Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Meeting Summary
April 21-22, 2005
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its fourth meeting at 9:00 a.m. on Thursday, April 21, 2005, in the Rotunda Ballroom at the Ronald Reagan Building and International Trade Center in Washington, D.C. The meeting was adjourned at 2:30 p.m. on Friday, April 22, 2005. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments from 1 p.m. to 2:00 p.m. on Thursday, April 21, 2005, and Friday, April 22, 2005.

Committee Members Present:

R. Rodney Howell, M.D.
Committee Chairperson
Professor
Department of Pediatrics
The University of Miami School of Medicine

Duane Alexander, M.D.*
National Institutes of Health

William J. Becker, D.O., M.P.H.
Medical Director
Bureau of Public Health Laboratories
Ohio Department of Public Health

Coleen Boyle, Ph.D., M.S.*
Centers for Disease Control and Prevention

Amy Brower, Ph.D.
Executive Director
Medical Informatics and Genetics
Third Wave Molecular Diagnostics

Peter B. Coggins, Ph.D.
Senior Vice President
PerkinElmer
President

Denise Dougherty, Ph.D.*
Agency for Healthcare Research and Quality

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*Ex officio member

**Liaison member

E. Stephen Edwards, M.D., FAAP
American Academy of Pediatrics
Past President

Gregory A. Hawkins, Ph.D.
Assistant Professor
Center for Human Genomics
Wake Forest University School of Medicine

Jennifer L. Howse, Ph.D.
President
March of Dimes Birth Defects Foundation

Piero Rinaldo, M.D., Ph.D.
Professor of Laboratory Medicine
Mayo Clinic College of Medicine
Department of Laboratory Medicine and Pathology
Mayo Clinic Rochester

Derek Robertson, J.D., M.B.A.
Attorney-at-Law
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Joseph Telfair, Dr.P.H., M.S.W., M.P.H.**
Secretary's Advisory Committee on Genetics, Health, and Society
Department of Maternal and Child Health
School of Public Health

Peter C. van Dyck, M.D., M.P.H., M.S.*
Health Resources and Services Administration
Associate Administrator

Executive Secretary
Michele A. Lloyd-Puryear, M.D., Ph.D.
Health Resources and Services Administration
Committee Executive Secretary

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WELCOME, OPENING REMARKS

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Dr. Howell opened the meeting by noting that the Committee would welcome suggestions for a new name and thanking Committee members and Dr. van Dyck and Dr. Lloyd-Puryear and the staff of the Health Resources and Services Administration (HRSA) for their hard work. He added that voting to approve the minutes for the third meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children held January 13-14, 2005, would be delayed to allow time for the Committee members to review the corrected minutes, which were not in their briefing books.

Next, Dr. Howell drew attention to the new Charter for the Committee, signed by the Secretary of Health and Human Services (HHS) on February 8, 2005. The new Charter is very similar to the previous Charter but makes Dr. Howse and Dr. Edwards voting members and includes a few other organizational changes. Dr. Howell also reported that Secretary Michael Leavitt had been confirmed as the new HHS Secretary.

Finally, Dr. Howell reviewed the agenda for the 2-day meeting:

- **The American College of Medical Genetics (ACMG) report on newborn screening.** Following an update by Dr van Dyck on the status of the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System,* Committee members would have an opportunity to ask both Dr. van Dyck and ACMG's Executive Director Dr. Michael Watson questions and to make comments about the report.
- **Two public comment sessions.** Members of the public would be given two opportunities to make statements to the Committee, one on Thursday and one on Friday.
- **Meetings of the three subcommittees of the Committee.** The three subcommittees established at the January 2005 meeting of the Committee—the Education & Training Subcommittee chaired by Dr. Howse, the Treatment & Follow-up Subcommittee chaired by Dr. Boyle, and Laboratory Standards & Procedures Subcommittee chaired by Dr. Brower—would hold concurrent meetings open to the public.
- **Educating parents about newborn screening.** Committee members would hear three presentations related to parental education.
- **Guidelines for newborn screening follow-up.** On Friday**,** Committee members would hear additional presentations related to guidelines for newborn screening follow-up and quality assurance.
- **Committee business—subcommittee reports.** Also on Friday, the three newly established subcommittees would report on their plans and activities to date.

ACMG REPORT ON NEWBORN SCREENING

Update on the American College of Medical Genetics (ACMG) Report on Newborn Screening

Peter van Dyck, M.D., M.P.H.
Associate Administrator
Health Resources and Services Administration (HRSA)

Dr. van Dyck reminded everyone that the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System* was prepared under contract to HRSA, which asked ACMG to analyze the scientific literature and gather expert opinion to develop recommendations in five areas: (1) a uniform condition panel, including implementation methodology; (2) model policies and procedures for state newborn screening programs, with consideration of a national model; (3) model minimum standards for state newborn screening programs, with consideration of national oversight; (4) a model decision matrix for consideration in state newborn screening expansion; and (5) the value of a national process for quality assurance and oversight. The report is available online at http://mchb/hrsa/gov/screening and can be downloaded for review.

After the January 2005 Advisory Committee meeting, HRSA received permission from the Secretary of HHS's office to release the ACMG report. The report was placed in the public domain for a 60-day comment period on March 8, 2005. Public comments may be sent via a special fax line (301) 443-8604; by e-mail to screening@hrsa.hhs.gov; or by mail to HRSA's Maternal and Child Health Bureau, 5600 Fishers Lane, Parklawn Bldg., Room 18A-19, Rockville, MD 20857. They must be received by HRSA's Maternal and Child Health Bureau by May 8, 2005. HHS is encouraging public comment. It's very important to us to receive a wide range of comments and to hear from everybody. HHS will take the public comments and inputs from the Committee and other sources and prepare a report and recommendations from HHS.

Committee Discussion of the ACMG Newborn Screening Report

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children
Professor of Pediatrics
University of Miami School of Medicine

Committee members discussed the ACMG newborn screening report at length, focusing on (1) the process for dealing with the ACMG newborn screening report; (2) the methodology used in the report; and (3) the process and criteria for evaluating the recommended newborn screening panel recommended in the ACMG report.

Process for Dealing with the ACMG Report. The first topic was what happens to the ACMG newborn screening report once the public comment period ends on May 8, 2005. Committee members asked the following questions, and Dr. van Dyck responded to them:

- **When and how will HRSA make available public comments on the ACMG report to the Committee?** Dr. van Dyck and Dr. Lloyd-Puryear said that HRSA has received dozens of public comments on the ACMG report. After May 8, 2005, HRSA will assemble the comments and

send them to the Committee in the form of a compilation. There was some discussion about whether the public comments should be dealt with by the Committee's subcommittees first or should be considered by the Committee as a whole. Several Committee members indicated that they would like to be able to read all of the comments. The final decision by Dr. Howell was to let all Committee members see all the public comments; then have a conference call to allow Committee members to comment on the public comments; and if needed, to ask the subcommittee members during the conference call to think about responses to specific issues.

- **What process will HRSA use to review the public comments?** Dr. van Dyck said that HHS would begin an internal department process of reviewing the public comments and making recommendations to the HHS Secretary. Federal agencies, which have already had an opportunity to make comments during the 60-day public comment period, would have an additional opportunity to weigh in on the report and public comments during this internal process. The timetable for completion of the internal process is not known.
- **What are the next steps with respect to communicating the Committee's comments regarding the ACMG report to the HHS Secretary**. Dr. van Dyck said the Committee's purpose at this meeting was to comment on the ACMG report during the public comment period, which ends on May 8th; then at its July meeting, the Committee could make additional comments related to the public comments.
- **How does HRSA plan to monitor the impact of the ACMG report?** Dr. van Dyck indicated it was important to examine the report and to examine the recommendations in the report. But HRSA feels a primary responsibility to monitor how well state programs are functioning rather than monitoring the report itself—and will report to the Committee on how programs are functioning as a whole. Dr. Howse, noting that no entity within the Federal Government has yet adopted a formal position with respect to disposition of the recommendations, said she thinks it is important to figure out how to advance the recommendations in the ACMG report. Dr. Howell said that many things seem to be happening as a result of the ACMG report, regardless of where it stands, and he is especially pleased that the National Library of Medicine is doing an information sheet on its genetics home reference page on each of the ACMG's core recommendations.

Comments about the ACMG Report's Methodology. Dr. Howell asked ACMG Executive Dr. Michael Watson to join Committee members at the table, so that Committee members could ask him questions and make comments on the report. Committee members engaged in a lengthy discussion about the methods used to arrive at the conclusions of the report and whether the findings were scientifically justified.

Dr. Edwards indicated that the American Academy of Pediatrics (AAP) would like to be reassured by the scientists on the Committee that the information in the report is very good information—if not the best, then at least among the best. Committee members, Dr. Boyle and Dr. Telfair, asked Dr. Watson to clarify the methodological approach used in the ACMG report.

Dr. Boyle commented it is not clear in the ACMG report how the expert review and scientific literature were brought together. The weight of the process seemed to be expert review, with scientific literature being brought in at the end of the process. In a systematic review, one would do just the opposite—that is, start with the science and then fill in the remaining information gaps with expert review. Dr. Boyle further noted that the scientific base on using expert review did not seem to have been brought into the report. Dr. Rinaldo asked whether Dr. Boyle was questioning the end product, the process that led to the end product, or had specific issues for specific diseases. Dr. Boyle

said that although she could not say that she had problems with the final product, as an epidemiologist, she considers understanding how the conclusions were derived essential to understanding the final product. Dr. Boyle said she believes that it is important for the Committee to arrive at a consensus about what process should be used in the future to evaluate conditions for inclusion in newborn screening programs. She also thinks that it is part of the Committee's responsibility to emphasize the importance of developing scientific evidence. Dr. Rinaldo said he thought the concerns that had been raised by Dr. Boyle were valid but he wanted to press people to provide specifics about what was wrong with the ACMG report or how it was done. Were we asking the wrong questions? Were we asking the wrong people? Should the questions have been different? What are the specifics?

ACMG Executive Director Dr. Watson indicated where there were higher levels of evidence available; either because there were clinical trials around therapeutics or in more common conditions like hyperbilirubinemia and such, there were certainly a large number of very strong evidence reports, such as the Cochrane reports and others in some of the more common conditions. But if the reference is to rare disorders, the findings in the literature about many of the rarer disorders are meager. Therefore the findings in the ACMG newborn screening report—especially for the newer and rarer disorders—were based on expert opinion. That expert opinion is not anecdotal but is based also on evidence. We ultimately did have to rely heavily upon experts in providing the information on which we based the evidence, on telling us whether or not they felt the evidence was strong or weak. In addition, in its contract with HRSA, ACMG was required to give credence to views of the public, consumers, scientists from state health laboratories, and a wide range of people. Thus, ACMG started by soliciting a wide range of opinion and then folded in the evidence base. Dr. Watson agreed that expert opinion is not the highest base of evidence, but he believes that the ACMG report presents the best evidence we have available. When higher levels of evidence (e.g., clinical trials) were available, that evidence was used. In addition, Dr. Watson explained, ACMG took into account that newborn screening yields benefits for affected children and their families even in the absence of effective treatment—value that is typically not acknowledged in the approaches taken in some of the more common evidence-based approaches that just analyze the literature and do not include input from the public.

Dr. Howell, noting that the ACMG report used experts who had published articles about the conditions, said he thinks the evidence in the ACMG report is the best evidence available to us at this point in time. Dr. Brower said that as a scientist, she thought the methodological approach used in the ACMG report was elegant—and that starting with a survey, though not standard, was a great thing to do in addressing these types of rare disorders. Dr. Watson stated his belief that the ACMG report advances the field in a very substantial way and presents a model that can be improved upon over time. Dr. Rinaldo observed that most decisions about newborn screening states made in the past were very subjective, but the ACMG report is a sizable step in the right direction, and we can now work to improve it. The whole process is moving to create an evidence base that currently does not exist. Dr. Alexander indicated that in a "perfect world," we could have gathered this information ahead of time for these rare disorders, but there's really been no organized way to do it. Only with implementation of screening for these disorders in a broad way, in a manner that we will be able to identify larger numbers of patients even with rare disorders and enter them with their parents' permission into studies of the available therapies is it ever going to be possible to gather the size of population that we need to get the evidence that we're all asking for.

Dr. Telfair suggested that the Committee think about how states and municipalities might use the information in the ACMG report to inform the way they make decisions. He would like the Committee to consider this as a next step, in addition to seeking clarification of what was done in the ACMG report. In addition, Dr. Telfair recommended that the Committee think about how to put the ACMG report's recommendations into some structure that is useful for people in decision-making positions that influence what happens at the national, state, local, and community level.

Dr. Howell asked Committee members to comment on the overarching principles of the ACMG report, which he thinks will be the basis on which the report will be used in the future. One of the principles calls for broadening the definition of potential benefit from newborn screening, with the idea that there are broader benefits from newborn screening than have historically been recognized and that benefits accrue to families even if there is not a curative treatment at the current time; for instance, knowing about a condition early and the possibility of other treatments such as early childhood intervention or something of that nature. Dr. Becker said that just as the ACMG report represents a bit of a paradigm shift in that it is not the traditional, well-controlled evidence-based study that we might like to see, it also represents a paradigm shift in terms of overarching principles, in that traditional public health screening programs do not just collect information without a specific benefit or intervention that has been shown to either be effective at the personal level or effective at the financial level to society as a whole. There may be a slight change in the perspective that communities or society as a whole are going to have to get used to thinking about.

Dr. Hawkins commented that parents and people such as those in the audience are interested in getting beyond methodology questions. They are interested in what we are going to do about the problems we have with not having a uniform panel of diseases to test for. Dr. Howell noted that there was tremendous effort to get input from parents with children who have the conditions, because their input is extremely important. One of the things that the ACMG report quantifies is the burden of disease, which is the greatest for affected families. Mr. Robertson concurred with Dr. Hawkins and Dr. Howell, saying it was important not to forget the babies and parents behind the listed conditions. As a parent, he said that one of the best things about the ACMG report was its emphasis on follow-up and training and on getting parents and providers to understand the diseases. There will never be a perfect list of diseases, because something is always going to be left off, no matter what the criteria. The important thing is to get to a point that it doesn't matter where your child is born that will determine whether the child will live or die.

Dr. Alexander urged the Committee in commenting on the ACMG report and in its future deliberations to take into account the fact that newborn screening yields benefits for affected children and their families even in the absence of effective treatment:

- Newborn screening can help families of affected children avoid a long and traumatic search for a diagnosis, which is valuable whether treatment is available or not.
- An early diagnosis can be useful to the families of affected children for family planning reasons (e.g., so parents can at least know about it before they make a decision about having another child or can consider options such as prenatal diagnosis, adoption, etc., to avoid another child affected).
- Affected children and their families can benefit from interventions other than treatment to foster healthy development, motor skills, or other functions even if the disorder cannot be directly treated.
- Newborn screening can yield a population for doing studies of interventions that will enable us to move from the realm of expert opinion to the realm of evidence-based practice based on clinical

trials. In the United States, 85 percent of children with cancer are entered into research protocols via the children's oncology groups that have been operating for the last 30 years or so, and these are responsible for marked improvements and cures for children. We have an opportunity to do something similar with newborn screening.

Following up Dr. Alexander's comments, Mr. Robertson said that if the intention is to try to enroll children into studies, an emphasis must be placed on educating the parents about enrolling kids in studies. In cancer, sometimes the alternative to not enrolling children in studies is extremely grave, but for other diseases, there may be other options. Probably the best way to get parents of affected newborns to enroll their children in studies is to get other parents who have enrolled their kids to encourage other parents to do it.

Dr. Howse thanked Dr. Edwards for putting the question on the table of the weight of the report and whether the scientific evidence in the report was justified. She said that what she had heard from the Committee's discussion reflects the opinion of the March of Dimes: (1) that the ACMG newborn screening report represents the best available information, the weight of expert opinion, and a rigorous and lengthy review involving families and consumers, experts, practitioners, clinicians, lab directors, etc.; and (2) that the uniform panel represents conditions for which there is a test, for which early detection is essential, and for which there is efficacious treatment. In Dr. Howse's view, this is a sufficient and appropriate basis for the Committee to support the report, especially with its recommendations for tracking and reporting back, follow-up, etc

Dr. Watson concluded by urging the Committee to recognize that its charge extends beyond newborn screening to include all heritable diseases and genetic disorders of newborns and children. For that reason, the Committee should think broadly about how it is going to collect information in the long term not just on the 50 or so newborn screening conditions but on 800 or 900 other genetic conditions, including lysosomal storage diseases, which include adult-onset as well as the infantile-onset form.

Recommending a Process for Modifying the ACMG-Recommended Uniform Newborn Screening Panel. Several Committee members recommended that the Committee provide guidance on the process for modifying—either adding to or removing from—the ACMG-report's recommended uniform screening panel in the future and on an ongoing basis. Among the ideas explored by the Committee were (1) getting a paper or presentation to the Committee on evidence-based decision-making in the context of newborn screening; (2) having the Committee review and perhaps make changes to the ACMG-recommended process for adding or subtracting conditions in newborn screening programs; (3) doing a trial run of the Committee's recommended process for adding conditions to the ACMG-recommended panel; and (4) recommending a body to advise HHS on changes to the uniform newborn screening panel.

Dr. Dougherty recommended that the Committee step back and consider whether the current fact sheets and approach used in the ACMG report represent the best mechanism for modifying the newborn screening panel. She suggested the possibility of commissioning a paper by an expert in evidence-based decision-making to help the Committee sort through these issues. Such a paper would lay out the current thinking about doing an evidence base for newborn screening, diagnosis, etc., and identify the other factors to consider in a systematic look at whether a procedure should be endorsed and paid for. Although the ACMG report tried to mix a lot of those kinds of things into one judgment, she noted, there are systematic ways of arriving at a systematic expert consensus and of doing a systematic evidence review and of bringing these things together to make a decision.

Dr. Becker agreed with Dr. Dougherty's suggestion, noting that the Committee is going to have to use the evidence base/expert opinion commentary as sort of a central tenet to whatever the Committee decides to do. Dr. Watson also agreed with Dr. Dougherty's suggestion but recommended asking someone to look very hard at the nature of genetic diseases and the difficulties that one has with an evidence base in genetic diseases such as cystic fibrosis for which outcomes may depend on genetic mutations that affect individual families.

Dr. van Dyck suggested that perhaps someone could be asked to give a presentation to the Committee at its July meeting rather than writing a paper. Agreeing that this approach would be more expeditious, Dr. Howell asked Dr. Dougherty and other Committee members to consult and get back to him or HRSA in a couple of weeks with recommendations for experts to make a presentation at the Committee's July meeting on evidence-based decision-making in the context of the Committee's work. Dr. Brower, following up on Dr. Watson's previous comment, recommended that the presentation in July or a second presentation include a discussion of genetic diseases, as well as the methodology for modifying the uniform newborn screening panel. Dr. Howell added that he also would like to have someone at the July meeting to give a presentation on designing a newborn screening long-term follow-up program.

Dr. Rinaldo suggested that the Committee institute a process that would allow proponents (e.g., parent support groups, experts) of adding a condition to the uniform panel of 29 conditions recommended in the ACMG report to come before the Committee and make the argument for inclusion of the condition to the Committee, using the ACMG report as a starting point. At every Committee meeting, one session could be devoted to a presentation by proponents of adding a condition. Dr. Alexander said that the Committee might consider going through the process of evaluating a few conditions as a trial run to gain first-hand experience in making such decisions, but he does not think the Committee should take on the task of modifying the uniform panel as part of its formal responsibilities.

Dr. Brower said she thinks the best thing the Committee can do is to communicate to the public and experts about what level of evidence they need to meet before the Committee will consider that a disorder or a test has been validated. She believes it is part of the charge of the Laboratory Standards & Procedures Subcommittee that she chairs to come up with a first step to define what the process for adding or subtracting conditions in the uniform panel ought to be and then present it to the entire Committee for comments.

Dr. van Dyck agreed that the Committee should not take on the task of modifying the uniform panel itself. He added that the process for modifying the uniform panel recommended in the ACMG report is a consideration that could be in the final output of whatever HHS recommends the best way to suggest to states to add new conditions. He said he thought that the HHS Secretary would be interested in the Committee's recommendations about the best way to suggest that states add conditions to their newborn screening programs. Dr. Rinaldo underscored his belief that HRSA and the Committee have a moral responsibility to make sure that that there is a process for modifying the panel so that the children affected with whatever diseases where there is a test and early intervention can be beneficially served. The newborn screening panel recommended in the ACMG report is now a HRSA product, he said, so it seems that HRSA should be the one to decide how to modify the panel.

Dr. Alexander suggested that the Committee might want to make recommendations about what type of organization might be best suited for the task of modifying the uniform panel. He said he thinks that an organization along the lines of the Advisory Committee on Immunization Practices might be

best suited to make such decisions, adding that perhaps the Committee should have some sort of presentation on the Advisory Committee on Immunization Practices model. Dr. Howse agreed that a connection to the Public Health Service as an ongoing mechanism to advise states in a formal and timely way as to the recommended newborn screening tests to be done might be a good idea. Dr. Howell summarized his understanding the Committee's discussion, saying that the Committee should have an opportunity to look at and comment about any changes in the recommended newborn screening panel, but there would be some other type of structure—whether a subcommittee or parallel committee or some other structure—that would review things and make recommendations that would come to the Committee, and then go to the HHS Secretary.

Dr. Alexander then returned to the idea of doing a trial run of a process to evaluate the process for deciding whether conditions should be added to the uniform panel to gain first-hand experience that would inform the Committee's recommendations as to how such a process might be carried out. Dr. Howell said he thought that was an excellent suggestion and that maybe the Committee could get some expert proponents of a condition that is moving toward prime time to come and make the presentation. Dr. Rinaldo suggested that they develop a short list of about 10 conditions rather than leave it to outside proponents, then the Committee could choose which ones it wanted to use for a trial run. Dr. Watson recommended that the Committee do a trial run of two conditions—one rare condition (e.g., any lysosomal storage disease) and one relatively common condition (e.g., use of pulse oximetry for congenital heart disease, hyperbilirubinemia, asthma). Dr. Howell suggested perhaps the Committee should -do a trial run of one condition with effective treatment and one where knowledge of early benefits is more predominant.

Mr. Robertson asked for clarification: Are you saying we would first look at developing a process and then pick two diseases? Dr. Alexander responded by suggesting that the Laboratory Standards & Procedures Subcommittee chaired by Dr. Brower take the lead in reviewing and suggesting modifications to the criteria that are currently in the ACMG report for making decisions and then put together a list of five to seven conditions that might be added to the panel. Then the Committee could review and possibly modify the criteria that the Laboratory Standards & Procedures Subcommittee suggests and go from there in terms of setting up a presentation by a proponent of adding a condition to the uniform panel as a trial run of the modified process for adding a condition. Dr. Dougherty agreed that the Committee might want to settle on a process for adding disorders before asking proponents for adding disorders to give presentations to the Committee as a trial run.

Dr. Rinaldo said he was thinking of something simpler than what Dr. Alexander proposed—asking someone with clear knowledge of a condition to look at conditions that did not make the cut for the ACMG-recommended uniform panel, review what happened in the ACMG survey process, and then come before the Committee to make the argument that the reason the condition did not make the cut for the ACMG-recommended uniform panel was that incorrect information was used. Then the Committee could agree or disagree.

Dr. van Dyck suggested that one way to approach things might be this. First, the Committee could hear from a couple of people who were involved in developing the ACMG report go through either a condition included in the uniform panel or one on the second panel to get a feeling for the process. Then, the Committee could hear from an outside speaker or speakers on a process that they would recommend. That way the Committee could absorb the differences if any between what was done in the ACMG report and what is recommended.

Dr. Alexander said that he was going to suggest something very similar to what Dr. van Dyck just suggested. He emphasized that the Committee does not want to get into revisiting the ACMG report

and making the judgments made in the report; it is just trying to gain some first-hand experience to guide its recommendations for adding new conditions to an existing list. In terms of process, Dr. Alexander suggested the following:

- At the Committee's July meeting, one item on the agenda would be a presentation by an expert in evidence-based decision-making on a process for modifying the uniform panel, as suggested by Dr. Dougherty. Another agenda item would be a report from the Laboratory Standards & Procedures Subcommittee on what information the Committee might ask a proponent of adding a new condition to provide that is relevant to the criteria that were used for the ACMG report and whatever modifications to those criteria the subcommittee recommends. Then Committee members would deliberate on what they liked from both pieces and come up with some final guidance for a process for modifying the uniform panel.
- At the Committee's October meeting, one item on the agenda would be a presentation from a proponent of adding a new condition to the ACMG-recommended uniform panel based on the guidance that the Committee gives in light of its discussions at the July meeting.

Dr. Howell got a sense from Dr. Robertson and other Committee members that they were comfortable with the process outlined by Dr. Alexander, and he asked Dr. Lloyd-Puryear to work on the agenda items for the next meeting. Dr. van Dyck summarized his understanding of what would happen next as follows: At the July 2005 meeting, the Committee would hear a presentation from the Laboratory Standards and Procedures Subcommittee chaired by Dr. Brower on the recommendations in the ACMG report, modified by whatever the subcommittee suggests, as well as a peer presentation by an outside expert on a process for modifying the ACMG-recommended uniform panel; then Committee members will deliberate on what they like from both pieces and come up with some final process for modifying a panel. Then at the Committee's October 2005 meeting, the Committee would have a proponent of adding a condition to the panel come before the Committee to give the newly recommended process a trial run. Dr. Howell said he believed that was what he heard, adding that the Laboratory Standards and Procedures Subcommittee would also come up with some suggestions about what conditions might be appropriate for the October meeting.

Dr. Edwards concluded the discussion by saying that while new conditions might be added to the ACMG-recommended uniform newborn screening panel, it is important to bear in mind that some conditions that are currently on the list potentially could leave the list and move around, move from a secondary target over to the primary, depending on developments.

PUBLIC COMMENT SESSION

The following individuals made public statements. The written text of their statements appears in Appendix A.

Bennett Lavenstein, M.D.
Childhood Neurology Society (CNS)

Dr. Lavenstein indicated that CNS supports national minimum standards for newborn screening for the specified genetic disorders. He believes that Federal oversight is necessary for all newborns to have equal access to identification and interventions for these disorders and that a combination of adequate Federal and state funding should be allocated to initiate and sustain statewide programs and limit the long-term effects of these disorders. Mandatory testing, counseling and follow-up requirements must be fully supported by designated Federal funds, since the U.S. health care system

currently either does not support such services in totality or perhaps does so somewhat inadequately. Every state has newborn screening, but there is variability among states. National minimum uniform standards would be helpful. Finally, Dr. Lavenstein commented on the need to draw upon lessons from clinical experience and expertise and evidence-based medicine to make things work.

Jana Monaco
Parent and Board Member
Organic Acidemia Association

Ms. Monaco, the parent of one child with isovaleric academia who suffered lifelong brain damage and another child leading a normal life because of newborn screening, said she strongly supports the recommendations for expanded newborn screening in the ACMG newborn screening report and hopes the goals of the report are fully achieved. She reported that Virginia has already expanded its newborn screening program in response to the report. She also reported her observations as one of two parents serving on the New York-Mid-Atlantic Regional Genetics and Newborn Screening Collaborative, which recently had its first meeting. She noted that the lack of coverage for metabolic formulas (medical food) leave families with a big burden and urged the Committee to address this issue. Finally, Ms. Monaco underscored the value of parents in educating, advocating, assisting, and translating information about newborn screening. In response to an issue raised during the Committee's discussion in the morning, Ms. Monaco stressed that parents of affected newborns want to know what disorder they are dealing with whether a cure or management exists or not.

Jill Fisch
Parent & National Director of Education and Awareness
Save the Babies through Screening Foundation

Ms. Fisch, the parent of two children affected with Short Chain Acyl-CoA Dehydrogenase Deficiency (SCADD), said she strongly supports expanded newborn screening so that all children in all states are treated equally and fairly. She also expressed concerns about legislative maneuverings in Texas that may prevent the expansion of newborn screening. Ms. Fisch said she is looking forward to learning about the Committee's approaches to evaluating new newborn screening tests and technologies. SCADD is one of the disorders on the secondary panel in the ACMG report, but there is still no natural history study for SCADD, which is necessary for the disorder to be added to the core panel. How can the Committee help get these studies implemented? Ms. Fisch said she is particularly concerned about the follow-up of children who are picked up by newborn screening, as well as children not detected via newborn screening, to ensure that every child gets what he or she needs. Ms. Fisch expressed her concern about several ethicists who have been speaking out against newborn screening in the past few months. Finally, Ms. Fisch stressed the importance and value of having parents serving on the subcommittees of the Committee.

Micki Gartzke
Parent & Director of Education and Awareness
Hunter's Hope Foundation

Ms. Gartzke, a parent who lost a child to Krabbe disease (a lysosomal storage disease) following a 6-month effort to get a diagnosis, said she is strongly committed to the expansion of newborn screening so that what happened to her family does not happen to others. She applauded the research and test development taking place for many different diseases, including the lysosomal storage diseases pilot in New York State, and said that she was particularly interested in how the Committee will review

new tests and technologies and how the Committee will recommend and evaluate translational research. Ms. Gartzke agreed with a point made earlier in the day - there are benefits to newborn screening even if treatment is not availablee.g., screening can keep parents of affected infants from having to go on a long diagnostic odyssey and can help develop populations to be studied. Ms. Gartzke stressed the importance of educating both parents and professionals about the need for newborn screening. She also emphasized the importance of involving parents who have lived through the lack of early detection and access to treatment in the deliberations of the Committee and its subcommittees.

John Adams
Parent & President/Chief Executive Officer
Elivery Solutions, Inc.

Mr. Adams, a parent who has an 18-year-old son with phenylketonuria (PKU) who is about to enter the University of Toronto, said the Canadian government is AWOL on the question of newborn screening—and it tears his heart out to know that there are babies who are dying or being damaged needlessly. The province of Ontario only screens for three disorders—PKU, congenital hyporthyroidism, and hearing loss, and it is not alone. Mr. Adams said that his sense of reading the ACMG newborn screening report was that it was a snapshot of the state of the art, the best available evidence, not yet perfected. He also said he is delighted to be able to participate in this open forum today, because the Canadian government is operating behind closed doors on newborn screening. As a Canadian, Mr. Adams also said he is grateful for the American taxpayers' investment in a number of things, including the National Newborn Screening and Genetics Resource Center. He said as the Committee moves forward, he hopes that it recognizes that it is performing a service for people in other countries, not just the United States. He also suggested that HRSA consider supporting the development of smart systems that put the intelligence and best practice available at the hands of a clinician when there's a child or an adult who is in a period of crisis.

Peter Sybinsky, Ph.D.
Chief Executive Officer
Association of Maternal and Child Health Programs (AMCHP)

Dr. Sybinsky explained that AMCHP represents state public health leaders who direct programs for mothers and children, many of which are funded in part by the Maternal and Child Health Services Block Grant, Title V of the Social Security Act. Although state newborn screening programs vary among the states, most Title V programs ensure follow-up and access to health services for children found to be affected. AMCHP believes the ACMG report on newborn screening is an exceptional example of bringing together expert opinion and evidence-based research to form national recommendations. Still, state Title V programs have concerns about issues that the report did not address: (1) the implications of the recommended uniform panel on the extensive state responsibility for providing long-term treatment and follow-up; (2) the adequacy of funding to meet the recommendations for implementation of a uniform panel; and (3) the lack of a national procedure for adding conditions to the uniform panel. AMCHP urges the Committee to address these issues. Finally, Dr. Sybinsky said, AMCHP would welcome an opportunity to designate a representative to the Committee to provide continuing input.

Scott Grosse, Ph.D.
Health Economist
National Center of Birth Defects and Developmental Disabilities
Centers for Disease Control and Prevention (CDC)

Dr. Grosse, who works with Dr. Boyle at CDC on newborn screening issues, responded to the question that Dr. Rinaldo asked earlier in the day about specific objections to the ACMG report. He said that CDC is concerned that certain statements in the fact sheets may be inaccurate or misleading. In particular, CDC believes that the fact sheets for congenital adrenal hyperplasia (CAH), cystic fibrosis, hearing loss, hemoglobin SC disease, and medium chain co-A dehydrogenase (MCAD) deficiency do not accurately reflect what is in the scientific literature.

Jerry Vockley, M.D., Ph.D.
President
Society for Inborn Metabolic Disorders (SIMD)

Dr. Vockley explained that SIMD members are scientists, physicians, nutritionists, nurses, and other health professionals involved in research or the diagnosis and treatment of individuals with inborn metabolic diseases. He said that SIMD unequivocally supports the ACMG report and urges the Committee to ask the HHS Secretary to move forward to implement its recommendations. SIMD looks forward to the work of the Committee's three newly established subcommittees and is particularly eager to be partner in the activities of the Treatment and Follow-up Subcommittee. SIMD urges the Committee to work to ensure the availability of adequate resources for long-term follow-up and treatment.

SUBCOMMITTEE MEETINGS

Each of the three subcommittees established at the Committee's January meeting—Education & Training Subcommittee chaired by Dr. Howse, Treatment & Follow-up Subcommittee chaired by Dr. Boyle, and Laboratory Standards & Procedures Subcommittee chaired by Dr. Brower—met for 45 minutes. The subcommittee meetings were open to the public.

EDUCATING PARENTS ABOUT NEWBORN SCREENING

NNSGRC Survey of States for Policies and Procedures for Public and Professional Education Related to Newborn Screening

Donna Williams, M.S.
Newborn Screening Project Coordinator
National Newborn Screening and Genetic Resources Center (NNSGRC)

Ms. Williams reported on the findings from an NNSGRC survey of state policies and procedures for public and professional education in newborn screening. The survey compared state practices to the set of recommendations presented in the American Academy of Pediatrics (AAP) Newborn Screening Task Force Report published in *Pediatrics* in August 2000. That report recommended that states and state public health agencies implement public, professional, and parent education efforts regarding newborn screening.

In the realm of professional education, the AAP Newborn Screening Task Force Report recommended that prenatal health care professionals, as well as an infant's primary care professional, be knowledgeable about the state's newborn screening program through educational efforts coordinated by the state's newborn screening program in conjunction with the newborn screening advisory board. The NNSGRC survey found the following with respect to professional education related to newborn screening:

1. One of the biggest gaps in professional education is in the provision of educational tools and resources to professionals responsible for prenatal care. Although the prenatal period has been identified as the optimal time for parent education on newborn screening, prenatal providers do not receive the necessary training or educational materials to provide appropriate education to parents. Only 20 percent of newborn screening programs provide brochures to obstetricians for distribution to parents.
2. States often spend much of their effort in providing education and resources to birthing facilities, with a primary focus on educational tools and resources for health professionals responsible for specimen collection (e.g., provider manuals, collection posters, newsletters, NCCLS newborn screening video, formal onsite training, Website).
3. States typically provide just-in-time information (e.g., disorder fact sheets, follow-up ACT sheets or procedures) to primary care providers responsible for follow-up of presumptive positive screens. Primary health care providers rely on sub specialists to educate parents of affected children in the specifics of the child's condition.

In the realm of public education, the AAP Newborn Screening Task Force Report recommended that pregnant women be made aware of the process and benefits of newborn screening and their right of refusal before testing, preferably before a routine third trimester prenatal care visit. The prenatal period has been shown to be the time when parents are most receptive to the information. The NNSGRC survey found the following with respect to public education related to newborn screening:

1. The need for public/parent education is well understood by newborn screening programs, and all make an effort to provide printed materials (e.g., brochures, posters), videos, and online materials and resources. All states have a newborn screening Website, but this is probably not the best means of trying to educate the entire population because of access and other issues.
2. The NNSGRC State Newborn Screening Parent Brochure with basic program information is the main educational tool for parents; however, it is generally not given at an optimal time to have the best impact.
3. Most newborn screening programs lack an education plan that includes assessment and monitoring of material distribution and an overall assessment of parent education efforts. They know they send 10,000 brochures out, but they don't know if education is effective.
4. Obstetricians, who should have a responsibility for prenatal education, are generally not involved with screening programs (e.g., advisory committees). They typically do not see parental education about newborn screening as being in their realm of responsibility.

Parental Education Project—Informing Parents about Newborn Screening

Terry C. Davis, Ph.D.
Professor
Department of Pediatrics & Medicine
Louisiana State University Health Sciences Center, Shreveport

Dr. Davis, a clinical psychologist and pioneer in the field of health literacy, began her presentation by noting that parents' informational and psychological needs change at different stages of newborn screening—initial screening, retesting, and confirmed positive diagnosis. She has performed qualitative research in six states on parental education related to newborn screening at the initial screening stage, and reported the findings to the Committee.

When talking about designing education materials for the parents of the 4 million newborns born in the United States each year, Dr. Davis said, it is important to pay attention to communicating effectively with parents about newborn screening. Data from the 1993 National Adult Literacy Survey indicate that 47 percent of adults in the United States have a very low level or low level functional literacy—21 % are at a fifth grade reading or below, and 26 % are at a sixth to eighth grade reading level. Such individuals cannot use a bus schedule or a bar graph. The high school dropout rate in this country is 29 %; among blacks, the dropout rate is about 50 %. In 2004, the Institute of Medicine published a health literacy report. It said that 90 million adults have low health literacy—that is, trouble understanding and acting on health information. Dr. Davis showed a video illustrating that people of all education levels may have trouble understanding and acting on health information. The agendas, communication styles, and knowledge levels among patients, providers, nurses, and state programs vary, and there are differences in patients' education, general literacy, and language skills.

Dr. Davis said she views newborn screening communication as a quality issue. She indicated that several things are known about patient education: (1) written materials, when used alone, will not adequately inform; (2) simplified materials are necessary but will not solve the communication problem; (3) the focus needs to be on "need-to-know" and "need-to-do"; and (4) it is important to work with patients to identify best practices. In the case of newborn screening programs, there is often a mismatch between the provider or state newborn screening program giving information and the patient's process of understanding it, remembering it, and being able to act on it.

Under a project funded by and in collaboration with HRSA, Dr. Davis and her colleagues undertook the following tasks:

- **Evaluation of the reader-friendliness of parent education materials on newborn screening.** The first task was to evaluate the user-friendliness, including readability and cultural appropriateness, of newborn screening parent education materials in English and Spanish. Materials were collected from 49 programs with the help of the National Newborn Screening and Genetic Resources Center (NNSGRC). The evaluation showed that the average brochure about newborn screening was written on high school level; more than one-fourth of the brochures were on a college level. Readability was the tip of the iceberg. Also important to reader-friendliness: good layout; pictures and captions that convey the message; a clear message; managing information by focusing on need to know" and avoiding information overload; and making the information personal and in a conversational tone. Furthermore, information should be sequenced along the lines of a newspaper model (most important information first) or health

belief model (your baby may be at risk; there is something you can do; your baby will get personal benefits if you do).

- **Focus group research on informing parents about newborn screening**. Dr. Davis and her colleagues conducted 22 focus groups and three interviews with English- and Spanish-speaking parents of babies recently screened; a few parents of babies who had a false positive; pediatric and prenatal care providers; and state newborn screening professionals. Parents view their primary care provider as the most credible source of information. They want oral information from the doctor about initial newborn screening and retesting when they are 7 to 8 months pregnant and a pamphlet to take home. Both parents and providers said the pamphlet should be to the point. "Need to know" information for parents was the following: all babies are screened, screening will benefit the baby; testing is safe not harmful; the baby may need to be retested; parents will be notified if retesting is needed; and it is important to act quickly if retesting is necessary. Prenatal providers indicated a willingness to educate parents. Obstetricians and family physicians are more likely to incorporate newborn screening information if it is on the American College of Obstetricians and Gynecologists (ACOG) checklist. Providers requested brief information in a handy notebook to prepare them for conversations with parents. This might include a list with concise definitions of the diseases screened; the specific diseases screened for in their state; and sources of additional information.
- **Development and evaluation of pilot materials to educate parents about newborn screening.** On the basis of their research, Dr. Davis and her colleagues developed and evaluated a brochure on newborn screening in English and Spanish for parents, and worked with NNSGRC to develop and evaluate educational tools for prenatal providers and toolkits for state programs. The vast majority of parents were highly satisfied with the newborn screening brochure. The materials for providers—a discussion guide with seven talking points, a quick reference (what is screened in your state, who do you need to call, the phone number, etc.), and a provider notebook to facilitate prenatal parent education—were also very well received. The toolkit for state newborn screening programs includes a CD in a jewel case with electronic templates for the parent brochure in English and Spanish, with pictures of babies and parents of different ethnicities that states can use to tailor the brochure to their needs.

To improve the quality of newborn screening communication, Dr. Davis said, information needs to be more *patient- and provider- centered.* Thus, it is important to involve parents and providers in the development of materials and the distribution plan. Plans for providing information about newborn screening should be systems-oriented. Brief education offered multiple times may be helpful. Providers should be in the loop. Parent education should be consistent and practical for usual practice. Professional organizations, state agencies, HRSA, and affiliated groups should collaborate more to prepare and motivate providers to educate parents.

In conclusion, Dr. Davis said, her newborn screening education ideal is that parent-centered materials and messages are delivered first prenatally; that messages are delivered multiple times; that obstetricians and pediatric providers are more involved in the system; that parents get provider-centered "need to know" and "need to do" education; that public awareness campaign are adopted; and that quality control or tracking is used to ensure consistency and the efficacy of the educational efforts.

Sickle Cell Disease Newborn Screening Education Project

Janet Ohene-Frempong, M.S.
President
J. O. Frempong & Associates

Ms. Ohene-Frempong, a plain-language and cross-cultural communication consultant who has been working with the Sickle Cell Disease Association of America (SCDAA), gave a presentation on the Sickle Cell Disease Newborn Screening Education Project funded by HRSA. She prefaced her remarks by noting that the Institute of Medicine published a 2004 report on health literacy that focused attention on health communication issues, which are closely related to the issue of racial and ethnic health disparities. The Agency for Healthcare Research and Quality (AHRQ) also did a systematic review of the literature in the area of health literacy to produce a good, solid evidence base, and many other Federal agencies and the Surgeon General are providing leadership on the issue.

SCDAA received funding from HRSA/MCHB's Genetic Services Branch to create and implement a national coordinating and evaluation center to increase the capacity of the 17 HRSA-funded, community-based programs that screen newborns for sickle cell disease (SCD) and to provide model education, counseling, and follow-up services to families identified with SCD or other hemoglobinopathies. The Sickle Cell Newborn Screening Education Project, which involves patient and family education for families of babies with SCD, carriers of SCD, and the providers who serve these families, is a component of this effort. The goal of the Sickle Cell Newborn Screening Education Project is, first, to create materials and methods of information delivery that will increase health literacy, particularly about SCD and genetics; and then, through the information created for families and providers, to establish a foundation to disseminate standardized information about SCD. Data from 1993 National Adult Literacy indicate that 75 percent of African American adults have low or very low levels of functional literacy. This situation is of immense importance in the case of SCD, because individuals with low literacy often get unintentionally left out of information giving.

The Sickle Cell Newborn Screening Education Project has been working to develop plain-language educational materials that can be used for patient and family education. The project has provided the following: technical assistance and training related to the production of reader-friendly format to staff at community-based programs that screen newborns for SCD; and evaluation of sickle cell trait notification letters from community-based programs and state agencies. It has begun to field test education materials for sickle cell trait and disease management that were collected from the community-based agencies that were part of the Sickle Cell Newborn Screening Education Project for SCD to see how effective such materials were with parents. Ms. Ohene-Frempong and her colleagues are now in the process of developing a toolkit for people who are producing educational materials on SCD. The toolkit includes: a guide to reader-friendly material development; a checklist for evaluating reader-friendliness; a template for an sickle cell trait notification letter; a template for a trait notification brochure; a "What if Future Baby" card;, a fact sheet on sickle cell trait that may be for the public; and the five things parents want to know. In the future, Ms. Ohene-Frempong and her colleagues also want to develop easy-to-read Web content for parents and providers.

Questions & Comments

Dr. Telfair asked the presenters in the parental education session to comment about how their research applies in the design of consent forms and materials to explain confidentiality and privacy

issues to parents of newborns. Ms. Donna Williams, National Newborn Screening Project Coordinator for NNSGRC, said that work by Dr. Davis for HRSA includes information for parents on what is going to happen to the screening residual blood spot after the screen; this information includes education on privacy and confidentiality issues and the right to refuse a screen. Ms. Ohene-Frempong said that she thinks that it is important to educate people who sit on institutional review boards about the importance of designing materials that consider literacy levels in obtaining consent. Ms. Williams said she hoped that efforts to get consent would not detract from the goal of getting every child tested.

Dr. Rinaldo said that the presentations and video had been an eye opener for him—demonstrating the challenges physicians and other health care professionals face in trying to communicate with parents about health issues. The low levels of literacy and accompanying challenges, he added, should be kept in mind by the Committee when it considers how to count newborn screening conditions. In addition, Dr. Rinaldo asked how to get obstetricians involved as providers of information about newborn screening to parents obstetricians tend to see the mother rather than the baby as their patient. Ms. Williams said the research done with Dr. Davis found that although obstetricians do not see the child as their responsibility, they do accept the fact that educating parents about newborn screening is necessary; if the obstetricians were asked to educate parents by the ACOG, they would do it. Next it may be important to get ACOG to outline or standardize throughout the states what that education should look like and what we expect to get out of it.

Dr. Boyle also said she found the presentations on parental education extremely informative and asked whether a national campaign is needed to increase awareness very globally and very generally of the importance of newborn screening among parents and providers. Such a campaign might be similar to the campaign for developmental screening ("Learn the Signs, Act Early") that CDC is supporting. Ms. Williams said she thinks this would be a good time for a national campaign on newborn screening and that it would help standardize information. Dr. Howell commented that although the March of Dimes had focused on this, the idea of a systematic national campaign is an idea that is worth thinking about.

Dr. Becker also said that the presentations on parental education were very helpful and that much of the material would be particularly useful to the Education & Training Subcommittee headed by Dr. Howse. He then asked whether the materials developed by Dr. Davis and her colleagues had been reviewed by someone familiar with legal issues. In the case of medical procedure such as newborn screening, a health care provider's desire to communicate effectively has to be balanced with the obligation to inform. Were the materials passed by some form of legal review that would satisfy a physician's or practitioner's obligation to inform? Dr. Davis had left the meeting, so she was unable to answer, but Ms. Ohene-Frempong said that a legal review should be a part of the process of developing materials to educate parents.

COMMITTEE BUSINESS—APPROVAL OF MINUTES

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Dr. Howell opened the second day of the meeting with a vote on the minutes of the meeting of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children held January 13-14, 2005. The Committee voted unanimously to approve the minutes. Dr. Howell then asked Committee members if they preferred more detailed minutes or a condensed version of those

minutes. Several Committee members said they preferred the more detailed minutes. Consequently, Dr. Howell indicated that the Committee would like to receive similarly detailed minutes in the future.

NEWBORN SCREENING FOLLOW-UP AND QUALITY ASSURANCE

Introduction

Robert Vogt, Jr., Ph.D.
Research Chemist
Newborn Screening Branch
Division of Laboratory Sciences
Centers for Disease Control and Prevention (CDC)

Dr. Vogt introduced this session by explaining that two of his colleagues would discuss two efforts related to enhancing the quality and standardization of certain non-laboratory aspects of newborn screening:

- **Proposed Clinical and Laboratory Standards Institute (CLSI) Guideline VLA27P: Newborn Screening Follow-up Activities and its Quality Assurance.** The primary goal of the proposed CLSI guideline on newborn screening follow-up is to improve and ensure the quality and effectiveness of follow-up on newborn screened-positive results to the point of resolution.
- **Newborn Screening Program Evaluation and Assessment System (PEAS).** The goal of the PEAS is to create model PEAS for various newborn screening system components and to combine them into a system-wide newborn screening PEAS. The model PEAS will be embedded into an interactive Website for widespread program use as a self-help tool.

According to Dr. Vogt, the subcommittee that developed CLSI Guideline VLA27P was chaired by Ms. Judith Tuerck, and the PEAS committee was chaired by Dr. Bradford Therrell of the National Newborn Screening and Genetics Research Project (NNSGRC). The two groups have worked closely together as these documents have been developed to enhance quality and standardization in newborn screening. The CLSI guideline is in a way a subset of the newborn screening PEAS.

Because Committee members were already quite familiar with NNSGRC, Dr. Vogt did not need to explain it. He did, however, give Committee members an overview of CLSI, an accredited developer of global voluntary consensus standards and guidelines within the health care community. Formerly known as the National Committee on Clinical Laboratory Standards, the organization recently changed its name to CLSI to become more globally engaged. CLSI's mission is "to enhance the value of medical testing and health care services through the development of standards, guidelines, and best practices."

The activities of CLSI are performed by a series of standing area committees, with members from industry, academia, and government that meet on an annual basis and have conference calls on a quarterly basis. CLSI standards and guidelines are developed via a consensus process. First, a document is approved by the subcommittee and goes through a little CLSI review; then it is sent out at the *proposed l*evel. If there is a "P" after a standard or guideline, the document has been proposed. Once the proposed document has been widely distributed to all the CLSI members and comments have been received, the subcommittee revises the document and completes the document at the

approved level. If there is an "A" after a standard or guideline, the document has been approved. CLSI standards, guidelines, and best practice documents are widely used in clinical, academic, regulatory, and industry settings. The Food and Drug Administration has used the documents in its review process for about 15 years. Of all the CLSI documents that have come out, one of the most popular is CLSI standard LA4-A4—blood collection on filter paper for newborn screening programs. There was a 6-year process from the proposed standard to the approved standard.

Proposed Clinical Laboratory Standards Institute (CLSI) Guideline on Newborn Screening Follow-up

Judith M. Tuerck, B.S.N., M.S.
Assistant Professor
Oregon Health & Sciences University
Child Development and Rehabilitation Center

Ms. Tuerck, who chairs the CLSI Newborn Screening Follow-up Guidelines Subcommittee, reported that guidelines for the analytical portions of newborn screening, the confirmatory tests, and various treatment modalities have been in existence for a while, but guidelines for follow-up are just now being developed. The follow-up community, Ms. Tuerck noted, has struggled for equal status within the screening system—and in fact, is not represented on this Committee or its subcommittees. Follow-up activities are often under funded, although HRSA and CDC have changed that in the last 5 to 10 years

The intent of the proposed CLSI guideline on newborn screening follow-up—CLSI Guideline VLA27P: Newborn Screening Follow-up Activities and its Quality Assurance—is to provide a framework and a best practices model for newborn screening follow-up. The proposed guideline focuses more on short-term follow-up (birth to diagnosis) than on long-term follow-up (diagnosis throughout life). The intended audience for the guideline includes not just newborn screening follow-up personnel but anyone who may be participating in follow-up activities—maternity and newborn health care providers, medical home provider, confirmatory services/subspecialty providers, and parents.

The CLSI Follow-up Subcommittee met in September of 2004 for a couple of days and agreed to a number of overarching principles: (1) follow-up is an integral part of the newborn screening system; (2) follow-up should be centralized; (3) follow-up should be uniform across conditions, jurisdictions; (4) follow-up activities should be prioritized; (5) follow-up should be active for abnormal and inadequate cases; (6) follow-up should be accomplished quickly; (7) all cases should be resolved and closed in a specified period of time; (8) follow-up activities need evaluation. In May 2005, the CLSI Newborn Screening Follow-up Guidelines Subcommittee will vote on a draft of the proposed guideline. By August 2005, it is expected that the proposed document will be ready to circulate for review. If all goes according to schedule, the approved CLSI guideline will be published in June 2006.

Questions & Comments

Dr. Edwards asked how the exponential increase in newborn screening tests might affect the need for additional follow-up personnel and the costs of follow-up. Ms. Tuerck said that although she could not speak for the whole country, in her five-state region that started tandem mass spectrometry testing 2 ½ years ago, the follow-up load for metabolic diseases initially tripled because of the large number

of false positives. The region's follow-up load is currently about double what it was before, and the region has doubled the number of follow-up personnel.

Dr. Rinaldo, a proponent of focusing on more accurate laboratory testing to reduce false positives, asked Ms. Tuerck if she had any idea of what the false positive rate for the program in her region is. She said she believes that it is now down to less than 1 percent.

Dr. Howell, in response to Ms. Tuerck's comment that the follow-up community is not represented on the Committee or its subcommittees, said that the Treatment & Follow-up Subcommittee headed by Dr. Boyle is still in the process of formation and that it would not be correct to assume at this point that any group has been excluded from participation.

The Newborn Screening Program Evaluation and Assessment System (PEAS)

Bradford Therrell, Ph.D.
Director
National Newborn Screening and Genetics Resource Center (NNSGRC)

Dr. Therrell gave a presentation on the Newborn Screening PEAS project. The PEAS project group, funded through a cooperative agreement with HRSA/MCHB has been meeting about a year. PEAS is also a collaborative project with CDC. The purpose of the project is to support the improvement of newborn screening systems, and ultimately, patient services. Dr. Therrell, HRSA collaborators Dr. Lloyd-Puryear and Dr. Marie Mann, Dr. Harry Hannon from CDC, and two subcontractors who worked at the New Jersey Department of Health Newborn Screening Program are involved in the overall direction of the project. Committee members Dr. Becker from the Association of Public Health Laboratories and Dr. Edwards from the American Academy of Pediatrics are among several individuals serving on the project's oversight committee.

The PEAS project group has been collecting and assessing tools that the states are currently using to evaluate and assess their newborn screening programs, and it plans to create a comprehensive PEAS for the newborn screening system. The project group will develop performance indicators and give states a self-assessment performance checklist so they can assess their programs in terms of whether they comply with a particular indicator, do not comply, or are working on it. If the answer is that they do not comply with a performance indicator, states will be given advice on how to improve that particular indicator. The PEAS project group also expects to develop an interactive means to allow states to use PEAS. Its final task will be to implement PEAS pilot testing and improvement efforts.

The two working committees of the PEAS project group are (1) the Laboratory Working Group and (2) the Follow-up/Education Working Group. Dr. Therrell reported that these groups have undertaken a number of activities.

The PEAS project's Laboratory Working Group has identified the general areas specified below for the development of PEAS indicators in various phases of newborn screening. For each of these areas there are very specific indicators evaluating different issues.

- *Preanalytic phase of newborn screening:*

- At birthing facility: (1) heelstick blood collection (specimen collection, specimen preparation, specimen information review, and recordkeeping); (2) specimen transport (transport process, data tracking).
- At screening laboratory: (1) employee training 7 (employee competency); (2) employee safety (laboratory safety training, laboratory safety manual, blood borne pathogens exposure control; chemical hygiene plan); (3) specimens (collection card quality, specimen verification during transport); (4) acceptability of dried blood specimens; (5) transport process; and (6) specimen quality (patient data/demographic information, patient confidentiality. *Analytic phase of newborn screening*: (1) analytical processes (e.g., procedure manuals, quality assurance for the screening process, kit validation, method validation, reagent validation, proficiency testing, quality control procedures, control validation, calibrators/standard validation, analytical quality assessment); (2) laboratory instrumentation (instrument calibration and validation, instrument operation, maintenance of lab instrumentation); (3) supplies/reagents (quality and quantity, storage procedures); (4) laboratory environmental conditions; and (5) laboratory information system.

- *Post analytic phase of newborn screening*: (1) screening test results (e.g., assay acceptability, specimen testing and result reporting, accuracy validation of computer data and test result reporting, report correction); (2) archival recordkeeping; (3) clinical feedback (differences between screening and clinical testing results, critical test results, diagnostic confirmation); and (4) contingency planning.

The PEAS project's Follow-up/Education Working Group has identified the following general areas for the development of PEAS indicators in various phases of newborn screening. Under each of the specified areas, there are very specific indicators evaluating different issues.

- *Preanalytic phase of newborn screening:* (1) prenatal and birthing facility education for parents and consumers (e.g., prenatal educational materials, distribution and evaluation of such materials); and (2) prenatal professional education (e.g., professional educational materials, distribution and evaluation of such materials).
- *Postanalytic phase of newborn screening:* (1) overall follow-up system evaluation (e.g., evaluation plan, minimum evaluation elements); (2) follow-up of presumptive positive results (e.g., written follow-up policies and procedures, communication of results, documentation of communication); (3) follow-up of unsatisfactory specimens (e.g., timely notification, specimen receipt monitoring); (4) mechanism for evaluating the timeliness and effectiveness of diagnosis and treatment; (5) parent/consumer education for newly diagnosed newborns (e.g., education, counseling); and (6) outcome measures for evaluating long-term follow-up (e.g., medical management, long-term outcome).
- *Cross-cutting issues:* (1) education; (2) data systems (e.g., integrity, integration); (3) monitoring of timely and universal screening; (4) program policy and financing issues (e.g., administration, financing). Dr. Therrell expects that by the end of the next year, the PEAS project group will have developed an electronic process for states to use PEAS, probably via the Internet, and will be in the process of evaluating how the system works.

Questions & Comments

Dr. Boyle asked whether there are plans to do a pilot test of PEAS at the state level. Dr. Therrell said that although they hope to do pilot testing at the state level and already have interested voluntary groups, they may run out of time on the project. If so, they may ask HRSA for an extension.

Dr. Rinaldo, noting that the data elements in the PEAS checklists and the College of American Pathologists (CAP) are remarkably close, suggested that perhaps laboratories complying with the PEAS list could consider this a step to becoming CAP accredited. Dr. Therrell replied that although CAP is applicable to the laboratory part of PEAS, PEAS goes beyond laboratories. He added that he does not expect the PEAS project group to require that laboratories be CAP certified.

Dr. Rinaldo also said that although the PEAS laboratory list is exhaustive in terms of documenting every aspect of laboratory activity, what seems to be missing (except a reference to proficiency testing) is an assessment of how the laboratory is performing. Dr. Therrell said that performance elements are built into some of the details of PEAS, but the PEAS Laboratory Working Group did not want to say, "Is your false positive rate greater than .1 percent or .05 percent?" It would rather say, "Are you meeting the Clinical Laboratory Improvement Amendments (CLIA) standards and doing the things that need to be done there?" Dr. Rinaldo emphasized the importance of addressing this issue, because he believes that minimizing the unnecessary load on follow-up activities by minimizing false positives is key to the success of expanding newborn screening. Dr. Therrell promised to take this issue back to the Laboratory Working Group for discussion, but noted that many newborn screening programs have developed their own follow-up laboratory algorithm in terms of what the system can bear without missing any cases.

Dr. Boyle followed up on Dr. Rinaldo's comment from the follow-up perspective. She attended a PEAS meeting last week and asked why there could not be specific standards with regard to follow-up. She was told that states do not want specific standards; they want general guidelines. Dr. Boyle would like to see both the Treatment & Follow-up Subcommittee and the Committee discuss the need to impose specific standards to push the newborn screening system forward. Dr. Howell suggested that Dr. Boyle take this issue up in her Treatment & Follow-up Subcommittee.

Dr. Telfair, also following up on Dr. Rinaldo's comment, said that in the whole assessment of performance under PEAS, there are questions about whether state programs did or did comply, but not about whether they were making progress toward achieving that objective or indicator linked to that objective. Dr. Therrell said PEAS is intended as a self-assessment tool, and state programs have said they want a comment box on the form to comment on their progress toward the achievement of specific objectives if they want to.

Finally, Dr. Becker said that Dr. Rinaldo's point on the issue of certification or accreditation is extremely important. He noted that all state public health laboratories are at least certified by the Clinical Laboratory Improvement Amendments (CLIA) standards, and he is aware of some that are CAP-accredited. Currently, there appears to be interest in the accreditation of public health organizations at the National Association of County and City Health Officials (NACCHO), the Association of State and Territorial Health Officials (ASTHO), and CDC. Any of several different models could be used to accredit public health organizations, but until we get to some standardization perhaps of the cutoffs, we are going to continue to have conversations about the impact of false positives across the newborn screening system.

COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS

Dr. Howell reported that the three subcommittees established at the January 2005 Committee meeting—Education & Training, chaired by Dr. Howse, Treatment & Follow-up, chaired by Dr. Boyle, and Laboratory Standards & Procedures, chaired by Dr. Brower—had been meeting by telephone and had also met on the previous day, April 21, 2005. At this session, he said, the subcommittee chairs would be presenting their first reports to the Committee as a whole. Dr. Howell emphasized that although the subcommittees have been discussing priorities and areas of interest, they are still in the process of development, both as far as their mission and their memberships.

Education & Training Subcommittee

Jennifer Howse, Ph.D.
President
March of Dimes Birth Defects Foundation

Dr. Howse, chair of the Education & Training Subcommittee, began by identifying subcommittee members—Dr. Edwards, Dr. Becker, and Dr. Hawkins—and the HRSA/MCHB staff assigned to the subcommittee, Ms. Penny Kyler in the Genetics Services Branch. She reported that prior to the meeting on the previous day, subcommittee members had two conference calls to begin formulating plans.

The Education & Training Subcommittee is proposing that its charge be to review existing educational and training resources, identify gaps, and make recommendations regarding newborn screening communication to the following five groups: (1) health professionals; (2) parents; (3) screening program staff; (4) hospital/birthing facility staff; and (5) the public.

The subcommittee has already begun a broad review of education and training materials—particularly for health professionals and parents—to get a sense of what is available in the various states, as well as some of the materials and recommendations from Dr. Davis and her group related to effective newborn screening communications. The model for the subcommittee's review of educational materials related to newborn screening, Dr. Howse explained, is a kind of funnel, with the broad cone of the funnel representing the education needs of the 4 million U.S. babies screened each year and the long, very narrow portion of the funnel representing the education and training needs of parents, health professionals, and associated support for the small number of children who have a positive screen and confirmed diagnosis of a serious condition. Furthermore, the subcommittee is very respectful of the tremendous responsibility of the states not only to provide outreach, information and technical services around screening but also to ensure the quality and provision of technical services related to screening.

Second, the subcommittee is interested in exploring how the stated public policies and recommendations of professional organizations align with the recommendations of the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System.* The subcommittee has begun reviewing the policies of the AAP, Academy of Family Physicians, College of Nurse Midwives, American College of Obstetricians and Gynecologists, the Association of Women's Health Obstetrics and Neonatology Nurses, and the Society of Teachers of Family Medicine. If such organizations' newborn screening policies and recommendations do not align with the recommendations in the ACMG report, their training and educational materials will not align with the recommendations either.

Dr. Howse concluded her presentation by asking the full Committee to give the subcommittee its perspectives on a somewhat delicate issue raised by Dr. Becker and Dr. Edwards—the relationship between a child's medical home and the state/private laboratories that do newborn screening. According to Dr. Becker, especially with the Health Insurance Portability and Accountability Act's (HIPAA) confidentiality requirements related to medical records and patient information, state laboratories struggle with the following issues on a daily basis; (1) how to find out what a child's medical home is; and (2) how to get information from that medical home back to the state laboratory. Dr. Edwards noted that the one-page action sheets for conditions are unclear with respect to policies and protocols related to reporting follow-up back to the newborn screening program.

Questions & Comments

Committee members first responded to Dr. Howse's request for comments on the issue of the relationship between a child's medical home and state/private laboratories that do newborn screening. Dr. Howell noted that decisions about communication lines tie into the issue of informed consent and asked whether there are clear rules and regulations governing communications between state laboratories and the medical home. Dr. Becker explained that a lot depends on state's interpretation. In the case of HIPAA, for example, if the state defines newborn screening information as public health information, it can be reported by most interpretations of HIPAA; if a state does not define such information as public health information, there may be a problem.

Dr. Rinaldo said that the relationship between a child's medical home and state/private laboratories is one that states are going to have to address. Minnesota now uses a secure Website with a restricted list of people permitted access (a commercial product from IBM) to help keep the screening lab in the loop. When someone posts information about a patient on the Website, an e-mail is sent to the defined and approved list of people. That way, they can start a string of information about the patient. Lawyers at the Minnesota Department of Health and the University of Minnesota reviewed this approach and all deemed it acceptable under HIPAA.

Next Committee members turned to other issues. Dr. Howell reported that several people had contacted him about being involved in the Education & Training Subcommittee, including one young attorney working on a Ph.D. in medical ethics who might be useful. Dr. Edwards asked Committee members to let the Education & Training Subcommittee know of any activities going on in the field of education related to newborn screening. Dr. Therrell said he knows two groups working with family practice on modules on newborn testing. Dr. Dougherty suggested the possibility of having large retail chains like Wal-Mart, Target, and Buy Buy Baby help with a public information education program for newborn screening. Dr. Howse said retail outlets have worked with the March of Dimes and AAP—and at the right time, the subcommittee would be able to have that discussion. Dr. Howell agreed that a public education information program at the right time would be a wonderful idea. Finally, Dr. Telfair recommended that the Education & Training Subcommittee consider not just what needs to be communicated in education and training related to newborn screening, but who should communicate it. He suggested that Dr. Davis and Ms. Ohene-Frempong might be helpful in this area.

Treatment & Follow-up Subcommittee

Colleen Boyle, Ph.D., M.S.
Centers for Disease Control and Prevention

Dr. Boyle, chair of the Treatment & Follow-up Subcommittee, identified subcommittee members—Dr. van Dyck, Dr. Telfair, Dr. Dougherty, and Mr. Robertson—and noted that they had been working under the guidance of HRSA/MCHB staff, Dr. Marie Mann. She added that the subcommittee conducted two conference calls to talk about what the subcommittee's charge should be and about standards for follow-up in the newborn screening system. Dr. Boyle said that the April 21, 2005 subcommittee meeting, which was open to the public, also had been very helpful in drafting a proposed charge for the Treatment & Follow-up Subcommittee.

The presentations to the Committee by Dr. Therrell on the Newborn Screening PEAS and by Ms. Tuerck on the proposed CLSI guideline on newborn screening follow-up are evidence that HRSA and other agencies are supporting and trying to develop standards for follow-up. Although there is much information in terms of guidelines and possibilities for state standards for follow-up, it appears that state programs are not adopting these standards. Currently, there is no formal accreditation or certification process for newborn screening follow-up beyond what is done at the laboratory level. The Treatment & Follow-up Subcommittee could develop some type of product relative to standards for follow-up and help move the accreditation or certification process along.

Dr. Boyle proposed that the Treatment & Follow-up Subcommittee have the following charge:

- Recommend standards of practice for short- and long-term follow-up of newborn screening. Begin by trying to understand the state of follow-up: (1) inventory of activities related to development of standards (e.g., PEAS, CLSI, ACMG guidelines, the California and Massachusetts tandem mass spectrometry projects); (2) inventory of state practices and impediments to follow-up cost, lab and clinical expertise); and (3) patient/caregiver perspectives. Identify models of care that work—identify common features or key elements of exemplary program or program components.
- Recommend a mechanism to disseminate information and educate key stakeholders about these standards. Test and establish models that would lead to adaptation of standards.
- Recommend a mechanism for accountability to the standards for short- and long-term follow-up (e.g., a formal accreditation process).

Other topics that came up in the subcommittee meeting included the following: (1) tracking the impact of implementation of the ACMG's newborn screening report recommendations regarding follow-up; (2) the importance of clear definitions of follow-up (e.g., how long, how often, and who is responsible), and that long-term follow-up is critical and important; (3) the importance of financing newborn screening follow-up—many state programs cannot deal adequately with the children identified via newborn screening today, let alone with the expansion of screening; and (4) potential uses of a uniform child health record in linking children with services.

Questions & Comments

Dr. Howse similarly suggested that the subcommittee make a distinction between establishing standards and identifying best practices and using all available methods to promulgate a variety of best practices. In addition, she asked whether the Subcommittee should make a distinction between

what newborn screening tests and reporting requirements are legislatively authorized in each state and how to forward those, as opposed to focusing entirely on best practices.

Dr. Edwards commented that if we do get electronic health records for children, and we do have the state programs having information about children, pediatricians who accept new patients are likely to encounter difficulties in getting the patient's old information, especially from another state, because of HIPAA and confidentiality requirements. He urged the Treatment & Follow-up Subcommittee to look at this issue.

Dr. Dougherty asked two questions: (1) What is the general expectation of states and HRSA with regard to long-term follow-up? (2) Are there any conditions where there is a good relationship between the state public health delivery system and the medical home?

With respect to the first question, Dr. Lloyd-Puryear said that published guidelines, including the Newborn Screening Task Force report that HRSA did with the AAP, do recommend long-term follow-up. Some states do long-term follow-up and others would like to but are too fiscally constrained to do it. Dr. Becker concurred that some states do long-term follow-up aggressively; other states are too fiscally constrained. Dr. Howell asked whether the new HRSA-funded Regional Genetics and Newborn Screening Collaboratives and the National Institutes of Health (NIH) Rare Diseases Clinical Research Network might be tapped as a resource to help states do follow-up. Dr. Boyle said that considering the role of the regional collaboratives was an excellent idea. Dr. van Dyck concurred that the regional collaboratives might be used to lessen the burden on states; with respect to having specialty centers or consultants to the regions for rare diseases and facilitating a referral mechanism.

With regard to the second question asked by Dr. Dougherty, Dr. Becker said there are infectious disease and other reporting mechanisms. In the infectious disease model, CDC establishes the national notifiable reportable infectious diseases—the table at the back of *Morbidity and Mortality Weekly Report* every week. The Committee might want to consider recommending that CDC establish a similar mechanism for national notifiable newborn screening disorders. Still, he noted, he does get calls and questions about reporting that information because of HIPAA patient confidentiality concerns. Dr. Dougherty added that it might be useful to talk to people working on bioterrorism-type reporting activities, as well.

Dr. Hawkins, noting the second component of the Treatment & Follow-up Subcommittee's draft charge has a strong education component, expressed a concern about overlap with the Education & Training Subcommittee's work. Dr. Telfair said that a lot of what goes on in follow-up is education, and he thinks some overlap may be necessary. Mr. Robertson suggested that perhaps the Treatment & Follow-up Subcommittee could recommend the provision of education but let the Education & Training Subcommittee recommend techniques. Dr. Howell added that the Laboratory Standards & Procedures Subcommittee would also have an education component—perhaps it could do content, and the Education & Training Subcommittee could do format.

Laboratory Standards & Procedures Subcommittee

Amy Brower, Ph.D.
Executive Director
Third Wave Molecular Diagnostics
Medical Informatics and Genetics

Dr. Brower, chair of the Laboratory Standards & Procedures Subcommittee, introduced subcommittee members present—Dr. Alexander, Dr. Coggins, Dr. Rinaldo, and Dr. Howell. The committee has been working under the guidance of HRSA staff person, Dr. Marie Mann, with HRSA staff support from Carrie Diener. Prior to the April 21, 2005 subcommittee meeting, this subcommittee had had three conference calls to begin formulating preliminary plans.

The Laboratory & Standards Subcommittee is proposing that its charge is to assess laboratory methodologies and standards for testing panels of inherited disorders in newborns and children. The subcommittee is further proposing that its first three focus areas are; (1) infrastructure services; (2) developing a process for modifying the uniform newborn screening panel; and (3) evaluation of new technologies. The subcommittee also will address the three crosscutting areas identified at the previous Committee meeting as being of importance to all of the subcommittees—namely, evaluation, information technology, and financing.

Infrastructure services. A slide presented at an earlier meeting by Dr. van Dyck, Dr. Boyer noted, showed a pyramid with direct health care services at the top, followed by enabling services, followed by population-based services, and finally, infrastructure building services at the bottom. In the area of infrastructure services, the subcommittee will consider the following:

- *Nomenclature.* The subcommittee believes it will be important to provide guidelines for the standardized counting of conditions with a focus on clinical phenotype, how to group conditions, the primary marker used to determine whether the condition is present or absent, the testing platform that is being used, the response to treatment, the number of loci, gene, and other analytes that we're targeting, and an hoc criteria to be established as we go further along. The subcommittee anticipates it will be able to help facilitate communication to professionals and consumers by providing structural feedback to the Education & Training Subcommittee.
- *Testing strategies.* The subcommittee will examine testing strategies in newborn screening, focusing on the evaluation and standardization of preanalytical, analytical, and postanalytical processes (e.g., time of collection, second collection, second-tier tests, profile evaluation, and timing of confirmatory testing).
- *Cutoff values.* The subcommittee will look at cutoff values for the following: disease range vs. normal range; use of analyte ratios; monitoring of abnormal results (true positives, reported abnormal false positives, interpreted as not significant); normalization (abnormals/10,000 cases) using models developed by Dr. Rinaldo in his regional collaborative; and the impact of second-tier tests.
- *Reporting.* The subcommittee will consider standardizing required elements in results reported by every laboratory and every state. It also will consider quantitative results, cutoffs, the prior experience (range), and the interpretation (differential diagnosis, if applicable and recommendations for confirmatory testing).

- *Performance metrics.* The subcommittee will look at performance metrics, including the definition of targets (detection rate, false positive rate, positive predictive value) and proficiency testing.

Process for modifying the uniform newborn screening panel. The uniform newborn screening panel should be driven by stakeholders—consumer advocates, clinical investigators, researchers, providers of laboratory services, and industry. The subcommittee will work on developing a dynamic, open-ended process for adding conditions to or deleting conditions from the uniform newborn screening panel. As part of that process, the subcommittee is proposing the use of a prospective evaluation tool—generally based on the evaluation flowchart for evaluating conditions in the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System*, which specified that secondary conditions and other conditions were to be reconsidered on the basis of (1) new screening methods; (2) new treatments; or (3) evolving understanding of the natural history of the condition. The subcommittee expects to create an outline and guidelines for modifying the uniform panel and expects to start collecting survey data from local groups, providers of services, and consumers. It then plans to apply the evaluation flowchart, modify this from the ACMG report, review updated literature evidence, and make recommendations for additions to the uniform panel.

New technologies. New technologies taking advantage of the knowledge gained from the Human Genome Project, expression targets, and proteomics are another important issue. There will be new approaches to conditions that are on the current panel, as well as the testing of additional conditions for which testing is not now available. The subcommittee also wants to address other technologies, including multiplex testing, point-of-care testing (e.g., for diabetes), and direct-to-consumer testing—things that will impact testing, not necessarily in the newborn phase but perhaps in child- and adult-onset diseases.

Crosscutting issues. In the area of evaluation, the Laboratory Standards & Procedures Subcommittee will be focusing the cost-effectiveness of testing the assessment of clinical validity and utility, and health outcomes. In the area of information technology, it will consider how to integrate diverse data sets and how to provide data access to clinicians, consumer groups and public health entities, and how to ensure privacy. Finally, the subcommittee will focus on how to ensure the necessary financing for laboratory tests and procedures.

Dr. Brower concluded her presentation by noting that the Laboratory Standards & Procedures Subcommittee has invited several individuals to participate in its work. Confirmed participants are: Dr. Don Chace, Pediatrix; Dr. Harry Hannon, CDC Biochemical Branch; Mr. Gary Hoffman, Wisconsin State Laboratory of Hygiene; Ms. Jana Monaco, parent; and Dr. Larry Sweetman, Baylor University. Dr. John Sherwin, Genetic Disease Branch, California Department of Health Services, may participate.

Questions & Comments

Dr. Becker commented that the CLSI is working on developing a protocol or standard document for tandem mass spectrometry testing. Dr. Chace is chairing the subcommittee, so his involvement with the Laboratory Standards & Procedures Subcommittee will be very useful.

Dr. Howell observed that the Laboratory Standards & Procedures Subcommittee has an enormous task before it and asked what its priorities would be. Dr. Brower said the subcommittee will address laboratory standards and methodology; in parallel, perhaps in a separate working group, the subcommittee will focus on adding new conditions to add to the uniform panel.

The Committee engaged in a lengthy discussion of how the Committee should develop recommendations to the Secretary regarding modifications to the uniform panel for newborn screening recommended in the ACMG newborn screening report. Dr. Brower suggested that the Laboratory Standards & Procedures Subcommittee evaluate the ACMG model for evaluating conditions and report back to the entire Committee. Some members, including Mr. Robertson, agreed that the subcommittee should take the lead in evaluating the ACMG model and reporting to the Committee. Other members, including Dr. Boyle and Dr. Howse, were of the opinion that it was important for the Committee as a whole to develop criteria for adding or removing conditions in the newborn screening panel. Dr. Boyle stated that the issue would continue being a thorn in the side of the Committee unless it comes to a consensus about the process.

Dr. Edwards, noting that he was impressed at the last meeting by the number of positives picked up on a second newborn screening test, asked whether that is part of the Laboratory Standards & Procedures Subcommittee's charge. Dr. Boyer confirmed that both the confirmatory testing and the second test are included in the subcommittee's purview. Dr. Howell agreed that the second test should be looked at very carefully.

Dr. Howse agreed with Dr. Boyle that the Committee as a whole should try to develop a consensus about the criteria of adding tests to the uniform panel. She also questioned whether the Committee is the right group to be recommending additional tests, suggesting that perhaps CDC or the National Institute of Child Health and Human Development should weigh in. Finally, Dr. Howse urged the Committee to focus on the poor coverage of children for the 29 tests in the ACMG-recommended uniform panel, reminding the Committee that the current list of 29 conditions has no Federal standing at this point.

Dr. Rinaldo emphasized that somebody has to take ownership of making sure that the process of adding conditions to the panel continue because the ACMG-recommended uniform panel was meant to be a baseline for future improvements. At the same time, Dr. Rinaldo said he had no problem tabling any activity on the issue of modifying the uniform panel until after the presentation being organized by Dr. Dougherty for the Committee's July 2005 meeting and hopes the Committee gets something tangible out of the presentations.

Dr. Dougherty said she expected that the presentation—tentatively titled "The Role of Evidence and Other Factors in Decision-making"—would be provided by a person knowledgeable about genetics and newborns and children. The presentation would focus heavily on the current state-of-the-art and science of evidence-based decision-making focused on screening. It would address approaches to decision-making that can be used in the absence of evidence. It would also address how the cost burden of disease, natural history, and test characteristics are systematically addressed. A subtopic of the presentation would be systematic ways to obtain expert opinion.

Dr. Rinaldo said he would hope that the presenters could be asked to use specific examples and, if possible, provide an evaluation of the tools used in the ACMG newborn screening report. Dr. Howell said perhaps the Laboratory Standards & Procedures Subcommittee could get some comments to the speaker or speakers about the specific types of information the subcommittee would like the presentation to include. Dr. Dougherty suggested that the Committee might want to hear more than one presenter, because people have widely different views on evidence and other factors to be used in decision-making.

Mr. Robertson suggested having presentations made to the Laboratory Standards & Procedures Subcommittee rather than the full group, but Dr. Boyle said she personally would like to hear the

presentations. Dr. Telfair proposed middle ground—letting the experts give the full report to the Laboratory Standards & Procedures Subcommittee, and then having the subcommittee distill the information and give a more targeted report to the full Committee.

Finally, Dr. Howell suggested the following approach: (1) first, having the experts identified by Dr. Dougherty meet with the Laboratory Standards & Procedures Subcommittee prior to the Committee's July 2005 meeting: (2) then having the experts make a presentation to the full Committee at the July 2005 meeting; and (3) finally, having Laboratory Standards & Procedures Subcommittee consider the presentations and other materials and come back to the full Committee with recommendations. Dr. Howell said he would work with Dr. Dougherty, Dr. Boyle, and Dr. Lloyd-Puryear to move the process along. Dr. Brower said that she would be happy to work with Dr. Dougherty and the speakers. She also agreed to Dr. Howell's request that the Laboratory Standards & Procedures Subcommittee hold off on other actions related to this topic until after the Committee's July 2005 meeting.

Dr. Dougherty then raised a larger question related to the appropriateness of the charges for the Committee's three subcommittees, noting that she thinks the process for modifying the uniform newborn screening panel is an issue that the entire Committee should deal with rather than just the Laboratory Standards & Procedures Subcommittee. Dr. Howell commented that the subcommittee's business is in all cases the business of the whole Committee. At the suggestion of Dr. van Dyck, Dr. Howell directed subcommittee chairs to send their charges and priorities electronically to Dr. Lloyd-Puryear to be distributed to Committee members for comments and approval before the Committee's next meeting. Dr. Howell also told subcommittee chairs to submit the names of individuals they would like to have as consultants to Dr. Lloyd-Puryear, so that he and HRSA can approve them.

At the end of the session, Dr. Edwards asked for clarification about what action the Committee will take and what the disposition of the ACMG newborn screening report will be once the 60-day public comment period ends on by May 8, 2005. Dr. Howell said that Dr. Lloyd-Puryear will arrange for the Committee to get copies of all of the public comments, so the Committee can write to the Secretary of Health and Human Services about the Committee's further deliberations related to the document and the public comments. He also suggested that the Committee not respond to the comments, many of which are similar, except to amplify them or correct misinformation. Dr. van Dyck explained that after the public comment period, there would be an internal process involving all HHS agencies with an interest in the ACMG report and public comments to determine what product or decision would be forthcoming from HHS. He said that he could not specify an exact time frame for when (or whether) there would be final recommendations or actions by the HHS Secretary.

Dr. Howse confirmed that the HHS Secretary receives many reports—and some of them are never acted upon. Referring to the letter that Dr. Howell previously sent to the Secretary on the Committee's behalf, she said that the Committee still needs to draft a letter from the Committee to the Secretary that says the Committee reviewed the public comments and final report in light of the public comments and is now requesting that HHS take specified actions to accept and move the recommendations as departmental advice or guidelines in newborn screening. Dr. Howse said she would hope that the Committee could move the letter forward at its next meeting. Dr. Howell and Dr. Lloyd-Puryear agreed to draft the letter to the HHS Secretary for the Committee's consideration at the July 2005 meeting.

Finally, Dr. Telfair commenting on the earlier presentations by Dr. Therrell and Ms. Tuerck on newborn screening follow-up, reminded the Committee to bear in mind that nongovernmental

organizations, community-based programs, and individuals are passionate about follow-up and can play an important role in ensuring that follow-up occurs.

PUBLIC COMMENT SESSION

At the second public comment session, the following individuals made comments. The written text of their statements appears in Appendix A.

Frances Downes, Dr.P.H.
Board Member
Association of Public Health Laboratories (APHL)

Dr. Downs explained that APHL represents public health laboratories in the 50 states and six territories, which currently conduct approximately 97 % of all newborn screening tests in the United States. APHL commends HRSA, ACMG, and the Committee for their roles in developing the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System.* The second section of the report contains recommendations related to aspects of the newborn screening system that lie beyond laboratory operations. Since these aspects of the system often interlock with laboratory functions, APHL would like to provide input on these recommendations. In addition, APHL would like to propose a wider vetting process for the recommendations from the ACMG report, perhaps in the form of a consensus conference or similar mechanism, along the lines of the Western blot consensus process for which APHL provided leadership in the past.

Jennifer Sullivan, M.S., C.G.C.
National Society of Genetic Counselors, Inc. (NSGC)

Ms. Sullivan stated that NSGC, which represents approximately 2,000 genetic counselors worldwide, enthusiastically endorses the ACMG newborn screening report's rationale for and designation of the core disorders for newborn screening. NSGC commends the Committee's dialogue regarding the lack of long-term follow-up for many of the conditions endorsed by the screening recommendations. It believes it is critical that high-risk infants and families identified in newborn screening programs receive high-quality and standardized medical care, regardless of geographical location or ability to pay. NSGC encourages the Committee to recommend periodic evaluation of the national and state directives regarding newborn screening to ensure the availability, accessibility, and efficacy of such programs and their adjunct follow-up services. NSGC would be pleased to work with the Committee as it continues to consider these issues.

Philip R. Vaughn, M.D., M.B.A.
Vice President, Newborn Screening
Pediatrix Medical Group, Inc.

Dr. Vaughn reported that by creating a consensus statement as to the scope of disorders that should be screened, the ACMG newborn screening report has provided significant guidance to newborn screening program developers about what disorders that should be included. Pediatrix will advocate for prompt implementation of expanded newborn screening recommended by the ACMG report, will endorse physician and parent awareness to encourage more screening of kids, and will look for constructive ways to become an active technology partner with program coordinators.

Carol Greene, M.D.
Clinical Geneticist, University of Maryland &

Membership Chair, Society for Inborn Metabolic Disorders (SIMD)

Dr. Greene made two separate comments. First, speaking as a private person, she addressed communication problems related to newborn screening that arise between public health departments, primary care physicians, and specialists under the Health Insurance Portability and Accountability Act (HIPAA). Referring Committee members to an Apr. 13, 2005, article in the *Journal of the American Medical Association* that discusses the inappropriate implementation of HIPAA by many states and institutions even when there are clear guidelines and FAQs (frequently asked questions), she noted that HIPAA explicitly exempts public health reporting and states that no patient authorization is needed for a clinician to talk to another treating clinician about a patient. A primary goal of HIPAA is not to interfere with quality medical care, and interfering with quality care can be a HIPAA violation. Clinicians and others who encounter problems, she suggested, should consider making reports to the Office of Civil Rights or ask for clarification. In addition, the Committee might want to hear from the Office of Civil Rights on this topic.

Second, speaking for SIMD, and as a follow-up to Dr. Vockley's formal public statement for the SIMD on the previous day, Dr. Greene appreciated the report on the Treatment and Follow-up subcommittee. She recommended that Dr. Boyle change the draft charge for the Treatment & Follow-up Subcommittee to explicitly include the word "treatment," to assure that issues of the need for efforts to assure treatment and funding of treatment are explored.

Marilyn C. Jones, M.D.
President
American College of Medical Genetics (ACMG)

Dr. Jones gave a brief overview of the development by ACMG of the report, *Newborn Screening: Toward a Uniform Screening Panel and System.* ACMG received a contract from the Maternal and Child Health Bureau of HRSA to assess the scientific and clinical evidence regarding the appropriateness of 78 conditions for newborn screening. This effort stemmed from a 1999 recommendation by the American Academy of Pediatrics (AAP) Newborn Screening Task Force that suggested that HRSA engage in the development of a national screening process. The steering committee for the report, she noted, included representatives from the leadership of the American Academy of Pediatrics, t March of Dimes, CDC, HRSA, AHRQ, and the Genetic Alliance. The project was organized around several workgroups, each of which included members with extensive knowledge and experience in newborn screening. Twenty-four (24) individuals whose expertise encompassed science, law, health policy, and ethics constituted the expert group that established the framework for the report, reviewed materials prepared by others, and made the final recommendations. There were three opportunities for public comment on the report. The ACMG Board unanimously endorsed the report in December 2004, recognizing the complexities involved in evaluating and comparing the many conditions and technologies but agreeing with the report's conclusions that the 29 conditions identified as appropriate for newborn screening are often devastating, are sufficiently well understood, have screening tests with strong performance characteristics, and are treatable with significant benefit to the infant. ACMG hopes that that the report will set the stage for a number of initiatives that will define a stronger national role in newborn screening to ensure that the outcomes expected from a child identified in a screening program are realized. For that reason, ACMG hopes that the Committee will establish an ongoing process by which conditions already included in newborn screening are reviewed and candidate conditions are considered for inclusion as new screening tests and treatments become available. Dr. Jones concluded by discussing ACMG's involvement in a variety of other projects—from the development of the National Coordinating Center for the new HRSA-funded Regional Genetics and Newborn

Screening Collaboratives to the pilot testing of management guidelines (ACT sheets) to improve the delivery of screening and diagnostic follow-up services.

COMMITTEE BUSINESS—SETTING COMMITTEE PRIORITIES

Rodney Howell, M.D.
Chair, Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Dr. Howell asked Committee members what thoughts they had about priority topics or agenda items for the Committee's next meeting, scheduled for July 21-22, 2005, or beyond. The following topics were suggested as potential agenda items:

- **The Committee's letter to the HHS Secretary about public comments on the ACMG newborn screening report**. Dr. Howell indicated that a substantial effort at the July meeting would be devoted to reviewing the draft letter to the HHS Secretary regarding the ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System* and public comments.
- **Update from Dr. Therrell, of NNSGRC, on where states are in terms of implementing the ACMG newborn screening report's recommendations**. Dr. Dougherty requested an update on where the states are in terms of implementation of the ACMG report's recommendations. Dr. Howell said he thinks an update by Dr. Therrell should be a permanent part of the Committee's agenda, so that the Committee can track what progress is made. Dr. Therrell reported that the translation from the previous way of counting to the ACMG way of counting was just put on the NNSGRC Website (http://genes-r-us.uthscsa.edu/); and the site is updated at least monthly, if not weekly. According to Ms. Williams, the key to the site is as follows: a dot = testing is universally required by law or rule; A = testing is universally offered but not yet required; B = testing is offered to select populations or by request; C = testing is mandated but not yet implemented. She added, however, that even in states where testing is mandated or offered to everybody, the states do not know what percentage of children actually get screened.
    - **Subcommittee reports.** Dr. Becker asked the Committee chair what the subcommittees should accomplish by the July meeting. Dr. Howell said the subcommittees should continue to meet by teleconference and in person and should come up with quite substantial plans and results by July. He reminded subcommittee chairs to provide their draft charges and agendas to Dr. Lloyd-Puryear so that they could be circulated and commented on by the group. He also said that he should hear from the subcommittees about recommendations for consulting persons to serve on the subcommittees. Dr. Brower reminded the subcommittee chairs not to forget to address the three crosscutting areas identified as being of importance to all three of the subcommittees—evaluation, information technology, and financing.
    - **Financing for newborn screening.** Dr. Edwards commented that several people making public comments had raised the issue of financing and asked whether the Committee would be discussing this. Dr. Edwards said he thought both state and Federal financing (e.g., financing for state health departments for testing and follow-up services) should be addressed by the Committee. Dr. Dougherty reminded Committee members that financing was one of the crosscutting issues to be addressed by the subcommittees. Dr. Boyle suggested that the Committee have speakers or talks around these crosscutting issues and that perhaps a speaker could talk about financing. Dr. Lloyd-Puryear reminded Committee members that Kay Johnson had given a presentation on state financing issues. Dr. Robertson suggested that

perhaps the Committee should just make broad recommendations about the importance of providing financing for certain things rather than getting into the details of specifying how much financing is needed. Dr. Telfair, quoting from the previous meeting's minutes, noted financing is not just for the expansion of newborn screening but also for new paradigms of working relationships identified as an area of shared need by the Regional Genetics and Newborn Screening Collaboratives. Dr. van Dyck said it is important to know how states do their financing and that it would not hurt to go back and revisit this. Dr. Howell decided to put financing on the agenda, with a view toward having the Committee make a clear statement about the need to finance a screening system, not just test. Dr. Becker suggested that in addition to having Dr. Therrell review his presentation about how states generally financing newborn screening, it might be helpful to invite some insurers to discuss how well newborn screening is reimbursed. Dr. Rinaldo said it might be of interest to the Committee to learn why the fees for newborn screening vary so much from state to state—ask a representative from a state with no fee and a state with a high fee to explain their approaches. He also suggested it would be helpful to learn more about unit costs of a generic short-term follow-up, so that the Committee could provide tangible practical guidance. Dr. Therrell said that a few studies of unit costs have been done (Kaiser, Jerry Berry, California). Dr. van Dyck sad that each of the subcommittees has an opportunity to put a cost on some set of standards, guidelines, or recommendations that might help make things more uniform. Dr. Edwards suggested that the larger question the Committee should consider is how funding relates to the provision of a good quality newborn screening program. Mr. Robertson recommended that the Committee hear a presentation related to mechanisms and best models for funding newborn screening programs. Dr. Becker said it would be interesting to hear what legislative activities are needed in different states to expand funding for newborn screening. Mr. Robertson agreed. Finally, Dr. Becker said he thought Dr. Therrell, of NNSGRC, had given a nice overview a couple of meetings ago about general funding strategies and that perhaps he could create a presentation tailored to the points made in the Committee's discussion. Dr. Howell directed that Dr. Therrell be asked to discuss financing at the Committee's October meeting.

In addition to suggesting the aforementioned agenda items, Committee members raised several other issues.

- **Invitation to the American College of Gynecologists and Obstetricians (ACOG).** Dr. Dougherty asked about the possibility of inviting a representative of the ACOG to serve on the Committee as a nonvoting member. Dr. Howell said he thinks that this would be very valuable. Dr. Rinaldo suggested that as a first step the Committee invite a representative of ACOG to make a presentation about ACOG's stance on newborn screening. Dr. Edwards said it would be helpful to invite ACOG to help implement Dr. Davis's recommendations about giving newborn screening information to parents in the prenatal period.
- **Paper on history of newborn screening**. Dr. Howell noted that there had been a great deal of lay press on newborn screening recently, and he believes this coverage is very valuable. One problem, however, is that the lay press suggests that there are often many adverse effects resulting from newborn screening, although the literature to support this view is not there. Dr. Howell would like to work with Dr. Lloyd-Puryear to get an expert to look at the history of newborn screening and adverse effects and get it published. He has been discussing this with Dr. Howse, and she is enthusiastic. Dr. Becker said that he liked the idea, as well, and added that Dr. Harry Hannon is also interested in the subject. Dr. Boyle said it might be helpful to have it a little

more generalized paper on the risks and benefits of screening, but Dr. Therrell said he was thinking of just clearly defined adverse effects. He will move ahead with this.

- **False positives in newborn screening.** Dr. Rinaldo suggested that it would be useful for the Committee to learn something about false negatives in newborn screening. It is a problem to have too many false positives, but it is deadly to have any false negatives. Dr. Therrell said that a joint study of false positive involving CDC and the NNSGRC is about to get underway but won't have results for at least a year.
- **Protocol for handling the press**. Mr. Robertson asked if there is a protocol to follow if contacted by the press. Dr. van Dyck said that Dr. Howell, as chair of the Committee, is free to comment to the press, and other Committee members can comment to the press as long as they keep their comments focused on issues in the public record. Dr. Howell said he would be happy to field the questions and to help with consistent messages. Dr. Howell talks about the Committee's message and what the Committee is doing, but does not talk on a public dialogue with what somebody else said.

Dr. Howell thanked the members, speakers, and audience members for their participation and adjourned the Committee meeting at 2:30 p.m.

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We certify that, to the best of our knowledge, the foregoing meeting minutes of the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children are accurate and correct.

/s/ _____

R. Rodney Howell, M.D., Ph.D.
ACHDGDNC, Chair

/s/_____

Michele A. Lloyd-Puryear, M.D., Ph.D.
ACHDGDNC, Executive Secretary

These minutes will be formally considered by the Committee at its next meeting, and any corrections or notations will be incorporated in the minutes of that meeting.