. It's having the trained people, it's doing the method validation, it's having the instruments, and it's having the people who can crunch the data and interpret the results. It's the entire package that's what's needed, and some of those things are barriers as well.

I did have one comment, I guess, Brad, for you. I guess I would be cautious when you say that, for example, cystic fibrosis is not on somebody's -- because it's not on your map, it's not on the radar screen. I know for a fact that cystic fibrosis is on the radar screen of several states right now, and in fact cystic fibrosis is legislatively to be added to the Kentucky menu as of a law that was passed in 2001 in addition to MCAD, and they have not been able to implement that due to a lot of reasons, and funding is certainly one of them. So just because a disorder is not being screened for or shows up on the map at this point in time doesn't necessarily mean it's lost in the consideration process.

I do agree with you, though, that there is a conundrum out there. It's almost a paralysis in some of the states right now because there's so much out there that could be added that I believe a lot of states, a lot of advisory committees, a lot of state health officers are looking for advice that we might provide and that's desperately wanted to guide them in the next steps in their process.

DR. HOWELL: Piero?

DR. RINALDO: Bill, I think that you're actually making a very important point, and that goes back to the discussion we were having this morning, that really in some key areas, there is no consolidated evidence. For example, let's take the downtime. It would be extremely important for your operation to know if your downtime is average, less than average, or perhaps you are way above average. That means there is an addressable problem. If you have an instrument that's down every other day, you do have a problem. That shouldn't happen.

So that means that you can go back, compare yourself to other labs and start to say, gee, this is really what we need to do, start doing a comparison in real time about all the aspects related to quality, the detection rate, false-positive rate, downtime, rate of repeats. That's what we tried to do, the regional collaborative, because there is a plan already that we will really go and start asking specifically all these questions.

Again, this is not a finger-pointing exercise, that you're trying to feel better or worse compared to your peers. It's about giving something tangible to programs to know how they are performing, and I would like to know if Brad agrees with that, because that's really where everybody knows his own right now. There are probably some enclaves where people may share data, but I remember when we were sort of trying to put together, and it was incredibly difficult to gather that information, even as simple as what is your false-positive rate for a given year, a given month. We should have it on a given week.

DR. VAN DYCK: Brad, are there any efficiencies or inefficiencies or problems or good things that you can discuss related to these little mini-regional setups across the United States? Do you see differences that are significant in those situations?

DR. THERRELL: Well, it is interesting that they are a little different. Oregon, for instance, as I mentioned, just sort of mandated to everybody in their region that everybody does the same panel or finds somebody else, as opposed to Massachusetts, which feels like they should not dictate to other states what to do and they customize for everybody, which does run the price up. So it's much cheaper -- the reason these people consolidate is generally because they have low numbers of births in their state and they recognize that by combining together they can get more cost-effective testing

done. Yet they still do it in some instances like Massachusetts. That's not such a cost-effective way to do things. Yet their philosophy is that we shouldn't be telling another state in our area what to do.

We've been able to demonstrate that while there are large geographic barriers here, for instance between Hawaii and Portland, that's not really a barrier in terms of sending the samples over and getting them done. When Delaware was sending samples to Oregon, it was also not a problem. The reason they came back to Delaware wasn't because they were having trouble getting them over there but because they felt like they could do the things themselves just as good as Oregon, and they started doing two tests on every baby so it gave them enough volume to do the testing.

It looks like it doesn't matter if you're an adjacent state, because you saw all the errors I have shooting around. What states do is they shop for prices and they send it to where they get the best deal in some cases.

So you can become very cost efficient if you do it that way. Pediatrix and Neogen has been able to demonstrate -- there's a very good model there, I think, because states will invariably say, well, you know, we have this privatization issue here, and they have a point, because if the state public health laboratory were to go away and the company that's doing the testing were then to go away, to start the state laboratory back up or to find another vendor is a monumental task. So they're very careful about privatization issues.

Now, what's happened with Mississippi, and you'll hear this later from Dan Bender, Mississippi and Nebraska have entered into a contract where they get a part of the fee back to help support the follow-up. So while Pediatrix does the laboratory, the state continues to do the follow-up with money that's generated out of the fee, as opposed to the District of Columbia, which I don't think has the same kind of arrangement and has a little different situation there.

DR. VAN DYCK: Are any of these little mini-regional setups, are they only for doing the test itself, or are there other arrangements that help in supporting follow-up or phone calling, things like that?

DR. THERRELL: They do support their follow-up because most of those smaller states don't have the subspecialists available. So, for instance, Oregon has a contract with Oregon Health Sciences Center to do the follow-up for the metabolic testing, and they also do the follow-up for the other labs in the region. Massachusetts also has a local person that does some of the footwork, but the subspecialty stuff comes out of Portland. In Massachusetts they have subspecialists on the staff of the Massachusetts laboratory who help those states out. They also have subspecialists in those states. So yes, there are follow-up considerations there. Yes, it's included in their fee, and these things are all calculated in, but it's possible not just to talk about laboratory centers but also follow-up centers.

DR. HOWELL: Dr. Alexander?

DR. ALEXANDER: Several questions about fees. They vary all over the place according to your chart. Do they bear any resemblance to the actual costs, or do they reflect other support from the state or whatever? Who pays these fees? Are they covered by insurance? Do the families pay them themselves? Does Medicaid cover these? And then where do the fees go? You said they sometimes don't go to the lab. Where do they go?

DR. THERRELL: I don't know how much Kay is going to talk about this. She's going to talk about it somewhat. Let me just briefly answer it, and then Kay can give you the specifics.

In general, the fees that are listed on there bear very little relationship to the number of disorders screened because they include various levels of follow-up and other support services, and

you'd have to call individual states to find out what their fee covers, and you'd have to get the right person in the state to really answer that question, which is not so easy.

In terms of insurers, it varies all over the map, again, in terms of what the insurers will cover, but basically the fees are the responsibility of the patient, so they have to be covered by somebody. If they're on Medicaid, then they're usually covered by Medicaid, but again that's an issue, and I know Kay is going to talk about that one because I've talked to her about that one. But for instance, in California, this was an issue, because when the program expands, it you've got a large Medicaid population, then the state has to kick in some money to cover their part of the Medicaid fee.

DR. ALEXANDER: Let me ask another related question. If Kay is going to cover that, we can wait. That is, parents doing this on their own if the state isn't covering it. This is a relatively recent phenomenon, but it's like having your core blood frozen privately, and pediatricians are often counseling parents about this to just avoid later claims for negligence in practice. Do we have any measurements yet on how this is catching on, how much parents are actually opting to buy this screening on their own?

DR. THERRELL: I don't have the figures. I'm sure that Pediatrix could help with that because they get most of those referrals, but also Baylor in Dallas gets some. Now, there are differences in what services are available in some of these labs. For instance, the Baylor laboratory offers only supplemental mass spec screening, as opposed to Pediatrix, which offers everything in the panel. So you can get a lot of different tests there. Mayo offers some testing and so on. We don't have those data, but I would say it's slowly increasing, but very slowly, because most people aren't aware of it still.

DR. HOWELL: Derek?

MR. ROBERTSON: Brad, I just wondered if there were any issues related to the quality of the services between public and private labs.

DR. THERRELL: Well, not the quality of the laboratory services, I don't think. All these labs are certified. They go through the CDC testing program. The state labs, the private labs all do well on those tests or they're not in existence. So in terms of the quality of the laboratory services, I think they're fine.

Where the difference is is when you talk about a state public health program, you're talking about laboratory and follow-up combined, and it makes sure that the patient is tracked down, they get into their follow-up tests, and track them all the way to completion, as opposed to the laboratory service that's provided is a laboratory service, and it doesn't necessarily mean that there's going to be follow-up from that laboratory, although Pediatrix are friends of mine and they have the baby's interest at heart. They are a laboratory right now and they provide laboratory services, and that leaves the physician or whoever ordered the test to worry about the follow-up.

They will offer consultation if you need it, but in terms of tracking the baby down to make sure that he gets into his tests, chasing him down, that's not what they do. They're a laboratory, and that's where the public health part comes in. So when you mandate a test, you mandate laboratory and follow-up. When you offer supplemental, it's a test, and the follow-up is handled separately.

DR. HOWELL: Let me welcome Dr. Alexander, who just commented. Dr. Alexander was not here when we introduced the panel this morning. He was busily helping dedicate the new Clinical Center at the National Institutes of Health today. Dr. Alexander is director of National Institutes of Child Health and Human Development.

Glad you're here, sir.

Piero, you had an additional comment?

DR. RINALDO: Yes. I'm a little skeptical that there are really no differences, and I don't know if this is sort of the elephant in the room that you don't want to talk about. That goes back, actually, to a question I was trying to ask you before. Do we have any data about efficiency, about performance, about downtime? Because that's really, I think, the objective answer to the question, rather than start debating opinions, who does it right, who doesn't.

DR. THERRELL: Well, we don't have data on downtime. We have data on babies that are tested, the number of those tests that are positive, the number of those positives that are diagnosed, the time from birth to diagnosis, the time from birth to treatment, the proficiency testing at the CDC. Those things are all available. I mean, downtime -- mass spec is your issue here, but that's not something that we've ever collected. We could go out and try to do that, and I'm sure what most of the states do is they compare notes with each other, because that's what I did when I was with a state.

DR. RINALDO: Well, I think that means indirectly probably there are data out there. I really wonder why we don't have real-time feedback about things like the rate of false positives, the rate of number of tests that are repeated, because these are the things that do greatly affect the operation of a laboratory.

DR. THERRELL: We have those data. We don't have real-time data, as you mentioned, but we have a system that's going online January 1 which has the capability to give us those real-time data. It's set up so that as a case is diagnosed, it's put into the system. But it's also set up so that the laboratory can download daily if they want to, which is a key issue here, the number of tests they did, the number of positives they reported out, so that you could get that kind of data.

In talking to the laboratories, most laboratories have been giving us that on an annual basis. They're not sure they want to give it yet on a monthly or a quarterly or a daily basis, but we have the capability to do that. It's just a matter of coming together as a community and deciding what we need to get, and how to do it, and getting agreement.

DR. HOWELL: Bill?

DR. BECKER: I want to expound a little bit on I think where Piero is going. First of all, there's no question there are differences. I've been in the laboratory field for a long time now, and no two laboratories are alike. I think that that's an accepted fact.

I think as Piero has alluded to, there's a tremendous opportunity for us, as also implied by some of the elements of the report that Mike gave, in a total quality management philosophical approach to newborn screening programs. Now, we're talking about laboratories here, but we could have the same conversation about follow-up and the veracity of the data we're getting about the clinical cases and making the diagnosis and the treatments, when it's implemented, how timely, how appropriate, and have some quality reviews and evaluations of those mechanisms.

So the laboratory is just a microcosm here of all of the elements of a quality process that should be in effect or enforced and recommended hopefully by this committee for the newborn screening system, and I would certainly welcome it. There's always improvement that can be made in any laboratory operation or any follow-up program or any public health program in general, and I think everything we can do to support that from this committee's work I'd certainly be in favor of.

DR. THERRELL: Yes, I don't disagree that there are differences in laboratories, but in terms of quality of the results coming out, I don't think you can say that, let's say, private laboratories are better than public laboratories or anything like that.

DR. BECKER: I don't think that's the issue.

DR. HOWELL: Brad, thank you very much. I think that reviewing a lot of these problems at the state level as far as implementation will be very helpful to think about mechanisms that could help the state move along.

We're going to move ahead this afternoon now and talk about financing the newborn screening programs. We're going to devote the rest of the afternoon to this, and we're going to lead off with Kay Johnson, who is going to talk about state financing mechanisms with an overview.

MS. JOHNSON: Hi. I am humbled by the amount of knowledge that the previous two speakers brought to you about this particular area, and also just to say I think all of us are humbled by a two-hour presentation this morning in which no one in the room fell asleep.

(Laughter.)

MS. JOHNSON: But here we are after lunch.

I do want to say, based on 20 years of very active engagement in the development of maternal and child health policies across a wide array of issues, of having sat where you are in an equivalent position on the National Vaccine Advisory Committee and thought about the financing and strategies and the role of states over these past 20 years, that just by way of personal commentary, I don't think there's any federal authority for the federal government to mandate that states do anything. I'm going to talk about that a little bit more in a moment.

I do encourage you to move toward a set of recommendations that grow into a standard of care, as has been done by the NCIP in the case of vaccines. I very much encourage you, and I think you'll see from these small number of cases studies, why I encourage you to quickly give states the tools, give them a uniform panel, give them new criteria. A lot of the barriers that Brad talked about have to do with people using old criteria and why cost-effectiveness may not be the right criterion anymore. And give them straightforward information about the evidence, and I think fact sheets are the right direction to go on that. Support the quality improvement as we've heard about it and to clarify their understanding about financing, which is where I want to go to now.

I want to credit both Michele Puryear and Lauren Raskin and ASTHO and HRSA for helping to shape what I did here, and these folks in these seven states. I won't read all of their names, but they gave permission and participated in our process, and particularly the people toward the right end who are actually operating and managing newborn screening programs.

Oh good, this is the one that says draft. Don't we like that? Let me just be sure these are the right slides. If they're not, it's my fault, and they are not the right slides. Can I have a moment to switch?

Let me talk to you a little bit about what the study questions were. I think we can do this this way. We really asked states to give us some more information about how they were handling the challenges that are out there for them, and one is state budget shortfalls. Another is consumer demand for more tests. A third is the rapid technology change. The fourth is the pressure to privatize. I guess I would say, echoing some of what I heard this morning, change is happening, and the states are managing change. They're not going to wait for you. So you can go along with them, help them figure out ways that HHS can have a role in helping them, or not. But they really do need your help, advice, and consultation.

So what did we wish for them to tell us? We wish for them to tell us why this change was happening in the way that it was and for them to actually put some dollars and cents behind this and so forth.

I remind you that newborn screening did not start out as a mandatory activity, that it wasn't legislated and it wasn't public health, that it started off in physicians offices, and I remind you that physicians were slow to adopt this new technology. Consumers took it into their own hands. Pediatricians and others pushed for change, and the result of that advocacy is that legislatures mandated screening in most states. Then the programs sort of bumped along for the next 40 years, but we really are in a similar kind of time of change and pressure today.

I'd also remind you, and this is back to my point about mandates, that I think as Neal Holtzman so eloquently put it, only public health agencies with their authority under the police powers, and it goes on like that, could implement systems that would mandate screening for all infants, ensure the quality and availability of testing, and provide follow-up on a population basis. Nobody else in the United States governmental Constitutional structure has the authority to do that. It's a very important point for you to remember as you're thinking about recommendations.

So starting from the framework of the task force, which is where I started my thinking about this, focusing on a system, and we got a little bit focused after Brad's presentation, although his presentation didn't go there, a little focused on that test part again and remembering that you're financing a whole system, that you need the right policies, that you're involving professionals and consumers, adopting mandates and privacy protections, establishing new criteria, and setting program guidelines for quality.

What did the task force say about financing? Well, they said, first of all, that it ought to be adequate, which it generally is but isn't always; that it first ought to be adequate for the screening, short-term follow-up, and diagnosis phase, and many states today only have the adequate financing for screening and perhaps short-term follow-up, but not even all that far. Then, there ought to be an approach so that children get to comprehensive care and treatment, and that we're doing the right thing by having good operations where we can do quality assurance, evaluation and good program management.

They also found, again, that the core funding, that fees in most states, ought to be sufficient to finance that first part, that other public health dollars ought to be used as necessary, and that there ought to be coordinated funds for treatment. The task force report talked specifically about ways to finance treatment and the role of government in doing so, and the role of states who have the opportunity to coordinate Medicaid, the state children's health insurance program, and Title V dollars, in order to be sure that families that can't afford treatment get it, and it doesn't have to be condition by condition, it doesn't have to be drug by drug or formula by formula, and that's a little bit the way we've gone in the past. It doesn't have to be that way.

Also, as they're doing managed care contracts, there are opportunities for them, and they have opportunities to regulate mandate coverage and health services, although that way they tend to only reach about a third of children who have private health insurance.

Thinking about the respective roles and responsibilities of the feds and the state, we looked at this and thought about that on the federal policy side you have the Health Insurance Portability and Accountability Act protecting genetics information, but you also have a much lesser known provision in your world, a provision which says a baby who is born with a condition with private health insurance coverage, that plan has to cover that condition. So long as that child remains continuously eligible for insurance, there are no preexisting conditions exclusions permitted. This is something that I, the March of Dimes, and many others worked to ensure was in that legislation. It's there. It's a protection for these babies if you're thinking about financing treatment.

There are rights under the Americans with Disabilities Act. There are rights and entitlements under the Individuals with Disabilities Education Act or special ed and early intervention programs, and a broad entitlement to treatment services under the Medicaid program, early periodic screening, diagnosis and treatment. On the state side, they're doing the mandates around newborn screening. They're putting the financing picture together, deciding what's important to finance. Insurance benefit mandates are the purview of the states. What benefits go into their state children's health insurance programs, known as CHIP, will be there, and how they're managing the dollars they get from the feds for children with special health care needs. States are making all those decisions, but there is policy interaction here.

This is a slide of where GAO saw the distribution of funds in 2001. As you'll see through this presentation, I think there has been a shift. We don't have a good comprehensive survey yet, I believe, to tell us where the dollars have shifted. But the key point here is that the majority of the dollars are from fees. What I think you'll find is shifting is that there's probably less maternal and child health block grant and maybe a little bit more Medicaid and related children's health insurance programs as they go on.

In framing up this conversation about finance, I also want to talk about three overlapping and sometimes conflicting myths, the first one being that newborn screening programs are fully funded by fees. That's a myth for the first reason that there are five states and the District of Columbia that are not actually collecting any fees. So it's not funding all of them, but it is funding a majority. So it's a myth that has some basis in reality, as most do.

It's also true, however, that in most states those fees typically only cover the test and the lab cost, and perhaps communication of results to the physician. They don't cover real contact with families, real follow-up and connection of families to treatment, or even strong information generation at the primary care level, let alone the specialty level. Fees may not support the expansion of new technology and equipment, and I think states are running into this again and again because they're set to be ongoing, covering fixed costs. I'll show you how states are getting around that one. And economic pressure may limit fee increases. States may just say, and I'm going to come back to this one, we're not prepared to increase the fee because we're not prepared to add another cost to the increasing cost of health care.

Now, that gets right to our second myth, tax dollars fund newborn screening. Because this has tended to be a public health program, because its basis is in public health, we act as if it's all taxpayers' dollars funding this, and probably two-thirds of the money, at least two-thirds of the money, comes from a private source. It's not that you're asking someone to raise taxes to buy more newborn screening tests in a panel. In all but those five states and the District of Columbia, you're talking about the core money actually coming from fees, and maybe some residual funding from some state and federal programs, and otherwise private insurance dollars.

Then the third, which Brad touched on, is about third-party reimbursement. They're not paying their share. They rarely do when something is a public health service. It's been years of struggle around the immunization, let alone around well child visits. The fee in and of itself is not always fully paid by Medicaid is the take-away point from this slide, and that is something I think could be changed.

So what did we learn? What did we go out to ask? Again, the recent challenges. Who did we ask? Our criteria for selecting this was a mix. We engaged input from ASTHO, from MCHB, from Brad and his resource center, and began to look at these various kinds of factors you'd want to know in an illustrative set of case studies. Are they across the country? Are they doing different patterns of testing? Are they using public and/or private labs? Are they using fees or not? You see this here.

I'm going to skip over this one and go to these because they tell you -- I'm going to be echoing some of what you heard from both of the previous speakers, but just to give you a very quick

profile of our sample. These check boxes are based on a combination of the resource center and March of Dimes. You can see there that there may be slight variation from one list to the other, and I tried to reconcile and justify those.

But as you look down these seven states, and here they are -- California, Maryland, Minnesota, Mississippi, New York, Oklahoma, and Oregon -- you see quite varied patterns of what they're actually including in their screening panel. If you look just at tandem mass spec, you can see a substantial variation. So having a check in the box on the left does not mean that everything you'd expect is going on on the right. Again, this is just illustrative of the variation in this sample.

Having seen those two, I actually had this, Duane, so that it showed you the alignment of who was testing what, and I decided there were too many columns on this slide and I took it out. But there is not a very good relationship between how many. I think it reflects historical trends, it reflects what it costs to do business in a lab and what it costs to do business in a health department, how health care financing goes generally in the state, and it's different, as you can imagine. It's different in Maryland, California, Mississippi, Minnesota, New York, Oklahoma and Oregon. What doctors get paid varies across those states. So the whole health care system is different.

DR. RINALDO: One quick question. Does it make sense to present these data divided by the number of tests? Because it's somewhat misleading, I think, to say that it was 620 percent --

MS. JOHNSON: Because I'm going at a very different point. Stay with me for a moment. I'm going at a very different point, because what I'm going to say to you is that I believe that all of these increases were justified and minimal, not that the percentage is big. I think that's the way that legislators see it, and I want to talk about another way to see it.

So there are the fees, where they're charged, and there are the contributions in at least three other categories. What was interesting to me was that in California, Minnesota and Mississippi, they said we used to use the maternal and child health block grant more, or they said we used the occasional grant dollar, but we're not really doing that routinely, that's not a regular source of core funding for our program. You can see that they're fairly limited in thinking about Medicaid as funding, and I think you can see here the reason for that. Brad alluded to it.

If you look down the middle column, you can see the percentage of births financed by Medicaid. It's large. It's running from a third to a half, in that 35 to 40 percent range on national average. So there's a lot of money on the table when you talk about changing something related to financing birth and Medicaid, and there's a lot of money on the table even if it's only a minimal amount, even if it's only $75. There's a lot of money in California, or in any of these states relative to their population.

So I'm going to go through these very quickly and talk to you just a little bit about the headlines, the financing approach in California. The fees are paying for the program, as I call it, that range of the first pieces, up to the diagnosis, and they're charging a dollar for the test form. As George told me, he said, you know, we don't want them to throw them away. We want them to have a little bit of value, so we charge for the form, and it seems to have worked for them. Then $59 per baby screened. The hospitals can keep something over and above that for themselves.

What were the challenges they faced in these times? Well, first of all, it's a huge undertaking to try to change a system for a half a million babies, just period, whatever they're changing. Then they had success with their project pilot, but they really have run smack dab into politics and state budget pressures and not being able to go forward with their plans. They have a model that I describe as public health management using private lab capacity, which I think has been a strong one for California and maybe one that's going to be working for others in the future. They're setting the way that things get done and then using the capacity that they have in the state.

In Maryland, the fees cover the lab tests. It's interesting that they actually got a loan to buy the equipment, and they're using the fee increase to pay back the loan. The state government got the loan in order to be able to do the up-front investment because they didn't have the money, and they're paying it off through their fee increase. They're using the maternal and child health block grant for both short-term and long-term follow-up and have a very extensive push in that area.

The challenges that they faced. They feel that there is now Pediatrix in competition with the state lab. They don't know entirely how that's going to play out in terms of the operation of their program. They have a philosophy about effective parent informing, which actually says in their legislation consent. They call it good will consent in terms of telling people, and changing the number of tests, and number of conditions, has made it much more complicated to communicate with families about what the tests would be, and to get that sort of good will basic consent. They are doing two screens, and therefore they have to think about everything they add they're doing twice over.

They are doing follow-up for many more families. Because they take their follow-up responsibility very seriously, adding a test means an enormous pressure on the follow-up side of the program. They've commented on state budget pressures.

In Minnesota, I'm going to say a few words about states that are in the room at my own risk. What I was told was that they hit the restart button and that they really changed. They financed a new approach with a fee increase, that they're focusing on the family as a consumer. They expanded the number of tests. They created this marvelous three-legged stool between the state public health agency, the Mayo Clinic, and the University of Minnesota, using the capacity that they have there.

They have sought really to develop structured, more formalized, more regularized linkages to the medical home, to the primary care pediatricians, and bring in the consultation functions with the subspecialists here. I think it's very important the extent that MCHB and others have talked about medical home, that we not forget the role of that linkage, a really good solid linkage, not just somebody calling the office with results but supporting them with training and new knowledge in these areas also.

In Mississippi, Mr. Bender is going to tell you more about this, but the expansion to really do what they see as today's state of the art comprehensive screening, and I think we have to be honest about that as a huge commitment from a state with limited resources. Their fiscal approach is that they did their fiscal analysis and decided what it would cost to make this change. It's not a frivolous number. They didn't make it up. They did the analysis to get to that number.

They also see that the hospital charges may actually vary. So it may be a little above the fee and the way that those things are getting paid through insurance and Medicaid today, it's part of the global payment. So the hospital is paying it out of what they get paid. So in essence, when the fee doubled, the hospital is getting less out of that global payment because the global payment and Medicaid wouldn't necessarily increase here or in another state.

They had political pressure to change from their Genetics Advisory Committee, as well as through parents and others going to the legislature. They did not have lab capacity before. They were part of a shared arrangement. They made the decision that they found the services they wanted at a price they wanted to pay with Pediatrix and, of course, had the good judgment to say that as part of that they needed to have money to fund their follow-up program, and they have added public health staff in each health district in order to make that follow-up much more real on the ground in real time.

New York is not a fee-based approach. Their public health dollars are financing newborn screening, by and large. They too had a lot of advocacy. They had a three-year push to add cystic fibrosis, so they've been through a battle around change. Again, this is a huge undertaking to change things in New York. Not a half a million births, only a quarter of a million babies we're talking

about in this case. They have undertaken innovations to link to the primary specialty care physicians, not the same kind of deliberate effort that's gone on in Minnesota, but an effort to think about how you provide the tools in practice that make the program operate well and help to ensure quality.

In Oklahoma, their finance approach was to have a fee and increase it when they needed to do more tests. They also saw the opportunity to move forward much more aggressively with Medicaid and private insurance billing, and they got the legislative commitment to financing I think in large part because they figured out how to use the third-party payers. The third-party payers were at the table as the decisions were being made. They saw that their federal support for planning was enormously important. They have their authority, they're moving ahead, and they're also adding more to their follow-up component as a result of this.

In Oregon in their fee-based approach, they actually have people buy the kit as they start off. They actually have had a process that said no to something in Oregon, and they were going to just go to the legislature to get money, and they had a task force to guide their decision, and they drew the conclusion that they were not ready to add cystic fibrosis. The regional lab for them as a vendor, they've had to make decisions that Brad has already described to you.

So, in short, what's driving change in the states and what's financing it? What happened at the federal level, at the national level, and the changes that federal agencies have promoted, genetics planning grants, program integration grants, the resource center demonstration projects, regional collaboratives, having an advisory committee, and looking at laboratory quality control and many things that go on that I haven't listed here, and combined with -- not to say anything less than, but what's really driving the change, that action and advocacy on the part of all those folks on the right-hand side.

So what's driving change from the state perspective? They told me the national task force, they told me that the advocacy by the parents, arguments for equity, HRSA efforts, and the science is carrying them forward. What did they do? They were focusing on their system, not just on a test. They expanded the number of tests. They invested in state of the art testing. They financed more follow-up. They made that commitment. They engaged the parents, the families, the consumers, the advocacy groups, as well as their experts on their advisory committees, and I think they've done a very effective job of negotiating issues around quality and privacy.

They all said to me these are remaining challenges for us, but we've negotiated them to date, nobody's effort at expansion has blown up in the face of privacy concerns, so I felt that they've done a good job.

So what do I see as affecting the future? What I heard was adding tandem mass spec capacity in the laboratory is simple compared to the fiscal, ethical and system of care decisions that lie before them. As goes genetic science, so goes newborn screening, and that introducing profit into these systems has changed everything. I've been working a great deal on Medicaid managed care issues over the past decade, working with states and working on national reports, and to me there is an incredible parallel that you have to pay attention when the private side comes in to something where there has been a longstanding public health role. It's not that it can't be done well; it's that you have to make deliberate decisions. As long as you're making deliberate decisions, you know what the pros and cons of that are, and you have ongoing oversight.

You don't want a situation, the extreme example of health plans that say okay, sure, we'll take the monthly payment for these managed care patients, and we'll take responsibility for these children and for their health and well-being, and six months later, after the first year or so, the money is gone, the business is bankrupt, and the state is on the hook for delivering services for which they've already given away the money.

The political pressure is against increasing health care costs for all the reasons that you know if you read the newspaper. Legislators tend to say or may say that's a nice idea but we can't afford it, it's a good idea but you should do it with no new money, and neither of those is really good for the manager of a state newborn screening program. Health insurance plans and Medicaid may come forward to say this is going to drive up costs overall, so there's a dilemma there for them. We know, as we talked about this morning, that many things drive policy decisions other than good evidence, and the fiscal constraints are often driving it.

I just want to close with this quote from one of the state officials that I think captured much of the spirit of what I heard. "Parents may go from doctor to doctor seeking diagnosis for their child, and generating costs without being prepared for the outcome. If you miss a child and miss the opportunity for intervention, the costs are much higher. Program managers have to look at all of the costs and make judgments that balance the interests of the individual child and the public."

Then just as a final reminder, by and large, we are not spending taxpayer money.

What now? The goals I heard consensus about were that every baby, regardless of where born, should have access, that every child receive screening, diagnosis and treatment, and that they need a new consensus for adding tests, and they need quality standards to help them get their job done.

Let me close with that.

DR. HOWELL: Thank you very much.

(Applause.)

DR. HOWELL: I'd like to hold questions for Kay's excellent presentation.

For those of you who have been looking at the agenda, you probably noticed one major deficiency in the agenda this afternoon, which I hope everyone has noticed. There's no break. But that has not gone unnoticed at this point, so let's take a 15-minute break and come back, and then we'll have questions about the financing after we hear from Mississippi and California.

Let's see you back in 15 minutes.

(Recess.)

DR. HOWELL: We're going to continue our important discussion about how states finance their systems. So if everybody could please come and have a seat before I have to come out and seat you.

(Laughter.)

DR. HOWELL: Excellent.

We're going to start with Ken Pass, who is director of the newborn screening program for the New York Department of Health.

Ken, welcome to the podium.

DR. PASS: Well, thank you for this invitation. I'm pleased to be able to tell you about our program.

The directions to me changed each time I asked what I should present, so I quit asking and I'm just presenting what I want to present.

(Laughter.)

DR. HOWELL: I think everybody knew you would do that anyway.

(Laughter.)

DR. PASS: I've chosen a very broad title for the talk, which means that it will be broad but not deep in substance.

First issue I wanted to look at was referred to before, financing. In New York we finance the program, as you know now, with no fees, but we do use state dollars, MCH dollars, and various grant funds from time to time when we can convince the agencies that we need them.

Historically, the ratio of those dollars is really in the same sense as they're listed there: more state dollars, less MCH, and less for grant support. But there are other ways that we have approached but decided to back away from.

This was a headline in the New York Post on January 20th, 1993: "Governor Wants $17 for Every Infant Born in New York." That's not quite what we had in mind. The same day in the late edition, still pounding home the point. So I can assure you now in New York State, there's no elected official who is willing to discuss a fee for newborn screening, because this reporter is still employed by the New York Post.

(Laughter.)

DR. PASS: We've heard a lot today about adjustments to panel, and I want to show you how it works out in New York. We started the program in the legislature in 1964 with Public Health Law 2500a that told us to screen for PKU. Since that time, we've amended that law several times to include some of the conditions in our panel. Other conditions in our panel have been hindered there through the regulatory component derived from the law. That is, Part 69-1 lays out in great detail how we do newborn screening in New York, the responsibilities of all the participating partners, from the hospital to the laboratory to the follow-up people, medical specialists and so forth. So we can change the program by amending Part 69 using a statement in the law that says "at the discretion of the Commissioner." So the Commissioner, through the rules and regs, can change the panel.

Sometimes we're simply told by the legislature to do it, without any amendments, without any changes in the regs beforehand, that coming afterwards.

So if we go back and look at our panel of 11 conditions, this is the way that panel has evolved. We started with PKU in 1965, with the creation of our public health screening law. Then in '68, '75, and '78, that law was amended to include galactosemia, MSUD, homocystinuria, sickle cell disease, and thyroid. So if you pull the law from the statute books, you'll find all of those listed there to be screened by the state.

In 1987, we were completing a HRSA-sponsored project looking at biotinidase deficiency. When we started that project, the enzyme for that assay was about $14 per baby. As we approached the end of the project, it was down to 10 cents. So we convinced then Commissioner

Axelrod that it was cheaper to keep the test in place than it would be to put it out, and we then lobbied to put it back in. But there was no cost to the program, essentially, and he agreed. So we modified the public health regulations.

HIV, a very special course, and I'll show you a little more detail on that. But just understand that New York, unlike other states, in 1987 when the CDC asked for a surveillance study, instead of doing a statistical sampling, we tested every baby. We had a very effective and complete blinding system so that there was no going backwards to link a child with a test result. Yet, from day one, we were accused of identifying babies with HIV disease and not telling anybody.

Well, that's true to a point. But, in fact, we were not allowed to test by name, and we had a system in place that did not allow us to go back one day, one week, one year and link those names. Nonetheless, the clamor continued until 1996, when a court in New York City agreed that that was not the right thing to do and told the state to unblind the testing. Well, we couldn't unblind the testing. So we went through an intermediate phase and then began, in 1997, testing under mandate for HIV exposure.

Then again an edict from the legislature actually in 2000, with the test coming on board in 2002, we were told to add CF, CAH, and MCAD to our panel. Until this day, no one has stepped forward to take credit for that. I cannot tell you how that originated in the legislature or why it came about.

I want to go back now and look at just two of those conditions to give you a feel for what can really happen here. As I said, we began the blinded testing in 1987. We were told by the courts to unblind, but we couldn't, and by that time -- this was actually '96 -- there was legislation in place that you could not be tested for HIV without informed consent. So that meant the mother had to consent to the baby's testing.

We instituted a program that ran for about seven months in which the mother was presented with the option of receiving her child's newborn HIV results and, planning for that, we estimated that approximately 15 percent of the mothers would say yes, I want to know, primarily because we made it very clear in the educational materials that by testing the baby, we would know the mother's HIV status even if she had not been tested previously.

So we estimated 15 percent. By six weeks, we were in excess of 90 percent. The legislature saw that and within the first six weeks of that consent program added HIV to our panel. We then very carefully over the next six months developed the program we have in place now so that the testing can take place, the appropriate care can be provided, and a minimum number of individuals involved can then transfer that information.

Now, contrast that with the most recent addition, MCAD. As I said, we were told by the legislature, and actually in the budget a line item, I received a call saying congratulations, you got some money. I went back and looked and there was a line item asking for MCAD, CAH and CEO. So then we formed a task force of physicians, metabolic specialists, CF specialists, endocrinologists, parents, other state programs, CDC. So we had a broad spectrum of people to advise us not on if we should add those three but how we should go about it.

We began testing for MCAD in 2002, but we were only testing for one condition, MCAD. That was the one we were directed to test for. When I met with the metabolic specialists, their first reaction was let's do the whole thing, whatever comes out of the instrument we will take. Then after some discussion they finally agreed or accepted the position that it would be better to start, get the system developed and working, and then expand, and that's what we are discussing now in New York State, an expansion of the MS/MS panel to some level. I'm not sure yet what level. We were waiting quite anxiously to see what would be presented here today in terms of an expanded panel.

I have to say that these parent groups played a big role in this. We had planned from 2000 to expand the panel stepwise. With some strong input from parents, that time frame has been condensed down to a very short time frame. We heard a little bit about this, but I'd like to comment that if, for instance, New York were to expand its MS/MS panel from one condition to 30 or 50, that's a trivial move for the laboratory. We simply re-program the mass spec to give us the results that we're not getting now. Our computer system, when we designed it, allows us to change the data handling so that we can handle that new data, and the only thing we would then need is more resources in our follow-up group.

But when you go outside that to the metabolic specialists, to the parents, to the people actually delivering the care, our estimate from -- say we expanded the panel by only 15, then we estimate we would be turning out another 1,200 presumptive positives per year. That's in addition to the group of metabolic specialists who are now receiving almost 1,000 referrals a year from us, screen positives. So they would see a more than doubling in their workload with the flick of a switch. I met with those folks last week and the point of discussion was not the capacity or willingness to handle the increased workload but the poor financing that comes along with it, and you heard it this morning. The Medicaid rates are trivial compared to the cost that they incur.

In fact, one of those metabolic specialists -- these are all operating out of medical centers, huge medical centers -- told us that they had had the conversation with a CEO that this money-losing process could not increase, that you can't add loss on top of loss. An expansion with the MS/MS panel has that potential.

So having said all of that, I have some wise observations for you. Yes, you do need an advisory committee. It's just too much for one individual or one institution, one laboratory to manage all the decisions, all the perspectives. You need an advisory group.

You need the proactive support of the health officer, in our case the commissioner, and/or the lab director. If any one of those is absent, you're not likely to expand the program or to change the program in any meaningful way.

You need the active support from the state legislature. I'm sure that every newborn screening program person in this room has a story to tell you about how a condition was added to their panel because of the personal experience of one of their state legislators, a very powerful influence. That legislator, in fact, that personal experience need not be in his or her own family. It can be in a friend's family, and I can show you equipment in our laboratory that was placed there because of that relationship. So this is a very potent point.

Now, I have my own list of barriers to change. Technology. I tend to think that newborn screening has always been driven by technology. I think back even to the thyroid testing. We only added that when the RIAs became sensitive enough that we could get the information out of the Guthrie spot. So now we've got the mass spec, and it's brought another interesting question to us. The question now is not can you screen but should you screen, a totally different question. You heard that this morning. I would submit to you that we're going to have to accept the fact that we are genetic testing programs, and DNA is the source of the genes. So we're going to at some point begin looking at the DNA, maybe first rather than a second tier.

Staffing levels. Not only the head count but in the experience. You've heard already this morning that to add mass spec technology, you need some very experienced people, usually at a Ph.D. level, with one exception behind me, to put that in place and make it work. It's not a simple procedure.

Another barrier is the absence of a support group. There are no support groups for G6PD that I'm aware of. There's no support groups for congenital toxoplasmosis. So without that push from the consumer side, it's not likely to happen.

With that I'll close and take your questions. Thank you.

DR. HOWELL: Thank you very much.

(Applause.)

DR. HOWELL: I think what we're going to do is to go ahead and have Mr. Dan Bender talk about Mississippi, and then we will have questions.

MR. BENDER: Thank you, first of all, for the opportunity to come and speak to you and talk about our program. We're very proud of it. I was director of genetic services for 17 years, and we started back in the early '80s, as many of the other programs did, with a nice grant from HRSA. We could not have accomplished what we did if we hadn't had that.

We started screening, and I was hired then. The law was passed. There were seven hospitals in our state that were volunteering to work on this when I was hired, and we had a mandated law passed by our legislature, and we went to 75 hospitals overnight. Then we decided at that same point in time that we'd better start charging. I think California was one of the only other states that charged back then. We decided to charge $2.50. Our former, two or three health officers ago, said that that was our baby tax. I shouldn't say that, but that's what he said. He called it a baby tax. It worked. It worked well.

The cost of the laboratory is one thing, but the follow-up cost is equal or even more important. I know most of you are laboratorians. I don't see a lot of MCH. Dr. van Dyck, you'll have to protect me here. But it's strange that more MCH people aren't involved, because that's the important follow-up. We tried to combine over the years our MCH dollars along with the fee we charged to make our program go and grow.

Another thing that was very helpful, I think our state and South Carolina, are the only two states that have a central office system, nine districts, and 108 or so health departments. We don't have any autonomous health departments. So that system lends itself to newborn screening. It helps a great deal to be able to make sure that all this happens out in those county rural areas.

We took that small amount of money that we charged and we added first PKU, hypothyroidism, sickle cell, and as we kept going we began to see the need. We only have one tertiary center in the state at the University Medical Center at Jackson. We only have one tertiary medical center in the whole state, so we felt like we needed some genetic satellite clinics. So we added those, and you'll see those circles all represent satellite clinics that we started by using our genetic staff at the University Medical Center and our nurses in the health department to start.

Then we also started something new, and Louisiana picked up on it. One of our proudest program or one I'm proudest of is sickle cell disease. Forty-nine percent of our deliveries in the State of Mississippi are non-white. We feel that we have an obligation to make sure that each baby in our state gets taken care of, and those non-white babies, if you've ever dealt with sickle cell and you've ever dealt with a sickle cell crisis, you know what a horrible thing that is. So we put satellite clinics all through the state for sickle cell as well. So they go there and they're tested, a laboratory test, and they see a specialist, and they're taken care of.

We did that and we went up to about $35. This was before we expanded newborn screening to the 40 tests. So that's some of the things that we did with our money over the years.

Now, at the same time, we tried to educate hospitals and make sure that they knew how to collect the specimens. Not a lot of programs did this, but we went out to each hospital, we made sure they knew how to collect the specimen, and we did it at least twice a year.

Then we added more and more TS, and every time we added TS at that point in time we had to go to the legislature and we had to ask them to add it. We had an advisory committee, but the legislature wanted us to come to them and they wanted to do it themselves, so that's what they did.

Then in the year 2000, we had a child up in the northern part of the state that died with MCAD. We got parent involvement. I'm sure many of you saw not too long ago the "Today Show" with Ms. Haygood on there, and our program really got started, and we started looking at what we could do or how we would move toward expanding newborn screening. We worked for 20 years with the State of Tennessee. Their laboratory worked with us, so I have a lot of experience with state labs, and they do a wonderful job. We had a great relationship. We had no problems. But when we went to them, they didn't feel at this point in time they could go to the expanded newborn screening and they couldn't help us, so we had to seek help elsewhere.

Dr. Pass, other people we contacted helped us, and it is so important, so very important when you put out a bid process, if that's what you're going to do, you'd better make sure that you're careful what you're asking for, you know what you want, and you know what you're going to get, because if you bite off more than you can chew, you're in trouble. But we were lucky. The University Medical Center, I heard a lot of discussion about cystic fibrosis. We had a wonderful team there that worked with us. We used our children's medical program for children with special health care needs, that we see these children a year after they're diagnosed to do the follow-up. We also used our early intervention program for other problems.

So we used these other programs that we had at our disposal to work together, to combine, to try to work together to expand and to make this program work. We have as many problems as any other state in the United States as far as economics is concerned. We're the poorest state in the United States. But we had a team that worked closely together. Somebody said, well, you can squeeze a dollar. No. I have people that helped me squeeze that dollar. They worked with us, the team from the medical center on all our metabolic disorders. We sent people off to get them trained, we worked together with them, and they helped us. We even have metabolic clinics now over the state where, if it's not convenient for that family with six and eight kids to come 200 miles, we go to them. That's one of the things that we've done.

Now, the first law that was passed was a law that -- somebody mentioned this morning about giving information out, passing out the information and saying this is what you might need to do, this would be good. The first law directed the physicians, pediatricians, GPs, everybody, all the physicians, to get information to the expectant mothers, and even the fathers, everybody. They had to give the entire family information as they came in to show them what tests were offered.

This put the physicians in a real uncomfortable position, a real liable position, and they said please, let's do something different, this won't work. We feel like the monkey is on our back and we don't know what to do. Just telling these people about it, we don't know if it will get done or not. We don't know the lab, we don't know the outcome, we don't have a central point computer system to put this in. It's just causing a lot of problems.

So then we moved on with our law as it reads now. What the law states is that the advisory committee will decide or will suggest to the board of health the tests that should be done, and then the board of health will instruct the health officer which tests to actually make sure are followed up on.

Now, I heard some discussion this morning about tests, different tests and what should we do, and I respect you guys for being experts, I really do. But if you know a test can be done and you don't do it, and there's a problem, my state recognized that as that was a good way for them to get in a lot of real hot water. So since we bid it out, we tried to look at any lab that would take it. Some labs wouldn't even consider it. Baylor is a good example. They would do the mass spec, but they wouldn't do the other tests. We couldn't find anybody.

So we only had two or three bids, and we felt like the private laboratory offered us the best situation for the money, and that's the way we went. We didn't want them to do follow-up. They said they would do follow-up, but we now our physicians, we know the communities, and we've been doing this for 20 years. So we wanted to continue the follow-up. The reason we were able to go from five tests to 40 tests was because we had a solid follow-up program, a system in place that could go out and find these children at Box 8, Route 62 and bring them in to the tertiary center, to the specialist, within 24 to 48 hours. All of ours, 100 percent of them, have been brought in in that length of time, and we're real proud of that fact.

Now, we went from $35 to $70. It's about $1.75 a test. Depending on how you count eggs, 30 tests, 40 tests, 50 tests, whatever. But at any rate, I think that's a bargain for that cost. We take the majority of that, over half of that $70 goes for follow-up. What we did on that map that I showed you, every one of those nine districts we had a social worker or a nurse in the district to make sure that child got taken care of, and also to make sure that child who had sickle cell disease, if they were on penicillin and it was January and it was 24 degrees in their house, all the penicillin in the world wasn't going to make any difference.

So we made sure that follow-up was done with our sickle cell patients. It was important to us that we do that, and we've continued to do that. With this money now, these additional dollars, we have put -- and by the way, we've cut back on the MCH dollars. Almost all of it is fees now, like 98 percent of it is fees. We've put a nurse, a social worker, and a clerk, a clerical person in each of those nine districts to make sure that not only newborn screening but child health is being accomplished. We've started up, through our tobacco funds, we have 51 nurses in the school systems that now are helping us with follow-up. We also have 24 new nurses that the University Medical Center School of Nursing has just piloted that are doing EPSDT in all the schools that they represent, 24 schools.

We're hoping with the 250 nurses statewide that we can go statewide with all child health and look at it as a child health project, not just newborn screening or tobacco nurses or EPSDT or whatever, but a holistic look at the whole situation.

Now, this was the first year of our testing. The first information that some of you saw me do in the past was 41,000. It's 42,000 because the children that were Mississippi babies that were born in the surrounding five states, now we've pulled in. There were about 1,000, so it kicked it up to 42,000. These are the numbers that we've come up with. They're not real large, but you multiply between 70 and 80 sickle cell disease, and that's SC, SS, thalassemia, that's what we consider sickle cell disease. We even follow up the traits with letters and information. But the sickle cell disease patients, you take that and add it up year after year after year after year, that number gets large.

Our children's medical program for children with special health care needs covers 500 sickle cell patients right now, and these other disorders, you can see we have large numbers. For some we have less than we should, PKU, and then we have congenital hypothyroidism at 21. Every one of these are confirmed. This is not just positives that we came up with. These are all confirmed in each one of these areas. They've all been gotten into the tertiary center, they're all being taken care of, and they're all being followed. They'll be followed through our children's medical program if need be until they're 21 years old.

Have any questions, I'll try to answer them.

(Applause.)

DR. HOWELL: The two of you, if we can get you up here.

Dan, it was very nice to have your comments. I think one of the things that you emphasized that has been discussed so broadly is a program both of diagnosis and follow-up that's comprehensive that the State of Mississippi has been able to put into place that you emphasized, and you emphasized that you're as challenged financially as any of the states, which I think is a very good example.

It's also nice to have someone present who doesn't have an accent. I appreciated that.

(Laughter.)

DR. HOWELL: Peter, you had a comment.

DR. VAN DYCK: I had a question, Dan, for you. Tell me a little bit more how you get the tests to the private lab and how they come back from the private lab and who they come to, and then how you follow-up.

MR. BENDER: The system that we have there, the private lab has contacted every delivering hospital in the state, each and every hospital, and they have given them overnight mailers. They go straight to Pennsylvania, and we use the telephone system. You mentioned earlier, you were talking about doing lots of tests, those machines putting out more and more. You have to make sure -- and I know this wasn't where you were going, but I've just got to say it. You've got to make sure when you follow up that when your laboratory is open, your follow-up is open, because if that laboratory is open and the follow-up is not, and I don't care if the laboratory is public or private, they're going to get rid of that positive. They want to get that positive out of their hair because they're afraid that something is going to happen.

So if you don't coordinate the times of testing with the times of follow-up, you've got problems, and you can't do follow-up 24 hours a day, seven days a week.

DR. VAN DYCK: So you mean the follow-up, the tests come out at 7 o'clock at night and you may not be --

MR. BENDER: Right, contacting the patient, making sure their family physician knows what's going on, and then making sure they get an appointment with that specialist the next day.

DR. VAN DYCK: So each hospital mails overnight their tests at the end of the day.

MR. BENDER: That's correct.

DR. VAN DYCK: And then the lab turns them around overnight?

MR. BENDER: Within about 48 hours, 72 hours the max. They call us on the phone on all positives or borderlines.

MR. BENDER: Okay. So when they call, they call the health department.

MR. BENDER: That's correct.

DR. VAN DYCK: They don't call the private physician.

MR. BENDER: They call the central genetics office, and we take it from there. That's the way it's been from the very beginning.

DR. BOYLE: I will direct my question to you as well, Dan. In terms of Medicare issues that Ken brought up in terms of reimbursement for private physician specialists, have you had the same type of challenges? I think Kay showed us that Mississippi has the highest percentage of children on Medicare.

MR. BENDER: Well, we have good Medicaid coverage, because it's like 54 percent I think your numbers showed, and I think that's correct. We have good coverage, but each hospital gets a per diem, a flat rate, and they have to take it out of there. Now, the hospital association has been very supportive. For 20 years, they've been very supportive of what we've done. When we went to the $70, I went to see them, and they said for what that patient is receiving and for what it costs for blood tests, we don't see a problem. The hospitals gave us no problems whatsoever.

They pay us directly. They don't deal with Medicaid at all. Hospitals collect third-party Medicaid. We charge per hospital per baby.

DR. BOYLE: But I thought the issue for Ken was more the specialist, the follow-up specialist, not so much the hospital.

MR. BENDER: The follow-up specialist, they're receiving their money from either -- the children's medical program or children with special health care needs is the payer of last resort. But if they don't have insurance, with our poverty, which I think is 185-some percent -- it's gone down some, but it's still 185 -- there's not too many people without Medicaid insurance, and if there are a few that fall between the cracks, we pick them up on the children's medical program or children with special health care needs.

MS. JOHNSON: I want to try to get at this issue because it's an important one. Brad and I have talked a lot about it, Michele and I have talked some about it, and we talked a great deal about it at the Newborn Screening Task Force.

Having worked intensively around Medicaid financing issues over the past 20 years, I guess my bottom line on this is that with a couple of exceptions for a few years here and there, I think there was one five-year period where California paid adequately and above commercial insurance for birth expenses. Medicaid does not pay well for any service it pays for. We've made a public policy decision in our country that that's the case.

On the other hand, the only people who get paid in any way well have gone to the legislature and demanded they get paid. I just have to be really clear about this. The only way newborn screening fees are going to go up and the only way anything around treatment is if the people in that state have the will to move the legislature to change the fees, because that's the only way it can happen.

DR. HOWELL: Peter?

DR. VAN DYCK: I would expect that in New York, no matter what disease or the rarity that's found on screening, you probably have specialists within the state who can deal with that. That may be a false assumption, but that's an assumption. Mississippi, however, makes me wonder. With one medical center, do you have specialists for all the conditions you're testing, or do you have to somehow arrange and find specialist care outside of your state?

MR. BENDER: We do have arrangements with Memphis particularly with contracts. We've done that for many, many, many, many years. But for Jackson, we have one pediatric endocrinologist, and bless his heart, he comes in on Saturday and Sunday, whatever it takes, and he helps us, and there are others that do the same thing. It's not for pay. It's a labor of caring about the patients, because a lot of times they don't get the money. I'm going to be quite frank with you; they don't. But we do have arrangements with Memphis, with the UT there, and they do see our patients and follow-up. A lot of times they do it taking money out of their pocket. They probably get more money for their own patients, their own Tennessee patients, than they would the Mississippi patients. But they do get our Medicaid dollars for that.

DR. VAN DYCK: Did you, before you increased the panel, go around seeking people that you knew you might need for referrals?

MR. BENDER: Yes. We had numerous meetings with all the different areas we knew were going to help, the metabolic disorders, that geneticists who worked with us on that. But we had the most meetings with the people helping us take care of cystic fibrosis, and we had to work that out. But between the medical center and our children's medical program, that's what really takes care of those children. You saw the ones we found. It's really an interesting situation.

I followed a couple myself just to see how it was working. One large hospital in our state made a mistake on one newborn and got the babies mixed up and thought they had a heart problem. Well, as luck would have it, that particular baby a week later, we had to tell them the child had cystic fibrosis. The daddy threw our social worker out of the house and all that sort of thing, but what it boils down to is we went to that family, and these weren't wealthy people, but they really cared about their child.

Even the churches supported us, and we do a lot of work in our state. You don't function in Mississippi very well if you don't work with the churches. The black churches are very strong in Mississippi, and so are the white churches, and they work with us to help make sure that money is available if that's what it's going to take to take care of that child.

DR. VAN DYCK: Ken, you mentioned there might be a capacity problem among specialists if you increase your tests significantly, even in New York.

DR. PASS: Yes. I was just going to make that point, that when we're looking at the numbers such as Dan put up there, those are the confirmed positives. What you don't see there are the diagnostic workups for the false positives, and those numbers can be 10, 20, 30 to 1, false to true. So the numbers that are on the screen are not the true workload. That's the outcome from a much, much larger workload. That's the point I was trying to make with the metabolic specialists who presented to me, that they lose money on every one of these workups.

Medicaid in New York, I think the number is correct. The Medicaid payout for a workup for an acylcarnitine disorder, true or false, no matter how it comes out, is less than $200. The actual incurred cost can be as high as $1,000.

DR. HOWELL: Dr. Rinaldo has had a comment.

MS. JOHNSON: Dr. Howell, can I just follow up on that and clarify what I said about Medicaid before? Do you mind?

DR. HOWELL: No, if you're brief.

MS. JOHNSON: Brief. I was talking about treatment. I do believe there is an opportunity for there to be a federal law which requires Medicaid agencies to pay cost-based reimbursement for the test.

MR. BENDER: One thing that did help is the ability to do the DNA. For instance, the sickle cell disease, we don't have to do those confirmatory tests that we were having to do so much of. Our number is a lot smaller than Dr. Pass', of course, but the nine tests that we do DNA on save us a tremendous amount of time.

DR. HOWELL: Piero?

DR. RINALDO: Ken, can you tell us a little more about how exactly you came up with those estimates? Clearly, when you talk about a load of 1,200, I believe you mentioned, additional cases that need evaluation, what rationale did you use? How did you define the number? Do you have figures? Were you just extrapolating the rate of false positives for MCAD, or were you doing it based on some other set of numbers?

The other question I have for you is if the limiting factor is the demand of specialists scarce, have you considered the possibility to perhaps do something similar to what Minnesota has done? That is, try to have an accelerated confirmatory testing before the specialists get involved, so that the specialists only see the ones that really need to be seen.

DR. PASS: Well, I hope you noticed my smile for your first question, because most of those numbers were worked up on the data that you gave me, with some references to the literature.

DR. RINALDO: Okay. But what rate of false positive did you pick, then?

DR. PASS: The highest. Five.

DR. RINALDO: Five? Point 5?

DR. PASS: Yes.

DR. RINALDO: Do you realize that the number, instead of being 1,200, could be 200 a year if performance were at the highest possible level, but an achievable level?

DR. PASS: Yes. I would certainly concede if you were in our laboratory, that would be the number. We don't have our expertise, we don't have your background, and until two years ago we couldn't even get that expertise in the City of Albany. So we tend to be very conservative in our screening program, and I would much rather generate the false positives than to have a false negative.

DR. VAN DYCK: When you say being conservative, you mean setting your cut points conservatively?

DR. RINALDO: No, setting a very high rate of false positives.

DR. VAN DYCK: But it's setting the cut point higher.

DR. PASS: The rate is a result of our cut point. We don't target a certain false positive rate. We don't even calculate it.

DR. RINALDO: You know, these are self-inflicted wounds to some extent.

(Laughter.)

DR. RINALDO: It can be done better, and it should be your goal to do it better, because that will have significant consequences downstream, especially at the financial level. That also goes with what you were saying about I don't believe, at least in the figures I gave you -- and remember, I wasn't going higher than .3, because I think if you go higher than .3 false positive rate, something is wrong. But besides that, no workup costs $1,000. They cost less.

DR. PASS: That was the number given to me. We haven't priced it out. I can only report what I heard.

DR. RINALDO: I know, but do you see? The point I'm making here is that we are sort of working with a potential picture of doom when in reality things might not be that bad. It could be much better, actually.

DR. HOWELL: I think the point has been made that there's a great virtue to try to reduce the number of patients requiring specialty workup by having a second-tier testing in some of the cases. You mentioned that. Apparently you're doing a second tier in nine of your --

MR. BENDER: That's done as soon as the positive is found. They do the DNA right away.

DR. HOWELL: That's what I mean, but at the same time. In other words, if you have a screen positive, you have a secondary level that will help reduce that.

MR. BENDER: That's done in the private lab.

DR. HOWELL: Yes. I'm sure everybody did the same number I have, but the interesting thing is that in your numbers, you had 1 in 365 patients in the State of Mississippi that had a confirmed positive diagnosis, which is a very interesting figure. The other thing that's remarkable is that you had an incidence of galactosemia of 1 in 4,700, which is dramatically different than the population.

MR. BENDER: And it's been that way for many years.

DR. HOWELL: That's because you've got a large African American population that has a high incidence of galactosemia.

There's great anxiety, so why don't we start with Bill since he's nearer? He may hit me. Then we'll go to you, Derek.

DR. BECKER: Rodney, I would never hit you.

Two comments. Actually, a comment and a question.

First, the burden to the laboratory and the burden to the program might not be as great as is otherwise predicted, and I can use my own state's anxiety in considering the expansion of our program from a few years ago. Much like another state that just described it, we took a phased-in approach. MCAD clearly was driving the process, and it was very easy for us to move amino acids over because of the applicability with the instrument. But it was much less clear to our advisory committee, again three or four years ago, what the total burden to our program would be by a full expansion.

So what we opted to do, our mandated list went from 5 to 7 to 12 very quickly, using MS/MS. Then we offered a supplemental panel which, as Brad has already mentioned, several states

are doing at this particular point in time, and there are pros and cons to that. But I think in the final analysis, our advisory committee was reluctant to do the massive expansion for some of the reasons that have already been discussed or mentioned, and after close to a two-year period of time, first of all nearly 96 percent of parents were opting in for the supplemental testing, and the burden to the system from the follow-up care perspective, the burden to the specialist was not as great as what might have been anticipated.

Now, that doesn't mean that we didn't go through some refinements. Something that Piero and I are very interested in, that early on our false positive rate was probably a little bit too high because we were conservative with our initial cut points. But we modified it. We learned as we went along. We learned from our colleagues in other states who already had expanded testing, and I think we were able to convince ourselves that the burden was not as great as the doom and gloomers.

I think now there's an opportunity for all of the rest of the states who don't have maybe the full panel to learn from those experiences, and particularly in the regional collaboratives, so that we can help perhaps lessen the anxiety and perhaps implement a screening process that doesn't have false positive rates that I think we would all consider unacceptable.

I'll make another comment from a clinical colleague of mine, and I think some of us around the table have already heard this. I'm not sure that the argument that there's going to be a burden certainly in the cases is all that valid, because you can choose to see the patients presymptomatically, or you can choose to see the patients symptomatically. I think most people, you're going to end up seeing those cases.

Now, it makes more sense to me to see them before they express their disease and you have to deal with some metabolic crisis than it ever would be. That's not a reason not to screen for a particular disorder.

The question that I have is more towards Kay and Dan. Our hospital association -- well, first of all, let me state that our fee in Ohio is like, Dan, yours, a slightly greater percentage to the program side. A portion of that goes to our regional genetic centers, our regional sickle cell project, a very successful program. We even can pay for selected items of formula, although that's a little bit dicey for us. PKU formula, we've got over 450 kids for life getting their PKU formula, but I can't get that for all the disorders.

More and more, when we go back to our advisory group and our legislative group that oversees the fee increase, our hospital association comes to us and says we have no problem justifying a fee increase when you're doing more testing. It's the cost of doing more business. It makes perfect sense to us. We're getting value there. But our point of departure from the hospital association perspective is when you're asking hospitals to up-front the cost for follow-up that largely they don't do, knowing that Medicaid does not reimburse or reimburses at 27 percent for the entire birth DRG.

They take great issue with that, and our hospital association is a reasonably powerful lobby. While we involved them early on, similar to what you described, they still testified in opposition to our most recent fee increase. Fortunately, our administrative body took that information and said, no, we think it's more important for us to expand, we need to increase the fee. But there's going to come a point in time when the hospitals are going to say enough is enough, and I would really like to know your thoughts on how we can address this.

Are there other models that we can perhaps look at that would help the hospitals, or is there a way for us to get better reimbursement from Medicaid in order to achieve our goals?

MR. BENDER: The difference is our hospitals do not have the specialists. The specialists only lie at the university medical center. We don't have any private physicians at that level. That's the difference.

MS. JOHNSON: That's the difference, but that may not be the whole answer to your question. It gets back to my point about the whole country thinking about what we pay for health care and the resistance to increasing health care costs, and increasingly over the past 10 to 15 years the whole issue of cost shifting as a mindset of saying, well, I'm paying my part, but this all costs too much and, therefore, I'm not paying your part, whether it's private insurance not willing to be paid the freight for Medicaid and so on.

I want to come back again on this point. It's not been evenly implemented in the United States, but we do have a federal law which requires Medicaid agencies to provide cost-based reimbursement for community health centers, for community and migrant health centers. It seems to me that whether it's at a federal level or at a state level, there is reason to have a dialogue with Medicaid about, at a minimum, the cost-based reimbursement around the testing, but then perhaps a larger portion of that.

If the follow-up is being provided in local health departments, I would encourage you to think about a Medicaid billing strategy for those local health departments, because it certainly is a part of the EPSDT program as a billable service.

MR. BENDER: It is. Thanks.

DR. HOWELL: Derek?

MR. ROBERTSON: Just a question. In New York, with the HIV testing, if you do find a positive child and the mother has not previously been tested, does the newborn screening program inform the mother or is that passed off to somebody else?

DR. PASS: That's no longer a possibility. Two or maybe three years ago, a law was passed in New York that the mother's HIV status must be known before she's discharged from the hospital, coincident with the test that allowed us to have testing. So it gets to be a tricky issue. You cannot ask a mother her HIV status. You can ask her if she knows her HIV status, and they're recorded. If she doesn't know her HIV status, then the test will be performed in the hospital before she's discharged. The whole intent there is to institute the perinatal care for the baby, not just the postnatal care.

MR. ROBERTSON: Another question for Kay. What was intriguing to me was seeing that they were not using tax dollars. That's a really compelling argument to make. Could you expand on that a little bit?

MS. JOHNSON: Well, by and large, and Medicaid being the exception and assuming Medicaid isn't paying very much, and it isn't paying its share, you have a situation where these dollars are coming from fees, which by and large are being paid by the person who pays for the birth. The majority of the births are still paid by private insurance or self-paid by the family, or they're uncompensated care at the hospital. So it's either coming out of the hospital's pocket, the private insurance pocket, the family's pocket, or in some cases a portion of it is coming out of the Medicaid pool. Then you have the residual dollars, Title V and others, wrapping around, but more around the public health function than the testing.

Now, that's not true in the five states and D.C. where they don't use fees, because in those states they are using public health dollars. But if you look at 45 states and the distribution of those dollars, and you see that two-thirds of the money is coming from fees, that is by and large private sector

money being managed and financing a public health program, but it's not that you're asking the taxpayer to pay for that. Does that help?

MR. ROBERTSON: Yes.

DR. HOWELL: Any more questions or comments for this distinguished group here?

(No response.)

DR. HOWELL: Thank you very much.

Since we are running a little early, I'm going to ask Michele, who has not had any warning that I'm going to ask her, one of the things that's been discussed several times today that I think will have potentially a very valuable role in newborn screening are the recently funded HRSA cooperative agreements, the regional cooperatives and so forth. I think it would be great for either you or Peter, or the both of you, to tell the group -- some of us are aware of what those are and some of the regionalization that's going forth.

DR. LLOYD-PURYEAR: Not everybody has received a notice of grant award, so I can't be entirely specific, but we have funded seven regional collaboratives. We divided the country up into regions based on birth rate, and also funded one cooperative agreement to help coordinate with us those regional collaboratives. The American College of Medical Genetics received the funding for the coordination as the national center. The seven regions are in the northwest, mountain states, Great Lakes, the Great Plains area. We included Texas in the mountain states because of similarities in border issues. The southeast, the northeast, and the mid-Atlantic and New York area.

The reason why we began that initiative is to address a lot of what has been talked about today and in the June meeting, to address the maldistribution of genetics and newborn screening metabolic expertise in the states, to try to approach that on a regional basis, and also to bring that expertise not only to the newborn screening programs but also to the community providers through special education programs to address the needs of the parents in those areas, with a background that if you're asking states to expand, then you need to have some mechanism to expand that expertise, and this was to address that immediately.

Several of the applications have put forth some remarkable proposals -- Piero has alluded to some of it -- to address some of the specific needs either in their newborn screening programs across states or specific genetics expertise capacity issues across those states. So they're interesting projects. Maybe next time we can present them.

DR. HOWELL: When are they scheduled to begin?

DR. LLOYD-PURYEAR: They're scheduled to begin October 1st -- September 31st, actually.

DR. HOWELL: Next week.

DR. LLOYD-PURYEAR: Next week, yes.

DR. HOWELL: I wonder, are there any comments or questions about the material that we've discussed today that you would like to come back and have a comment on at this time?

(No response.)

DR. HOWELL: It's a lovely, sunny day. Everybody has noticed that and so forth. Apparently there are no questions about anything.

George has a question.

DR. CUNNINGHAM: I'd just like to make a brief statement about financing of newborn screening. Kay Johnson has given a broad overview of the many and varied ways in which newborn screening is funded at the state level, and the committee has to deal with the many interrelated and interlocked aspects of newborn screening as illustrated by the issue of funding. There are political, ethical and pragmatic considerations.

One first has to take a position on whether newborn screening is a public health program resulting in net benefits to the community at large and entitled to public resources as the responsibility of government to its citizens, or whether newborn screening benefits should be made available to those who can afford to pay via any willing private provider. That is, is newborn screening mainly an issue of personal responsibility.

The consensus of the earlier American Academy of Pediatrics study and the American College of Medical Genetics report which you heard this morning is that it is a public health benefit and deserves to be supported by public funds. There are, in fact, several states that work their programs from general tax funds, make no charges to patients. As you heard, though, most states support their programs with fees. The programs using state-collected fees include the fact that there were two previous studies of fees, one by the General Accounting Office that was requested by Don Devine, and another one was made by the March of Dimes with an accounting firm.

But the GAO study found that the fee covered on average only 64 percent of the true costs of the program. Fees are established in a political context. The legislature can see the newborn screening fee as a way to supplement general revenues. Fees in these states are deposited in the general treasury, and the newborn screening program competes with other state needs for their support. Some states, like California, put the fee in a special fund, restricting their use to the supported genetic or newborn screening, and our statute requires us to set the fee to support the entire program. This latter design forces the true costs of the total program to be included in the fee.

One of the objectives of the committee is to address the ethical issue of ensuring that a minimum uniform level of protection is extended to newborns irrespective of the state of birth, and to make recommendations to the Secretary on how the federal government can best meet this objective. However, the use of federal authority imposes, in all fairness, a responsibility as well; namely, to work with the states to ensure that the resources will be made available to meet the minimum standards for content and operation being proposed.

I would urge the committee not to be content with the vagaries of the many discordant and sometimes dysfunctional means currently used by states to fund newborn screening as a reliable base to build a proposed high-quality, equitably distributed, national newborn screening system envisioned. I would like to suggest to the committee and to the Secretary to give serious consideration to regarding this universal program as -- and I dare use the disdained and despised "E" word -- an entitlement. Instead of small sums to provide marginal and unsustained support to states, I suggest an effective, consistent, systematic approach.

I had the pleasure in 1999 to work with Dr. Carol Green, who is in the audience, who was the government fellow for the American Society of Human Genetics and worked with Senator Edward Kennedy's office to develop S. 1981. This legislation would have created a federal/state partnership to share the burden of developing and maintaining newborn screening services modeled on the existing Title V child health program. Newborn screening is a three-legged stool, with state

governments, federal government, and private sector all having to provide support. That support today is very unequal.

The GAO study of newborn screening financing indicated that in 2001, $120 million was spent to screen the nation's 4 million newborns, or about $30 on average. While it's difficult to separate out federal maternal and child health and Medicaid funds, the best estimate is that only $18 million, or 15 percent, is provided by federal taxpayers. That's only $4.50 per birth. California's program, which screens 540,000 newborns annually, will in fiscal '04-'05, in order to meet the American College of Medical Genetics' proposed standards for coverage and operational effectiveness, spend over $42 million, or $78 per birth.

The federal government has just awarded California $13 million to preserve and protect the native salmon, to which the state has added $8 million. Now, I know salmon is a beautiful athletic animal, and that newborns are unsightly, homely, and uncoordinated. And I know that salmon have great commercial value, whereas there's no market for newborns. But I can't help observing that somebody somewhere has a very distorted sense of priorities.

While I strongly support the conservation efforts on behalf of the salmon, I also feel a wealthy nation such as ours could do better by our newborns.

(Applause.)

DR. HOWELL: Thank you very much, George.

Are there other comments?

(No response.)

DR. HOWELL: I think that if we have no other comments, we will adjourn. We've got a busy day tomorrow. We've got a lot of material to present, and we've got a distinguished group of people providing public comments.

So we'll see you back at 8:30 a.m. on the button. Thank you very much for your attention.

(Whereupon, at 4:27 p.m., the meeting was recessed, to reconvene at 8:30 a.m. on Thursday, September 23, 2004.)

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

Second Meeting
Thursday, September 23, 2004
Burlington Rooms A/B
Jurys Washington Hotel
1500 New Hampshire 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 (8:37 a.m.)

DR. HOWELL: Ladies and gentlemen, let me welcome you to the second day of the meeting of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. We've got a busy, exciting day with a lot of presentations. We are, as usual, looking forward to the public comments in the afternoon. There is a new list of persons scheduled to comment. There are 13 this afternoon.

We are going to start off this morning with a review of a report that we have often discussed. We're delighted to have Dr. Judy Wagner from the Institute of Medicine to present that report.

DR. WAGNER: Yes. Is --

DR. LLOYD-PURYEAR: Julie's on the phone.

DR. WAGNER: Can you hear, Julie?

MS. OSTROWSKY: Mostly. Not the voices further away.

DR. WAGNER: Can you hear me now?

MS. OSTROWSKY: Yes. That sounds better.

DR. HOWELL: Can we announce who is on the telephone?

DR. WAGNER: Yes, I will do that.

DR. HOWELL: Thank you.

DR. WAGNER: Okay. Am I on now?

DR. HOWELL: You are on.

DR. WAGNER: Well, thank you for inviting me and Julie. This presentation is joint between me and Julie Ostrowsky, who is actually the brains behind the chapter on Newborn Screening. Julie's background is in medical genetics. I'm an economist who knows the verbs and adjectives, and how to put things together. I spent much of my time trying to learn to pronounce these inborn errors of metabolism, or even to pronounce inborn errors of metabolism.

We are now 18 years out from the publication of the report, and neither Julie nor I have been active in the field since then very much. So actually I think Julie especially with her science background has been most interested in going back. I will be talking for much of this presentation, and then Julie will pick up in the last part for some of the extensions and questions.

I do have handouts, which in the interest of time, I'll leave with the group. It was a surprise for us to be contacted on this. As I said, this is a report that is 18 years old now. In trying to find excuses for why our study had the limitations that it did, I'm not even sure we had PCs at the time. I know we didn't have Excel or Lotus loaded on those PCs. I think we had just transferred from Wang word processing, and we had no access at OTA to any kind of mainframes or modeling software.

Much of what we did we thought was pretty cool with paper and pen. I think that is a good metaphor for what has happened in newborn screening as well from the little reading we've done as

we awoke. But at any rate, Julie and my biographical sketches are in your background material, so I won't sing our praises. I'm semi-retired, so you can forgive my difficulty in pronouncing the new diseases.

So now to the first slide. Let me get this under control. OTA's Newborn Screening Study, as I began to say, the analysis was conducted in 1986 and 1987. It was first published in February, 1988, and it was simply a chapter in a larger study that had been commissioned by the House Energy and Commerce Committee called "Healthy Children: Investing in the Future."

That report was a response to the Congressional Committee's request, which was tell us what preventive measures, really new measures are cost-effective for infants and children. They were especially interested in asking, what can we mandate through Medicaid? Or what can we foster through maternal and child health programs? So they were looking for new initiatives.

We studied early prenatal care, newborn screening, well child care, accidental injuries, and child maltreatment all as chapters in that report. I think one of the down sides of a report that has a lot of separate analytic issues is that one of the areas that I think was most important was efforts to prevent child maltreatment. It didn't get the kind of visibility that I think it should have then, and almost 20 years later, certainly should today. That is for another group.

Now, our findings on newborn screening boiled down to just a few. I'll go over them very briefly. The first one was that the USA and Canada, at that time, we're not up to date now, were the only developed countries without a national screening program. Secondly, the lack of a coordinated network of newborn screening services in some areas were possibly reducing the overall effectiveness of newborn screening.

Third, which gets to the cost- effectiveness/cost-benefit question, expanding newborn screening strategies to include additional diseases. We looked at -- I'm blanking. I am having a big birthday coming up in a month. You know what HC means, galactosemia, and maple syrup urine disease, which I worked on this morning, saying it. But I forgot HC. So you know what it is. Julie certainly does. Beyond PKU and congenital hypothyroidism.

PARTICIPANT: It's homocystinuria.

DR. WAGNER: Yes, thank you. Yes, of course, that important one, homocystinuria. Thank you. Or to take a second specimen would save more newborns from death and disability. But the incremental cost per case found would be high.

So that is where we ended. Of course actually now, having our dinosaur bones surface again, looking at it recently, Julie and I concluded and agreed first of all, cost-effectiveness analyses are maps, and maps are not the territory. So they are useful, but they are never the absolute reality. They never represent absolute reality.

The major limitation of our study even then was that we used a very limited outcome measure. We did not go to what would be the standard of care today, which would be to look at, at the very least, a year of healthy life lost, and more ideally, some kind of quality-adjusted life year measure.

We stayed with cases detected per 100,000 infants screened. It is obvious from anybody's analysis, including our own, the implications of detecting cases in the various diseases we looked at are quite heterogeneous. So that is one major limitation that today we certainly would have dealt with differently.

But I must say that the QALY measures, especially the weights for various outcomes associated with these conditions, still leave one with a sense of unease. In my view, and this is my

personal view, the methods for eliciting preferences about various outcomes of severe mental retardation, you know, well, they may never be settled. But certainly there is a certain amount of uncertainty about how the community behind a veil of ignorance, which is what we have to deal with here in investments and screening when nobody knows whether or not the QALYs that I have seen applied to newborn screening really are the best.

In any case, we didn't even go there. As a result, I think our interpretation was faulty. Remember our result was doing more, doing a second screen under various circumstances could add, find more cases, but the cost would be high. I think if we had taken a QALY approach, or even a life years approach, the cost probably would not have been as high per unit of effectiveness as we concluded from the cases.

I think that was due to our naivety, to be perfectly honest. So today I think we would come out with a very different result. Even given the cost, effects, and technologies available at that time.

The third limitation was at the time the standard for discounting future costs of treating affected babies throughout their lifetime, there was a 7 percent annual discount rate. That is what OMB was using at the time. Since then, the field of cost-effectiveness analysis has evolved. The current CEA standard, as a result of a panel on cost-effectiveness, is 3 percent. That would undoubtedly have -- well, it is unclear what effect that would have had. But it is likely to have -- well, I can't really predict. It could have worked both to reduce the cost of treating a particular condition found, but it also would reduce the cost of the sequela. But at any rate, certainly these results don't transfer.

Of course the data were limited at the time on the outcomes of the diseases, and of the screening and treatment programs per se. So today, we do a better job because there would be more evidence out there. Finally, as you all know so well, the screening technologies we looked at are old.

So really the OTA analysis has to be looked at in a historical context, perhaps paving the way for thinking about screening in the context of benefits and costs. So I'd like to turn, rather than spend much more time on the OTA report and its conclusions, which are clearly out of date, I'd like to use the OTA and some more recent studies just to illustrate an important point or two. That is that the cost effectiveness of an intervention that you find depends to a great extent on how you structure the range of alternative event interventions.

So what do we mean by an intervention? First, one point that I think is very important is that an intervention isn't simply whether one tests for a specific disease or not. It has to do with the entire organization, even down to the minutia in cases of the specific screening intervention. The number of samples, the timing of those samples relative to birth, and the locations of sample collections OTA found were a major source of cost, especially the location and number of samples. Sampling and collection costs were a major part of the total cost of a program.

Also of course what diseases would be tested for at those various points, and what screening technologies would be used. And around that, how those screening technologies would be organized, especially when there are fixed capital costs associated with acquiring capacity.

Laboratory procedures which might improve sensitivity and specificity are very important. What confirmatory procedures are used, and of course what follow up and treatment regimens are assumed. These are all really parts of the decision about what you are going to test in a cost-effectiveness analysis. So how those interventions are defined are important.

Perhaps even more important, not only what is compared with what, but how these things are compared with a baseline program, which is considered the status quo. Those influence both the findings, usefulness, and analysis. I'm going to say a little bit more about that in the context of the OTA study.

Now, in our study, we looked at this kind of a framework, which was we found that a one-specimen regime for PKU and congenital hypothyroidism at the hospital was universal at the time, in 1986 or 1987, across the states. So we chose that as the baseline. If we had said, well, what is the value of PKU plus CH with one specimen versus doing nothing, we actually would have found that newborn screening was not only cost-effective, but cost-saving. That is, if you look at all the averted health care supportive costs of the diseases themselves, that you could save costs by the baseline.

We didn't look at that. What we looked at was let's assume that is the status quo. What are the implications of all these follow on, or all of these expanded alternatives involving second specimens, or additional tests on the first specimen, or combinations of additional tests on the first specimen and the second specimen.

I have to say all these strategies were devised largely as a result of Julie's research on what were the current questions in the field.

So these were our numbers. That is the net cost compared with the baseline. The net resource cost in millions of dollars for each 100,000 newborns screened. The extra cases found compared to the baseline, and then the cost per extra case found. These numbers themselves are irrelevant today, as I have indicated, but for each one of these strategies, that is what we found. These were all compared with the baseline, so they all were cost-raising technologies, or strategies. They all led to additional cases.

Now, this is how the conclusions would map in what is called a cost-effectiveness frontier mapping. On the X axis is the cost per 100,000 newborns measured, and on the Y axis, the ost per case found in 100,000 newborns. This really says it all. It shows that there are really two truly superior strategies. They are said to dominate all the other strategies.

There is Strategy 6 and 7 in this case, and they rely on what is called the cost-effectiveness frontier. Strategy 6 offers the highest gain in cases per extra cost, and the incremental cost of finding even more cases by switching to Strategy 7 is higher. This is the important point. Barring any kind of fixed aggregate budget constraint, it would make no sense to invest in any of the other strategies, say Strategy 4, for example, when the returns in cases found, if that is the measure you accept, are so much greater for Strategy 7.

Even though it costs a great deal more to reach Strategy 7, from a resource allocation standpoint, all those other strategies are clearly inferior. Between 6 and 7, you have a clear tradeoff. That is to get more benefit, you have to pay more per unit of effectiveness. The other strategies are not good buys.

Remember that Strategy 6 was one specimen expansion, to include the extra tests of homocystinuria, maple syrup urine disease, and the third, which escapes me. Strategy 7 was a no holds barred strategy, which said not only do those -- oh, galactosemia and maple syrup urine disease. I'm sorry. Then 7 was the second specimen, which included PKU, congenital hypothyroidism, and homocystinuria on all infants. I'm not advocating those today, but that is how you would interpret this.

Now, to make the point about the importance of baseline and what you choose to compare. In fact there really weren't seven alternatives, well, there were seven alternatives, but in fact there were really three mutually exclusive alternatives. That is at the first level, you couldn't do a second specimen on PKU and congenital hypothyroidism for early discharge patients, and at the same time, do a second specimen on only CH for all infants.

So these were in essence three different strategies that you wouldn't do at the same time. But if we had taken the first column and said, we are only going to compare to baseline Strategies 3, 2, and 5, if we had not even defined any of the additional strategies, we would have had a cost-

effectiveness frontier that would have found Strategy 3, which was the second specimen added to the PKU, plus congenital hypothyroidism on the first specimen, only for early discharge patients -- I think I've got my numbers wrong. I'll doublecheck .

At any rate, it doesn't really matter. The point is that we would have come out with a different set of preferred alternatives. We would have been recommending something that really was truly inferior, because we hadn't considered other unmeasured alternatives.

Now I want to talk about how this relates to two studies that I looked at very briefly with admitted ignorance. The study published in 2002 based on the Wisconsin program, in which the researchers looked at the cost-effectiveness of tandem mass spectrometry screening for MCAD. I won't even try to pronounce MCAD.

The baseline that the Wisconsin people chose was no screening for MCAD, and no tie-in with using tandem mass spectrometry for PKU screening, or any other kind of screening. They found that there was a positive benefit in terms of cases and years of life lived, but they also found that it would lead to additional costs. That is, it was probably cost-effective in terms of the number of years, the cost per year of life gained. But it certainly was not cost-saving to choose tandem mass spectrometry for MCAD.

Contrast that with the recent Health Technology Assessment put out by the National Health Service in Britain, their baseline started with the existing PKU only screening system. Essentially their first level of comparison was to change the nature of that screening, to change the technology to mass spectrometry, and add to that one specimen test, MCAD.

That move from the baseline to the first level was cost-saving. Then the incremental move to additional tests, which basically piggybacked on, were not cost- saving, but had cost per added year of life that appeared to be relative to common benchmarks that we use today, and appeared to be relatively good buys for society.

So one turns out to show that MCAD testing by tandem mass spectrometry, the previous study, showed that it was not cost-saving, and this study shows that it is cost-saving. The critical difference was the choice of the baseline, and how these alternatives were aligned.

So now I'm going to turn to Julie. I hope you have heard what I have said, Julie.

MS. OSTROWSKY: Yes.

DR. WAGNER: You were able to hear. She is going to make some final remarks about what the impact of what is going on today might have on cost-effectiveness analysis.

MS. OSTROWSKY: Let me just say first of all, I'm sorry I can't be there in person. This would have been great for me to sit and listen to the discussion yesterday and the rest of today. But given that I have a really bad cold, I think you all lucked out. It is great that I'm not there physically.

Anyway, I'd just like to pick up on a few of Judy's points that link to the current situation. These were things that really jumped out at me as I looked into a quick review of the current literature, just to see what we could possibly link here with the decisionmaking framework of cost-effectiveness analysis, and the current reality of screening, which obviously has changed, from my point of view, quite dramatically since the last time I really poked my nose into this.

If we were designing a cost-effectiveness framework for newborn screening now, there are clearly from what Judy said in looking at those other studies, lots of different ways of structuring it,

depending on what your questions are. One of the things that really popped out at me at first was the issue of the private sector labs, which was always an issue with newborn screening, but now it seems to be a bigger issue, and has taken on quite a complexity.

One of the things I would note here is that the OTA analysis looked at, in a global sense, cost and savings to the health care sector. There are different ways of looking at this. There is a cost-benefit analysis out of California that looked just at the ins and outs of costs to the Kaiser Permanente system, the HMO. You can ask a question about the whole value of doing screening a certain way and consider it globally, or you can look at a specific contained system, or just the state.

So one of the things that would pop up right away would be what effect does the private sector lab have on the cost? One thing, since there is such a huge capital investment involved in the new screening technology there, there would obviously be a cost-savings to the state if it were the figure we're looking at, not having to pay for the specialized training of the personnel. But then on the other hand, I gather that the fees that are collected for screening at the moment are really a huge source of income.

The possible loss of that would make a big difference as far as the costs incurred, and the costs avoided, if you're looking at the state.

One of the other issues here obviously is the equity issue of offering a supplemental test panel for an additional fee to those who can pay for it. So I think that if equity is considered to be a high value, you can structure a cost-effectiveness analysis to come up with an estimate of the costs that would achieve that in screening. That can be built into it.

As far as the private sector labs overall, you can look at it in different ways. There can be a constructive effect of having somebody else out there with more flexibility, and possibly more ability to incorporate innovation to bring screening along. This is also competing with public sector funds for screening.

So I just wanted to point that out as something that would be an additional complexity that we'd have to face now for doing cost-effectiveness analysis.

On the next slide, one of the other things that struck me here was with the tandem MS technology, you are all of a sudden dealing with a much wider range of screening outcomes than was the case when you were looking clearly at the PKU and similar disorders. So right away you've got at least four different categories of outcomes that you may be considering.

The first being effective treatment to put that neonatal mortality and severe mental disability as in PKU and other other legacy diseases. There is a bigger category there apparently with treatment being available, but the long-term effectiveness of that treatment has a lot of uncertainties. The outcome being uncertain. That goes with a whole bunch of diseases that are in that long list, that create the 30 or more tests that we're talking about here. Though what may be included in that is disorders that you would test for in order to provide genetic counseling services, family planning advice, that sort of thing. Then there could even be just purely research functions of that.

I think that the cost-effectiveness framework could incorporate multiple outcome measures like this, depending on what tests you're looking at. The larger issue here is what criteria. Of course this links into what I'm sure you were discussing yesterday, criteria that should be applied to screening tests, given that this technology can deliver results on so many disorders at minimal extra cost. We probably wouldn't be looking at the kind of framework we set up in the OTA analysis where you'd look at the incremental cost of adding additional tests onto a single specimen, as long as they were done within that system.

Just finally on the last slide there, I just wanted to point out that to my surprise in looking at this, we used to be talking about two to six disorders, and now the range is three to over 30. This wide disparity among the states in test availability is really quite a striking issue. It brings up all the same issues that have always been discussed in newborn screening about the impact of the screening organization, whether it is state by state, or states included in regional systems, whether you are centralizing that within that structure in public, or public and private together.

There really is a greater urgency here for looking at outcomes and effectiveness, whether or not it is really part of the process to develop minimum standards or core services to all newborns. Some of the other issues I would just mention here are of no surprise to anybody.

If you are looking at the effects of reducing the disparities between states in testing, you could structure this in the analysis to make a very clear statement about the fewer number of missed cases that would be a result of such a system. You could look at the cost- savings and the benefit of having that.

Another issue is the role of federal involvement here, as was seen with the sickle cell disease screening. The federal involvement, through direct partnership with the state, can be very effective in promoting the greater access to screening tests. So you would have a role here for the financing and guiding implementation of those goals that could make a big difference. You can look at that in this kind of structure as well.

But this is just a quick overview on the kinds of things that we were thinking about in looking at the relevancy of our OTA analysis from so long ago, how we would apply that to the situation now. The devil's always in the details. So I didn't want to lose track of the overview issue that Judy was talking about, but there is also these current points, which I think would really loom quite large if you were designing a cost-effectiveness analysis that would take into account the kind of comprehensive look at the different strategies, and what that meant for the groups that were doing the screening.

DR. HOWELL: Thank you very much, Dr. Wagner and Ms. Ostrowsky. I hope, Ms. Ostrowsky, you can stay on the phone. What I would suggest is that we have two other presentations about cost-effectiveness, and I think it would be appropriate to discuss all of them at one time. Thank you very much.

But if we could now go to Dr. Stephen Downs from the University of Indiana School of Medicine, who will present on the cost-effectiveness analysis of newborn screening.

Dr. Downs?

DR. DOWNS: Thank you. Thank you very much. This is a pleasure and an honor, and a lot of fun to be here. It is particularly nice to follow Dr. Wagner's comments, because some of what she has said will resonate in what I'm presenting.

This work was done in collaboration with one of my colleagues, Aaron Carroll, at Indiana University's Children's Health Services Research Program. I want to open with some acknowledgments, because as you'll see from this presentation, this work is evolving a little bit, largely due to the very thoughtful input from people who have been reviewing this work, such as Alex Kemper at the University of Michigan, Tracy Lieu at Harvard University, and Scott Grosse at the CDC.

I'm going to breeze through this quickly, because everyone knows these things who is here. Inborn errors in metabolism competed to be a significant cause of mortality and morbidity. New technologies have enhanced our ability to detect these conditions, particularly tandem mass spectrometry, which is one of the focuses of this presentation. But there are questions of cost-effectiveness for the reasons brought up.

That is that despite the fact that these technologies can reduce morbidity and mortality, these are rare conditions, and there is significant cost to screening and follow up.

Our objective was to look at a range of newborn screening tests, including tandem mass spectrometry, to determine the incremental costs and clinical effects. I want to emphasize that this is some preliminary work that was intended to kind of cross-check the findings of the American College's Panel Task Force.

We kind of did this on a shoestring budget. In spite of the fact that it is preliminary, I think there are some insights that we gain from it. I do have to say that Dr. Wagner, at the time that she did her work, was working with paper and Wang computers. The sad reality is I have a laptop in my hotel room here, and have made changes even since I've been to D.C.

Basically we are evaluating tradeoffs here. Our motivation was to understand the total costs and effects of the various screening tests, including the costs of testing, the costs of treatment, and disease-induced costs that we might reduce by screening and detecting conditions early, and to make the tradeoffs in screening explicit.

What I'm going to talk about here is first the initial analysis, the baseline analysis that we did that looked at costs and effects of individual screening tests. Now, this is of limited interest, because we aren't usually interested in looking at the costs of individual tests, as Dr. Wagner pointed out, compared to a baseline of no screening.

Our cost estimates for the actual costs of doing the tests are dubious. I'm going to come back to that in a moment. The second thing I want to talk about is a comparison of tandem mass spectrometry versus a panel of individual tests, which is closer to the question that I think this panel is trying to grapple with.

That is, given that we have the possibility of this new tandem mass spectrometry being used in all states or regions, what is the tradeoff of switching to that technology. Then finally, I'm going to briefly present what I call the pessimistic analysis. It is not quite what is referred to as a worst case analysis, but I would call it pessimistic because we removed several potential biases that had been pointed out by our reviewers.

So we did this analysis using decision trees, which is just one formalism for doing cost-effectiveness analysis. This is just to make sure, and many of you have seen this, but I just want to make sure that you understand what we are doing here.

This is a simplified generic version of a decision tree. We make a choice here at this blue node between screening or not screening. If we screen, disease may be present in an individual child, and the probability that it corresponds to the prevalence of the condition, otherwise, the disease is absent. The same is true if we don't screen.

The screening tests may be positive. That probability corresponds to the sensitivity of the test. If the disease is absent, the screen will be negative with the probability that corresponds to the specificity of the test. So these represent true positives, false negatives, false positives, and true negatives. Of course, we can categorize each of those outcomes as disease detected early and treated, disease missed, I said disease untreated, it would be a late treatment. This case would be a false positive, which would require an evaluation of a positive test that would lead to no detection of disease. Then finally, disease untreated, certainly the most common thing.

Each of these pathways can be associated with a cost and effect. If we multiply the probability of following one of these paths times the cost or the effect, and we add up across all the things that can happen, you end up with an average cost for a screening test, and an average effect for the screening test. We can compare that to the average cost and the average effect of not screening, and the differences between those two lead to the cost-effectiveness ratio.

These were the screening tests that we looked at. There are eight of them. Phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, biotinidase deficiency, maple syrup urine disease, galactosemia, homocystinuria, and tandem mass spectrometry to look at MCAD, PKU, biotinidase, and homocystinuria to use the multiplexing capability of tandem mass spectrometry.

This is what the decision tree we built looks like. I am only showing a few of the branches, because there is absolutely no way to fit the entire tree on a slide. At least in a way that would look like anything more than kind of an interference pattern on the screen.

But the first branch shows all of the different testing tests that can be done, including tandem mass spectrometry as a panel. Each one of these is followed by the list of conditions that may be present, including no disease being present. Then for each one of these, we have a set of outcomes which relate to what the disease condition is.

So there is a probability associated with each of the outcomes, and then there is a value, both in terms of cost, and in terms of quality-adjusted life years attached to each of these potential outcomes.

This is the way we modeled the probability of each of the outcomes. We took the baseline probability of the outcome taken from the literature, and we derived an efficacy and a sensitivity. The efficacy of early detection and treatment in terms of reducing that, the probability of the outcome, and the sensitivity of the tests in terms of detecting that outcome in the newborn period.

The values of the outcome were done in terms of costs. We did do a quality-adjusted life expectancy model, as Dr. Wagner mentioned. We used a multiattribute model for doing that, as it is termed, in which we looked at the life expectancy associated with each of these outcomes, and we multiplied it times quality adjustments that relate to the quality of life associated with those different outcomes. We can talk about that in more detail later.

These were the variables that we needed to obtain by the literature review. Prevalence of disease, sensitivity and specificity of the tests, the costs of testing, the costs of treatment, disease outcomes, costs of disease outcomes, and the values associated with disease outcomes.

We took what is referred to as the societal perspective, meaning that we tried to look at all of the costs involved. This is not the sort of thing you can do on a shoestring, but we did the best we could. We did use the current standard, at least in the U.S. of 3 percent discount rate.

These are just some of the sources that we used. I'm going to go through this fairly briefly today. To look at the prevalence of conditions, we looked at the National Newborn Screening Report from the National Newborn Screening and Genetics Resource Center, the Newborn Screening Fact Sheet from the AAP. We also used another paper from the literature by Naylor and Chase.

Looking at sensitivity and specificity, again, we looked at the National Newborn Screening and Genetics Resource Center, and a couple of other papers there, Kwon. The baseline cost of testing we took from the PriceWaterhouseCoopers report that was sponsored by the March of Dimes.

Now, the methodology used there is a matter of significant contention, because it was done as a simple survey of newborn screening programs around the country. There were a variety of costs that different newborn screening programs reported within the cost numbers that they had. The numbers were simply divided up among the tests. So this doesn't tease out the fixed and incremental costs of adding tests that Dr. Wagner talked about.

Unfortunately, there isn't much else out there in the literature, and we didn't have the budget to do a

full microeconomic analysis of the costs. We did get some of the numbers from the prior CEA of tandem mass spec that Dr. Wagner mentioned.

The cost of treatment we derived from the OTA "Analysis of Strategies for Newborn Screening," the disease outcomes with and without early detection we took from the AAP's Newborn Screening Fact Sheet, and then a number of other papers that are briefly listed here.

The costs of disease outcomes, most of these we derived from the MMWR report on the costs of developmental delay, cerebral palsy, vision impairment, and hearing impairment. The baseline numbers we took included both direct and indirect costs. We did a sensitivity analysis on that, which I'll show you toward the end here.

We also looked at the previous cost-effectiveness analysis done by Karen, et al., and the study of end of life costs done by Angus in 2004.

The values of the disease outcomes, as Dr. Wagner pointed out, this is, well, the life expectancy data are relatively hard. Those come from CDC vital statistics, and a cohort study of the impact of developmental delays on life expectancy. The quality of life or utilities, we did take those from the literature. There is probably an unending debate on exactly how you quantify quality of life adjustments.

What we chose to use was actually a paper by Bennett, et al. that actually assessed parent preferences for these outcomes. It was done for a study of outcomes of occult bacteremia in infants, but the outcomes were essentially identical to the ones that we're talking about here, although that did not include blindness, which is one of the outcomes in our model and we obtained that from a paper by Sharma, et al.

This is a cost-effectiveness frontier. This is the direct output of our software. It may drive me nuts because the axis here are the opposite of what Dr. Wagner showed.

I'm not going to linger on this too long, except to say that in the top left corner, and I'll point to it here, this is a baseline of no screening. Again, as Dr. Wagner pointed out, this may not be the best baseline. But if we take that as a baseline, everything that falls down and to the right of this would be cost-saving relative to not testing. So in that sense, I think we are consistent with what Dr. Wagner had said, that if you started with a baseline of no testing, you probably could save money by doing newborn screening.

This is what is called a league table. It may not be a good idea to show the entire league table, because there is some confusion. It can induce some confusion. I'll explain what the columns are, and then point you to what I want you to pay attention to.

This is the list of tests, the strategies. This is the average cost per test per child screened. Now, that is not the cost of testing, it is the cost of everything, and it is an average cost. What we are really interested in is comparisons between different strategies.

This is the difference in cost between each test. We compared them all to the baseline of no testing, which is down here. This is the average effect in

quality-adjusted life years associated with each strategy. This is the incremental effect, and that is the difference between that strategy and no testing.

This is the average cost-effectiveness ratio, not really a particularly interesting number. The one I want you to pay attention to is the incremental cost-effectiveness. What we found is compared to not testing, and again, we'll come back to looking at alternative baselines in a moment, but what we found at baseline is that all of the screening tests saved money and improved quality-adjusted life expectancy over not testing, with the exception of galactosemia testing all by itself, or CAH testing all by itself.

I will comment that CAH testing at $20,000 per quality-adjusted life year saved would be considered reasonable by the sort of standard benchmarks that people use in health-related cost-effectiveness analyses.

We did run some sensitivity analysis on this baseline. We found that test characteristics were not sensitive within a reasonable range, meaning within the range of sensitivities and specificities reported in the literature. Disease prevalence was not sensitive to disease prevalence in the most sensitive cases within an order of magnitude, and that is a tenfold change in the prevalence of disease.

The probability of different sequela, we found that testing for congenital hypothyroidism was, if developmental delay occurred at half the rate that is reported in the literature, that would begin to cost more to screen for than not to screen for. Blindness in the case of homocystinuria, if that occurred at half the baseline, then there would be a cost associated with screening for that test.

Effectiveness of early detection and treatment was not sensitive to within less than half of the baseline numbers that we use for effectiveness. I'm giving very short summaries of what are actually tables and tables of numbers. The cost of tests, we did look at threshold values for costs of tests. It is probably not worth focusing too much on this, because I think that baseline cost numbers may not be particularly helpful.

I want to point out that the threshold numbers, what is shown here, is each of the tests taken in isolation from the other tests, that the column that shows baseline are the costs taken from the PriceWaterhouse report. The threshold on the right side is the cost above which there would be additional costs. How do I want to put this? The threshold represents the costs above which it costs more to screen than to not screen. So it is a pure economic consideration, regardless of the benefits of it. The costs to society, if the cost of the individual test was below that, then society as a whole would save money by screening, rather than not screening.

So we also wanted to look at a comparison. So what we did was we looked at the cost of doing tandem mass spectrometry, and at the benefits of doing tandem mass spectrometry as compared to a panel to look at the same set of conditions. So we're looking at MCAD, PKU, biotinidase, homocystinuria, and galactosemia.

Except of course without tandem mass spec, it is impossible to screen for MCAD. What we found, again, is that the panel was dominated, that is tandem mass spectrometry was less expensive and more effective than the comparable panel of tests. Now, I'm going to show you one other brief set of analyses that are based on some weaknesses in the data I have just shown you.

We had poor data on the incremental costs of testing. As I mentioned, we used the PriceWaterhouse data, and it doesn't really break out fixed and incremental costs. We included indirect

costs of the health outcomes that were reported in the MMWR. So that includes things like lost productivity, which the panel on cost-effectiveness analysis and health recommended not including those. So that was another weakness.

The cost associated with cerebral palsy and developmental delay in the MMWR report are not completely independent of one another. Dr. Grosse pointed out that we may be double counting the benefits of screening, because we treated those as if those costs were additive. They're not additive, there is some overlap in the costs that are incurred in children who suffer from both cerebral palsy and developmental delay.

There are a range of cost estimates for MS/MS, and we picked something sort of in the middle of the road. It may be somewhat more expensive. The confirmatory, it was suggested that the costs of confirmatory or false positive testing may be too modest. We used a baseline number of 300.

The rates of adverse outcomes for MCAD in the unscreened population are unknown. Now, I don't know which way this would push it. There are probably some patients that go undetected with MCAD. Therefore, we may be overestimating the severity of outcomes in children with MCAD. There is no such thing as a population of identified children with MCAD who have gone untreated. But on the other hand, there may be several unexplained deaths that are attributable to MCAD, such as SIDS. So this could play either way.

The prevalence of MCAD and PKU may be overestimated in our baseline model. The risks of death from undetected congenital adrenal hyperplasia may have been overestimated in our model. These comments are based on the very helpful critique we got from Dr. Grosse.

So I constructed what I would call a pessimistic case model. We eliminated indirect costs, which account for 42 to 81 percent of the costs in the MMWR report. So if we just wipe out from the model those costs, that makes the financial benefit of newborn screening less.

DR. VAN DYCK: What would be an example of an indirect cost?

DR. DOWNS: An example of an indirect cost would be the loss of earnings for a child who, for example, a child who had PKU, as an example, who suffered severe developmental delays because it is undetected. They would be less productive to society than the same child if he or she had grown up with normal development.

We eliminated all of the costs attributable to developmental delay in cases where cerebral palsy was also part of the outcome. That is probably a little swing of the pendulum in the other direction, but we wanted to completely eliminate that double counting. We used a higher estimate of the cost of tandem mass spectrometry, $20 per test. We used high estimates of the false positive costs. We basically tripled and used $1,000 for evaluating any positive screen on tandem mass spectrometry.

We used lower estimates for risk of MCAD, 1 in 18,000, which was a little lower than our baseline, and the risk of PKU was 1 in 20,000, which was a little bit lower than our baseline. We used a lower estimate of the risk of death from congenital adrenal hyperplasia, 3 percent.

This is the result of the analysis. Again, what we have got here is no testing, the incremental cost of testing based on a panel, and then the incremental cost of tandem mass spectrometry. I'm going to draw your focus to the bottom right corner here. This is the incremental cost-effectiveness studies, the cost per quality-adjusted life year saved using each strategy compared to the next less expensive strategy.

With this pessimistic model, we found that it would cost basically $300 per quality-adjusted life year saved to screen versus not screening. To go from a panel to tandem mass spectrometry would cost just under $5,000 per quality-adjusted life year saved.

Now, if we compare this to sort of a standard benchmark of $25,000 per quality-adjusted life year saved, which is less expensive than things like treating hypertension to prevent cardiovascular disease, or screening for breast cancer between the ages of 40 and 50, a number of different things which use this benchmark, then this turns out to be quite a bargain, even in our pessimistic case.

DR. WAGNER: Is that compared to no testing? The $4,800?

DR. DOWNS: No. The $4,800 is compared to the panel. So each of these increments is compared to the one above it, which is different from the earlier ones I showed.

Because there is concern about what the costs are, the final analysis I ran was to figure out what would be the threshold cost of tandem mass spectrometry that would make it actually cost-saving. In this pessimistic scenario, it would be $16. So if it was possible to carry a tandem mass spectrometry at an average of $16 per child screened, it would save money to society overall.

So a quick conclusion. Screening for most inborn metabolic and endocrine disorders is cost-saving or reasonably cost-effective. Possible exceptions would be congenital adrenal hyperplasia or galactosemia. Galactosemia in fact looked at by itself may be prohibitively expensive, but I want to temper that comment by saying that this is an absolute cost difference for the total cost of galactosemia screening, and that cost shrinks down quite a bit when it is just added, as Dr. Wagner pointed out, when it is just added to an existing program.

Tandem mass spectrometry appears to be cost- saving or, at worst, reasonably cost-effective. This is largely because of its ability to multiplex, the ability of it to replace other testing modalities and add its ability to detect MCAD.

This analysis is preliminary, and this is why it is not complete. The fixed and incremental cost of screening programs have not been teased out. A much more ambitious undertaking would be required, more like what the OTA did many years ago, would be required to separate out the fixed costs of having a baseline screening program from the incremental costs of adding new tests.

Risks of sequela from undetected disease, MCAD and CAH remain uncertain. The cost to evaluate, there are two tradeoff costs that we didn't take into account with MCAD. There may be others, but these are the ones that we have been thinking about.

There are going to be costs associated with evaluating what the task force called secondary targets that would be detected by tandem mass spectrometry. For a few of these, there may not be direct benefit, because we don't know what the natural history of these conditions might be. We don't know what benefit treatment may offer. So that remains uncertain in that area of secondary targets.

There may be cost savings from avoiding diagnostic odysseys. Everyone has heard plenty of stories, and had plenty of experience with children who had one of these undetected conditions and went through an expensive and elaborate diagnostic odyssey that could have been avoided if it was detected early. My analysis here is not going to quantitatively help you with those considerations.

I'm going to close with a comment about societal perspective. This is not part of the analysis, except that we use the societal perspective. This is something that the panel is going to have to grapple with. That is that the real problem with the societal perspective is that no one has it. No one has

the societal perspective. Newborn screening programs bear the costs of screening, but the benefits are going to be incurred by others, insurance companies, educational programs, families, and others that I haven't listed here. With that, I'll close.

(Applause.)

DR. HOWELL: Thank you very much, Steve.

We will now go ahead and hear from Dr. Cunningham about the cost-benefit analysis of tandem mass spectrometry in the newborn screening program in California.

DR. CUNNINGHAM: I want to thank the organizers and the committee for the invitation to contribute to your important work. I will report today on a preliminary economic evaluation of a pilot project conducted in California to evaluate how best to incorporate the new tandem mass spectrometry technology into an existing newborn screening program.

I would first of all like to acknowledge the support of the Maternal and Child Health Bureau's Genetic Services Branch at HRSA which funded the staff to conduct this study. Briefly, a pilot project in tandem mass was authorized and funded by the state legislature, and was conducted from January, 2002 to June, 2003.

During that period, 353,894 newborns were screened. We found 51 cases with one of these disorders. This gave us a rounded off overall incidence in California of one case for every 65,000 newborns screened. So this takes into consideration what Steve talked to, the sensitivity and specificity of the test in actual operation.

Based on that, and applied to our entire birth cohort, we would expect the operation to detect by the methods, 83 cases. Now, my cost-benefit analysis is based on a practical policy decision that has to be made by a state agency. We are already operating a newborn screening program. What is going to be the incremental tests of adding tandem mass to the existing program? What are the incremental benefits?

We already have costs of specimen collection, we already have follow-up systems in place, and so forth. What are the additional costs? What are the additional benefits? It is also based on California costs and California experience. This is what my legislature and my Department of Finance wants to know.

So first of all, we did not include phenylketonuria in our analysis since we are evaluating a marginal gain of tandem mass versus the incremental costs of adding the technology. In California, the ethnic breakdown is 50.6 percent Hispanic, 28.4 percent Caucasian, 8.6 percent Asian, and 6.3 percent African American. So the prevalence figures that are quoted in the general literature may or may not apply to our population. So this is why we're using our pilot project figures as our actual experience.

So first we conducted a classic cost-benefit analysis using what we considered conservative estimates, the cost to include the annual costs of screening and treatment costs of individuals detected or missed. These are based on the actual personnel needs for the comprehensive program, which includes educational materials, testing, interpretation reporting, the costs of paying for follow-up contracts, and for quality control for laboratory and clinical elements of the screening.

This cost, which is based on our experience with purchasing and contracting, came to $5,664,500. We depreciated the cost of equipment over eight years. To that, we added treatment costs, which were $5,117,905. So the total cost of adding tandem mass came to $10,782,405.

DR. VAN DYCK: That's the total cost of adding MS, or the total cost after MS is added?

DR. CUNNINGHAM: That is a total incremental cost to add tandem mass.

So the next thing we calculated were the benefits of the program. Again, we took as a baseline, the cost of care avoided. This is based on the distribution of the 83 cases in terms of probabilities of outcomes, based on the reports in the literature from the natural history of the disorders.

Based on that, we anticipated ten cases would die, ten would have severe neurological, ten mild, and so forth. Then we took the number of cases times the lifetime treatment costs per case. We used $30,000 as the cost of death, because at a minimum, most of these kids will be admitted to an emergency room, they may spend a day or two in intensive care before dying. We had anecdotal evidence of $100,000 cost for a kid who ends up dying. So it is not cost-free.

The cost of severe neurological impairment, $635,000, is based on an exhaustive study done by a Blue Cross grant, published by the University Press of America. In California, based on the costs of our disability programs, based on the costs of our Medicare reimbursements, based on the costs of care in California for severe mental retardation, and adjusted from the study that was done in 1994. It was adjusted by using the general CPI, not the medical CPI cost of living, which would have been higher, to 2004 figures.

Now, we did not use the higher cost that Steve used from the MMR that the CDC gave, which is $1,042,000, which would have doubled the benefit, or the costs of not treating. We are concerned what it is going to cost California, in California rates.

The mild to moderate, we had to estimate based on it being approximately half of what it would cost for the firm figure on severe. We figured there would be 18 cases that have acute complications that may require minimum visits to the hospital or extra laboratory tests, and 35 cases would be asymptomatic. So we came to total lifetime costs of $10,568,350.

So compared to that, we want to know what is the cost with tandem mass. Again, we estimate that based on the efficacy of screening, it would be 70 percent effective in preventing deaths and severe mental retardation, but those cases would be completely effective, so we added to the number of mild to moderate, acute complications, and asymptomatic cases.

So based on our assessment of the redistribution that would occur due to early intervention, we came up with a cost of MS screening, a treatment cost associated with it of $5,117,905.

Now, in our effort to meet the time deadlines, I did notice that they transmitted a disc for this PowerPoint, which has some errors in it. So you'll have to correct your data whenever I indicate that. Where is the pointer?

This is really treatment costs without tandem mass. That is the figure I gave you of $10 million. This is treatment costs with tandem mass, so that is the net cost avoidance of $5.4 million. Now, to this we added the economic value of lives saved. In this, we accepted the official EPA value of $6.1 million, which would give a net benefit of $42,700,000.

Everyone debates the economic value of a life saved. We picked that figure because EPA uses it in their regulations. Net benefits then would be $48,150,000. So if you take the total cost then, $48,000,000, and you divide it by the figure, and here is where I think one of the errors is. This is the cost of screening and treatment. We get a cost-benefit ratio of $4.46 for each dollar invested in the program.

Now, cost-benefit analysis has been criticized on the basis that human life, IQ points and the like, have a value that cannot be translated in a universal way to dollars. So as a result, modern health economists prefer cost-effective or cost-utility analysis.

Now, this method assumes outcomes are assigned a relative value called utility, with perfect health being one, and death being zero. We assigned a utility of 0.9 to newborns who are asymptomatic, 0.87 to those with acute complications, 0.6 to mild to moderate neurological complications, and 0.3 to severe neurological complications.

I compared these with Steve's utilities, and they are fairly close. This is one of the elements that you can change in doing sensitivity analysis. In these economic analyses, just for the newborn screening people, sensitivity analysis is different for what we call sensitivity. It is varying all the variables to see how it changes your cost-benefit ratio.

You could say, well, suppose these only live 60 years, what would that do? Suppose this cost-utility was 0.4? You can do exhaustive sensitivity analyses. But based on these, and based on the 75-year life expectancy, we estimated the quality-adjusted years of life without tandem mass would total $4,212.

In terms of the changes that would be introduced, applying the same utilities and longevity, we came up with a total quality-adjusted years of $5,071. So this is wrong. There should be no dollar signs here. This is quality-adjusted years of life, the 5,000. This is quality-adjusted years with the screening, it is years, not dollars.

The point of this is that there is a net gain of quality-adjusted years of life of 859.5. Then we took the total program costs for screening and treatment of $10 million, divided it by the gain and quality-adjusted years of life. We came up with a figure of $12,544 per quality-adjusted year of life, which is higher than Steve's, but we think more realistic.

Our Senate Office of Research did an analysis which was more like Steve's, and came up with a much lower quality-adjusted years of life. But if you consider $25,000 as a cutoff, that is obviously a cost adjusted.

Lastly, a figure that I like to use as a rough comparison in terms of making screening decisions is the cost per case detected. Our total cost of the program, including screening, treatment, follow up of false positives, everything comes to $10 million and we net 83 cases, it is $130,000 per case detected. If we just look at our screening costs, it only comes up to $68,000 per case detected.

So the economic analysis that we presented here is a high-level product designed for practical program needs, and not a detailed study for a peer review journal. Like all economic analysis, it is subject to criticism of the assumptions and the lack of precision.

I'd like to close my presentation with a brief commentary on the practical and moral aspects of econometric analysis as an instrument of public policy. These analyses, cost-benefit and cost-utility have been criticized and discredited for some time, but have survived because even though flawed, they were better, we were told, than nothing, and at least should be part of the policy decision process.

I have done my share of such analysis, because fiscal control agencies have demanded that. However, I basically agree with authors Frank Ackerman and Lisa Heinzirling who wrote a damning indictment of cost-benefit analysis applied to health entitled "Priceless."

In a pamphlet version of the book, "Pricing the Priceless," which was published by Georgetown University Law Center, they concluded "Cost-benefit analysis is exceedingly time and

resource intensive. Its flaws are so deep and so large that, at this time, these resources are wasted on it."

It should not even be kept around as an interesting but not decisive policy decision aid, because it is fatally flawed, and ultimately unreliable when it comes to making health care decisions. The economist knows the price of everything, but the value of nothing.

(Laughter.)

DR. HOWELL: Thank you very much, Dr. Cunningham. I think that your last comment certainly opened up the podium for discussion of the very fine presentations that we've heard on cost-benefit analysis. So we will start with questions and comments of the three speakers.

I believe that our other colleague is still on the phone. Is that correct?

MS. OSTROWSKY: Yes, I'm still here.

DR. HOWELL: Excellent. Maybe we could put a microphone over there so that we can hear her comments and so forth.

Dr. Hawkins?

DR. HAWKINS: I just have one quick question. Yesterday we heard about the unique -- we're looking at Mississippi have a high minority population. But with California having a high Hispanic population, is there anything that is unique about that situation that would apply to California versus some other state? I'm just curious.

DR. CUNNINGHAM: Well, it depends on the disorder. For example, they have much higher incidences of congenital hypothyroidism. They have a higher incidence. We have a prenatal screening program. They have a higher incidence of anacephaly.

When we do cystic fibrosis screening, we have been working hard on getting a Hispanic testing panel, because our incidence is much lower than a 97 percent angle of population, where you could use just 28 mutations to get a 97 percent detection rate. So we have to take that into consideration.

It also adds to the cost of our program. We publish educational materials in English and Spanish, and we have 14 languages that are available on the web, or can be ordered by the doctors. So there are costs associated with dealing with minority populations.

DR. HOWELL: It was interesting that the data for Mississippi had an overall incidence of all these conditions of 1 in 360, which was quite striking with a dramatic number of galactosemics being detected in their early screening.

DR. CUNNINGHAM: Well, I think one cost -- the Mississippi figures were based on a relatively small population for screening, 42,000.

DR. HOWELL: Yes.

DR. CUNNINGHAM: I cannot imagine Mississippi, they have three times the amount of hypothyroidism that we have in the rest of the country. In the next 40,000, those figures could change fairly dramatically. But we screened 80,000 when we started our PKU program. We had eight cases, that is 1 in 10,000. Our overall incidence now is 1 in 20,000.

DR. HOWELL: Well, the numbers you have of course are enormous with a significant portion of the births in this country with 400,000 or 500,000 out of slightly over 4 million.

Dr. Rinaldo?

DR. RINALDO: Dr. Cunningham, first of all, I completely agree with your finding statement. So in light of the fact that perhaps we can get too deep in numbers and lose perspective, I really have a compassion to do some of what you call sensitivity analysis.

It is based on two things. One is that I was intrigued by your first slide about the rate of detection. The 83 cases in the California population based on some calculation seems to be a little high. I think you should add more cases, perhaps excluding PKU.

According to the calculation they did, the detection rate was actually very conservative, and could be actually more like 1 in 5,500 rather than 6,500. So that perhaps can even make the overall picture even more significant.

As I asked Dr. Pass yesterday, and I really have to ask you the same question. I see something missing in your cost analysis, and that is the impact of false positives. Again, looking at the California numbers, if my calculations are correct, in California the number of cases that require evaluation and turn out to be false positive can vary anywhere between say 30 a week, if the false positive rate was 0.3 percent, to about 50, 60 a week, if the rate is the same chosen by New York of 0.5 percent.

That will add a lot. So I wonder if you can elaborate on sort of how you have included in your calculation that, or why you didn't include it.

The other one, I'm wondering if you can tell us more about how you sorted out the outcome of patients, the proportion of your case. How many are remaining, how many are symptomatic, how many resulted in death? That is clearly another variable that can greatly change.

I think if anything, what I want to say is your figures are very conservative, especially when it comes to the cost savings. So I'm just wondering if there is a need to make it even more impressive. I think that there is probably some room to make it so.

DR. CUNNINGHAM: Well, I agree with you. These are very conservative figures. First of all, the costs of false positives. We have $742,000 available in follow-up contracts. Those go to metabolic centers to produce the follow up, and that includes the false positives.

One thing that is sure about California is that our costs include all the costs. Everything is covered. The tracking of the false positives, the computer system, everything is included in the cost.

Your point about the false positive rate is also good. When we started the program, we were running a false positive rate of 0.4. Then we refined our cutoffs, we looked at all of our results, and we changed them and adjusted them. Now it is 0.2.

When the program starts, it might even be less, because in the pilot project, we used only analyte cutoffs. We didn't include ratios, but now we are including ratios.

So that will probably further reduce the cost.

But my argument is to make it not the worst case scenario, but pessimistic, make it very conservative so I could say that we aren't presenting a rosy picture and underestimating the costs, and

the state is going to get burned because we have sold them, which is the criticism that we would get from the legislature and Department of Finance.

I agree with you. These are very conservative, and our actual experience may be better.

DR. HOWELL: I found these presentations personally very informative. At least as I interpret them simplistically, they all show that virtually all of the newborn screening programs as they currently are looked at are sound from the public health view economically. Is that a general gestalt that would be fair to say? That they seem sound investments from the public health standpoint for getting any of the other --

DR. WAGNER: If you're addressing me, I'm simply an economist. So therefore, I don't know anything.

(Laughter.)

DR. WAGNER: Given that I actually don't know anything because I have been out of this area for 15 years, I don't think I can comment on that.

I do have a question of Dr. Cunningham with regards to the cost-benefit analysis, the cost-benefit ratio. As I read your slides, you have indicated a net cost of MS screening at $10,782,000. That is the treatment and screening costs together. Then you come up with savings in terms of dollar savings from averted treatment costs of $5 million.

I see what you have done. You have put that in a numerator. I see what you have done. Never mind.

I honestly don't know how to respond to a comment that essentially -- I don't know what I did here. My emotional state just caused a burnout. I really do think that these analyses, our analysis is not really an analysis anymore. It is me.

DR. HOWELL: Actually, I think there was an economist in the hallway. They closed off the power after George's comment.

DR. WAGNER: Over the years, you know, I have worked at the office, Julie and I, and actually Denise Dougherty spent years at the Office of Technology Assessment in which we advised the Congress on a variety of issues, often including the cost aspects of those. They can't be denied.

What cost-effectiveness or cost-benefit analysis does provide is a way of thinking about a problem that I think has introduced a measure of rationality into public debate that I have seen evolve over 15 years. So I just have to express my complete disagreement with these essentially assaults on what seem to be modest and humble contributions by the economics field to try to bring in some decisionmaking rationale.

DR. HOWELL: I think the power has returned.

DR. WAGNER: And now I just ended my diatribe.

DR. HOWELL: Dr. Wagner, I think your comments were extremely valuable.

DR. WAGNER: I mean, I couldn't leave that broadside unanswered at all. I think I'll stop talking, because I really don't have much to say.

I do think, though, that on the MS, the tandem mass spectrometry question, I'm a little confused. Having read the British study which came up with a very low estimate of the cost, and I'm not sure whether that had to do with high volume decisions, or whether it had to do with a different costing structure.

It seems as if that cost does make a difference. It made a difference in the Indiana study. I'd be interested in knowing what it is. Actually, the cost of the procedure itself, you know, what it is that makes the cost of the procedure itself so varied across those studies. I'd be interested from the experts in finding out.

DR. HOWELL: Piero, you're an expert in tandem mass spectroscopy.

DR. RINALDO: What exactly would you like to know?

(Laughter.)

DR. WAGNER: Well, why did the British study come out with, I believe it was a procedure that cost something like $4, or four pounds. So $8, let's say? I may be wrong on this. I'm sorry, Steve. The analysis was $16 to $20 per. I'm just curious, what is the truth here? It seems to matter. What is the truth?

DR. RINALDO: I can talk a few comments about that. The first one, I believe that the cost of equipment is a variable where you find a great, vast degree of variability. Still, I don't know.

For example, look at this slide. The slide says $500,000. I assume that is for how many instruments, Dr. Cunningham?

DR. CUNNINGHAM: Twelve.

DR. RINALDO: For 12 instruments. It's $500,000 for 12 instruments. Four million?

DR. CUNNINGHAM: It is $4 million for 12 instruments.

DR. RINALDO: Okay. So the instrument that we're talking about -- well, that's a comment I made yesterday. Mine will be a standard, but I believe you can buy an instrument like from one of the vendors now, especially the older models. So they are not trendy, they are not the high sensitivity, but you really don't need a high level of sensitivity. Those can cost really in the ballpark of $100,000 an instrument.

The second point, and again, supplies can vary. People can buy kits, or can try to do it themselves. But the other one I can tell you, I come from an institution were recording is a religious experience. I actually was really intrigued by looking at the numbers Steve presented. Our calculation is $15 and something, of all things considered. So we are very below that threshold. So I believe from what I can tell, what our experience is is very accurate. I don't know if that helps.

DR. CUNNINGHAM: Well, our costs average $18 a test for the total program. Our costs are based on what the state can actually purchase in the market in terms of market rates. They are not based on the WaterhouseCoopers annual survey or averaging costs from one lab that does a lot of manual stuff versus another lab that uses a lot of automated equipment.

Our costs are actual costs that we pay to private labs on a labor basis, and on the cost of the equipment, the maintenance, the quality assurance, and the proficiency test program that we can conduct. Those are real California costs.

DR. RINALDO: But I believe that there is a very high sort of purchasing power. Think about if APHL for once collectively went to vendors and said for X number of instruments that can go to all our members, what the cost could be.

I think some of the figures I have seen quite frankly in the past, I just cannot believe them. I know it is not the real market. If I can make one more comment. Going back to your follow up centers, can you please clarify, is the $742,000 for everything, including medical services like clinical evaluation and laboratory tests? Or just for laboratory tests?

DR. CUNNINGHAM: The $742,000 pays for tests and personnel that are not covered in fee for service. So most laboratory tests can be covered fee for service, but genetic counseling can't be covered in fee for service. Dietician services might not be covered, so we'll pay the salary of the dietician.

DR. RINALDO: Okay. That again goes back to the point I made earlier. Even if you take the old costs of follow up centers, again, my calculations go back that there would be the follow-up cost per patient of around $259.

This is where I think we are dealing with -- just look at the two presentations we had from California and New York. California, yesterday Ken Pass told us that they expect a false positive rate of 0.5 percent, and a follow-up cost of $1,000 per patient. You today are telling us that you are in the ballpark of 0.2 percent rate of false positive, with a cost of $259 per patient.

That is where the problem really is. By looking at two of the largest states, the gap between their estimates and your estimate is enormous from a financial point of view. It goes back a point that I was trying to make yesterday. There must be some goal defined of what is acceptable, and what is an outlier.

I believe the potential benefits strictly from a financial point of view can be enormous if we try to achieve common goals.

DR. HOWELL: Bill?

DR. BECKER: Yes, two comments. One, I believe Judy had asked a question about some of the potential discrepancies with the British MCAD study, and the cost-effectiveness analysis. It is certainly true that the cost of the instruments is a bit variable. I believe that study was done at a time when the instruments were at least twice as expensive as they are right now. The instrument costs have certainly decreased in the last couple of years.

DR. WAGNER: That is a 2004 study.

DR. BECKER: Yes, but I believe that their data was collected from earlier, because they have been looking at MCAD for several years now.

DR. WAGNER: It has changed so dramatically.

DR. BECKER: It has changed reasonably significantly. I mean, the analogy is like calculators. I mean, everybody bought them for several hundred dollars, and now you can go buy them at the grocery store for $20, and they do more than most of your computers.

The other thing, Piero is exactly right. His observation is correct. The cost for follow-up diagnostic services does seem to span a wide degree of variability from the numbers we heard yesterday. I think Steve actually summarized it fairly well. His initial analysis used a number of about

$300 and demonstrated a cost value savings. Then even in his pessimistic model, closer to what Ken was mentioning yesterday of $1,000, even then showed cost-effectiveness savings.

So I think without dissecting the numbers anymore than that, realizing that the savings is probably somewhere in between, I suspect that there is enough variability in medical treatments that $300 might not be the average, and $1,000 might not be the average, and the answer is somewhere in between. So Steve's analysis shows us from both ends of the spectrum that this is a value. I think that is what I take away from this.

Is that accurate, Steve?

DR. DOWNS: That's accurate. In fact, my comment was going to be a couple of things. First, I admittedly came into this as a skeptic about the cost-effectiveness of newborn screening as a strategy, because the conditions are so much more rare than the other medical conditions that have been evaluated this way.

I was surprised at how nicely it does in a cost-effectiveness analysis. I'm struck by the fact that several analyses of this have gone everywhere from cost savings to a real bargain compared to other things we spend money on.

So I think that there are still a lot of uncertainties. I wouldn't go so far as the quote that Dr. Cunningham put forward about cost-effectiveness analysis. There are certainly lots of unknowns. In defense of cost-effectiveness analysis, I will say that every dollar you spend on a very good cause is a dollar that you can't spend on another good cause.

So we do need to be thoughtful in where we put our money. Having said that, I don't think the question before the panel is anymore whether this is a good financial investment. It seems pretty clear to me we're for society. Overall, we are going to either save money, or we're at least going to get good value by investing in this.

I think the bigger question has to do with the societal perspective, and how do we make it happen, given the competing economic and individual interests of the parties involved.

Derek?

MR. ROBERTSON: Thank you. I guess my point has been kind of echoed by both Bill and Steve's comments. I think being an economist as well, at least in a prior life, it is always going to be difficult when you are comparing quantity to qualitative issues.

I think if we get too much into trying to do that, we digress. I think the overall issues, this is something of value. I like that term in terms of societal perspective, because if it is of value, then the perspective really has to be what is the least cost alternative of doing this. Because you are going to say that this is something that is value, we need to do it. How can we do it in the least cost way? The least cost alternative?

That is something I learned, again, a long time ago in trying to move from a financial analysis to an economic analysis, and trying to place economic values on what are really qualitative matters. That is always going to be an issue. I think we really want to focus on what Steve just said, which is is this of value, yes or no. Once you say yes, then you have to get society to understand that, and then what is the least cost alternative of doing that.

DR. HOWELL: Excellent. Thank you very much.

Any other comments? We have some comments I think from the audience that we'll take at this time. There has been the first hand, and there is a hand back in the back that I can't see to who it is attached. It is attached to Dr. Grosse. After we hear from Kay.

MS. JOHNSON: I want to go back on the point around follow-up care. I think part of the variability, Piero, the ranges around the number of false positives clearly is an issue related to quality decisions that have inside labs and inside state agencies.

The follow-up decision is likewise. It sounds very simple in the context that it has been described this morning about what does it take to follow up through the diagnostic workup. What is very clear is that the amount of effort expended by states and the amount of, if you will, care and handling they give to that situation is really quite variable.

Whether they go to the pediatrician and give the information there, whether they go to the hospital and put the burden on informing there, or they take responsibility for informing the family themselves and the public health agency takes responsibility for ensuring that that connection is made all the way through diagnosis and treatment is the kind of range of variability you see in what states have invested in the context of follow up.

I think it is very important to remember that it is different if the public health agency says we're calling the hospital and letting them know, and the burden of actually finding the family and making sure that it is done moves to the private sector, and moves to the pediatrician, or primary care physician, in essence.

It is a very different view of the roles and responsibilities of public health. You can place your own value on that, but I think you have to think about it in that range. It isn't happening by magic, and not all public health agencies are taking the same burden on themselves.

DR. HOWELL: Thank you, Kay.

Dr. Grosse is coming. Dr. Grosse, of course, is a health economist from the Centers for Disease Control.

DR. GROSSE: Thanks. First I just wanted to clarify about the U.K. HTA report, which I served as a reviewer on. The cost estimate for mass spec was about $2.5 dollars. It was 1.45 pounds. They assumed the cost of about $300,000 for the machine, and assumed an asset life of seven years, which is reasonable.

They assumed that there would be only one machine for a screening laboratory with an annual volume of 50,000 births. They assumed that a 0.2 FTE skilled interpreter would be sufficient. Of course salary costs are much lower in the U.K. than they are in the U.S., so they were very conservative assumptions. I think it is realistic based on how the National Health Service operates. Costs are definitely going to be higher in this country.

The reason they find screening for MCAD to be cost-saving added to the PKU was they used an old estimate from the United States of the number of false positives for PKU screening using fluorometry. The more recent California data that Fred Lowrey presented suggests that the false positive rate with fluorometry is much lower, so there would be far fewer false positives averted than was assumed in the U.K. analysis.

The cost estimate aspect was somewhere between $5 and $20. I think there is a consensus, it is cost-effective, if not cost-saving. Whether it is cost-saving or cost-effective, we could debate all day long. It is not important. It is good value for money.

What I have not heard is evidence related to some of the other conditions on the recommended panel, which is G6PD deficiency, CF. I'd be curious to know more about those conditions. Thank you.

DR. HOWELL: Would anybody like to respond to the question of the G6PD and the CF?

DR. DOWNS: It wasn't in our analysis, so I don't have a comment about that.

DR. CUNNINGHAM: I think the proper way to do the analysis is to approach tandem mass screening not as a single screening program, but as a screening for a series of disorders. For MCAD, it is extremely good. If you get a positive, it is going to be 80 or 90 percent, and when you send it in, you're going to get a case.

For SCAD, it really has a large number of false positives. For a lot of these other disorders, we don't have the numbers to say how sensitive or how specific it is. We don't have data. Part of our project in California is to go back to the metabolic centers and collect all of the cross-data for working up these various different kinds of cases.

But in any given year, you're going to have a miscellaneous mix of cases. You're going to have maybe three glutaric acid type 2s one year, and none the next year. So there is always going to be a mix. But the symptomatology and the treatment of these fatty acid disorders is very similar.

The justification for the most effective is MCAD. So I think it is reasonable to assume and base the justification on what can be accomplished with that.

DR. HOWELL: Let me make one question and one comment, and I'll ask Dr. Watson to perhaps comment. I'm not aware of the details, but I think Scott's question about G6PD and CF is very appropriate. I know that has been discussed, but I don't know whether you have any comment about that or not, Mike, some of the concerns that have been raised about that. Would you like to come to the microphone and say something?

DR. WATSON: I have nothing with me today that I had yesterday to look at. The G6PD I think has some serious caveats that are expressed in the report that you don't see in the fact sheet, except in the comment area. We had some very serious questions about whether newborn screening was the right time to be finding out about G6PD status, whether it was better to be done at the time that a prescription related to a G6PD deficiency might be prescribed. That might be a more effective place to apply it.

I don't know of any cost-effectiveness information. In fact, G6PD bothers me mostly because compared to everything else, the overwhelming lack of data that has been published by the programs that have been doing that screening. I think I covered the CF caveats yesterday.

DR. HOWELL: So the bottom line is there are obviously "caveats" and so forth.

Derek has some comments, and then we'll hear from Brad.

MR. ROBERTSON: I guess the comment that I would make is I don't know about G6PD. I know a little bit about CF. But what I think I do know is that the cost-effectiveness, again, would have to be just one perspective.

I know if I were a parent of a child with G6PD, and a parent of a child with CF, I would hope that we'd be looking at more than just the cost-effectiveness. It may not be cost-effective anywhere in the numbers, but it certainly would be cost-effective to saving that child.

DR. HOWELL: And Brad has a comment.

DR. THERRELL: Just another comment on G6PD. I have just gotten back from a meeting in Asia. Even in Asia, there is a lot of discussion about the cost-effectiveness of doing G6PD, because the mutations are so different.

So there are many Asian populations where the incidence is very, very high, 1 in 50, 1 in 60. But when they look at the mutations and the clinical significance, there is no clinical significance. So they are really rethinking G6PD even in Asian populations. We just don't have any data in this population, in the U.S. to say anything about G6PD.

DR. HOWELL: But the rethinking is along the scientific base, because of the value of the mutation. I think Derek's comment is about the importance of a clinically significant mutation and so forth.

I think one of the things that is probably not in any of the cost-benefit analyses are the direct costs to the families that are incurred when they have a child with a condition that is missed. I think all of us who have been in this field are aware of families that have had extraordinarily expensive odysseys. They fundamentally end up picking up the tab for this through time off from work, travel, confusion, the whole nine yards, and so forth. That's another.

We probably are never going to be able to get those accurately, but I think we need to think about that when considering some of these conditions from an economic standpoint. Again, I think Derek's point is extremely well made. You decide if there is a value, and try to figure out how to do it in the most cost-effective way that can be appropriate for the limited dollars that we have.

Piero?

DR. RINALDO: Just one other comment. People are familiar with sort of long-term follow up on metabolic patients. They are well aware that the rate of divorce and disintegration of families when one or more children are affected with metabolic disorders is extremely high.

That certainly would be a challenge that I would like to pose to the economists, what kind of value you put on that.

DR. HOWELL: This committee is certainly not charged to focus on research activities. But one of the research things that continues to surface is as we define these conditions and screen for them, the absolute necessities to get these children enrolled in a national program to see what is the long-term effect.

Obviously we need to know if you were to go back 20 years into the states that have saved all of their blood samples, and you did our current panel on all those blood samples, how many persons are in that group who are 20 years old and are totally asymptomatic? That is something we do not know. That would be an important research tool and so forth.

Are there other burning questions? These were very informative presentations, and I appreciate all of those. Does anybody else have any great comments before we go to a break? Oh, excuse me.

Colleen?

Julie, let me thank you on the telephone while we're waiting for Colleen.

DR. BOYLE: No, it is just more of a comment. I just wanted to follow up on what Scott had pointed out.

First of all, I really thank you for all of your work and your analysis. I know for me personally it really does help clarify a lot of issues. I think as Rodney had said earlier, that it really drives home a point that tandem mass spectrometry is cost-effective.

As you said, we have to balance the dollars that we have, the small amount of money we have here in terms of what we actually pay for. I just wanted to make a point for our committee. That is that what we heard really doesn't directly apply to all of the conditions that were identified at the ACMG report. So we still have some thinking to do in terms of the recommendations for the 30 conditions. But I do appreciate it. It was very, very helpful.

DR. HOWELL: Thank you very much. We will return at a touch after 11:00.

(Recess.)

DR. HOWELL: We have a block of time now for some fairly open discussion. Bill has brought up an issue that he'd like to bring up from the report yesterday. I think there are a number of other aspects of the report that we'd like to discuss at this time.

Bill?

DR. BECKER: Thanks, Rod.

A couple of people from the audience, and then indirectly a couple of the questions that were asked even just this morning, revolved around the issue of the ACMG report dealing with the issue of the report only category of disorders.

There are a couple of levels of conversation that we could have about this. First, what exactly does that mean? I think there are a couple of ways you can approach that. What does that mean to the testing laboratories, and how should they approach this, because that is a little bit of a paradigm shift from the way newborn screening laboratories I think, with the possible exception of hemoglobinopathies, tend to approach pattern reporting, as opposed to analyte-specific reporting.

There is also a little bit of a paradigm shift from the clinical perspective. Again, that is a little bit driven by what the labs report. In other words, they are going to be receiving reports for perhaps disorders that states are not officially "screening for" if that is what they decided to do.

That might be a paradigm shift, but yet that creates a burden in the clinical community for exactly what to do with that kind of information. Then the third issue about the report only which was a little bit implied by some of the questions in the cost analysis discussion from earlier this morning is we have data for MCAD, and I think it is clear for MCAD that there is savings, value, and benefit by doing MS/MS testing for that particular disorder. But we really haven't looked at the other disorders.

So there are several levels that could be discussed about this report only category. A couple of folks approached me earlier this morning and at the break to ask if we could get a discussion out there. I think I'd like to open it by asking Mike Watson to just review for us what he described yesterday about this report only category, and how it was sort of set up.

I believe that is going to open the conversation. There was quite a bit, just so everybody on the committee and in the audience knows, there was quite a bit of discussion about this at the expert group. Piero and I, and certainly Derek and George, who were on the group as well, and a couple of others, Brad, Harry and everybody, and Rod certainly, will all probably chip into this conversation.

But I think I'd like to get the basic definition of the report only category on the table for discussion, and hopefully address the issues that have been expressed. Mike has to leave this afternoon, so we wanted to do this before he got away from us.

DR. WATSON: Well, he's still in an improvisational mode. I suppose sort of hierarchically it stemmed from one of the overarching principles that the group agreed on, which was that any clinically significant result obtained in the course of screening ought to be reported out of the screening laboratory.

The range of options included carrier information that might be identified,. Obviously it only occurs in some conditions. Certainly you don't get carrier information in all conditions that are screened, but depending upon how you approach it and the nature of either the biochemistry, or if it is a DNA-based test, one might get that information.

Other examples, and I suppose the biggest group would stem from PKU as the classic example. There are, as I said, a number of conditions under PKU, including the biopterin biosynthesis defects, and the biopterin regeneration defects. In tandem mass spectrometry, if you sort of think about the biochemical phenotype of MCAD, when one sends out a presumptive positive or screen positive MCAD out into the world to be worked up diagnostically, one of a couple of things is going to happen.

They may come back to you and say false positive. The state gets information back regardless, hopefully. They are either told it is MCAD, or they are told it is a false positive. If it is MCAD, the program, if it is mandated, brings their full newborn screening program to bear on the follow up, outcome, and everything else related to MCAD.

However, there is a possibility that the diagnostic report that comes back to the lab could be that it is MSCHAD. Now, there may have been one more added. If there has been one more added since I looked, it means there has been a 15 percent increase in the total number of patients known. There are, I think, five or six MSCHAD patients. Now, MSCHAD is apparently a clinically significant condition.

Obviously it is rare. We haven't looked at a general population at the newborn screening level to see really what is the background going to be. But the sense was, what are you going to do with that information? Certainly the diagnostic people will tell you it is an MSCHAD.

I don't know that report only is the best word I could have chosen, but it boils down to the fact that the state now has an option. You are going to be told it is clinically significant, as MSCHAD was determined to be. You now have an option to say, I can treat it like a false positive, because there is not an expectation perhaps if it is an untreatable condition found.

You don't expect to see a change in outcome from the fact that they were identified early. So perhaps the state shouldn't be putting its money into the long-term tracking and follow up of that particular patient. It is important that that information got to the diagnostician who now can appropriately manage that patient.

The state may choose to keep that information, but there are certainly other options available. I was actually just talking to Steve Groft from the Rare Disease Center about this very issue. It

sort of stems from the fact that I think there are tremendous opportunities to be had in beginning to bridge some of the interest that everybody has in these conditions.

Ideally, if there was a rare disease center perhaps for fatty acid disorders out there somewhere, the possibility is that patients with MSCHAD, their data collection, could get centralized so that we could really learn much more rapidly through a rare disease center. There is a rare disease center for the urea cycle disorders. So the citrullinemia type 1 I think is in the core, and cit 2 is in the report only category.

It is an ideal opportunity to develop the natural history of that condition since we have identified it, and to centralize it into systems similar to the children's oncology group kind of model where one was able to aggregate as many patients, and I shouldn't say large, because MSCHAD is incredibly rare, but at least aggregate what information there is so that you can learn more rapidly, adjust your programs as you need to, and really have a more evidence driven process around some of those conditions. So that was the general framework I think around which the category was developed.

DR. HOWELL: Dr. Rinaldo?

DR. RINALDO: Bill, excellent question. I'm really glad you asked it. I think we need to sort of address what I think in some part of the report is a reference to the apparent gaps in clinical knowledge that seems to affect here the whole process.

I would like you if you have a copy of the report, to look at page 84. Page 84 is where Table 7 is. That lists all the conditions in the report only. Now, Bill, the truth is that if you look at that list, and please look at it, because it is very important.

Of all the conditions listed here, only a handful are not included in the differential diagnosis for one of the primary targets in the core panel. Again, I want to say that again, because this is one of the points that has been really a key in the whole process.

Making people understand that when they say they are screening for MCAD, they are screening for other things, like it or not. So let's look at the list. Of all the conditions listed in this table, the only ones that are not linked to one of the primary targets are malonic aciduria.

DR. VAN DYCK: Piero, are we all looking at the same table?

DR. RINALDO: Page 84.

DR. VAN DYCK: Table 7.

DR. RINALDO: It is on page 84. At least on the copy I have here. So let's look at malonic aciduria. There are less than five cases known in the world. We know that it seems to be that the test is highly sensitive and specific, because there are cases reported by numerous screenings. But the likelihood that any given program -- we think incidence is probably in the ballpark of 1 in 100,000 to 200,000. So let's say Ohio is 150,000?

DR. BECKER: Right.

DR. RINALDO: You might see one abnormal a year.

DR. BECKER: Right.

DR. RINALDO: Let's go down the list. Isobutyryl glycinuria or isobutyryl CoA dehydrogenase. These are other conditions with a limited number of cases described. Now, that is for the organic acids. So can anybody really make a claim that testing for these disorders will break the back of clinical centers involved with the follow up? No. They will not.

So let's look at the organic fatty acid oxidation disorders. We still have listed, because it is actually part of selection of main program, DNA CoA (inaudible) deficiency. It still is only a single case confirmed in the old literature, and none picked up by newborn screening. Is this going to break the back of clinical centers? No.

SCAD. SCAD is an issue, but I have to say that I disagree with Dr. Cunningham when he said a higher rate of false positives. There is excellent evidence published in Pediatrics last year by one of my colleagues, Dr. McTurn, that shows that being homozygous for one of the common polymorphisms will not lead to an elevated C4, at least high enough to be above the cutoffs. It's higher than the wild type, but it is still well below what is, in general, the accepted ballpark of cutoffs. People carrying the polymorphism will not be picked up on newborn screening.

I don't know where the data about the high rate of false positives comes. That's certainly not my experience, and I believe we can probably ask the people from Pediatrics. I don't think they have any evidence of a high rate of false positives.

DR. BECKER: Well, if I could jump in there. I think as you and I have discussed in another related venue, this discussion about false positive rate offers the opportunity for regional collaboratives to learn from each other's experiences.

DR. RINALDO: Absolutely.

DR. BECKER: In order for all the screening laboratories, whether you have one in the region, or you have four, five, or six in a region, for all of us to get that false positive rate down to what would be a clinically, and I use the term clinically accepted level slightly differently from what the laboratory would report.

DR. RINALDO: And I agree with you. The point here we are debating is somewhat different.

DR. BECKER: Right.

DR. RINALDO: We are talking about this perception that adopting the secondary targets will clog the system. That is the point I'm trying to emphatically make here. That is not true.

The last condition in all of this, and this is related to MS/MS, is argininemia. Again, an extremely rare disorder. I believe that one or two have been prospectively picked up by newborn screening. I really challenge anybody to come here and tell me that in other newborn screening programs, it's a daily problem.

I can go back to our data and tell you that I don't recall having an abnormal for arginine so far. So at least in my hands, I haven't seen one. So again, I don't see that making a line outside a clinical center.

The issue of course changes somewhat with the variant hemoglobinopathies. I'm really no expert there, and I defer entirely to others. Of course, there is the issue about galactokinase and galactoepimerase if you are going to screen.

But I really argue with anybody making a point in adopting this panel is like a burden and it is going to explode in an exponential way the number of conditions that have to be followed. It really reflects I think some serious misunderstanding of the incidence of these conditions and what their real clinical impact is.

DR. WATSON: I need to add a couple of caveats that underlie some of this discussion. I think because you have a core panel, I think your screening laboratory is going to be setting your threshold to get that core condition. You may get the other, so I don't think it would be appropriate to imply that you have a liability, or someone has a liability for not finding one of those report only's, because you're not setting your cutoffs to get them necessarily. So that is something to consider in defining what that category is all about.

There is that liability issue attached to it. I think the programs have to think about how they define a false positive. When you are in a biochemical mode where you have an elevation of a peak that is associated with several disorders, a false positive, it may be a false positive for MCAD, but not say a false positive for a clinically significant condition associated with that elevated analyte that you found.

So that is an issue. Then I think there is a technology issue that also comes to play here. As you know, we discussed the difference between tandem mass spec profiling and tandem mass spec selective reaction monitoring. One can run a tandem mass spectrometer, such that you can filter out a lot of other information and target mass ratios, and filter everything out and not see some of that stuff.

The committee's general sense and recommendation, for a number of reasons, including the fact that interpretation is improved by doing a profile, because you're able to see contaminants and other things on the baseline of the tandem mass spec profile that have implications for how you are going to interpret that information.

So ultimately, we recommended that a profile was the preferred analytical approach to tandem mass spectrometry as opposed to selective reaction monitoring, but recognize that lots of people do SRM and filter out a lot of things that might be in our report only category, or reduce their chance of detecting them in that category.

That is as far as I'll go saying anything technical about tandem mass spec, because I don't know. I have never touched one. So Piero might want to elaborate on that.

DR. HOWELL: Peter, I think, had a comment.

DR. VAN DYCK: Just a question to help me. Within that report only group that we're talking about, there are a mix of either clinically significant or treatable conditions or both within that category.

DR. RINALDO: In my opinion, they are all clinically significant, and many certainly have a spectrum of treatment options that may be less or more effective. The only conditions that in my opinion are truly untreatable in the context of a metabolic disorder are the form of neonatal CPT2 deficiency and a form of glutaric acidemia type 2. These are the forms with severe congenital anomalies, and usually dysplastic kidneys. These are children that cannot survive. Those are the only two untreatable conditions among the metabolic disorders.

DR. VAN DYCK: So generally speaking, they all have clinical significance and generally are treatable to some extent?

DR. WATSON: Yes. We acknowledge what is probably a deficiency in our knowledge of natural history. Those were the two things that moved things into that category. Malonic aciduria and MSCHAD, five, six patients known. That is a limited natural history, no matter what you do about it.

If you are going to ask the state to track all these outcome measures, yet you don't really know what to expect in the outcome, it seems that by collecting the information and aggregating it to learn, and then decide whether or not you should bring your full program to bear on it was the more appropriate sort of --

DR. VAN DYCK: So if they're identified, whether or not the state follows up themselves, those children are going to get followed up, because whoever does the diagnosis is going to follow them.

DR. WATSON: Yes, and that was certainly one of the most important aspects of this to the families, was the fact that this information was getting out into the system. The diagnostic odyssey was avoided, the futile therapies, or the wrong therapy, while figuring it out was going to be avoided. There was significant potential for both saving money, and helping families.

DR. HOWELL: But this seems to underline clearly the fact that these children should clearly be included in a research agenda. There is so little known about them and so forth, so they ought to all be enrolled in some situation that would permit follow up and see what happens to them, and be certain that if a treatment is available and they are treated, what happens and so forth.

DR. WATSON: Yes, and as you know, I prefer the word "clinical investigation" around things we think are clinically significant, as opposed to research. I think the connotations in the media are very different.

DR. HOWELL: We are in a compromising mood. We can call it clinical research. How's that?

Bill?

DR. BECKER: Many of the comments that Mike and Piero have made I would certainly agree with. One of the things I didn't mention yesterday when I was describing Ohio's evolution in implementation of MS/MS was the conclusion to the story, if you want to know the rest of the story, the Paul Harvey version of it.

After two years of having a supplemental program, we felt that the impact and the burden to the clinical community was not as great as we had perhaps feared when we initially started, and we mandated all those disorders. So they are now all part of the mandated program for us. We are at 30, including a full spectrum of MS/MS testing.

The other thing I need to point out is Colleen was also on the ACMG task force, and I didn't mean to leave you out, Colleen.

DR. HOWELL: But I think underlying this report only category was a sense of the group working that information that was derived from the newborn screening test should be available and reported, rather than some secret thing if you had anything that seemed to be relevant to the situation.

DR. WATSON: And one of the benefits of the category is that this is not a new phenomenon at all. This has been the case in PKU screening since day one. We didn't know about the biopterin defects on day one, but over time, we identified those as a subset of the hyperphenylalaninemias. I think just bringing that level of granularity to what you call people in the

databases allows for us to get better incidence data across the board. I think a lot of the databases call it PKU and variants of. But now that we have true etiologies, we can really get the granularity that allows us to collect the information in a more appropriate and useful way.

DR. HOWELL: Piero?

DR. RINALDO: The point I would like to make, it is really the report only is a way to document the rigor that went into the selection of a core panel. This exercise was not a free for all. It was really a very deliberate, and at times difficult, decision about what really belongs in a uniform panel and what on its own merit is not there yet.

I think on the evaluation flow chart, there was enough emphasis placed on the loop. They return to the top and go forward again anytime something new happened.

Think of tyrosinemia type 1. Not many years ago, it was a deadly disease. Now NTBC has changed that almost overnight. So all the epidemiology and evaluation done not many years ago is now worthless. You can ask Rand Mitchell in Montreal. He has beautiful data about the before and after NTBC and what happened in Quebec. It is some of the most compelling evidence you can ever see in terms of something has changed not over a long period of time, but because of a very specific event.

There was discussion in Amsterdam a few weeks ago about a new drug for urea cycle disorders. I think it is called carbaglue. The preliminary data are phenomenal now. Maybe there is a little hype there, as usual, but that seems to be a new, very effective opportunity to treat patients with hyperanemic episodes.

If that is proven true, our old perspective of the lack of response or lack of treatment -- you know, right now, there is another metabolic condition, Peter, that many consider lethal. It is a male newborn with OTC deficiency. They have what Jean Marie over in France, with over 40, 50 years of experience said. If a baby has a pneumonia greater than 3,000 in the first 48 hours of life, he's gone. Maybe, just maybe, if we can pick them up and treat them aggressively, that might not be the case.

So this goes back to the point of evolution, and I think that is where the line was drawn. These are the conditions. The report only are secondary targets that don't "deserve" to be in a uniform panel on their own merit, but they could very well be when something new comes up in terms of tests, treatment, or knowledge. You know, who knows? Maybe there are metabolic disorders that somebody will find out that in middle age, when you're 40, 50, you have a very high incidence of whatever other. Right now, it is a totally unrelated condition. It is just a matter of the way medicine evolves. But we need to collect the data. We need to have the patients for that. That is why it is important to keep them there.

DR. WATSON: It's very high on our list in the regional collaboratives as an issue to try to figure out how to deal. I think it was you yesterday that said traditionally, and for the most part, newborn screening programs are service-oriented entities. I think it is a mechanism to broaden their capabilities by taking advantage of other relationships that can be built around the programs.

DR. HOWELL: And Dr. Watson is alluding to the newly funded regional collaborative programs that HRSA has funded. Again, there will be an opportunity to collect data from those regional. On the next meeting of this committee, we are going to ask Dr. Puryear and her colleagues to tell us more about those in some detail.

Dr. Cunningham?

DR. CUNNINGHAM: Actually, in screening programs, we don't report out diseases. I report out abnormal biochemical findings that have been associated with diseases. I report out hyperphenylalaninemia consistent with prematurity, consistent with classical PKU, consistent with biopterin deficiencies. We send them to metabolic centers, and they make a diagnosis. But we follow every elevated phenylalanine, and we track it until we get a diagnosis.

The same thing with tandem mass. We will list even rare conditions. Piero just described methylmalonic encephalopathy. Okay, that's one of the differentials. We don't know how well they will pick it up. We're going to call it to the attention of our metabolic experts. Most of them will turn out to be something different.

But if it is detectable by the biochemical abnormality, we want it in the differential, and then they will report to us what they find.

DR. HOWELL: We have a great deal of interest in this. We'll start with Piero briefly, and then we'll go to Brad, and then to Jill.

DR. RINALDO: First of all, I want to say that I found myself agreeing with Dr. Cunningham four times today. That is probably a record.

(Laughter.)

DR. HOWELL: Maybe we should go to lunch.

(Laughter.)

DR. RINALDO: But Dr. Cunningham is absolutely correct. You know, we often discuss about what the perceived difference is between screening and biochemical genetics. But in reality, there are none. Screening done by tandem mass spectrometry is a form of biochemical genetics. As such, because we look at the phenotype, we do not make diagnoses.

We find what abnormalities are consistent with, or indicative of a certain disease, and if we do our job right, we are really supposed to give a differential diagnosis. We say well, it could be this, it could be this, or another thing.

Again, if according to the standard of the guidelines we follow in the American College of Medical Genetics, we are supposed to give some options about what to do next.

The reason why I really want to emphasize all of this is because one of the biggest obstacles I have encountered over the last few years when we deal with all of these issues is like a stereotype position. When I try to bring some of these, and Mike loves the word "granularity," but when I'm trying to bring a higher level of detail to the discussion, I'm always turned back when I hear people say, remember, this is screening, not diagnostic.

I really encourage whoever is responsible for the perpetuation of the stereotype to drop it. If you start doing newborn screening by tandem mass spectrometry, that is just a known stereotype that has no real reason to continue to exist. There is no difference between screening and whatever you call it, diagnostic, if you do it in a multiplex platform.

DR. HOWELL: You've raised even more hands. We are going to go to Brad, and then Jill.

DR. THERRELL: I thought I could agree with Piero until the last comments. I'm not going to go there.

What I do want to talk about a minute is this numbering thing in 30 and 25. I really hate to see this coming, because we are already having trouble when we ask the states, you know, how many disorders do you screen for?

The trend among advisory committees lately has been to say, whatever detectable disorders we can find. So if you ask North Carolina, give me your list, they'll say, well here it is today, but it is going to change tomorrow if we find another case.

So there is another way to think of these things. You have to think of them rather in numbers as all fatty acid oxidation disorders detectable by tandem mass as a group, and so on and so forth. Now, there has been a lot of rigor applied to the mass spec part of this report, and not very much rigor at all to the hemoglobinopathies and to the endocrinopathies.

In fact, if you look at what the states are doing with respect to, let's say, CAH, CAH is a magnitude of disorders, a magnitude of different numbers of disorders. We are only looking for 21-hydroxylase deficiency CAH. Some states would say they are only looking for salt-wasting 21-hydroxylase deficiency CAH. That is not broken out that way in these numbers.

Hemoglobinopathies, there has been no attention paid to E, and as George has mentioned recently on the Internet, if you look at what California is reporting out, 27 hemoglobinopathies, or 23 hemoglobinopathies. So if you are going to get into numbers, I think you need to pay some rigor to these other disorders beyond the metabolic disorders.

DR. HOWELL: Jill?

MS. FISCH: I'm trying to think of the best way to phrase my question. I guess it would be coming from an SCAD family where there are four of us now, my father, myself, and two out of three of my children clinically diagnosed, it is an official diagnosis.

Having that diagnosis been made through the private sector, and my youngest son who spurred us to find these other diagnoses in the family not being picked up in the screen because New York did not screen for SCAD, is there anyone who follows them other than the private physician so that treatment can be watched in how it is affecting us as a family to benefit other people down the road?

Because if you don't pick up the babies, and you don't treat them, you won't be able to provide treatment for them. Do you understand what I'm saying? What I'm wondering is what mechanism can there be in place for babies who are not picked up during the screen, but are picked up privately? Do they get reported anywhere? What happens to them so that they can be followed as well, and we can learn from them, too?

DR. HOWELL: Again, I would ask others in the room to comment. I'm not aware of a mechanism at the current time to have those children diagnosed privately to come into some common repository. But that may be incorrect.

DR. THERRELL: If you make them a reportable disease within the state, if you classify them as a reportable disease within the state --

DR. HOWELL: What states have such recording?

DR. THERRELL: Every state has some diseases which are reportable to the state.

DR. HOWELL: I know that, but are any of the conditions that we're talking about on that list?

DR. THERRELL: They could be.

DR. HOWELL: Such as?

DR. BOYLE: I was going to say, they could come in under birth defect registry programs. Some states do collect information on that. It would be easy to augment those types of data collection systems that are already established.

DR. WATSON: And I think it is fairly routine in every program to request that the diagnostic community, make them aware of a case they find that was not detected by screening. I think invariably, and I know at Washington University when a case came into our center, one of the first things we did was go back to the newborn screening side to really find out why we're getting them now instead of at the time of newborn screening.

DR. HOWELL: Dr. Hannon obviously has some comments on this area.

DR. HANNON: I know that Dr. Rinaldo and I have had many discussions about screening versus clinical testing. But no matter how good the mass spec is, it is no better than the sample that you use to analyze.

Blood spots are highly variable. You can take a good blood spot, and you can get an equivalent answer to serum. But in many cases, there are a lot of variances you cannot control, such as the size of the spot that is collected, the hematocrit of the sample, and the age of the spot. These all create uncontrollable variances.

So when you do a blood spot, it is not like doing a serum sample which doesn't have these same sorts of variances. Go ahead.

DR. RINALDO: It's exactly the same. A serum can be analyzed, a sample could be a known fasting, it could be a short sample. The number of variables that you encounter in clinical practice that are affecting the testing are the same, if not more, of what you encounter testing blood spots. It is a myth.

DR. HANNON: I don't believe it, because the size of the spot has different volumes of serum. You can say that contamination of serum might have different volumes also. The aging is a fact that you're gong to have a hard problem equating to serum sample.

These variances are part of the problem with putting the screening situation in place. If you're going to standardize mass spec, you're going to have to standardize the quality of the blood spot collected.

DR. RINALDO: Harry, it is the same. Think about it. How long the sample was refrigerated, was frozen, was frozen and thawed several times. There are equal, if not greater, number of variables that affect the quality of a specimen. So that is not a difference.

Can I say one more thing?

DR. HOWELL: One more only.

DR. RINALDO: Only one. The solution is very simple. Read the emails that were exchanged on some of the listservs. Dr. Cunningham and I have already sort of come together to it.

Let's count markers. That is a finite number that cannot be manipulated. If you count the analytes, you will tell what the program is doing. Then you will ask for every analyte, what the differential diagnosis is. That's the end of story. That will achieve standardization.

DR. HOWELL: Thank you.

DR. LICHTER-KONECKI: This is Uta Lichter from Children's National Medical Center in Washington. I wanted to comment on the clogging up of the system that Piero Rinaldo referred to earlier.

As one of the people on the front line, what is clogging up the system is the cutoff values. We see newborn screening from Maryland, the northern part of Virginia, West Virginia, we see some from Pennsylvania and Delaware. We have the whole spectrum of what is being screened and not screened.

Since Maryland went on with tandem mass spectrometry, all the MCADs I have seen were heterozygous for the common mutation, but if Maryland would apply the cutoff value Dr. Militen has taught me to use, the C8/C10 ratio, I would have not seen any of these children. The same with leucine.

Obviously not every screening program lab is run by Piero Rinaldo, but that's what is clogging up the cutoff values.

(Laughter.)

DR. LICHTER-KONECKI: No, there has to be a consensus. If every lab uses different cutoff values and reports every mild elevation, that is what is clogging up the system.

But at the same time, with the report only category, I had a patient recently who was creened in Virginia, which screens for MCAD, but does not report other acylcarnitine profile abnormalities, and had CPT2 deficiency, and it would have been very helpful to me if it had been reported to me. It would have speeded up a diagnosis tremendously.

So I think if the real pathological values would get reported, it would be very helpful. What is driving us crazy is all these very mild elevations that are getting reported.

DR. HOWELL: I think your point is obviously a very important one, and one that has been brought up I think in different contexts this morning about the cutoff points and the laboratory false positives.

DR. RINALDO: It is all the false positives. That is a key issue. It is the elephant in the room that we're not addressing. The rate of false positive is what drives all these downstream negative mostly, well, completely negative effects. She is absolutely right.

The point is not being able to discriminate. Again, it is another one of the old ones, the Singleton test. Aligning it below this level is normal, above is abnormal. Where these lines are drawn without any interpretation of the data is what causes unnecessary numbers of false positives. We have to address the rate of false positives. It is a key element.

DR. HOWELL: It was very helpful to hear from one of the metabolic experts in the center today looking at some of the referrals from three states that underline that importance. You had something? Brad has more to say.

DR. THERRELL: Let me just mention on that. We actually tried to bring together the community to help with this problem about two years ago. We had everybody who is doing mass spec in a room here in Baltimore, including your group and other groups. They all sat down and decided that they were willing to share cutoffs, and willing to share diagnoses on the Internet system.

We set it up. Everybody is volunteering to put their data in, we are to collect it in a library, and then re-analyze it. That system has been still in place for two years, and the only people who have contributed to it are Wisconsin and California. Nothing from your lab, nothing from Baylor. I know that takes time, but unless we do that sort of thing, we are really not going to come up with those.

DR. RINALDO: I'm sorry. I think part of the problem is really there is no clear understanding of what is going to be done with those data, and by who.

DR. THERRELL: Well, the agreement of the group was, and Steve Goodman was the Chair of this group from Colorado, was that we would put this into a library, and then this group of experts could decide how to help come up with these cutoffs.

DR. HOWELL: We were just having a sidebar here. One of the things we will discuss later today are subcommittees, or working groups, whatever you would like to call them. Apparently in this system they are essentially the same. But one of the early groups obviously should address this kind of issue, QA and so forth.

Are there other comments about this?

(No response.)

DR. HOWELL: Any further comments about report only, which was the overarching subject that we have been on for the past bit of time?

(No response.)

DR. HOWELL: Other comments on the report per se that we've heard about yesterday, and that people have thought about overnight? While Mike is still here before he flees the city.

(No response.)

DR. HOWELL: Total silence? Excellent. Mike, have a seat. Thank you. Wait.

MS. MONACO: I didn't know you were leaving. I was going to save this for my public comment this afternoon, but since you're leaving. I wanted to commend you for your work and your efforts in compiling this panel.

I have to admit that I have been listening to all these presentations, and it is somewhat appalling as a parent to listen to the cost-effectiveness issues, and putting dollar signs on these children's lives, and bargain shopping, as you will.

The work has been done in place. I don't think we need to reinvent the wheel. This serves as a real foundation for something to grow. All these issues will take place and be handled in the future.

So like anything else, everything has kinks in it, and I think this is one. But I just wanted to thank you, because I think we owe him a lot to this.

DR. HOWELL: Thank you very much.

(Applause.)

DR. HOWELL: I might point out that Mike will obviously have access to all the public comments this afternoon. That will be important.

I think in view of the fact that we have reached a silent lull in our conversation, let's go to lunch. We're coming back at 1:00. We've got a number of folks who are scheduled to present this afternoon, and some discussion and planning. We'll return promptly at 1:00. Thank you.

(Whereupon, at 11:51 a.m., the meeting was recessed for lunch, to reconvene at 1:00 p.m.)

AFTERNOON SESSION (1:05 p.m.)

DR. HOWELL: Ladies and gentlemen, we have a number of folks who are going to speak this afternoon. We are very pleased that they have joined us to provide information to us. Since we do have a considerable number of folks -- we have 12 people who have signed up to report during this time -- we're going to have to be quite rigid about staying within the five minutes, or otherwise we will have a problem with time.

I'd like to begin and welcome Dr. George Hardy, who is Executive Director of the Association of State and Territorial Health Officials. Dr. Hardy?

DR. HARDY: Thank you, Mr. Chairman, very much, and members of the committee. I am George Hardy, the Executive Director of ASTHO, the Association of State and Territorial Health Officials. Our members are the chief health officials of the 50 states, 6 territories, and the District of Columbia.

I will certainly honor the time constraint. I would just like to make three key points with you today, and I think that you know all of them. One is that clearly newborn screening programs are a true public health success story. State public health agencies have had a pivotal role in their administration. Two, that the state public health agencies will need adequate resources to support any expanded newborn screening programs in their states. And three, that we would hope that you all could add additional representatives from state public health agencies, particularly the policymakers at the state health official level and other program administrators, particularly at Title V level in your deliberations to bring that perspective to your recommendations.

Newborn screening programs, as you know, are obviously complex systems that save lives and improve programs. They have five major components. Screening, follow up, diagnosis, treatment, management, and evaluation. Across the country, the state public health agencies have been responsible for assuring the provision of that full range of services.

For a newborn screening program to function optimally, adequate funding is going to be needed to support that integrated system, from specimen collection, through the follow up, and evaluation. Failure to consider the system in its entirety will result in a fragmented system, which is unable to effectively benefit the public's health.

State programs have developed and expanded differently over the years as a result of differing state infrastructure, financing mechanisms, as well as varying statutory requirements defining the scope of mandated services.

Each state has been responsible for designing and implementing its own program in the context of that individual state's economic, demographic, geographic, and political manifestations.

While the structure allows for great flexibility for newborn screening programs, it also creates significant variation among the states. To date, as you well know, there has been little federal guidance in relation to optimal program models.

This committee has discussed the possibility of recommending a uniform panel of tests for states to adopt. Scientifically based recommendations to aid states in making decisions about the number of disorders for which to screen would certainly be welcome.

However, such recommendations must also be responsive to the state needs and fiscal realities. We urge the committee to recommend that HHS provide not only guidance, but sufficient funding to states to support every component of the newborn screening program.

Again, because state public health agencies have a leading role in the administration of these programs, it really is important for representatives of state health agencies to serve as members with this group. We are delighted that Dr. Becker from Ohio is on the committee, who brings a very important perspective to this. We trust that you can also appreciate the need for inclusion of the prospective of agency's chief policymakers, and other public health officials with the responsibility for other parts of the program. Including these would be vital to making recommendations that are feasible and reflective of state needs and fiscal circumstances.

So in conclusion, the state newborn screening programs as they expand, the state agencies are going to be faced with new challenges and opportunities. Your committee is in a unique position of providing recommendations to states to strengthen these programs, and to contribute to the improved health of infants and children in the U.S.

We certainly appreciate your efforts in that regard, and we look forward to assisting you in any way that we possibly can. I thank you for the opportunity. If I can answer any questions, I'd be glad to do so.

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

Are there any questions of Dr. Hardy at this point?

(No response.)

DR. HOWELL: I think we appreciate your perspective. I think the committee is very much aware of the importance of your organization as we move forward with any recommendations.

DR. HARDY: Great.

DR. HOWELL: We appreciate your willingness to participate.

DR. HARDY: Thank you very much for the opportunity.

DR. HOWELL: Thank you.

Our next presenter is Dr. Norman Kahn, who is President of the Society of Teachers of Family Medicine.

Dr. Kahn?

DR. KAHN: Thank you, Dr. Howell and members of the committee. Only one correction. My role with the Society of Teachers of Family Medicine is left over from a previous project. I'm here as Vice President for Science and Education with the American Academy of Family Physicians.

But in reality, at this hearing today, I am sitting here representing more than the nation's family physicians, but the general internists, the general pediatricians, the obstetricians, the nurse practitioners, and the physician assistants who practice primary care.

I had the privilege of serving as Project Director of the Genetics in Primary Care Project, which was funded by the Maternal and Child Health Bureau, and the National Human Genome Research Institute, with co-funding from the Agency for Healthcare Research and Quality, and the Division of Medicine and Dentistry of HRSA.

I'm now serving as Project Director of a new project called Annual Clinical Focus 2005 in Genomics. This project is produced by the American Academy of Family Physicians, but in cooperation with the disciplines of internal medicine, pediatrics, OB/GYN, nurse practitioners, physician assistants, and the American College of Medical Genetics.

What we're going to be doing with your support, and thank you for your support, is to provide a monthly online curriculum for the nation's primary care clinicians in the area of genomics. Newborn screening is going to be one of the most important of those particular curricula. Actually, there is probably going to be a little bit more content in newborn screening than in some of the other curricula.

You all will have an opportunity next year when this is launched in 2005 to have access to the monthly archived online curriculum. The newborn screening module will probably come out in the spring. We will be subcontracting for some additional support to provide some additional newborn screening modules as part of that.

One of the things that will happen for the nation's primary care clinicians is that these 30-minute programs will end with a web tour. The web tour will identify websites for clinicians, but also for patients. They will identify resources for clinicians, as well as for patients. We are looking forward to utilizing the support and the participation with you, and with the Maternal and Child Health Bureau, and other agencies involved to provide the newborn screening materials as part of that curriculum.

The program will be launched at the World Meeting of the Nation's Family Physicians and the World's Family Physicians, which is two weeks from now. Francis Collins will be the keynote speaker at that particular meeting. We will be then putting the first programming online for the primary care clinicians in the United States in January, and then monthly thereafter.

I'm not asking you for anything, because you have already been very supportive. I just want this committee to be aware of the role that the federal government in concert with the private sector has played in making sure that the primary care clinicians in the United States have the information that they need to provide adequate services. Particularly in an area as rapidly growing as genomics, and in this case, focusing on newborn screening.

So in closing, I'd just like to thank Michele Lloyd-Puryear for her strong support, Dr. Howell for your support, and Dr. Hanson's support as well. Also, from the National Human Genome Research Institute, we've had a great deal of support from Alan Guttmacher, Francis Collins, and particularly Jean Jenkins, as well as Dan Wotendorf, and finally from the National Coalition for Health Professional Education in Genetics with Joe McInerny.

If you have any questions about this program, I'd be happy to answer them.

DR. HOWELL: Thank you, Dr. Kahn. I think it is very encouraging to hear that you as a leader of a broad group of primary health care providers are, shall we say, tooling up to deal with what is clearly happening nationwide in the expanded area of newborn screening.

You seem from your comments to be rather fearless as you and your group move forward in this new area.

DR. KAHN: I didn't realize there was something to be afraid of, Dr. Howell.

(Laughter.)

DR. HOWELL: I commend you. There are those weak-kneed folks that worry about these things, but I'm glad to see that you are rather than worrying about it, are really tooling up to deal with the inevitable and clear cut changes in that area.

Are there questions of Dr. Kahn about his program? It is a very exciting program for 2005 that will have a broad swath of genetic impact and so forth.

Dr. Boyle?

DR. BOYLE: Is there a way that we can learn a little bit more about the content of the newborn screen module?

DR. KAHN: Yes. We are developing this in concert with both the National Institute for Child Health and Human Development, as well as the Maternal and Child Health Bureau. Marie Mann from MCHB is our primary contact on this. So there will be plenty of opportunity for learning more as this is developed. It will probably be taped in April of 2005 for online delivery sometime thereafter.

DR. HOWELL: Anymore questions of Dr. Kahn?

(No response.)

DR. HOWELL: Norman, thank you very much.

DR. KAHN: Thank you.

DR. HOWELL: We will next go to Mr. Martin Kharrazi from California, who is speaking to the group today as a parent.

MR. KHARRAZI: Thank you, Dr. Howell. It is an honor to be able to speak with all of you during this public comment period. My name is Martin Kharrazi, and I live in Alameda, California. My wife and I have five children. Our middle child, our son, has cystic fibrosis.

Our son was diagnosed 11 years ago on his third birthday. During his first years of life, we struggled to learn of his diagnosis, because at the time, California did not have a newborn screening program which included cystic fibrosis, nor does it currently, as you know.

Despite a five-day hospitalization for respiratory infection at four months of age, poor growth even after dietary changes, foul smelling, runny, and frequent stools, an insatiable appetite, chronic bronchitis and coughing, sleepless nights, and many, many other symptoms, we have discovered that our son's diagnostic odyssey is mild in comparison to many others.

We cannot expect that our pediatric care providers can consistently make a cystic fibrosis diagnosis when far more common reasons exist for these kinds of signs and symptoms. Dr. Watson and other speakers yesterday pointed out that the criteria for newborn screening are changing in the wake of recent technological advances like tandem mass spectrometry and DNA analysis, and due to increasing public advocacy.

A new category of report only disorders has been created for those disorders picked up in the course of multiplex testing protocols. It was great to hear the discussion this morning around that particular issue, because it is very important. It appears to me that there is a perception by the expert panel that providing such information early in a child's life is important for families and their care providers, and is in the best interest of the affected infant, even though demonstrated health benefits from early intervention have not been clearly established.

In support of this perception, I would like to provide the committee with a summary of the impact of delayed diagnoses on families provided to me over the last couple of years by over 40 families with cystic fibrosis as a simple email request over one of the CF listservs.

Families reported that a delayed diagnosis of CF comes with large and irreversibly negative impacts on the affected person's health and development, their quality of life, longevity, compliance with medical regimens, self-image, family structure, and major life decisions.

There were serious impacts on the relationship between family members. The stress around not knowing what was wrong damaged the family. Economic losses were common during the prediagnostic period. Parents developed strong views about the incompetence of the medical care profession. Negative effects on families were compounded the later the diagnosis of CF was made. Trust in the medical system was lost at a time when it could offer so much good.

Long-term parental guilt around not finding out sooner was difficult to avert altogether, or remove later. Delayed diagnosis meant that opportunities were lost to make informed decisions about health care, employment, housing, insurance, reproduction, and a host of other matters.

Parents felt that appropriate steps could have been taken to prevent their child's now irreparable lung disease, had they known sooner about the diagnosis. A few parents had had a first child diagnosed on account of a second child being diagnosed early in life via newborn screening.

We summed it up by saying that it is far better knowing the diagnosis rather than being tormented by not knowing it. It is extremely hard to plan for the future when it is unclear what was wrong with the undiagnosed child with CF. There was parental regret, anger, and pity for the older CF child who was not able to benefit in the way the younger child could now through preventive and focused CF care.

This care is considered to be most effective for persons who present early, without damaged lungs or nutritional deprivation. So as the committee goes forward with making recommendations to the Secretary, it would be my hope that research funding becomes available through one of the possible federal mechanisms to comprehensively measure and evaluate the costs, risks, and

benefits of an early diagnosis to not just the affected child, but the broader family of that affected child and children.

This is an area in newborn screening research that has been largely neglected here in the United States. Report only disorders, if I can call them that, may offer a golden opportunity to evaluate the impact of providing information to families and physicians about disorders that do not yet have a clear treatment benefit.

The results of such work would help policymakers solidify the criteria for newborn screening, as the availability of tests for genetic disorders is going to increase dramatically over time.

In closing, I want to express my appreciation to those on the ACMG Expert Panel who have decided to include cystic fibrosis on the National Core Panel of Disorders for Newborn Screening, a decision which is in line with recommendations to be coming out of the CDC and CF Foundation later this fall.

Finally, I want to just conclude with saying with from my eyes as a parent, I see newborn screening as the first step in the proper, routine medical care for cystic fibrosis, and many, many other disorders. I think that should be seen as its new place.

DR. HOWELL: Thank you very much, Mr. Kharrazi. Unfortunately for time, we'd better move along. I'm sure there are many issues that we would like to discuss with you, and perhaps we can later.

We are going now to Dr. Nancy Green, who is the Medical Director of the March of Dimes.

DR. GREEN: Thank you, Dr. Howell. I have several brief comments, because I think that the March of Dimes position was read by Dr. Howell yesterday at the meeting, so I'm going to keep my comments then brief. Plus I want to commend the leadership of HRSA and other federal agencies -- NICHD, CDC, and others -- in accomplishing this quite monumental task. Certainly the March of Dimes is committed to continuing to collaborate with you in newborn screening.

Since you have read the letter, I just want to for emphasis sake, just simply read the punch line of the letter, and then leave it at that. That is, "The March of Dimes supports the findings and recommendations in the report, and urges its swift and positive consideration by the Secretary of Health and Human Services."

I wanted to, in addition to our principles around newborn screening, which I think are very well matched by the committee's report, just to remind you that the March of Dimes will continue to work at the state and federal levels to improve screening to the level of the report's recommendations, and with high-quality follow up, as well as to continue our commitment to public and professional education to facilitate the diagnosis and treatment of affected children.

I also would like to emphasize the need for prospective evaluation of expanded newborn screening, and the responsible application and validation of new technologies and clinical applications, as well as the need for coordination between states and national and federal efforts for implementation and evaluation, as exemplified by the new regional project that HRSA is funding. Certainly you have the March of Dimes' support in those efforts.

You know, the report is a landmark for newborn screening, but newborn screening itself remains an open book. So I think that this advisory committee is in an excellent position to consider

additional paradigms for newborn screening, as well as new technologies and applications with rigorous and transparent processes for expert review and evaluation.

So I'm going to suggest that the advisory committee consider the formation of some subcommittees to look at several important aspects in this open book of newborn screening. The subcommittees I'd like to suggest are four, at least. One is the consideration of application of new technologies and clinical applications. Two, the evaluation of identified affected children. I think we had some discussion this morning that was fruitful around incorporation in existing programs in birth defect surveillance, and the possibility of a Children's Oncology Group kind of model for prospective evaluation of treatments and outcomes.

Three, certainly three is a need for a laboratory component in terms of quality assurance and quality control. And four, certainly the ever pressing need for education and training around newborn screening.

That concludes my comments. Thank you.

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

We are going to clip ahead. Each of these presentations we should have half a day on, I must confess, but I'd like to welcome Ms. Sharon Terry, who is Executive Director of the Genetic Alliance.

Sharon?

MS. TERRY: Thank you for the opportunity to make public comment today. Thank you also for the work of your committee, and for the vision and leadership of the Genetic Services Branch of MCHB/HRSA.

My name is Sharon Terry, and I'm the President and CEO of the Genetic Alliance, a coalition of 600 advocacy organizations representing over 14 million individuals affected by genetic conditions, both common and rare.

I hold this position not as a professional, but because I am the mother of two children affected by a genetic condition, and the founder of a small

disease-specific advocacy organization. The advocacy community has a number of concerns regarding newborn screening. My comments will be both general and specific.

There are a number of premises that must be articulated when newborn screening is considered on the federal level. The first is overarching. We are constrained by economic models developed within a crippled health care system. This conversation would be a different one in a nation with a more equitable alignment of resources.

Next, there are a series of basic premises for consumers. Parents want healthy babies at any cost. Often parents do not know that their infants are being screened, and that screening across states is variable, that the attributes of tests such as sensitivity and specificity, analytical and clinical utility, and validity are variable.

In lived experience, the odds of being affected are either zero or 100 percent. Benefit analysis is not conducted from a medical model. I'd like to comment more fully on the last two points.

In the lived experience, the odds of being affected are either zero or 100. In the moment that one receives a diagnosis, a line is crossed. One's world view is quite different from the moment before the diagnosis. In the new experience, the discussion of odds, whether one will or will not get a disease becomes irrelevant, and individuals have a poignant, though unconscious understanding of public health perspectives versus personal issues.

The public generally assumes that odds apply to individuals. Consumers do not experience the screening, the tests, the diagnosis, and the day to day struggles on a population level. It is completely personal. The affected family, individual, and newborn, uses their lived experience as a prison through which all life is assessed.

The other point, consumers do not engage in benefit harms analysis using a medical model, nor do they consider just the affected child in their decisionmaking . In the minds of consumers and parents, decisionmaking about which test should be part of a newborn screening panel is based on more than just a narrow medical model. Families see benefit even in screening for conditions for which there is no treatment.

I recently asked our members about this issue. Here is an example of a reply from a mother who has two sons with Niemann-Pick disease that poignantly illustrates one reason why one might want to know about conditions for which there is no treatment, a criteria that in some systems is considered a hurdle.

After the death of her younger son, she had her older son tested. This is a quote from her. "A year or two after Rick's diagnosis, when he was apparently still well, I asked him if he ever wished that he did not know that he had Niemann-Pick, and that he had never been tested. He said, 'Oh no, mom. Now I know that I'm not stupid. I know there is a reason for some of the things that I can't do.' When we had thought that he had no obvious symptoms, Rick had been struggling to understand why he was not able to keep up with his peers, why there were some things that he could not do as well as he felt he should."

Parents reported over and over to me that they need to know about genetic conditions in their family, because they need to make informed decisions about lifestyle for the family and the child, choosing care givers and specialists, financial planning, choice of job, educational choices, finding a support group, securing insurance, aiding and building registries, and participating in research.

Thus, the global context of decisionmaking and lived experience for parents includes more than what is traditionally considered in the medical world. Now I turn to issues that are more specific. The Genetic Alliance has a Public Health Action Team, an active group of people concerned about newborn screening and other public health issues.

Parents and professionals engage in daily discussion about many of the problems and potential solutions. I would like to share a brief synopsis of the more frequently discussed concepts.

Number one, it is a problem that there is inadequate understanding about newborn screening and diseases associated with newborn screening. One part of the solution is the proactive work of parents and advocacy groups to raise the awareness of health professionals and the public.

Number two, it is a problem that many communities lack necessary information and resources. Using the proposed uniform screening panel is a welcome recommendation, but the implementation goes well beyond the tests. Parents and advocacy organizations stand ready to be part of the solution to promote effective public decisionmaking .

It is a problem that technologies are advancing faster than policies, legislation, and treatments. Advocates have and will continue to promote this dialogue. It is a problem that consistent,

uniform, and continuous care is not available to all babies, all families, and all Americans. The advocacy community initiates and sustains strong partnerships between parents, professionals, and the public.

Although your attention these days is rightfully focused on the uniform screening panel, I offer specific recommendations of the advocacy community for both the panel and the system. We request proactive outreach to families and parents, input from underserved and underrepresented communities, a uniform newborn screening panel of at least the 30 recommended tests from state to state, resources for the medical home, and for necessary health professional education, health information accessible when and where it is needed, national standards, and increased resources.

We ask this committee to recommend the uniform screening panel as determined by the ACMG report to the Secretary. We also ask that you recommend the panel not as a stand-alone entity, but as part of a larger comprehensive package that would include the above requests, that would allow for resources to support the screening, mechanisms for collecting data after testing postmarket, systems that include resources beyond those usually included in the traditional medical model, including genetic counseling and services.

Finally, we are aware there are many elephants in the room. Tension between public and private labs, a lack of coordination among federal agencies, paternalistic and patronizing attitudes, and even special interest in earmarking behavior among advocates.

I am, in the face of all these obstacles, reminded of what an advocate for newborn screening said in a recent email discussion about the Genetic Services Branch of MCHB. "For their leaders, it's all about the babies." In the name of all of us who have crossed the affected line, I ask you to boldly, bravely make it all about the babies.

Thank you.

(Applause.)

DR. HOWELL: Thank you very much, Sharon.

We are going to next hear from Dean Jerrehian, National Coalition for PKU and Allied Disorders. I probably have murdered your name, so maybe you can tell us how we properly should pronounce it.

MR. JERREHIAN: I've heard worse than that. It is Dean Jerrehian. You were very close. I am with the National Coalition for PKU and Allied Disorders. I'm also here representing a success story of newborn screening. My son was born 12 years ago with PKU.

Back 35, 40 years ago, a lot of people worked very hard to see that every baby was screened for PKU, even though at that point in time, testing wasn't perfect, treatment wasn't perfect, and outcomes weren't perfect. That testing went into effect, and so when my son was born, he was identified. He has been treated ever since then, and he is leading a perfectly normal life, going to school, playing with his friends, fighting with his sister, things that kids do.

What we at the National Coalition would like to see is I think what everybody in this room would like to see is implementation of the American College of Medical Genetics report recommendations as soon as possible. We'd like to see this committee recommend them without any qualification, and just to see it happen quickly.

We miss a kid probably every eight hours right now under the current system. I was last in Washington talking about newborn screening about four or five years ago. I can't even count how

many kids were born since then. I stood somewhere else and said the same thing, let's do it now, it is being done, it needs to be done. There are probably thousands of kids that have been missed in the last four years. So what we're asking for really is let's move this forward as quickly as possible.

I wanted to just bring up a couple of issues that came up in the last couple of days, and just touch on them. I think yesterday Dr. Watson said that he wasn't suggesting in the report that the screening panel represented the current standard of care for newborns. I'm not sure whether he meant that it should be the same, or if he meant that it should be the standard of care. I think the committee should make that clear that that is what we're trying to create here is a standard of care for all newborns in this country.

Second, I understand and totally agree that a good follow-up program is important. I also agree with what was said yesterday, that whether these kids are screened or not, there is going to be follow up required. In cases where they are not screened and they are caught post-symptomatically, the follow up is most likely going to be much more difficult.

What I don't want to see is a situation where states can use the lack of follow up as a reason not to perform the tests sooner rather than later. Maybe what you can do is think about a situation where until the follow up is in place, create another report only category for the disorders that there is no adequate follow up currently.

As an example, I'm from Pennsylvania. We have some great success stories there on newborn screening. The Amish who get by very well without electricity, without telephones, without televisions, without cars, without any government support, happily pay for some very sophisticated lab equipment for their local clinic to help care for their disproportionately large population of children with genetic disorders.

Parents have a way of fending for their children when push comes to shove. So the lack of follow up I think should not be a bar to any state for any particular test at this time.

With respect to the question of public labs versus private labs, I think parents would also agree that we don't really care, as long as it is done right. If the barriers that Dr. Therrell talked about yesterday would prevent a state lab from implementing a particular test in a timely and competent way, we would just ask that the state labs step aside and let a private lab do the testing at that point. Either the way it is done in Mississippi, contract out to the private lab, or the way it is done in Pennsylvania, which I don't think was discussed here at all today or yesterday.

My understanding is that hospitals in Pennsylvania can choose between sending test results to the state lab, or sending them directly to a private lab. The private lab happens to give a wider array of tests. I believe every hospital in Pennsylvania will end up sending to the private lab. You give the consumer, the hospital, the choice as to where the test will be. Competition will improve the success for the children.

I guess I'd just like to conclude by asking the committee when they think about what to do here, what they would do for their child or grandchild who was born next week. If you think knowing what you know now you would have this test done for your child or grandchild, I think that we should pass that information along to the parents everywhere in this country as soon as we can.

Again, we applaud the efforts of this committee, and I know that babies in years to come are going to benefit from what you guys are doing. We just ask that you act quickly and forcefully with your recommendation. We all know where this is going.

Thank you.

(Applause.)

DR. HOWELL: Thank you very much, Mr. Jerrehian.

We are now moving to Ms. Jana Monaco who, again, is a parent. She is speaking as a parent.

MS. MONACO: Good afternoon. It is a privilege to be here once again to address the issue of expanded newborn screening, and represent the Organic Acidemia Association.

When we last met, I shared with you the story of my son, Steven, and his unfortunate fate of brain damage due to the late diagnosis of isovaleric acidemia, as well as the joys and the triumphs with our daughter, Caroline, who just celebrated a happy and healthy second birthday on Monday, thanks to early detection of her having IVA also.

I brought along photos of my children to put a face on these disorders, because many of you probably have never even seen a child with one of these disorders. I have seen and heard a lot of statistics and names of disorders in your presentations. But I remind you that these are real children.

Take notice of the top two photos, for they depict what 24 hours can do to a child gone unscreened. Since the previous meeting, our life continues to depict its ability to drastically change when a child has one of these disorders, and brain damage on top of it.

Shortly after our last meeting here, Steven contracted a strep infection from me, and was hospitalized. To our surprise, he went into septic shock. Once again, my husband and I found ourselves on the fast track of medical intervention to save Steven's life as his blood pressure plummeted to life threatening levels.

Dopamine had to be administered to stabilize his blood pressure in order to transfer him from Virginia to the National Children's Medical Center's PICU, where a metabolic team could closely monitor him. After ten days and another $48,000 added to our infinite pile of medical statements, Steven was well again.

I know cost-effectiveness. We recently found out that one of his surgically corrected testicles had once again moved out of place, and a prolonged bout of hiccups just last week threatened us with another hospitalization. This is all in a day's work with a brain damaged child.

I wish to thank the committee for the letter that went out regarding the need for states to notify parents of supplemental screening. I understand that our parent testimony has played a significant role in the development of that document, for which I am proud of. However, we must not be complacent and stop there.

I commend Dr. Watson and his team for the time and effort that went into developing a uniform screening program and system that we all await to be approved. We want all 30 disorders, with more to be added, and I urge the committee to approve it and get it published.

This plan is crucial for those of us needing the leverage on a state level. I have sat here in amazement listening to the presentations and a lengthy discussion of this matter, and find it difficult to put a cost figure on the life of a child, but I know we all have a budget.

The American College of Medical Genetics has proposed a phenomenal plan. Is it perfect? No. Is there room for development and change? Absolutely. Are there issues to be addressed? Yes. That's the glory of it. It is an excellent foundation for expanding newborn screening nationwide. Like everything else in history, there has to be a beginning, with a prospect of growth and fine tuning.

Without grassroots and a solid foundation, we cannot move forward, and there will be more Stevens. With the support and guidelines of the government, states are going to be willing and able to develop their screening programs, and ensure every baby a healthy start in life, whether it be with developing their own labs, or using the public and private partnership.

Let's face it, the money is out there. We need to know where and how to put it to good use. One aspect that I have heard complaints about, but no suggestions is the lack of specialists in the field. However, this too should not deter from the proposed plan.

I hope that considerations will also be made to provide funding for the development of more metabolic specialist positions, both physicians and dieticians, throughout the country. Though few in numbers, they are an integral component in the follow-up care and management of these disorders. I can tell you that out of all the specialists that oversee Steven's care, and there are several, our metabolic team is by far the most critical and readily available of all.

They have put in more hours than one can imagine on limited funds, yet have a level of commitment and dedication that we should all be so lucky to have. As you leave here today, think about the life that my husband and I go home to like so many other families. Consider the fact that you have a hand in preventing further situations like ours. I thank you once again for your time and dedication to newborn screening.

(Applause.)

DR. HOWELL: Thank you very much, Ms. Monaco.

We now move to Ms. Jill Fisch, who is the National Director of Education and Awareness at Save Babies Through Screening Foundation.

MS. FISCH: I'm a little emotional. I'm sorry. Thank you for the opportunity to speak today. My name is Jill Fisch. I am the President of Matthew's Mission, a not for profit corporation formed to create awareness about newborn screening and to promote SCAD research. I am also the National Director of Education and Awareness and a member of the Board of Directors of Save Babies Through Screening Foundation.

We are a family severely affected by SCAD. My father, two of my three children, and I, have all been diagnosed as having SCAD. My son, Matthew, was the first to be diagnosed after two years of searching for answers as to why he failed to thrive and suffered from developmental delays.

At the June advisory committee meeting, I spoke about parental notification of supplemental screening. I would like to thank the committee for taking the action that it did in sending letters to the states regarding parental notification. It is imperative that parental notification be mandated across the country.

This information must be given to families in the early stages of pregnancy, which would allow the family to weigh its options and make an informed decision. It is a known fact officials involved in newborn screening programs in various states have admitted to having supplemental

screening performed on their children and grandchildren. It is quite unfortunate that the general public does not have the opportunity to obtain the same knowledge and give their babies the same healthy start.

We also need to have a plan under which low income families can obtain supplemental screening, possibly through the use of grant money, or a voucher program. Perhaps this can be accomplished through the Healthy Start Program. Until the states screen for all disorders, it cannot become an issue of only the rich being able to obtain supplemental newborn screening.

There has been much discussion regarding screening only for disorders considered to be treatable. If disorders are not screened based upon treatment availability, how will the medical community develop treatment for these disorders? There is substantial value in knowing.

The use of the word "treatable" is an issue due to the fact that in the 1960s, the World Health Organization decided that you can only screen for disorders that have known effective treatments. That was then, and this is now. Whose language should be updated to screen for disorders for which there is substantial value in knowing? Genetic disorders can and do happen again.

Regardless of treatability, parents need to know before they decide to attempt further pregnancies. While the death of a first child may not always be prevented, with comprehensive newborn screening, subsequent deaths can be prevented.

Kileen Hall, a board member of Save Babies, and her husband lost their first child 28 hours after birth. Supplemental screening would not have saved him. The medical examiner concluded incorrectly that a heart defect was the cause of death. The couple had another son who also died 28 hours after birth. The second death was preventable.

Kileen and her husband suspected a connection between the two deaths. They found out their second child had VLCAD. They went back and had other testing performed on their first son. He also had VLCAD. Supplemental screening on Kileen's first son would have prevented the second death.

Regardless of degree of treatability and evidence or lack of evidence to support such, supplemental newborn screening prevents or lessens serious consequences in many cases. Some doctors and state officials are still saying that some of the disorders are so rare, it is not worth the expense of testing for them.

It is as though a child with a very rare disorder is worth less than a child with a more common disorder. Let's all remember, it is not disorders that are excluded, it is the children with these disorders who are excluded.

The incremental costs for running the additional test is insignificant. How many damaged or dead children do we need to document before we learn that early detection improves the quality of their lives? Let's screen them, find out who has what, and collect data about interventions that are provided in a positive, proactive way.

I finally wanted to present to the committee as I prepare with Micki Gartzke to attend a follow-up meeting with high ranking health officials at the capital in Albany next week. I anticipated, as did others, that Dr. Pass would take this opportunity to share that New York is making what are supposed to be exciting changes in the New York Newborn Screening Program.

However, I am very concerned based on Dr. Pass' presentation as to the high rate of false positives. Not knowing what New York has planned at this point, this to me is a perfect example of

where a public/private partnership for screening might be highly beneficial while New York continues to go through the tandem mass learning curve.

I look forward to contacting the committee next week with whatever progress has been made. We also need to address the manner in which states are counting disorders for which they screen. Am I taking too long?

DR. HOWELL: You're getting close.

MS. FISCH: Okay. I knew that would happen.

DR. HOWELL: Yes.

MS. FISCH: Many states are inflating their counts. There must be national standards set. The state should list the markers they are testing for, as that must be a precise number, and list separately the conditions to be considered in the differential diagnosis of an abnormal result for each of them alone, and in combination. Do I have time for the last paragraph if I talk fast?

DR. HOWELL: Yes.

MS. FISCH: Okay. That's how I can talk quickly, because I'm from New York. The last issue I would like to address is the resistance shown by members of the medical community when asked to perform supplemental newborn screening.

I have had many cases brought to my attention where a family has prepared to have their child supplementally screened, and have been talked out of it while still at the hospital. These families then had to seek the screening through their pediatricians. It would be quite tragic if a child suffered from a disorder and had serious complications while the family was trying to get the child screened.

One pediatrician told a mother, it is too time consuming to perform the tests. Perhaps most disturbing was the call I received from a New York family. The mother had G6PD and wanted to have her baby screened. The pediatrician refused to perform the testing, and called it a marketing ploy. I had to make arrangements for the mother to have the screening performed. I also had to help her find a new pediatrician.

There needs to be an educational program in place for the medical community so that they become informed, and this does not happen. The best thing we can do is arm the doctors with proper knowledge so that they can provide the best care for their patients. When a parent is looking to have their child supplementally screened, they should be met with encouragement, not discouragement.

Thank you for letting me run long. I thank you for all the advancements you've made. Thank you.

DR. HOWELL: Thank you, Ms. Fisch.

We now go to Ms. Micki Gartzke, who is Director of Education and Awareness for the Hunter's Hope Foundation.

MS. GARTZKE: Mr. Chairman, members of the committee, and HRSA, thank you for the opportunity to share my comments. My name is Micki Gartzke. I'm the Director of Education and Awareness for Hunter's Hope, as you just said.

I, along with many thousands of families who have gained awareness of the need to improve newborn screening applaud you for your hard work and your commitment to helping improve this large national health care problem. Expanded newborn screening is something of great value to the overall well being of the United States.

After hearing the presentations earlier today on costs, which needless to say I found very interesting, and the ensuing questions and discussions that followed the presentations of costs, some of which I noted earlier today in my notes of cost-benefit analysis, validity of costs, variables of costs, manipulations of variables of cost, I just am compelled to share that we need to remember that the one real cost are the stake of children's lives. That's the one real cost in everything that is at hand.

As did Dr. Edwards at the opening of his presentation to this committee at the last meeting, I urge you to please remember always first and foremost that you are dealing with children and families, and not just diseases. Please remember that the range of benefits extends far beyond infant morbidity and mortality.

I come to the newborn screening world from the perspective of a parent who has a lost a child to lack of early identification, and consequently lack of access to effective treatment, as you may recall from my previous public comments at the last meeting.

I am a childless mother, and it is not by choice. It is not a role that I relish. I will do whatever I can to prevent this unnecessary thing from happening to other parents.

The media and solutions are my two messages today. I believe policy development should de driven by what is in the best interest of the newborn. And from a mom's perspective, this is all about immediacy, and keeping the babies in mind always first and foremost. I can't help but wonder if there is enough time for the state health departments that need to get up to speed, to get up to speed on all the aspects of newborn screening before many more thousands of children die or become permanently disabled.

Children continue to die while waiting for the state programs to be tried, and in some cases, to be retried. I thank you for your leadership on the parental notification issue. It seems like you have kicked off your committee's work with your first action by sending a letter to the states urging them to pursue this important lifesaving, low cost educational avenue. Thank you very much.

You are victorious in your pragmatism in this area. I, along with others, hope there will be a significant impact in a relatively short amount of time because of your immediate response to the public comments you heard from parents at the last meeting on this.

I will not expand on what we have already heard about various screening health officials who have informed their own families about the value of supplemental screening, but to date have not felt compelled to share it with families and the states for which they have a responsibility to provide public health.

Rather, I will share my concerns about the type of turf behavior that that exhibits. I don't know if that behavior is the right thing to do. You guys are the experts. You need to help me understand why or how that type of leadership needs to be allowed to be continued, because I don't understand that.

I firmly believe that there is some sort of potential role between the federal and the state, some kind of partnership and oversight compliance, financing, and implementation of the national goals for newborn screening.

We have seen too much resistance to change on the part of many states that desperately need to change. I firmly believe in the innovation through regional testing, contracted public and private partnerships will be the key to improving the overall quality and scope of newborn screening programs. This, of course, again keeping the focus on the health of the newborns, and an efficient use of resources at the top of mind.

I don't need to tell you that state programs are under capacity, and often without funds for increasing competencies or capacity. You know the solutions are available today in regional networks and through public and private partnerships. We heard a few, the Mayo Minnesota model, and the Mississippi Pediatrics model. The solutions are out there, we just need to use them.

I look forward to hearing later today that the committee will be adopting the ACMG report with the initial list of the 30 recommended diseases, as well as the guidelines for adding additional diseases in the near future. I look forward to the day when we have a comprehensive standard of care for every baby born in this country.

The disease that killed my little blonde haired girl when she was two is one of the five lysosomal diseases that Dr. Watson described yesterday as a moving target. That will meet the guidelines once a test is ready. I am working very hard, along with a number of others, to get a pilot program initiated for this multiplex lysosomal test, and I look forward to when it is completed to share it with you so that we can get added to the new list of diseases that can be screened.

We need your help to move forward. I know this committee continues to work hard and to progress quickly on these and other issues. I look forward to continued participation, along with my colleague at Hunter's Hope, Jim Kelly. We want to help however we can. I thank you very much for everything you've done to date, and I look forward to seeing you in three months.

(Applause.)

DR. HOWELL: Thank you very much, Ms. Gartzke.

We are next going to hear from Dr. Karen Dixon from the Parents of Infants and Children with Kernicterus.

DR. DIXON: Good afternoon. I'm Karen Dixon. I'm a cofounder and President of Parents of Infants and Children with Kernicterus.

The short video you are about to see focuses on the value of screening for hyperbilirubinemia. In the last four years, PICK has been very diligent in changing the practice of newborn jaundice management. We have certainly met the bar for evidence for screening. Recently in the AAP guidelines that came out in July of this year, they stated that bilirubin testing is the best documented method to determine the risk of hyperbilirubinemia. I'm also the parent of a 15-year-old with kernicterus.

(Videotape shown.)

DR. DIXON: I'd like to close by asking the committee to remember that we can only prevent kernicterus. There is no treatment for it. Thank you.

(Applause.)

DR. HOWELL: Thank you very much. Thank you very much, Dr. Dixon, for your presentation.

We are going to next move to Dr. Michael Rock, Professor of Pediatrics at the CF Center at the University of Wisconsin in Madison.

DR. ROCK: I appreciate the opportunity to address the committee. I wanted to provide some more information about CF, and clarify some statements that have been made over the past two days.

First, this morning Dr. Scott Grosse brought up the question about cost analysis. That has been done in Wisconsin. I would point you towards the Journal of Pediatrics 2003 Volume 142, an article by Don Lee and colleagues, in which we looked at the cost of newborn screening, and diagnosing patients through newborn screening versus conventional diagnosis. We found that they were equivalent. There was a cost savings of fewer sweat tests done in Wisconsin with newborn screening.

I'm grateful that CF made an ACMG panel of 30 disorders. In looking at the CF fact sheet, the comment section was somewhat less than enthusiastic, and I'll read this verbatim. "Cystic fibrosis screening remains controversial. Nutritional benefits shown by improved growth were less pronounced after five years. However, recent evidence suggests that nutritional benefits may have a positive influence on cognitive abilities, though the data is yet to be published."

The slide prior to this from Dr. Watson showed the AAP evidence guidelines. Level 1 is evidence from randomized controlled trials. I would point out that CF is one of the very few newborn screening disorders that has had a well designed randomized control trial. One cannot say that for most of the disorders.

The evidence, in my opinion, is quite strong and compelling. With regard to nutritional benefits, that has been published in my written comments, reference number 3, Pediatrics, January, 2001. We showed nutritional benefits actually beyond five years of age into the early teen years.

We have extended our observations. There will be a supplement of the Journal of Pediatrics coming out next month in which we have extended these nutritional benefits into the late teen years.

With regard to cognitive benefits, we actually have published that data. This is reference number 4, Rebecca Koscik and colleagues, in which we showed that patients diagnosed conventionally had a longer period of Vitamin E deficiency. They scored lower on a cognitive abilities test compared to newborn screen patients.

Benefits have been a little bit more difficult to get a handle on. We have not seen benefits in Wisconsin or in a study in Brittany, France, but there were significant differences in pulmonary function parameters using newborn screening in the Netherlands. Reference number 7 by Merelle by colleagues, and in New South Wales, Australia, Waters and colleagues, reference number 9 in my written comments.

There have been some studies showing improved survival of newborn screening in two observational studies. Again, Netherlands by Merelle and colleagues, and Wales West Midlands United Kingdom, Doull and colleagues, reference number 10, Pediatric Pulmonology, 2001.

There was some concern yesterday that in some metabolic disorders, the system could be overwhelmed. Not enough physicians to take care of all of the positive screens. I think that is not the case in CF, in that if there is well planned, well implemented studies, newborn screening programs, we already have a network of 115 cystic fibrosis centers funded and accredited by the Cystic Fibrosis Foundation. There are additional 40 to 50 affiliate centers. We can handle the load of patients that gets generated by newborn screening.

Lastly, if one looks at economy of scale, this is not one of the rarer conditions picked up by newborn screening. Data from Wisconsin in 2003, we had 39 patients with congenital hypothyroidism, 26 with hemoglobinopathies, and 16 with CF. So it was the third most common. We do tandem mass spec. We do more than 26 disorders in Wisconsin.

There are approximately 900 to 1,000 newly diagnosed patients with CF every year in this country. Patients don't need to go through the diagnostic odyssey that Dr. Kharrazi described. I'm looking forward to all of us working together to strengthen CF newborn screening, and see that it is implemented across the country.

(Applause.)

DR. HOWELL: Thank you very much, Dr. Rock, for your input.

We will end the public comment with Dr. Philip Vaughn, who is speaking from Pediatrix. Dr. Vaughn?

DR. VAUGHN: Thank you. Before I begin my comments, I wanted to personally thank again the members of the committee for their important work, as well as the other attendees for their comments.

I am Philip Vaughn, a board certified neonatologist. I am currently serving in an administrative capacity at Pediatrix Screening.

Pediatrix Medical Group just in brief is the nation's largest health care company focused on physician services in neonatology and maternal fetal medicine. The company's roots lay in neonatology, but our commitment to the health and welfare of newborns has allowed us to branch out into other related subspecialty services.

Pediatrix Medical Group is comprised of over 700 physicians, and hundreds of nurse practitioners as well. Our clinical practice daily serves the needs of over 3,000 infants. Our research and education department demonstrates our commitment to improving the lives of infants we care for.

Our research expertise includes database management on nearly one million patient days per year. This database now has expanded to include outcomes representing more than 4 million patient days. It has been instrumental to numerous publications and retrospective research, as well as prospective randomized control clinical trials.

Our educational outreach, in addition, provides continuing physician and nursing education from across the nation to over 70 countries around the world through a

web-based system.

Our interest as an organization in newborn screening began over a decade ago now with newborn hearing screening. Since that time, we have been strong advocates for the evolution of newborn hearing screening programs, and have participated in the development of those programs. Today our programs screen over a quarter of a million babies a year using the most advanced technology available.

Our obligation we feel doesn't end with the screening. We have identified these patients through screening, and continue to track their outcomes through diagnostic and therapeutic care by our case managers with a case management system that we developed in support.

Now with the addition of genetic and metabolic disease screening, Pediatrix tests more than a half million babies a year for disorders with the common theme that early testing, identification, and introduction of appropriate therapeutic interventions will prevent adverse outcomes, and offer the best possible hope of long-term improvement.

Recent indications from this committee, as well as national advocacy organizations, have acknowledged a need for a broader spectrum of testing and for parent notification, which we've heard about today. We are proud to have participated in a number of public/private partnerships, which is a logical conclusion of how we can help to fulfill that need.

We are proud to participate in these various models of public/private partnership to help get this done. Again, with the intent of supporting and not supplanting any other public health participants. We tailor the programs that we participate in to meet the needs of the public health programs.

Our newborn screening services are readily available through a variety of channels, and include a comprehensive spectrum of testing and follow-up services. Elements of some of the successful partnerships we've participated in include complete outsourcing of laboratory testing, partial outsourcing of laboratory testing, and licensing of our tandem mass spec intellectual property.

We feel that all of these models are important, in that they are currently in use today, real world experience that is ongoing. Yesterday we heard some about the Mississippi experience and some about the Pennsylvania experience. We are the private labs that performs the testing for those programs.

In addition, Pediatrix also licenses our interpretative algorithms to a number of laboratories performing newborn screening, including Mayo Medical Labs. Now in conjunction with the Minnesota Department of Health, they have provided another very useful, I believe, model of public/private partnership that has allowed for expanded newborn screening.

Dr. Rinaldo has indicated his concern regarding unnecessarily high false positive rates that some programs are seeing, and we share those concerns. Rather than incur those unnecessary costs created by those false positives, we feel that with appropriate testing algorithms such as those shared by Pediatrix screening in Mayo, acceptable program metrics can be established to avoid the unnecessary costs of false positives, which could submarine the efforts well intended of expanded screening.

This demonstrates another partnership model between in this case, the Minnesota Department of Health, and a private lab Mayo. Finally, to fulfill the immediate testing need that has been discussed as well, Pediatrix also offers a supplemental program, step one program of comprehensive spectrum, the most comprehensive spectrum of supplemental testing available today to parents, physicians, and hospitals.

This service is provided across the U.S., and is an excellent method of delivering a high quality testing program to those in need who don't have access to it through a mandated public health program.

In closing, let me reiterate that Pediatrix is deeply committed to the health and wellness of the infants under our care. We look forward to supporting the continued evolution of expanded newborn screening nationwide, and remain at the ready to support this group with any further needs. We are ready to participate in the subcommittees as needed. We feel that our experience and expertise with data management, clinical investigation, and testing services and operational support for the implementation of testing services might be valuable.

Thank you.

DR. HOWELL: Thank you very much for your comments, Dr. Vaughn.

Let me on behalf of the committee thank the folks who have presented this afternoon. I congratulate you on presenting the material, and equally congratulate you on getting through a long list of participants in a timely fashion. Thank you very much for that.

We have an hour and a half left. Many of the people are on very clear schedules to leave at 3:30, so we're going to leave at 3:30. We have a lot of issues, and as you see on the thing, there are a series of priority issues that we need to deal with in the next period of time.

Some of those are business-type activities, and others are very substantive issues. I think that obviously the substantive issue before this committee is consideration and discussion of the HRSA report, the ACMG/HRSA report. Let me again, at the risk of beating a dead horse, point out that the report that Dr. Watson presented to you was prepared by the American College of Medical Genetics under a contract from HRSA. That document will be going to HRSA, that particular document you heard about.

It was obviously an important document with a huge amount of deliberations, and it was considered that that would be a very important document that this committee should hear about, think about, talk about, and consider as a possible basis for recommendations, and so forth. It is in that format that we need to discuss that particular document and so forth, and get the pleasure of the committee in how you would like to proceed from this point with regard to that specific document.

Bill?

DR. BECKER: Rodney, I would like to move that this committee officially accept the ACMG/HRSA report and forward it to the Secretary when it is available. I would also like to move in consideration of the comments that we heard yesterday, that we allow written comments to be included, both public and committee comments about the report to be included with the report that is submitted to the Secretary.

DR. HOWELL: Can we have a second for that recommendation so that we will be in order to discuss that recommendation?

DR. BROWER: I second that recommendation.

DR. HOWELL: Before we open for general discussion of the committee, let me bring up two things. One is that I read yesterday two of the committee members are not here. They are Dr. Edwards and Dr. Howse. I read those recommendations. Each of you have those letters in your folder from those two people. I remind you that since they are not here, that their letters of support are there.

I'll open this for discussion, and again, I'll take counsel from my colleagues on the right. What I understand will be the appropriate procedure for this is that we will not be modifying the document. The document is a document that goes to HRSA. I think what this committee will be doing will be accepting this report as core recommendations, and then having it proceed however with comments and specific materials that would address some of the questions. I think that is what we're discussing.

Peter, is that correct? Dr. Van Dyck says that is correct.

DR. RINALDO: I have a question. What kind of review do you anticipate for this additional material on the part of the committee? There will be things that will be attached to the report without review by the committee? Because it is out of our hands? Or how will that work?

DR. HOWELL: Let me make a comment. Again, there are two things. One, certainly the material that has been presented at this meeting and so forth will be in the public arena. So we would like public comments on that, and conceivably during the short period of time, even more of the report may be. I think that's a legal decision on HRSA's part. Certainly we will be inviting public comment on the document, in addition to this group.

The point is that I would anticipate that all the comments that come in, either from committee members or otherwise, will come back to the committee. I might point out, and maybe it goes back to my pediatric background, but I share the urgency that we've heard so often today. I would like to be sure that we review this as carefully as possible.

But on the other hand, I would like our work to proceed in the most expeditious way possible so that we can keep things moving. Perhaps those comments and reviews and so forth can be sent to the committee electronically. Is that possible? I see no reason it shouldn't be. The answer is yes, I think.

DR. VAN DYCK: We have planned to make this report public as soon as possible. We'll be inviting comments on the report, and there is every expectation we'll have a number of comments to us, because we ultimately have to make the recommendation.

I would think that the sum of those comments would be done and reviewed before our next meeting, and could come to this committee then for review and additional final comments before we have to make a recommendation.

DR. RINALDO: That's really my question. In terms of the logistics between now and the next meeting, is that something that will require further action at the next meeting? Meaning that no progress is made before January. Is that an acceptable time? That's really what I was asking, how this additional material will be evaluated by the committee. Will it be attached, or will it get a life of its own?

DR. HOWELL: I would like for the committee's recommendations to proceed more rapidly than that. That's a personal opinion, but there may be reasons that is not possible. I think the thing is is that the committee's recommendations, as opposed to the world at large, there are some important comments that have particularly come from Colleen and from Denise about specific parts of this report.

Our report should embody those recommendations, and other recommendations from the committee. Those, we should be able to do those before our next meeting.

DR. RINALDO: Okay. So that means that the report as it stands now is final. I was wondering if there was an expeditious way to incorporate some of the comments, just to improve it, if necessary. It goes back to the point of when you are 95 percent there, if that really makes a difference. I was just wondering about that. I'm not trying to create difficulty.

DR. BOYLE: Can I just ask for clarification? I'm very confused at what the motion is that is on the table at the moment.

DR. LLOYD-PURYEAR: The motion is to accept the ACMG report and forward it to the Secretary with public and committee comments.

DR. BOYLE: But then we're having discussion about having formal comments about the report from the committee, which is what I would like to see happen. I don't feel like the report as we saw or heard yesterday, and what we have read, there are a lot of discrepancies.

I'm feeling uncomfortable about that next step. I feel like we can be very responsive and get our written comments to the committee to be shared within the committee and outside, fairly rapidly.

DR. HOWELL: It would be my anticipation that the committee report should be done expeditiously and could go forward. Is that not correct?

DR. VAN DYCK: The recommendations from committee can come forward whenever they come, absolutely.

DR. LLOYD-PURYEAR: There's the committee's recommendations, and then this HRSA report. They are two separate things.

DR. DOUGHERTY: Well, I guess now I'm confused, because of the various FACA rules, and about having all discussions in public. Then if there is this separate set of comments from the committee about changing the report, that gets laid on top of the report as it is, and the public doesn't hear that?

I'm just thinking about what the implications are of us then sending stuff to HRSA or the Chair, and then what happens to what we say if it hasn't been said?

DR. VAN DYCK: It gets posted on the website, it gets put into the minutes.

DR. HOWELL: This committee reports to the Secretary, I might point out, directly.

DR. DOUGHERTY: Right. So we make comments and recommendations about the report, and then there is a document that goes forward to the Secretary that includes our comments, and the report that we saw yesterday?

DR. BOYLE: And the report recommendations.

DR. DOUGHERTY: And the report recommendations.

DR. HOWELL: But the comments of this committee can go on the HRSA website, which we have there.

DR. DOUGHERTY: But what is going to the Secretary I guess once we send in our comments?

PARTICIPANT: Whatever the committee decides goes to the Secretary.

DR. HOWELL: Dr. Alexander has a comment. He's an expert in this area.

DR. DOUGHERTY: Yes, he is.

DR. ALEXANDER: I'm no expert, but I would like to suggest a way to proceed with this that might meet most people's interest and concerns. We have a document that has been presented to

this committee that this committee did not solicit. It is a HRSA document. It is a report to HRSA prepared under a contract from HRSA.

We have been privileged to share in that before it is actually formally transmitted. But essentially it is now basically a public document, because it has been presented in a public session of a federal advisory committee. So that document should be essentially available.

I have no problem at all with Bill Becker's motion that we would forward this to the Secretary. In fact, I would suggest that we agree to do that. I would also suggest that we do it in the following context. That the letter to the Secretary indicate that the committee has been privileged to receive this report, we have accepted it, but we want to have an opportunity for further examination of that report ourselves, and an opportunity for further public input to this report, because this is really the first time that it has been aired to the public.

I would suggest that we indicate to the Secretary that we, together with HRSA, are making this report available for public comment, that we will specifically send it to all the state screening programs and invite their written comment, and that as a major part of the agenda for our next committee meeting that we set aside time for discussion by the committee, as well as an opportunity for additional public input to the extent people wish to provide it, for comments on this report.

Following this, the committee will be forwarding any recommendations that it has about this report to the Secretary with a hope that much of that can come in the January meeting. Again, keeping in mind that any action that the committee takes in this regard has to be done in the public session.

So I would suggest that if we did it that way, we could meet the desire of many members of the committee and the public that this go forward to the Secretary for information and the fact that we have accepted it. But at the same time, I don't think it is particularly responsible for the committee to imply that we have endorsed it when we have had really little opportunity to discuss it, that it really is still a draft report for HRSA, and that there has not been the full opportunity for public input and comment from the state screening programs, from advocacy groups, and so forth that we would like to receive before this committee takes any official action on it.

That's what I would suggest.

DR. HOWELL: Any comments?

DR. DOUGHERTY: I guess, Duane, you weren't here yesterday when we had some discussion about what we felt needed to be in the report itself to make it more transparent about what the methods were and so forth. We heard a lot of information yesterday and it was great, and we really got a good understanding of how the conclusions came about.

I'm wondering, are you recommending that we send the report forth as it is, as this draft final? Or that some changes be made before it gets put up for public comment to the Secretary? I'm just wondering. No preference one way or the other?

DR. ALEXANDER: Yes. The document that exists that is essentially the public document is the document that we have in hand. Any comments that we wish to make on that can be taken in public session today, or in public session the next time.

I see no problem with sending out that report for comment as it exists, and with the understanding that there will be opportunity for people from the public, as well as members of this

committee, to suggest additions, modifications, conditions, or whatever might be applied to it before we as a committee take any action in terms of recommending it to the Secretary.

DR. HOWELL: Derek, and then Piero.

DR. RINALDO: I think in asking for clarifications now, how HRSA perceives this report, is it perceived as the final document delivered at the completion of a contract? Or is it perceived as still a work in progress?

I think they are the ones -- I believe HRSA is eventually bringing this to the committee, is that correct?

DR. LLOYD-PURYEAR: To the Secretary?

DR. RINALDO: But the group, the expert panel, reported to HRSA. The report went back to HRSA, is that correct?

DR. LLOYD-PURYEAR: We still have modifications to do to the final report.

DR. RINALDO: Okay. So that is in line. I wanted just to make sure that we are talking about making changes or something that might have been considered final at some point. That, I think collides a little bit with this issue about how public this document becomes, and how you are going to modify it. We have to say version one, version two, version three.

MR. ROBERTSON: I guess I'm trying to clarify the process. I think one of the issues as well is that several people around this table were also involved in the initial report. If it goes to HRSA, it is probably the same question. Do we need to, or are we required here to approve that report?

It would seem to me that that is a report that HRSA is going to get, and would then ask us to look at and give comment, and then HRSA takes those comments. So the report is almost outside of the purview of this committee to the extent that it was written on the contract, it was sent to HRSA, and then HRSA can solicit comments from whomever they please, including this committee.

I guess what I'm saying is that we would just be submitting our comments on the report as can members of the public submit comments on the report.

DR. HOWELL: There's a very big difference. That is that this committee, which is a federally chartered committee, is specifically charged with making recommendations to the Secretary specifically in the area of newborn screening.

So that indeed, and the reason this report was presented here, and I'm beating a dead horse, is because it was felt that this report, which had been worked on for a long time, would be a very nice basis to begin that process.

MR. ROBERTSON: Right. So I'm saying that would come from us, a recommendation that would be based on our comments. So we would have comments, and we would say words to the effect that this report was written by ACMG, and we recommend it, and here are our comments to this report. We'd say, Mr. Secretary, this great report was written by ACMG, we have reviewed it, and we have these additional comments that we think could enhance the document.

DR. HOWELL: And so you would view those comments to encompass the concerns that came around the table about areas that could be strengthened, and areas that needed to be added. So you would visualize that our comments would include the methods section and things of that nature?

MR. ROBERTSON: I guess we would discuss it. I mean, I think that is a general consensus that the report, even as it is, does not have any major issues related to the report. I mean, I think both here and from the public comment.

What I'm saying is that it seems as though the role of this committee would be to recommend to the Secretary not only the report itself, but our own comments related to that report.

DR. HOWELL: You have a comment?

DR. RINALDO: I'm wondering if it would be appropriate to have, after all, I understand that this committee has voting and ex officio members. I'm wondering if a vote is in order about accepting and endorsing the recommendation of the report, and then compile it. Put it together for sure with the comments that may come for the committee and the public at large, but basically set a milestone on it. Are we in a position to endorse this report?

MR. ROBERTSON: I guess maybe, Michele or Dr. Van Dyck, is this report final in its form? Even from the perspective of ACMG, have they presented a final report?

DR. VAN DYCK: I think we're thinking about this report as being a next to a final report, a draft report. There has to be some point that we say, this is a final report, and any comments that come in after that are added to it. I mean, they are additional to the report that we will take into consideration before we make a final recommendation to the Secretary on what to adopt.

We want the report to be as reflective of all the comments as possible, but there clearly is a point when we say we have a final product, and any additional comments are added for our benefit, but don't become part of the final report. We want to make as good a document as possible.

MR. ROBERTSON: And that's the thing. Who determines when it is final?

DR. VAN DYCK: We do.

DR. HOWELL: HRSA does.

MR. ROBERTSON: Okay. So I guess we would need to see a final report to make comments on it. Because my understanding in reading the report was that it still wasn't final. It was very close to final. So I don't know if this committee today would be recommending to the Secretary a report that is not final. The motion on the floor is to recommend the report.

DR. BECKER: No, that wasn't the motion.

MR. ROBERTSON: With comments.

DR. BECKER: No, that's not the motion.

MR. ROBERTSON: Okay. Maybe I need to hear it again.

DR. BECKER: The motion was --

DR. LLOYD-PURYEAR: To accept.

DR. BECKER: -- to accept the ACMG HRSA report and forward it to the Secretary.

DR. LLOYD-PURYEAR: With public and committee comments.

DR. BECKER: And to also allow written comments to be included, both public and committee comments to be included with the report to be submitted to the Secretary.

DR. RINALDO: One point I would like to make, though, is that the group that was assembled to generate the report has been disbanded. It is no longer active. So I'm wondering, what is the expectation that a former member of that group will continue to work on this? We had three years of time to make comments and provide feedback. So in other words, you are providing resources for this group to still keep getting together and discuss it? Are you expected to do it besides your day job?

The report is being submitted as a final part of the group that no longer exists. So I'm really confused of what expectation you have of this being still work in progress.

DR. VAN DYCK: I think that because it is next to or near to a final report, there are editorial changes and there are other things that can improve the report. Those are the kinds of things we're talking about. I don't think we're talking about making major changes.

Part of the reason we're having this discussion, it would be wonderful to present a final report to the committee. It doesn't coincide in timing necessarily with the days that the committee is meeting, and our desire to move as quickly as possible towards implementation of many of the findings in the report.

You have the advantage, and we have the advantage of hearing your comments and getting your comments perhaps before there is a final report. Maybe that's a little less tidy than having them after you get a final report, but it will further speed up the process and our ability to implement them.

MR. ROBERTSON: So I guess we will recommend to the Secretary that we are accepting the report as presented? I mean, when it becomes final, we think that this would be a good report for him to follow.

DR. ALEXANDER: No.

DR. HOWELL: Let's hear a comment from Duane, who has been sending things to the Secretary for a long time.

DR. ALEXANDER: Let me try again. Basically the letter to the Secretary would be along the following lines. The committee has received this report, it has had a presentation of it, and has accepted it as a basis for further discussion and opinion.

We, in the course of the time between this meeting and the next, we will be circulating this report together with HRSA to state genetic screening and testing programs, newborn screening programs, and other interested parties for comment. It will be a major agenda item at our January meeting, at which time there will be another opportunity for public input.

The committee plans to have extensive discussions at our January meeting and take further action on the report at that time. That leaves all kind of opportunity for this committee to make

comments on things that we think need more clarification, more discussion, but it does not say to the Secretary that we have accepted, or that we are recommending anything in this report at this time.

DR. HOWELL: Let me make one comment. That is that having talked at lunch and other things in the group and so forth, the discussions around the table and so forth, I think that that would be a satisfactory thing, except that I think that the majority of the committee members who have spoken feel much more firmly about agreeing with the content.

In other words, not the details, but I think many of the committee members who have spoken out unfortunately during yesterday and today feel strongly about the guts of the report. That's not the proper word, but the core recommendations of the report are very consistent with what they would like to see happening.

Now, the thing is that that would not preclude modifications in the report and so forth, and additions to the report. Let me read one thing before we go on, because Dr. Hawkins had to leave, and he wrote me a note that he left. It is addressed to this committee by all of its initials, which go halfway across the page.

It says, "After reviewing the report from the American College of Medical Genetics on newborn screening towards the uniform screening program, hearing testimony and considering comments, I favor sending the report forward for public review and comment, and after modifications, sending the report to the Secretary for review for possible legislation."

DR. DOUGHERTY: But I have a question. We are talking about the core recommendations and recommending what is in the report. The report has more than the 30 conditions in it. Is that also what we're recommending? Mostly we have discussed how they got to the 30 conditions, and not a lot about the rest of the recommendations, about the medical home, storage facilities, and that kind of thing. We haven't discussed that at all. So I'm wondering where we are with that.

DR. RINALDO: Well, that's a different topic.

DR. DOUGHERTY: But that's in the report.

DR. RINALDO: Medical homes?

DR. DOUGHERTY: Yes.

DR. RINALDO: Sure.

DR. DOUGHERTY: That's why I'm asking.

DR. RINALDO: But that goes back to my point. Is it the distinction between voting and non-voting members, a totally artificial one, or meaningless? What is the difference?

DR. HOWELL: All the members of the committee are voting except the liaison members. The two liaison members are Dr. Edwards and Dr. Howse.

DR. RINALDO: So the voting members are the committee members and the ex officio members?

DR. HOWELL: That's correct.

DR. RINALDO: Okay.

DR. HOWELL: The ex officio members, let me be sure I'm right, are voting.

DR. LLOYD-PURYEAR: On this committee.

DR. HOWELL: On this committee.

DR. LLOYD-PURYEAR: Congress intended the ex officios to vote.

DR. RINALDO: Do we have a quorum? That is usually the first -- so even with Dr. Hawkins not being here?

DR. LLOYD-PURYEAR: The only ones that are missing, except for one voting member, are the ex officios.

DR. RINALDO: And how that works is it works from majority? A quorum? Do you know? Assuming there is not 100 percent consensus.

DR. VAN DYCK: A majority.

DR. HOWELL: It would be a majority of the quorum. Fortunately, you have to your left our attorney member.

MR. ROBERTSON: I think we just need to ask a fundamental question. That is it comes down to whether we recommend the report or not. I think there is some hesitation on some members of the committee to recommend the report without having discussed it in full.

So I might say, I think we should recommend a report, but I have also been involved in the process a lot longer than some, and others might not. So I think we want to put it in as many ways. But it really comes down to if I were the Secretary and I got what was that letter, which said okay, I'm going to wait.

What you are really saying is we are recommending this report to you, but we're going to get some more comments, and we're going to take a look at it as well. So if I were the Secretary, I'd say okay, fine, then I'm going to wait until I hear what you have to say.

When you finish saying what you have to say, then tell me about it. I think either we are going to recommend the report, and if we can, I'm wondering if we can, as much as we might want to, if the report is not yet final, if you are still taking comments, and if you still want to make changes, I don't see how you can recommend the report.

We might want to, but it is either that or we say, it is final. This is the report, and we recommend it. I think that the consensus I think generally is that we recommend the report, and then you have a comment period. But I don't know if we might want to make different grades, but that is what I think it comes down to.

DR. HOWELL: I would assume, and again, I'm assuming that the Secretary would be much more interested in our final opinion after the document had been public. Although a number of people have seen this document, it hasn't really been public. It has not been up on the website or anything of that nature for the public at large to comment.

I would think the Secretary may be interested in our wisdom, shall we say, as far as the final word after that public comment. I don't know that to be a fact.

Peter?

DR. COGGINS: It seems there is agreement, this is fairly close to being a final document, there is a need to get the commentary in. Isn't there a way that we can come together, finalize the document, and get it to the Secretary, rather than having to wait another four months until the next meeting comes up?

DR. HOWELL: I'm very unimpressed with waiting four months. Let me be very clear. That's a personal opinion.

(Applause.)

DR. HOWELL: But I want to do the things properly, but I would like to get something moving, if we can, and do it appropriately and so forth. There can be electronic things, and we can do it get it cooking. But maybe everyone else feels that that is precipitous.

DR. BROWER: And I guess I just want to say, I think this document was provided to us over two weeks ago. So I think the committee has had time to read and digest it. If there are specific issues we want to discuss, maybe we can take some time today and do that.

DR. VAN DYCK: Clearly, this committee has staff, and an Executive Secretary. Anything you want to happen as far as electronic communications, submission and collation of comments, getting them back out to the committee electronically for review and approval, coming back, you can call, you can set up a call of the committee before another formal meeting.

All of these processes can be done. We stand ready to assist the committee. So any kind of time lines, comments, any of that you want to do, we'll stand ready to make those work.

DR. RINALDO: But I really would like to make again the point. For example, Mike Watson is not part of this committee. A report is being filed, again, as a result of somewhat overlapping, a different group of people.

This is the report of that group. It sounds a little strange. Now you want to have a different group of people with overlap that will start making changes to it, that is where I get lost.

DR. BOYLE: No changes.

DR. RINALDO: And again, in the context of a time frame, what exactly is so important that we need to do -- I think the clock is ticking, as we heard this over and over. What exactly are we going to do?

DR. BOYLE: I guess I'd like to make a suggestion. That is to move things along expeditiously, and not to wait until the next meeting, and that we follow Duane's recommendation in terms of forwarding the report to the Secretary. But in the meantime, put together a small writing committee over the next month, 30 days, whatever seems reasonable, put together our collective comments, and then a recommendation from our group that we feel is appropriate for the document.

DR. DOUGHERTY: And maybe a piece of clarification of how government agencies very often will take a contract or report and then have further work done on it to write it, to edit it. It happens at AHRQ all the time, before it gets released publicly. This happens all the time.

You don't have to reconvene. I mean, you want to consult back to make sure you've got the sense of the original group, but you don't actually have to have them do another year's work and that kind of thing.

Is that what you're thinking, Peter and Michele?

DR. HOWELL: I think it would be important for any modifications to the document to take into consideration the extraordinary expertise that has gone into it.

DR. DOUGHERTY: Absolutely.

DR. HOWELL: That certainly adding and so forth wouldn't be an issue. So what is the sense of this group? What are we going to do to keep things in the air here?

PARTICIPANT: We have a motion on the floor.

DR. HOWELL: All right. Do you want to repeat your motion? It was seconded by Amy, but you have said it a number of times.

DR. DOUGHERTY: Does your motion include what Duane said? Or is Duane putting a different motion on the table?

DR. HOWELL: No.

DR. BECKER: I think Duane and I are in agreement on this. The word is not "recommend." It is "accept." Okay? If you want to amend the motion, we can discuss that. But I think that is where some of the discord really lies. But the motion as it currently stands is accept the ACMG/HRSA report, and forward it to the Secretary.

A secondary motion related to this is to allow by the mechanisms we have already sort of outlined here, written comments to be included, both public and private, and those be forwarded to the Secretary as well.

MR. ROBERTSON: Let me just ask a question in terms of the clarification. When we say we accept, are you saying that we agree with what is in it? Or do you mean we are in receipt of?

DR. BECKER: Well, I think there is the implication that we do agree. Now, we are stopping short of recommending certain aspects of it? I have several recommendations I'd like to make here, but some of those get down to the disorder panel that we have spent quite a bit of time talking about. We might be mature enough in those conversations to make a voting decision here today.

That is not what I'm saying in this motion. I'm saying that we accept it, and we submit it to the Secretary, and allow and include written public and committee comments.

DR. RINALDO: So that begs a question. You have seen this evolving from the beginning. You had this report for more than two weeks. We have been here for two days, and half an hour before we sort of close the proceedings, you tell us that you have changes you'd like to make. Why haven't we heard it sooner?

DR. BECKER: I've not suggested any changes, Piero.

DR. RINALDO: Well, maybe I understood what you just said.

DR. BECKER: Accept the report and submit it to the Secretary.

DR. LLOYD-PURYEAR: Can you clarify for me what accept is?

DR. RINALDO: Yes. That's really the question. Endorse it?

MR. ROBERTSON: Again, I think again we're just trying to create shades of gray. We're either going to recommend the report or we're not. I'm wondering whether or not the report -- the report has been submitted. We didn't write the report. It was done under contract.

So if HRSA says to us, this is the final report, are we in a position with whatever the reservations are to accept the report or not? Or to recommend it to the Secretary? If we can't, then I think Amy is correct. Let's talk about it. Why can't we just simply say, we recommend the report?

If you have some reservations, why don't you just say them and say what they are about the report?

DR. HOWELL: Dr. van Dyck?

DR. VAN DYCK: Well, one way perhaps to solve in a way both issues is hold the recommendation of the report for those 30 days it takes to produce the committee's comments, and then recommend the report accompanied by the comments that you have very expeditiously developed. Then they go together, and perhaps that will solve some of the people's issues.

DR. HOWELL: Dr. Alexander?

DR. ALEXANDER: Just from experience, the way these things work is that if a report comes from an advisory committee to the Secretary with recommendations, one of the first things the Secretary, or the staff of the Secretary will ask, is what opportunity has there been for public comment on this?

How did you arrive at your recommendations? How much public input did you get? The truth is that we have had some, but this document really was not a circulated public document until this meeting. So we can't say that we have circulated it to the state screening programs, we can't say that we've circulated it to all advocacy groups.

Although many of them knew many parts of it beforehand, this really has not been a public document. If the Secretary asked that, and he probably will, we cannot honestly say that we have circulated it for public comment, we have asked for in a public hearing format for comments. Our deliberations on this have been very, very brief, without the advantage of that input.

We got some in the last hour and a half, much of it endorsing it, and laudably so. I think that what we can legitimately do as an advisory group without coming under criticism for precipitous action without an opportunity for the public input that the Department always likes to have, it to say we have accepted this, we will be getting additional information and public comment, and we will be forwarding recommendations to the Secretary for action based on that report with the benefit of that opportunity for additional put input, comment, and discussion within the committee. That is I think the most responsible thing to do.

DR. RINALDO: But I think both Derek and I have been asking a question. I think we have to keep separate the comments from the public, or people that truly didn't have a chance to see this document before today, and people who did.

That is I don't understand why a delay should take place, because we are expecting sort of comments, contribution or criticism, as it may appear, from inside, from the committee. That is a different thing. So I do not accept the fact that somebody comes now half an hour before we adjourn saying I have problems with the report. Where have you been for the last two days? Why you didn't speak up? Why you didn't bring it up? It really seems to me a stalling tactic, and that is what concerns me.

DR. HOWELL: I guess the situation at hand is how can we get the document moving most rapidly? You think there is substantial advantage of sending the document now and commenting later? Or would it be advantageous to say that we're going to get public comment and so forth from the committee, and within 30 days, we'll have a definite time line, not six months. We would put those comments together and send forth an updated report and so forth with the comments. Which would be the most expeditious way to do business?

DR. COGGINS: It depends on how we send it in, whether we are recommending it, or just accepting it, I think.

DR. DOUGHERTY: If we send it in now and say we accept the report, and we are seeking public comment, then the Secretary's office has a chance to see it and act on it if he wants, right? I mean, if we don't send it to him --

DR. COGGINS: But if we send it with a recommendation, it is more likely to go that route.

DR. RINALDO: If you send it accepted and don't recommend it, that really sounds like an endorsement.

DR. COGGINS: If you send it in with acceptance but want to come back with written comments within 30 days, I think they are going to wait at least 30 days.

DR. DOUGHERTY: But I'm afraid that what Duane is saying is correct. If we do send it with a recommendation, then questions will be raised about have we sought public input.

DR. COGGINS: Isn't that what we're saying? We want to get 30 days for written comments to come in.

DR. HOWELL: The idea would be to have a public comment period before it goes.

DR. RINALDO: But it is different. The public, I think, I really insist on the distinction that one thing is to give a chance to who hasn't seen it to comment. The other one is to deal with what seems to be like at the last minute, an attempt to stop it.

DR. DOUGHERTY: Could I say something?

DR. HOWELL: Yes.

DR. COGGINS: I'm not in favor of delaying much beyond this 30-day period. I think that is appropriate. Yeah, the committee saw the report, but we only got a few of the fact sheets, we haven't seen all of those to consider. I just don't think we have the entire report. I mean, we've had most if it, and we haven't discussed a lot of it.

DR. HOWELL: Who has comments around the table? We're interested in the most rapid responsive way to get this moving.

Duane, you think it would be helpful for the Secretary to see it without a formal endorsement of the committee? Or would it be more efficient long-term to wait 30 days and have it in the public for 30 days or something?

DR. ALEXANDER: There is very clear strong sentiment both on the committee and in the public among the advocacy groups for getting this document to the Secretary. I think the way we have talked about here is a way to get that to the attention of the Secretary, saying that this report has been submitted, we think what is it it has merit, and we will be seeking additional public input before we make any final recommendations to you, which will be forthcoming shortly.

But by sending the document itself, even in its current stage without a formal endorsement by this committee, it brings it to the attention of the Secretary. It also gives us a way to get it out for public comment, in a formal way of soliciting that, so that we'll have the advantage of that in formulating whatever recommendations we do.

DR. LLOYD-PURYEAR: Does the committee want to accompany it by any recommendations? Preliminary recommendations based on the report?

DR. RINALDO: There must be something positive. I really am concerned about the perception of this being just a punt.

DR. BECKER: Well, Piero, can we take this in a step wise manner, though? Can we vote on the motion that currently is on the table, that we accept the report and submit it to the Secretary? We'll get that off the table, and then start talking about if there is a recommendation, that we as a group feel comfortable enough sending forward.

DR. HOWELL: At this time.

DR. BECKER: At this time.

DR. RINALDO: Well, I don't know what is a proper process to suggest an amendment to the motion. I really think the key here is what word we choose. Accept or recommend, accept or recommend. That really to me makes an enormous difference.

DR. BECKER: I would agree. The word "accept" was chosen carefully for a lot of the reasons that Denise and Duane have already expressed.

DR. COGGINS: Well, what about changing the motion that we recommend with the proviso that we need a period of 30 days to collate any further input from the public? We will respond in writing within 30 days?

I think if we send this in saying we accept it, it lacks some credibility.

DR. BECKER: That's a fair comment. All right. I'll tell you what. In order to be parliamentary about this, I'll withdraw the motion.

DR. HOWELL: Do you accept his withdrawal?

DR. BROWER: I accept it.

DR. BECKER: All right.

DR. HOWELL: We're going to go back to Bill.

DR. BECKER: We're going to go for the gusto this time. Mr. Chair, I would like to move that we accept and recommend the ACMG/HRSA report and forward it to the Secretary. That we also allow for written comments to be included, both public and committee member comments to be also forwarded to the Secretary.

DR. BROWER: I second that with an amendment or addition that it is a 30-day time line.

DR. BECKER: Yes, within the parameters that we have been discussing.

DR. HOWELL: So do you have that, Dr. Puryear?

DR. LLOYD-PURYEAR: Accept and recommend ACMG report and forward to Secretary, and allow for written comments from the public and committee to be included.

DR. HOWELL: With a?

DR. LLOYD-PURYEAR: Within a 30-day time period.

DR. RINALDO: Sorry if I ask the same question again. What kind of review, if any, by the committee, there will be of all these comments? And what kind of action? They will just be appended no matter what?

PARTICIPANT: No.

DR. RINALDO: Or there will be an acceptance by the committee of these comments?

DR. HOWELL: I would think that we'll need someone, an expert from HRSA, unfortunately.

DR. VAN DYCK: How you do it is up to you.

DR. HOWELL: I would think that the public comment should be included as an appendix. Maybe there is a disagreement, but I would think so, frankly, unless there is some reason not to. I can't see why we would take it upon ourselves to modify, sequester, or exclude public comments. It seems to me that is not our role.

On the other hand, the recommendations of the committee clearly would have to be seen, reviewed, and approved by the committee. No question about that, because we would not send through an individual comment.

So the recommendations to the committee would be reviewed electronically and accepted as a committee recommendation, and I would recommend that we append all public comments. So we have a motion on the floor, and we have a motion and a second. So we can discuss it, I hope not extensively. The day is wearing on, and the sun is still out.

DR. DOUGHERTY: When would this letter go forward? If we're appending committee comments and public comments, that means it can't go forward tomorrow.

DR. HOWELL: Thirty days.

DR. LLOYD-PURYEAR: A 30-day time period.

DR. HOWELL: Thirty days.

DR. DOUGHERTY: So we still are waiting for these comments?

DR. HOWELL: Thirty days after its posting. But the letter that would go with the ACMG report as it exists today would go promptly. Is that not correct? Yes. So it would go forth -- well, read the motion, please.

DR. LLOYD-PURYEAR: The committee accepts and recommends the ACMG report and will forward to the Secretary. Allow for written comments from the public and committee to be included within a 30-day time period.

DR. RINALDO: Can we say "to be appended"? That the committee will send forth its recommendations and the appended public comments within the 30-day period? The report will come, it will say that recommendations are coming, and within 30 days.

DR. HOWELL: Is that how you have it written?

DR. LLOYD-PURYEAR: No, because you guys have changed the wording along the lines. But the gist of it is accept and recommend the ACMG report and forward to the Secretary.

DR. HOWELL: Now.

DR. LLOYD-PURYEAR: Now. Allow for written comments, and we're doing to do it in an appendage, from the public and the committee to be included.

DR. HOWELL: I would say, "Additional comments and recommendations from the committee," because the committee will be making recommendations.

DR. BOYLE: I just don't feel like that is acting responsibly, in fact that we are recommending, and then allowing others to have comment. I feel like we need to let others have comment, and then we can make our recommendations based on those comments.

I feel like part of our committee's responsibility is to get comments from the public. That is my issue with that.

DR. RINALDO: That is why we have votes. I think it might be time to see.

DR. HOWELL: Well, let's discuss that word. I mean, is there another word that would convey the sense of the committee that would be better? The committee clearly, and I can see all the nodding heads, and you call can't unfortunately , and they are going one way and the other way.

But anyway, there is enthusiasm for the core part of the thing, and there is concern about certain parts. I guess that is what we're trying to get across.

DR. BROWER: And I think in working with the ACMG to put this project together, the community was included. Not the community at large, but several of the key stakeholders were included in compiling this report.

So given my background and my complete review of this report, I don't feel like there is going to be comments from the public that may need clarification of why this decision or that decision was made, but I don't think the fundamental core recommendations will change based on this 30-day time period. That is what I would base my recommendation and endorsement of this project report today on.

DR. HOWELL: We could add in the motion if folks would do it, and the committee will forward its final recommendation, rather than its recommendation in 30 days.

PARTICIPANT: No, no.

DR. HOWELL: Okay. That was not popular.

DR. VAN DYCK: Just to put on the table, this report will be widely circulated for comment by the Department.

DR. HOWELL: Yes.

DR. VAN DYCK: The committee can collect whatever information they want as the motion says, but I just want to make clear to folks here and in the group that there will be a wide public comment, and then extensive review.

DR. HOWELL: And the public comment, let me be sure I understand the legality. The public comment on the document, however, would be available for the committee to include to send to the Secretary with its recommendations, or not? How would that go?

DR. VAN DYCK: The document that we receive will take longer than 30 days.

DR. HOWELL: Okay. There is a lot of interest in the audience, and unfortunately, we need to resolve the thing with the committee to get this in. What other wisdom do you have? We have a motion on the table.

DR. DOUGHERTY: I'm just wondering. When we say core recommendations, I think people around here, if I'm inferring this correctly, means the 30 conditions. So is it possible -- no? Okay.

PARTICIPANT: No.

DR. DOUGHERTY: Okay. I think we need to spell it out. We can't just recommend the report, recommend the conclusions of the report. What are we recommending?

DR. HOWELL: The report.

DR. DOUGHERTY: The report.

DR. RINALDO: You know, there is one fundamental. If you look at the report at the 30,000-feet level, the report in essence has considered 84 conditions, and in the end, recommends 30 as a uniform panel, and an additional 25 as ones that ought to be reported, because they are clinically significant. That it the report.

If you had to summarize the report in a telegram, that is what it is. That is what the recommendations should be about.

DR. HOWELL: And I think that is, in essence, there are a number of things discussed in the report that are important areas to consider that have not really been considered substantively in the report. They are mentioned, and they are things we need to do.

Dr. Alexander, would this motion be consistent with your thoughts about the thing? Would that work, do you think?

DR. ALEXANDER: I will vote for the motion, although I must say I have some reservations about it. The usual public process for an advisory committee is to get a report like this, provide an opportunity for public comment and discussion, and then have a discussion among the committee, taking into account those comments.

We are short circuiting that process. We have had limited public availability of the report. We have had some opportunity for input, and we must recognize, I think, that there has been a lot of opportunity for input to the committee that prepared the report.

So given that fact, I'm willing to vote for this motion and forward it to the Secretary with the knowledge that I'm sure the Secretary will seek additional public comment. I was uncomfortable.

I really believe in this report. I think it is an excellent report. There is hardly anything in there that I have any hesitance about supporting. I think the ACMG did an absolutely outstanding job in preparing it, and I support what is in there.

My only reservations have been related to process, not content. So given the fact that the vote is going to be on forwarding the report to the Secretary with the concept that this committee supports what is in there, I'm okay with that, and I will vote to support it.

My preference would be to have provided some more opportunity for the process to occur that usually occurs with federal advisory committees, but if that is not to be, that is not to be.

DR. HOWELL: I appreciate those comments. I think that most of us would really prefer to follow a rigid process, but I feel such urgency in getting this process moving along. We do indeed, I mean, there is evidence that states are not moving, and they are not ready to go, and that babies are dying. I guess that makes me quite comfortable in "short circuiting" it. I really feel that way. Is there anymore discussion on this and so forth?

Coleen, do you have a final word before we call the question? We're getting close.

DR. BOYLE: I guess I still have concern. There are some errors in the report as written. Again, these are just issues, and you could say they are minor. What is recommended in the table and what is in the text is different. So to me, those are somewhat major issues. G6PD deficiency is in the table, and it is not in the text.

I feel like we have to vote on the report to that. I mean, you can clarify that and tell me which way we're going here. But if I'm recommending a panel, I want to know what I'm recommending.

DR. RINALDO: But those are typographical errors.

DR. BOYLE: No, but listen. No, they are typographical. We don't have all the fact sheets there, and I am there with you in terms of moving this process along, but I feel like we ought to move it along in a responsible way.

I feel your passion, it comes across loud and clear, and I'm there with you. But I do feel like we need to be responsible here.

DR. HOWELL: I think the thing is is that there is every indication from HRSA's point that they will want to work with the folks that prepared the report, and work with them to correct things that are obvious errors.

We'll have an opportunity to comment then and so forth. But unless there is some burning issue and so forth, I'd like to call the question.

Do you have a burning issue, Denise?

DR. DOUGHERTY: Yes. I think that given what Coleen said, and given my confusion when I first read the report, that somebody could choose from the executive summary either the scores of all conditions table or the uniform panel that is on page 19.

I would like to suggest that we clarify that we are recommending the uniform panel on page 19, the uniform panel in the reporting report only, to clarify for people that that is what is being recommended. Otherwise, recommending the report is a little vague.

PARTICIPANT: But that's just typographical.

DR. DOUGHERTY: No, there were decisions that were --

DR. RINALDO: You have seen the formal recommendations. The presentation that Mike made yesterday is the final version. If there are typographical errors, some of you probably do know and appreciate how hectic it has been for Mike in putting together and going through all the phases. It has been very pressing trying to meet the deadline and be ready for this meeting. Now, you cannot in good conscience delay the process because of a few meaningless typographical errors.

DR. BOYLE: I am not delaying the process. I am trying to clarify what it is we are recommending. I am suggesting that we recommend something specific versus recommending the report.

DR. DOUGHERTY: Because there is nowhere in this executive summary that says we recommend the following uniform panel and report only. It does not say that actually.

DR. LLOYD-PURYEAR: It does.

DR. DOUGHERTY: Where?

DR. HOWELL: The time I think this late on Thursday is too -- the thing is, we're going to vote. Madam Secretary, will you read the motion? She is getting good at it.

DR. LLOYD-PURYEAR: Accept and recommend the ACMG report and forward to the Secretary, and allow for written comments and recommendations from the public and the committee to be included. The public's comments will be included as an appendix within 30 days.

DR. HOWELL: We're going to send it forth at the current time. At the current time, we are going to make the document public, and we are going to within 30 days send the recommendations of this committee, which will be derived electronically, and we will append the public comments with further commentary to the Secretary. That's the motion. Do you have that down?

DR. LLOYD-PURYEAR: Okay.

DR. HOWELL: Any further comments about the motion?

(No response.)

DR. HOWELL: Those favoring the motion, please raise his or her hand. One at a time, please.

(Show of hands.)

MR. ROBERTSON: Can I abstain?

DR. VAN DYCK: Yes.

DR. HOWELL: Madam Secretary, are you getting all these numbers?

MR. ROBERTSON: Can you abstain?

DR. VAN DYCK: Yes, you can.

DR. HOWELL: Sure you can. Why not? You think that we can't abstain? That members can't abstain? Why would we not be able to abstain? I mean, I'm not abstaining, but why would someone not be able to abstain?

MR. ROBERTSON: I think an abstention is registered as a no vote.

DR. HOWELL: Well, we can record it as an abstention, and then the other lawyers can do it. Are there abstentions? Are there abstentions?

(Show of hands.)

DR. HOWELL: We have two abstentions, Denise and Colleen.

Thank you very much. We will get a note off, and we'll send this to the Secretary promptly.

However, Michele will be working with you aggressively over the next short period of time to get your comments so that we can put them together, and we will communicate with you about those and so forth, so that we can get those off the table. Thank you very much. That was very helpful, and I think we can get the process moving along.

Are there any other recommendations today? I hope not. I don't think so.

One of the things is that we have discussed in the past, subcommittees to proceed to work. Let's back up. I'm going to back up a little bit, because the time is getting awfully short. One of the things we've got to discuss is the next meeting.

In the back of your thing, you have a calendar. The tentative schedule for the next meeting is January 20th and 21st. I know Michele has been in communication with you about trying to identify the best days for each of you. Would anybody like to comment about that?

DR. LLOYD-PURYEAR: There were no conflicts.

DR. HOWELL: There were no conflicts. So please, since there were no conflicts, put that in stone on your calendar.

Peter, is that going to work for you? You have January, and you are out and about a good bit.

DR. COGGINS: As things stand right now, that will work out. Things may change, but I'll try and work around it.

DR. HOWELL: We don't allow change. Anyway, super. April will be the next one, the 21st and the 22nd of April.

DR. LLOYD-PURYEAR: No conflicts.

DR. HOWELL: No conflicts. And the next one, July 21st and 22nd. October 20th and 21st, and that takes us through a year from now. So we will settle for those dates, and those are the best dates that we have available and so forth.

I'd like to hear some comments about the agenda for next time. We will clearly have on the agenda revisiting our work on this particular document, and the communications that go forth and so forth. What other things would the committee like to have on the agenda for next time?

DR. RINALDO: I believe you already decided to have some discussion of regional collaboratives.

DR. HOWELL: We had discussed the regional collaboratives, which I think would be very, very profitable. I would like to suggest to the group if it would be acceptable, to ask Dr. Groft to come and talk about the new rare disease network that he is putting up at NIH that might be a useful site for information of some of the rare genetic conditions, some of which will be focused on conditions of interest to this committee.

Would that be something the group would be interested in hearing about? We'll ask Steve Groft to come, the Director of the Office of Rare Diseases.

DR. BECKER: Yes, Rod, a couple of things. One, I think Dr. Kahn mentioned that their online curriculum for newborn screening, the module would be available in the next month or two. I was wondering if we might get a preview of that, and have some information maybe available in our agenda book so that folks could take a look at that.

I think that speaks to the larger topic of the educational needs, both in terms of providers, and also parents, something that has rang through as one of the obvious needs as we go forward. It certainly was one of the potential subcommittees that Dr. Green mentioned earlier in her comments.

The second area that I would like to see us continue to evolve in is in the way of making recommendations about the financing. We need to I think dissect a little better how we are going to recommend to the Secretary the financial needs and issues of providing support for the funding that's needed at the state, and also reimbursement levels for the practitioners for support of expanded newborn screening that we have just recommended. That's enough for now.

DR. HOWELL: What would be the best mechanism to get information to this committee about directions that we could suggest that would enhance newborn screening follow-up services, and anything else that would have to do with funding?

DR. RINALDO: Well, one specific would be to talk about training programs. I think we have heard over and over again the lack of specialists, which I think is pervasive both at the laboratory level and the clinical level.

I believe there are very few training programs even less able to provide adequate laboratory training. Things are not going to get better just by spontaneous combustion. They need help, and I believe it will be very important thinking about ABMG, and the group, and just have somebody tell us how the status of training in the various branches of genetics. I think this is not only about newborn screening, but we are talking about we need, sure, biochemical geneticists, but what about cytogeneticists, molecular, and medical geneticists.

There is a new track they are proposing, and I believe soon will be. So I think it would be very important to have a discussion about what the gaps are, and about what this committee can do to help improve really the numbers of people properly trained to deal with all the aspects of genetics.

DR. HOWELL: So training in the field of medical genetics.

Denise had a first comment about training.

DR. DOUGHERTY: Well, now that we've started off the committee with this splash, I don't think any other committee in Washington has ever made recommendations in their second meeting.

DR. HOWELL: We're just getting started.

DR. DOUGHERTY: Yes. Splash is good. I guess I would like to recommend that we take some time and figure out what else it is we need to sort of a year-long work plan, and say what the nature of what kinds of recommendations we think we should be making, and have a time line for them.

For example, training, financing. There is a lot of stuff in this report that has gaps. The medical home for the kids, the link between primary care and specialists. There are a lot of things that need to be gone into in a lot more detail, and I'm sure if we send this to the Secretary and recommend the report, he may come back to us and say well, how would you fix the financing system?

So I think if we went through some of the issues that we heard yesterday, how are we going to deal with future recommendations, how are we going to collect the data if we need cost-effectiveness? So I guess that's what I would suggest, rather than have it meeting by meeting.

DR. HOWELL: Do you have some thoughts about how we identify them? What sort of a mechanism? For example, if you go through this report, you will find on every other page, a need, whether or not it is research, education, or financing, professional education, parent education, and so forth. One simple way may be to go through the report and see what surfaces.

DR. DOUGHERTY: I think that would be good. The Executive Secretary if he does his report, say here are all the issues that need further work, and perhaps recommendations by this committee. And then we can decide as a group whether we're going to take on the task of making recommendations.

DR. HOWELL: Right. We probably will need a substantial module on training. For example, I would visualize that Dr. Alexander would want to weigh in on that about the federal role and

training of professional specialists. But there are also obviously the whole group of non-genetic folks that are essential. They range from nurses to social workers, to any number of people that we need to be thinking about as far as training is concerned. So that is a very good thing, to think about the missions, and then maybe we can prioritize some of those for the later meeting and so forth.

Are there other things, Michele, that we need to do at the next meeting that comes to mind?

DR. LLOYD-PURYEAR: Thinking about the need for subcommittees.

DR. HOWELL: Yes?

MR. ROBERTSON: I was just going to follow up on something that Bill said in his comments related to training. I think we can't forget the role of the parents and the families and education about newborn screening in general, and beyond, in terms of follow up and care. I think that that has to be a really critical component. I know that's in the report as well. So in moving forward, not just training for the professionals, but education for the parents and families.

DR. HOWELL: You know, one enormous resource that we'll want to have is representatives come to this committee at some point is the National Library of Medicine. It has some terrific online programs, but they have not expanded much in this area yet. But they are, number one, interested.

Again, some of their public websites are extremely popular for other health issues. That's another group that we can get.

DR. RINALDO: Another point, actually not for the next meeting, but as we have already a schedule for 2005, perhaps a year from now in the October meeting of next year to have a first assessment of the impact of the report and the recommendations. Probably a year is a period of time just to see what happened.

DR. BECKER: Like another state of the states?

DR. RINALDO: Pretty much.

DR. HOWELL: That brings up an issue. Someone was suggesting to me that they had served on another Secretary advisory committee. One of the things that they had done, which I thought was a very good idea, is to ask one of the senior persons from the Secretary's front office to come to a meeting and say what had happened to the report that they got. That may be interesting. At least it would mean that someone would have to look in the in box to see where it was. That might be interesting. But obviously we'll have to look at the time and so forth.

DR. BOYLE: Rodney, can I just make a suggestion? I guess one of the keys for me in terms of the recommendation that we just made is to understand, or begin to build the data systems actually as what Piero just mentioned to try to evaluate the impact, and to collect the data so that we can have data to assess some of the data gaps we have. I feel like that needs to be a strong recommendation of our committee.

Coming back to what Denise had said, not just to deliver this report and hope it works, but to actually have some action items relative to what we need to do to ensure that it works, and to come back so that we can make this field more robust.

DR. HOWELL: We are in the waning minutes of this committee. We need, again, to talk briefly about subcommittees, because those have come up several times today. Nancy mentioned several, and we have been talking about several.

The discussion before had been that we will establish subcommittees, and people can decide what they would like to -- and subcommittees are important, because they are critical because you can involve other members of the professional and lay community, which adds a great deal of richness to the discussion. Let's hear your thoughts about subcommittees before we catch our plane.

Michele is saying that the committees could really be plugged in on the work plan that comes out the next time, and that probably makes sense. If we prioritize

committees, obviously there are major areas of technology, there are major areas of data, training, and so forth. They are fairly obvious things, and I think Nancy gave a long list today.

We will plan to next time have subcommittees earlier, and not at the day. Earlier on the agenda so that we can try to plug them into the thing. Are there any last minute critical issues of this meeting today?

(No response.)

DR. HOWELL: Is there a motion that we adjourn? We have a word before we adjourn.

MR. ROBERTSON: Just to thank the Chairman for running a very excellent meeting over the past two days. Thank you very much.

(Applause.)

DR. HOWELL: Thank you, Derek.

Is there a motion that we adjourn?

PARTICIPANT: So moved.

DR. HOWELL: So moved. Everyone is saying yes. Thank you very much.

(Whereupon, at 3:31 p.m., the meeting was adjourned.)