

**Report from the Advisory Committee on Heritable Disorders and  
Genetic Diseases in Newborns and Children**  
*R. Rodney Howell, M.D.*

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DR. TUCKSON: Rodney Howell is known to all of us. He is the chair of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, and they're facing many of the same challenges that we are regarding access, education, and appropriate standards for validation of genetic tests. In recognition of the liaison relationship and our common interest, there's a liaison we have between these two committees, and as I mentioned Dr. Joe Telfair is our liaison to that group. The advisory committee has been considering recommendations regarding a uniform newborn screening panel and system, and in light of the interest and overlap between the two committees, Chris Hook suggested this occur.

Chris is on the line. Is that right? Do I have to do anything? Hey, Chris, are you there?

DR. HOOK: Yes, sir, Reed. I've been listening in the last few minutes. I didn't say hello so that I wouldn't interfere with anything, but thank you for letting me call in. I appreciate it very much.

DR. TUCKSON: Well, I want you to know that you are beaming out of the ceiling. You have a celestial presence at this meeting. It's extraordinarily impressive, Chris. Thanks a lot.

DR. HOOK: Thank you.

DR. TUCKSON: With that, I'm pleased to welcome Dr. Rodney Howell, the advisory committee's chair, to speak to us about the work. You know Dr. Howell as professor of pediatrics and Chairman Emeritus with the Department of Pediatrics, University of Miami School of Medicine, a long history and considerable expertise surrounding genetics and child health.

Thank you.

DR. HOWELL: Reed, thank you very much. I'm delighted to be with this distinguished group this morning to discuss the work of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. One of the things I would welcome is anyone who can think of a worthwhile acronym for this committee. We have not so far been successful.

I'm going to spend a mercifully brief time with you this morning, but I'd like to discuss three areas. I'd like to discuss a little bit about the environment in which this committee was formed and the environment surrounding it. I want to talk a fair amount about newborn screening and so forth, and I will obviously also talk about the charge to this committee and some of the work that the committee has undertaken.

A central focus to this committee -- and I'll talk about the charge in some detail -- has to do with newborn screening. The environment in which this committee begins its work in the area of newborn genetic testing is that there's an enormously rapidly changing technology, literally by the week, with multiplex testing platforms that have moved the whole paradigm from the classic Guthrie newborn screening test where you had one blood spot and you did one test -- that is with phenylalanine -- to a new paradigm of tandem mass spectroscopy, where you have one blood spot and you do many, many tests simultaneously on that same spot.

The problem has been around for a long time and has increased in recent years, the fact that there are large numbers of extremely rare conditions and few providers with great expertise in this area. There's new technology on the horizons that will clearly supplant even tandem mass spectroscopy.

In addition to that, there was specific legislation for heritable disorders program that established the Advisory Committee on Heritable Disorders, and also established grant programs at HRSA for regional collaboratives. At the same time, HRSA had had a contract that had been under way for some time, at this point about three years, with the American College of Medical Genetics, to develop with a large expert and diverse group, under a contract, a panel of information that would provide for a uniform panel in newborn screening. There were other parts to that contract, but that was the core part of the contract, to think of the mechanisms by which you would decide what to screen for and to recommend those long term.

The legislation that established this committee was actually a congressionally mandated committee in the Health Care Act of 2000. It established this committee, as well as a couple of other areas that I'll comment briefly about because they're relevant to this. Section 1109 directed HHS to provide screening, counseling and health care services that would be of benefit to newborns and children at risk for heritable disorders. It also authorized the Secretary to award grants for demonstration programs that we hope will be very valuable to evaluate the effectiveness of screening, counseling and health care services, morbidity and mortality caused by heritable disorders of the newborn and children.

Section 111 of that act established the Secretary's Advisory Committee that I'm reporting to you about this morning. The purpose of this committee is very extensively spelled out in the legislation. The prime purpose is to provide the Secretary with advice and recommendations concerning grants and projects authorized under these previous sections that I mentioned, and also to provide technical information to develop policies and priorities that will help the states and local health agencies provide for newborn and child screening, counseling and health services for newborns and children at risk for heritable disorders.

Specifically, and it goes down into even greater detail, to provide guidance to the Secretary regarding the most appropriate application of universal newborn screening tests, and you'll see why the ACMG report was highly relevant to that particular requirement; technologies, policies, guidelines and programs that will effectively reduce morbidity and mortality in newborns and children at risk for heritable disorders.

The advisory committee's constitution was also further spelled out, and it said that the members should have medical, technical and scientific expertise in heritable disorders or in providing screening, counseling, testing, or specialty services for newborns and children at risk for heritable disorders; members of the public with special expertise about or concern with these conditions; and representatives from such federal agencies, public health constituencies, and medical professional societies as deemed necessary to fulfill the duties of this committee by the Secretary.

I'll go through briefly the members of this advisory committee to simply point out what they do so you'll be aware of that. This is an alphabetical list. Bill Becker is an active member of the committee and runs the Newborn Screening Public Health Laboratories in Ohio State. Amy Brower represents a major industry. She happens to also have a Ph.D. in a biologic science and happens to be the parent of children with genetic conditions that could have been detected in the newborn. Peter Coggins is with PerkinElmer Life and Analytical Sciences and, as I think many

of the laboratory people are aware, that particular company has a major interest in the technology of newborn screening.

Steve Edwards, at the time this committee was appointed, was president of the American Academy of Pediatrics, and the American Academy of Pediatrics has had a long and abiding interest in newborn screening and has provided data and advice for a very long time. Greg Hawkins from the Department of Internal Medicine at Wake Forest University in North Carolina. Jennifer Howse, the president of the March of Dimes, again a large public organization that has had a major commitment to newborn screening really for many decades, and continues to have that activity.

I chair the committee, as has been mentioned. Other committee members are Piero Rinaldo, who directs the biochemical and genetics laboratory at the Mayo Clinic and arguably one of the world's experts in technology, particularly tandem mass spectroscopy, and he's been very valuable to the committee. Derek Robertson is an attorney and a parent who has been very much involved in discussions in working these areas for a long time.

The ex officio members of this committee are voting, which I gather is not common, but at least the federal ex officio members are voting. Peter van Dyck represents HRSA, and he is head of Maternal and Child Health at HRSA, as I think you're aware. Denise Dougherty is from the AHRQ. Coleen Boyle has been appointed to represent the CDC, and Duane Alexander has been appointed to represent the National Institutes of Health. He is director of NICHD, again a group that's had a long interest in the research in this area.

There are important liaison members from other advisory committees. Jim Collins, a neonatologist, represents the Advisory Committee on Infant Mortality, and Dr. Telfair you've already heard represents this committee. He replaces the able Reed Tuckson, who began representing this committee until he was chosen as chair of this committee.

I'll talk very briefly about screening for metabolic disease. The tenets under which newborn screening has taken place really were laid out in 1968. The World Health Organization at that time released a statement that outlined kind of the general principles that you would want in a test to apply to newborns as far as screening is concerned, and those commentaries have really been in place since that time, and they basically have been used more or less by people who thought about this.

Newborn screening for genetic disease is a state administered program. I think many of you know that, but let me underline this. Although there are a lot of professional guidelines, et cetera, what a state screens for in the newborn period is decided at the state level. Ordinarily that decision takes place in concert with an advisory committee, and those advisory committees range from folks who have essentially no information on this to areas where there's extraordinary talent and depth, both in technology and the science and so forth.

I might point out last year 4.1 million babies were screened in the United States. Every state and jurisdiction has a newborn screening program, making this the most common form of genetic testing that's done today. Newborn screening has, interestingly enough, not been thought about as genetic testing, but obviously the vast majority of these conditions are genetically determined. I might point out, and we won't get into this today -- we could spend a long time on this -- most states have a program to fund this mechanism that's similar. Most charge fees that are charged back to the hospital that appears in your hospital bill or as a part of your room service. There are

exceptions to this, New York State being one that doesn't charge anybody, and the State Health Department, through its various fundings, picks up the whole tab.

I've mentioned that all 50 states have had this since the 1970s. Phenylketonuria is the hallmark of this that you can detect in the newborn period, and it's been a target since the mid-1960s. Congenital hypothyroidism soon appeared, and there's extraordinary variation from state to state in this program. Again, I've mentioned the fact that technology has really changed the field because of the fact that you can identify a large number of analytes on a single sample, and the experts certainly recommend that when you look at a mass spectrum from a tandem mass readout, that you look at the entire spectrum and that you don't set the instrument so that you only see one little corner you're interested in, that you basically look at those that are done.

I might point out, one of the questions that has been posed to me frequently is should we expand newborn screening. That question has been answered, and we can talk about it as much as you like. But the point is that expanded newborn screening is moving across the country extremely rapidly, and as we stand here today 36 states currently have mass spec programs in line. I simply show this very complicated map -- don't pay much attention to it, but I wanted simply to point out that all those little stars indicate the location of mass spec labs, and those arrows indicate that certain states send their samples to other areas. There are certain private labs that have contracts. One of the most visible is Mississippi that has a contract for a private lab. Mississippi, I might point out, has the largest number of mandated screening tests of any jurisdiction in the United States today.

But if you look at that in 2004 and you look at it in January, it's changed a lot, and I might point out it's changed even since then, because my home state of Florida that is still there in green, that means that we are not screening for many things, that's now changed to purple, and it, as of February 1, is again screening for actually the ACMG recommended list.

This gives you a little more feedback into the diversity from state to state, and I might point out that there's one state, one of those square states up in the middle of the country, that currently, as we are here today, screen newborn infants for three disorders. Then you can see the other states that screen for more than eight, and usually that's the so-called 30. Again, there is one condition that the expert panel working with ACMG and most experts in metabolic disease feel should be screened for in the newborn period is probably one of the least controversial, and that's MCAD deficiency, a disorder of fatty acid metabolism that can be very simply and effectively treated, and if untreated a certain percentage of those babies clearly and unquestionably die. So there's considerable feeling that that should be screened for.

Now, MCAD can only be detected reliably with tandem mass spectroscopy, and if you adopt the idea that it should be screened for, and that's the reason I show you the states that have either mandated screening for MCAD -- some states have it mandated. Florida is now doing it but it's not yet been implemented because they're working on it, and California has found the money. They started and stopped, and now they've returned to mass spectroscopy.

This is a graphic demonstration of what people are screening for. All the states and jurisdictions screen for PKU, hypothyroidism and galactosemia. Strangely enough, there are two areas that still don't screen for the hemoglobinopathies, which, as a personal comment and not as the chair of the committee, is quite amazing to me. Then it drifts off so that just a few places screen for this, and you can see the MCAD deficiency on the right.

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I will not go into this. This is very recent changes in screening programs, and I want to emphasize the fact that these programs are moving rapidly.

The committee has held three meetings which have focused on newborn screening and related technology. The next meeting is scheduled in April on the date you see here in the Ronald Reagan Building, and we certainly welcome anybody appearing for that to discuss anything of interest at that meeting.

What has the committee done? The committee has focused, as I said, on newborn screening and has seen major presentations of drafts of the report of the American College of Medical Genetics. The committee has been very positive about the premises that are set out there and felt that, because of the importance of this, that the committee would like to send a note to the Secretary as soon as the full report is available saying that the premises in there have been supported by the committee. However, the committee and its letter conveying that to the Secretary -- and I might point out it has not yet gone -- also points out that the committee has not had a chance to review the final document and will comment on the final document as it's received going forward.

Let me comment about this report, because this report has created more interest, shall I say -- I use that term politely -- than most anything you might imagine. The report is a report that was done under contract with HRSA, and HRSA quite properly doesn't release draft reports. In other words, a report is still working. Once the report is done and is to HRSA, then HRSA will post that. The report has been accepted I've been told, and it is anticipated that the entire report will be on the HRSA website by the middle of this week. Let's give it a few days. But the bottom line is the report has been accepted and it will be up there.

I might point out that folks who have gotten small parts of the report have commented about things that were not in the report. The draft report that was seen earlier by the committee was 60 pages long. The report that goes up on the website this week is 380 pages, to give you some idea of the scope of it. It's an extensive report that has involved a great number of people over the years.

But anyway, that's been a major focus, and that will clearly continue to be a focus as we review the final report of this committee.

As the committee has looked at things that are derived from this report, what do you do with these things and how do you implement them? The group decided that they would like to form three subcommittees, and I've listed those subcommittees here. There's a subcommittee that has been formed on education and training, one on follow-up and treatment, and one on laboratory standards and procedures. Now, these committees were formed at the last meeting of the group, and they are currently having email exchanges and meetings by telephone to lay out what their agenda will be and what exactly they're going to approach, and they will be reporting on their subcommittees the next time.

It is anticipated that these subcommittees, as you will see here, will identify experts all around, people who are certainly not members of the committee but anybody in the country who has expertise in these areas are likely to be asked to either be a consultant, and perhaps in time they could become a formal member of these subcommittees to work on these. But these are obviously, for everybody in this room and particularly the people around the table, understand extraordinary things that need to be done in those areas. But anyway, we expect that we will hear about that subcommittee.

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The report I alluded to will be put up on an individual website, and it will be at [mchb.hrsa.gov/screening](http://mchb.hrsa.gov/screening). For those of you who would like to spend quite a lot of time, I would suggest that if you decide to push "Print," that you fill up your printer before you do that because of the length of the document. You've all had that thing, you decide you'll print something quickly so you can read it quickly, and you come back and your printer is out of paper. This is clearly the thing to do.

But this is the website for the committee, and at that current website all of the minutes of the previous meetings are there, along with the presenters, and I might point out there's been a very gratifying input from the public. There's always an area of public comment, and public represents parents and industry and a variety of professional organizations have had a lot of comment, and we would look forward to that. Dr. Michele Puryear at HRSA is executive secretary of the committee.

So with those brief remarks, I will end. Thank you.

DR. TUCKSON: Thank you very much, Dr. Howell. Why don't you stay there for a couple of questions? I'm sure we'll have a few.

Emily?

DR. WINN-DEEN: Obviously, newborn screening identifies individuals who have genetic disease. So have you dealt with the issue of how those individuals go on in their lifetimes to experience or not experience discrimination?

DR. HOWELL: Interestingly enough, I don't think that there's been any formal look at that. Interestingly enough, some of us have been involved in newborn screening before most of the distinguished group at this table was born. For example, when the NIH had a consensus conference on the diagnosis and treatment of phenylketonuria, one of the panel members of that committee was a college student who had phenylketonuria. So we see now adults who had these conditions, and we have a lot of sidewalk conversations, but I'm not aware of any formal effort to look at -- the biggest cadre that would be out today I think would be patients with phenylketonuria, hypothyroidism and things of that nature that were back in the general community.

DR. TUCKSON: Any other questions, and Chris, also with you on the phone?

I've got Francis, and then Willie, and then if, Chris, you want to get in, just let us know.

DR. COLLINS: Rod, I appreciate your report. It sounds like this is coming along quite nicely.

With regard to the tandem mass spec, what's the current information that's been derived from the states that have been doing this about the concern about creating great anxiety amongst parents when you find something and you're not quite sure what it means, because that's been one of the major issues about introducing this into newborn screening. With the caveat of first do no harm, are we in fact creating in some circumstances unnecessary anxiety amongst parents by a finding of uncertain significance? Is that a real concern or are people handling that pretty well? What's the preliminary data on the consequences of greatly enlarging the number of conditions that can be screened for, including many for which nothing really is known or no intervention is available?

DR. HOWELL: I think that that has been discussed extensively over the past couple of years, Francis, while this whole effort was under way. One of the recommendations that will appear in this report is to systematically look at that, because there has not been any systematic look. I'm talking about other than people talking at a cocktail party, et cetera. But I think that there are a few things that are clearly important.

There are conditions that you pick out with the tandem mass spectroscopy that we know very little about, and I think one of those is SCAD deficiency, a short-chain fatty acid defect. You pick that up. However, it is clearly known that families who have this condition, and one of the people who commented at this meeting happens to organize a group of families with SCAD deficiency, those people do have problems when they get sick. When they fast, they have problems with acidosis and so forth.

So the thing is that it has been felt by most that certainly when you pick up something you don't know a lot about, you certainly should tell the health professionals at least that you have an abnormality. But on the other hand, I think a major research agenda is going to be to follow all these people and see what the condition is really like, and that's a key part to find out what they really are like.

Let me comment about one thing, because this report has been wonderfully interesting to a lot of people. But one of the things that has to do with what has been called secondary conditions is that when you're looking with tandem mass or anything else right now for a primary condition that no one argues about, and I'll use phenylketonuria as an example, you pick up a variety of conditions related to elevated phenylalanine that are not PKU. Those have been termed secondary conditions. You are not running a test for those secondary conditions. However, if you send me back a phenylalanine that's 18 milligrams percent, as a person who is doing the diagnostic follow-up, I must study those secondary conditions, because the secondary conditions include hyperphenylalaninemia that may not require treatment. It also includes a group of conditions related to bipterin metabolism, related to bipterin deficiency, bipterin recycling.

The thing is, if you've got a child that has a bipterin deficiency, you don't put that person on a low phenylalanine diet. You add bipterin. So the secondary conditions tie into the primary conditions tightly. Then there are other conditions that you just know very little about, and those clearly fall into the category of research things that need to be looked at. But they're going to be there.

DR. TUCKSON: Let me just quickly get Willie and then Ed.

DR. MAY: I'm from the Department of Commerce, but the NIST specifically, so I have to ask you this question. Certainly, tandem mass spectroscopy is a powerful technique. You get lots of data. But there are different platforms, there are different practices of the art. So have there been any studies on the accuracy or, let's say, comparability of results that you get across all of these tests that are being performed, either qualitatively or quantitatively?

DR. HOWELL: Yes, there have been, but not to the extent you would like. For instance, there is a quality assurance program that is currently done by the CDC. The CDC does quality assurance programs, as you know, on newborn screening in general. But there is additional quality assurance programs done by the College of American Pathologists and ACMG that specifically look at some of the rare metabolic conditions.

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In the regional cooperative groups that we talked about that HRSA has funded, one of the states is piloting a training and education program for people doing mass spectroscopy, and I think that's going to be a model for training other people because you obviously need people who are highly qualified. You need to keep the false positive rate as low as humanly possible, but you can't miss an affected person. So I think that quality assurance programs and the laboratory standards committee of the Secretary's Advisory Committee I alluded to, that clearly would be one of the things that they will be focusing on.

DR. TUCKSON: Ed?

DR. McCABE: I just wanted to reiterate that since we don't know the natural history or the influence of treatment on many of these disorders, I think it brings home the need for large studies like the Children's Oncology Group, which was done for children with cancer so that we should look to follow-up studies.

The other thing is that in our table folder is the article from Gina Kolata that you sort of alluded to and many of us read, and I just want to quote one point so that those who haven't been involved in newborn screening recognize that many of us take exception to it. It's a quote from the second page. "'The majority of newborn screening tests have failed,' said Dr. Norman Fost, a professor of pediatrics and director of the program in medical ethics at the University of Wisconsin. Over the years, Dr. Fost said thousands," and I quote thousands, "of normal kids have been killed or gotten brain damage by screening tests and treatments that turned out to be ineffective and very dangerous." End of quote.

Some of us have talked about where those thousands of kids are. There were some studies early on with PKU where they were trying to figure out the treatment. The best is a handful of children, and I've been on panels with Dr. Fost at the American Academy of Pediatrics a couple of years ago, when it was only hundreds, which I still think was way overstating the case, and suddenly that's grown to thousands. These are extremely effective tests. We always need to fine-tune testing and management whenever we introduce a disorder. But I think a quote like that that is completely unfounded in the medical literature or in the experience of the clinicians does a huge disservice to a very effective public health strategy.

DR. TUCKSON: Listen, I want to thank, first of all, Rodney.

Chris, I'm sorry. Did you have any comment you wanted to make?

DR. HOOK: I'm very appreciative of the presentation, the opportunity to hear it, but I don't have any additional questions.

DR. TUCKSON: Okay, thank you.

Well, Rod, thank you again. Your committee is different from ours and separate. You're doing the work that you need to do.

I would urge our committee members who would like to ensure that your comments are introduced into the discourse to really contact Joe. Joe is our liaison and is well able to represent any concerns, questions, suggestions or guidance.

Of course, Rodney, we want to really thank you for taking the time.

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DR. HOWELL: Thank you very much.

I would certainly like to underline that it would be wonderfully appreciated to have information. Ed and I have discussed the fact that we love controversy, but we do like to have the facts have some justification.

DR. TUCKSON: All right. With that, I'm running the train a few minutes late. I apologize. Be angry with me, but I'm going to give everybody at least their 15 minutes that they're due. So why don't we come back? We'll have public testimony, the first person at the microphone, at 25 after 11:00. So that means, committee, you have to be back here at 25 after.

(Recess.)