Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children

Summary of Ninth Meeting
December 18-19, 2006
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children was convened for its ninth meeting at 9:00 a.m. on Monday, December 18, 2006, at the Hilton Washington Hotel in Washington, D.C. The meeting was adjourned at 2:47 p.m. on Tuesday, December 19, 2006. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments on December 19, 2006. The Committee members and organizational representatives present are listed below:

Committee Members Present:

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I. WELCOME, OPENING REMARKS

A. Letter from HRSA Administrator to the Committee

Peter C. van Dyck, M.D., M.P.H., M.S.
Associate Administrator
Maternal and Child Health Bureau
Health Resources and Services Administration (HRSA)

Dr. van Dyck read a letter from HRSA Administrator Dr. Elizabeth Duke, who was unable to attend the meeting. In her letter, Dr. Duke welcomed members of the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. She noted that HRSA continues to be concerned about the patchwork of newborn screening programs in the States. She stated that the Federal Government, without imposing standards, can provide guidance on steps that States can take to assure that all American children get the same basic standard of care. She also underscored the importance of making sure that voices of parents are represented. Finally, Dr. Duke asked Advisory Committee members to advise the Department of Health and Human Services (HHS) on how to develop a transparent and evidence-based process for modifying the conditions in the uniform newborn screening panel recommended by the American College of Medical Genetics.

B. Welcome and Committee Business

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

New Committee Members. After welcoming participants to the meeting, Dr. Howell announced that the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC) had two new members: Ms. Jana Monaco, the mother of two children with isolaveric acidemia and a board member of the Organic Acidemia Association; and Dr. Michael Skeels, the director of the Oregon State Public Health Laboratory. Dr. Howell also thanked retiring Committee members Dr. William Becker and Mr. Derek Robertson for their service and presented them with letters of appreciation from HHS Secretary Michael Leavitt.

Approval of Minutes. The minutes from the June 5–6, 2006, meeting of the ACHDGDNC, were approved as amended. Amendment: In the last paragraph on page 26, in the sentence "Dr. Dougherty discussed what steps the Committee should take," change the word "should" to "could."

Correspondence re Adding a New Organization Member. Dr. Howell reported that Dr. Sharon Terry, the president and CEO of the Genetic Alliance, had written a letter dated June 21, 2006, requesting that the Genetic Alliance be permitted to send an organization representative to the Advisory Committee. He asked Advisory Committee members for comments.

Dr. Edwards, noting that the Committee is already near the size limit for sitting around the table, whether there should be some consideration of the size of the Committee before adding new

people. Dr. Lloyd-Puryear explained that the Committee's charter limits the number of members but not the number of organization representatives. She suggested one procedural way to handle the size of the Committee would be to separate the representatives from the Committee members; other Advisory Committee structure their Committee meetings using this method.

There was a consensus among Committee members that an organizational liaison from the Genetic Alliance would be an asset to the Committee, given the fact that it represents a broad area of interest to the Committee. Thus, the Committee voted to approve the following motion:

- ***MOTION #1: The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children accepts the Genetic Alliance's application to send an organization representative to the Committee***.

Several Committee members stressed the importance of developing some overall guidance about which organizations would be permitted to send organization representatives. Dr. Howell explained that organization representatives had been accepted in the past because they seemed to represent a large body of people or situations that were deemed relevant to the discussion of the Committee. He also stated that he did not think that the Committee should be proactive in seeking out organizations. Ms. Monaco said she would like to have an organization with expertise in followup and treatment, such as the Society for Inherited Metabolic Disorders, send an organization representative. The following decision was made:

- ***DECISION #1: Dr. Howell and Dr. Lloyd-Puryear will draft written criteria that the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children might use in deciding which organizations to permit to send an organization representative to the Committee, so that Committee members can review and modify these criteria at the next meeting.***

Agenda for the Day. Dr. Howell said that during the first day of the meeting, the Committee would hear an update from the Criteria Workgroup on the process for nominating and reviewing conditions to be added to the uniform newborn screening panel recommended by the American College of Medical Genetics (ACMG). Dr. Green, Dr. Alex Kemper from Duke University, and Dr. Stephen Downs from Indiana University School of Medicine would report on a small meeting with experts in evidence-based review held in October 2006. Dr. Howell said he added that he hoped the Committee would make a final decision about advising HRSA on the establishment of a group to review evidence conditions nominated for inclusion in the uniform newborn screening panel, so that the real nomination and review process could begin in the near future. A new item on the agenda for the first day of the meeting, Dr. Howell said, was a presentation from Dr. Gregory Downing on HHS Secretary Leavitt's priority initiative to facilitate adoption of personalized medicine. The viewing of the March of Dimes video on newborn screening, *A Parent's Guide to Newborn Screening,* would be postponed to the following day.

During the second day of the meeting, Dr. Howell said, Committee members would view the March of Dimes video on newborn screening for parents and hear reports from the Followup & Treatment Subcommittee, the Laboratory Standards & Procedures Subcommittee, and the Education & Training Subcommittee. In addition, Committee members would hear presentations related to the concepts of benefit and treatment in the newborn screening from Drs. Jeffrey Brosco, Don Bailey, and Ellen Wright Clayton.

Meeting Dates. Indicating that a decision had been made to reschedule the February 2007 meeting for April or May (preferably on a Monday or Tuesday), and to reschedule the June 2007

meeting for August or September (again preferably on a Monday or Tuesday), Dr. Howell asked Committee members to fill out calendars indicating their preferences for new dates to Dr. Lloyd-Puryear, so that the precise dates for the meetings could be determined.

II. ESTABLISHING AN EVIDENCE-BASED PROCESS FOR MODIFYING THE UNIFORM NEWBORN SCREENING PANEL

In this session, Dr. Nancy Green, Dr. Alex Kemper from the Duke University Department of Pediatrics, and Dr. Stephen Downs from Indiana University School of Medicine discussed how the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children might apply evidence-based review to the process of nominating, evaluating, and making decisions related to the inclusion of conditions in the uniform newborn screening panel recommended by the American College of Medical Genetics (ACMG).

A. Criteria Workgroup's Update on the Proposed Evidence-Based Nomination and Review Process

Nancy S. Green, M.D.
Medical Director
March of Dimes Birth Defects Foundation

Dr. Green reported on a small meeting convened by HRSA on October 23, 2006, with experts in evidence-based review, pediatrics, and rare genetic diseases, and members of the Criteria Workgroup. The October 23, 2006 meeting, entitled "Process for Evaluation and Gathering Evidence," was chaired by Dr. James Perrin, a Professor of Pediatrics at Harvard Medical School. The meeting was convened for two main purposes:

- To review the full Advisory Committee's proposed nomination form for adding conditions to the ACMG uniform newborn screening panel; and
- To develop a proposal for reviewing and grading evidence pertaining to the inclusion of conditions in the uniform panel.

(The minutes for the meeting were included under TAB #6 of the binder prepared for Advisory Committee members for the December 18-19, 2006, Advisory Committee meeting.)

As background for her report on the October meeting, Dr. Green briefly summarized the progress that the Advisory Committee and its Criteria Workgroup had previously made in developing a structured process for adding conditions to the ACMG uniform newborn screening panel prior to the meeting. First, the Advisory Committee had agreed that the process for nominating and evaluating conditions would be based on the following concepts: (a) broad access to nomination process; (b) evidence review; (c) streamlined processes; (d) transparency; and (e) consistent criteria throughout the process. The process would encompass three broad areas of consideration: the condition, the test, and the treatment.

Second, the Advisory Committee had agreed that the process would include the following steps:

- **Step #1:** Nomination form submitted by proponent(s) of adding a condition
- **Step #2:** Federal administrative review of the nomination form
- **Step #3:** Review by the ACHDGDNC

a. Advisory Committee review

b. Evidence-based review by an external body

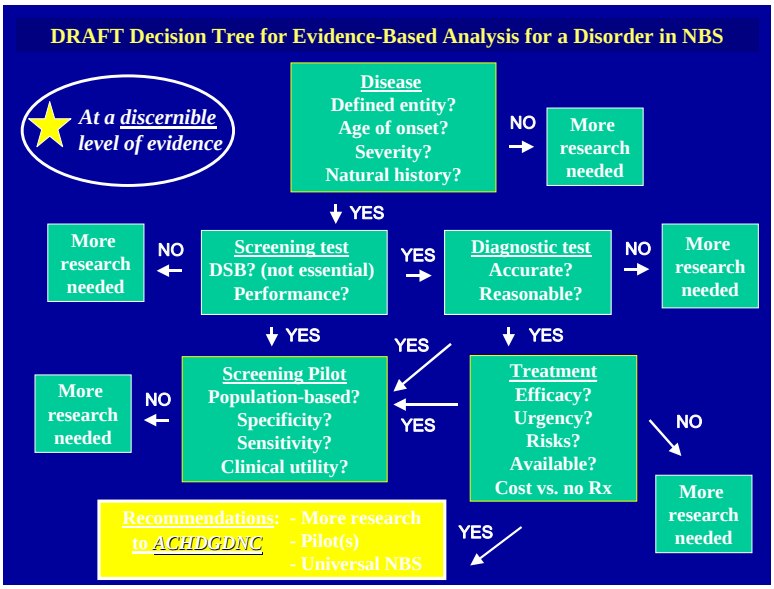
c. Advisory Committee review and decision

According to Dr. Green, participants at the October meeting generally supported the Committee's proposed nomination process and approved nomination form (Step #1 of the process outlined above); however, they did suggest some additions to the nomination form (e.g., related to the inclusion of pilot studies and quantitative/specificity/ sensitivity data) and indicated that additional tweaking of the form might be needed as the external evidence-based group moved along in its work.

Much of the October meeting was focused on a component of Step #3 (b)—specifically, having an external body review and report on the evidence to the full ACHDGDNC so that the Advisory Committee is able to make recommendations to HHS. Participants at the meeting agreed that evidence-based review could be applied to newborn screening. They also developed an overall framework for evaluating and making decisions about adding conditions to the newborn screening panel. They emphasized that the data in evidence-based reviews for newborn screening will necessarily be different from the data used in other evidence-based reviews. One reason is that there is generally considerably more evidence for interventions considered by groups such as the U.S. Preventive Services Task Force (USPSTF) or the Advisory Committee on Immunization Practices (ACIP) than there is for newborn screening tests and treatments. Another reason is that newborn screening disorders are unusual (as opposed to the underlying assumptions for these other groups, that the disorders are common), and the impact of early intervention and the natural history of the disorder and later intervention may not be crisply defined.

There was a consensus at the October meeting that some sort of consistent decision analysis should be applied for a disorder in newborn screening, perhaps using a decision tree along the lines of the rough draft of a decision tree developed by Dr. Green (see below). The focus of the evidence-based review in newborn screening incorporate the following questions: (a) what are the outcomes of screening and their implications: true positives, true negative, false positive, false negative?; (b) what disorders and what spectrum does screening identify?; and (c) how to assess the impact of treatment? Additional questions pertaining to the evidence review that remain to be addressed include the following:

- How to weigh evidence, especially where sparse or inconclusive?
- How does cost analysis influence decisions? What is the cost of screening and early treatment vs. not screening and late treatment and possible increase in mortality?
- How to define and prioritize the benefits of newborn screening?



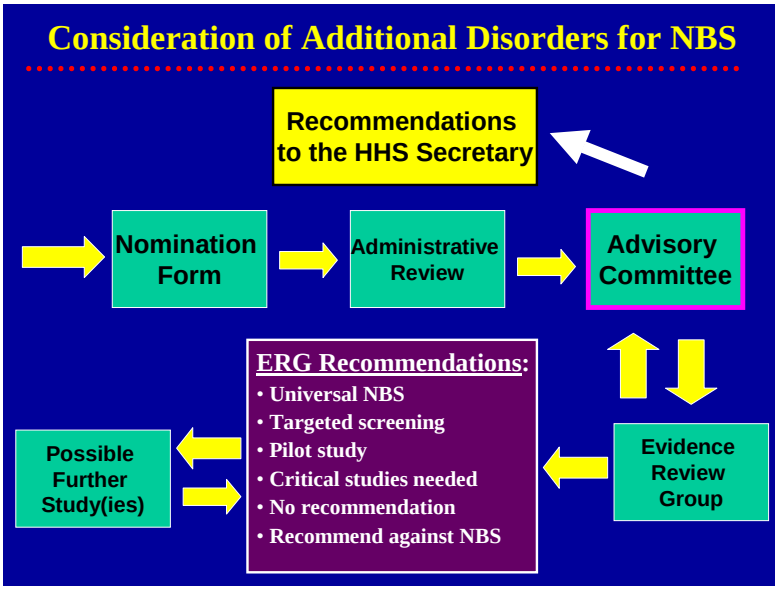
Participants at the October meeting agreed that an external Evidence Review Group (ERG) could advise the full Advisory Committee. They suggested that the ERG be composed of two parts. The first would be composed of a stable core of experts: clinical experts (genetics, pediatrics, and others), as well as experts in epidemiology, public health, consumers, methodology, and economic assessment. The other would be composed of individuals with ad hoc expertise thought to be necessary—for example, expertise related to the specific disorder or group of disorders (e.g., lysosomal storage disorders, immune deficiency) being considered.

The ERG's recommendations to the full Advisory Committee might take the form of a range such as the following:

1. Acceptable for universal newborn screening
2. Unacceptable for newborn screening
3. Reservations:
    1. Need to improve screening or diagnostic test
    2. Need more data on natural history
    3. Need more data on the impact of treatment
    4. Need more pilot data, especially trials of population-based screening (e.g., at State or local level)

Participants at the meeting said that when disorders are being considered for inclusion in the uniform newborn screening panel, an iterative process between the Advisory Committee and the ERG will probably be required.

As shown in the figure below, the first steps would be the submission of the nomination form and administrative review. Next would be the receipt of the nomination by the Advisory Committee, passing the nomination to the ERG for its recommendations to the Committee, then some potential further studies and additional recommendations to the Committee. Finally, the Advisory Committee would make recommendations to the HHS Secretary.



Dr. Green concluded her presentation by outlining next steps for the Advisory Committee in developing a process for making evidence-based decisions related to the inclusion of new conditions in the uniform newborn screening panel:

4. Review and ratify the evidence-based review concept and proposed framework.
5. Establish the responsibilities, composition, operating principles, and format of the external ERG.
6. Establish priorities for disorders to enter the nomination process.

Questions & Comments

Expertise Needed on the Evidence Review Group. In response to a request for additional comments related to the composition of ERG, several Committee members made suggestions. Dr. Boyle recommended including an "evidence-based methodologist" as a core person on the ERG. Dr. Brower recommended including a person with broad technical knowledge of tandem mass spectrometry, genetic testing, chips, the things that would be in review as part of the evidence-based review of whether there is a test available. Dr. Telfair recommended including as a core member of the ERG a person with experience related to the actual treatment process (e.g., a parent/scientist).

Dr. Perrin said that he thought the core group of the ERG should include a methodological expert who could handle the decision analysis and a content expert, noting that the presentation on Pompe disease by Dr. Kemper and Dr. Downs would be illuminating in this regard. Dr. Perrin also stated that he thought that consumers should play a very active role in really examining how questions are being asked and answered.

Dr. Rinaldo raised the question of whether people in the group nominating a condition for inclusion in the uniform newborn screening panel might be involved in the evidence review. Dr. Dougherty said there is precedent for involving nominators at the Agency for Healthcare Research and Quality's (AHRQ) Evidence-Based Practice Centers; groups such as the American Academy of Pediatrics (AAP) that recommend a topic to the centers often have representatives on

the telephone when the questions are being developed, as well as consider the evidence as it gets developed. Dr. Perrin agreed that nominators should participate in some way in the evidence discussions, but he underscored the need for the full Advisory Committee to think through and address the problem of conflicts of interest if nominators were allowed to participate.

Process for the ERG. Dr. Dougherty said she was concerned that Dr. Green had indicated that the external ERG would both review the evidence and make recommendations. Noting that AHRQ has found is better to have two separate groups, one to perform the evidence review and the other to make recommendations, Dr. Dougherty recommended that the Committee modify the process along the following lines:

1. Issue a contract with an objective independent group to do the evidence review and then make a report on the evidence *without* recommendations.
2. Have a subcommittee of the full Advisory Committee examine the evidence review and make a recommendation to the full Committee. (This is how the USPSTF works.)
3. Have the full Advisory Committee consider the evidence review and make its own recommendations to the HHS Secretary.

Dr. Perrin said he agreed with Dr. Dougherty that the ERG should simply pull the evidence together, and then let the full Advisory Committee weigh the evidence and make the recommendations. He explained that many steps in the evaluation process will require discussion by subcommittees and the full Advisory Committee about what constitutes "adequate evidence." Dr. Green pointed out that the Committee always has the option of recommending something for newborn screening even if more research is needed or pilots are needed.

An audience member, Dr. Alan Hinman from the Public Health Informatics Institute, proposed that the Advisory Committee consider instituting a process similar to what the Center for Disease Control and Prevention's (CDC) Task Force on Community Preventive Services uses.

A working group that includes two members of the Task Force on Community Preventive Services plus evidence review staff from CDC, the National Institutes of Health, and other agencies performs an evidence review, working with rules about what constitutes a good study.

1. The working group proposes a recommendation to the Task Force on Community Preventive Services.
2. The Task Force on Community Preventive Services acts on the working group's recommendation.

Draft Decision Tree. Committee members said they liked the decision tree drafted by Dr. Green (see above) and some offered suggestions to improve it. Dr. Rinaldo suggested changing it as follows:

- Diagnostic test— not so much is the test "reasonable" but is a test "available".
- Treatment—consider adding a step or a box for considering effects for the extended family, carriers (i.e., benefits of early identification rather than early intervention).
- Screening pilot-—should we have discussion of defining minimum targets for the performance of the test?

- “More research needed"—perhaps change to "gaps to be addressed" as a reminder that this is not meant to be a rejection, but rather an indication of what was recognized by the evidence review process as missing links so people can go back and work on those missing links.

Speaking from the audience, Dr. Don Bailey from RTI International said that in the box in the draft decision tree listing ERG recommendations, the Committee might want to think about changing the recommendation for universal screening to a two-tiered recommendation: universal screening or voluntary screening with informed consent. Noting that there are a number of places where the arrows go to a "more research needed" box, Dr. Bailey also said there is no natural infrastructure or mechanism for more research to occur right now. A national newborn screening research network is sorely needed and missing in our infrastructure.

Dr. Anne Comeau from the New England Newborn Screening Program, also speaking from the audience, made several points. First, she said she was confused by the diagonal line after diagnostic test, because it implied that one would go to a “screening pilot” without a treatment. Dr. van Dyck explained that there are benefits to the family from just knowing that a newborn has a condition; if that is added to the treatment box, as suggested by Dr. Rinaldo, the diagonal line might not be needed. Dr. Green said she favored that solution. Dr. Bailey said he liked the idea of changing “Treatment” to “Benefit.”

Second, Dr. Comeau asked what the Committee’s definition of "screening pilot" is—a deidentified research pilot or human subjects research. The question is important because there is a different level of consent required for these two types of research. Dr. Rinaldo agreed, explaining that one type of pilot study could examine the technical feasibility of a test in an anonymized way to determine whether the test is ready for prime time; however, a different kind of pilot would be required when there is a good screening test and a good diagnostic test, but no treatment.

Finally, Dr. Comeau suggested that the Committee needed a human subjects review panel with expertise in dealing with population-based human subjects studies. Dr. Perrin asked Dr. Comeau to clarify this comment, noting that the ERG would be reviewing available data, not doing primary data collection. Dr. Comeau said some States that have attempted to do population-based screening or population-based research have run into problems of having to gather very conventional informed consent, which basically prohibits that kind of research from going forward. She noted that the ongoing Massachusetts informed consent based studies provide one route for gathering evidence in an informed population-based trial, adding that guidance from the Federal agency regulating institutional review boards for such kinds of population-based research would be very helpful.

Nature of Reports from the ERG. Dr. Perrin noted that one of the advantages of AHRQ’s Evidence-Based Practice Centers is that when they say there is insufficient evidence, they lay out a research agenda for the next 5 years. Committee members agreed with Dr. Brower that giving feedback and concrete steps back to nominators when nominations were not accepted so they would know what additional information was essential.

Other Comments. Speaking from the audience, Dr. Bailey said the Committee should think futuristically about what might happen in 5 years if someone develops a platform that allows 100 conditions to be tested for immediately for the same price as one. The Committee might want to change the question of why screen for something to why *not* screen. Also speaking from the

audience, Dr. Ellen Clayton, agreed, saying she believes the Committee must address the question of whether the results should be reported just because a condition can be tested for. Dr. Clayton subsequently elaborated on her views during her formal presentation to the Committee.

Next Steps for the Committee. Dr. Howell instructed the Criteria Workgroup to meet at lunch to make changes to the draft decision tree and present additional recommendations to the full Committee after lunch, so that with HRSA's approval of the financial aspects of any plan, the Advisory Committee could vote on a plan to move forward with the process for adding conditions in the uniform newborn screening panel.

B. Criteria Workgroup's Additional Recommendations to the Advisory Committee About Nominating/Evaluating Conditions for Inclusion in the Uniform Screening Panel

Nancy S. Green, M.D.
Medical Director
March of Dimes Birth Defects Foundation

Following the lunch break, Dr. Green reported that the Criteria Workgroup's additional recommendations to the Advisory Committee were as follows:

1. Establish a core Evidence Review Group (ERG) via contract.
2. Considerations for the ERG are the following:

    —*Composition of the ERG*

    1. Core experts on genetics and on evidence-based review, including expertise on methodology, public health, consumer
    2. Two Advisory Committee members (rotating)

    —*Three immediate tasks for the ERG*

    3. Determine definitions of terms used in the form used to nominate conditions for possible inclusion in the uniform newborn screening panel
    4. Delineate the processes for gathering and weighing evidence
    5. Work through the two aforementioned items while piloting the considerations of two to three additional disorders for newborn screening

3. Determine what to assess in a different context (i.e., *NOT the ERG*):

    —*Cost analysis*

    —*Certain ethical, legal, and social implications issues, such as defining nonmedical benefits*

4. Relationship between the Advisory Committee and the ERG:

    —*Iterative and dynamic. Two overlapping members of the Advisory Committee to sit on the ERG. Rotate Advisory Committee membership on the ERG.*

    —*ERG reports to a subgroup of the Advisory Committee*

Dr. Green said the Criteria Workgroup believes that the next steps for the Advisory Committee with respect to process for nominating and evaluating conditions for inclusion in the uniform

newborn screening panel are (1) to advise HRSA on terms of a contract for an ERG, probable framework and leadership; and (2) to solicit nominations for the two to three disorders to be considered for evaluation as possible additions to the uniform newborn screening panel.

Questions & Comments

Following Dr. Green's presentation, several Committee members made important points and corrections about the Criteria Workgroup's plan:

- Dr. Lloyd-Puryear stated that the ERG's consideration of two to three additional disorders for newborn screening would be real, not a pilot.
- Dr. Dougherty said that because Advisory Committee members could not serve on the ERG if the group was established via contract, the two rotating members of the Advisory Group should be considered liaisons to the ERG rather than members. Dr. Green agreed.
- Dr. van Dyck noted that in Dr. Green's slides, the abbreviation EWG and ERG were both used. Dr. Green clarified that they all referred to the same body. (They are corrected in the outline above.)
- Finally, Dr. Dougherty said that she was not quite sure what was meant by following certain ethical, legal, and social implications issues, but she believed that where there is evidence in any evidence reviews about the impacts of treatment or diagnoses that actually address things like quality of life for families or children; that that kind of evidence should be gathered as well. The Committee would have to work with whoever the ERG is to define the outcomes that we mean by treatment, risks, benefits, etc. Dr. Green agreed.

Dr. Howell asked the Committee to vote formally on the plan, so that HRSA could move ahead with implementation. The Committee unanimously approved the following motion:

- ***MOTION #2: The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children accepts the recommendations of the Criteria Workgroup with respect to the process of establishing an evidence review group (ERG) presented by Dr. Green, as amended, and requests that HRSA move ahead with implementation of the recommendations.***

Dr. van Dyck indicated that HRSA would report to the full Advisory Committee at its next meeting on what HRSA had done to implement the Criteria Workgroup's recommendations.

Dr. Dougherty asked when the Committee would make a recommendation about how to deal with the cost analysis and the ethical, legal, and social implications issues. Dr. Howell replied that the Committee could consider those issues in a global way after a formal recommendation had been brought back to the Committee.

C. Lessons Learned from "Newborn Screening for Pompe Disease: A Synthesis of the Evidence"

Alex Kemper, M.D., M.P.H., M.S.
Associate Professor
Department of Pediatrics
Duke University

Dr. Kemper discussed lessons about conducting systematic reviews of the evidence for conditions being considered for newborn screening learned in developing the report "Newborn Screening for Pompe Disease: A Synthesis of the Evidence" for the October 23, 2006, meeting, "Process for Evaluation and Gathering Evidence." (The Pompe disease evidence report prepared by Dr. Kemper and Dr. Priya Kishnani was included under TAB #6 of the binder prepared for Committee members for the December 18-19, 2006, Advisory Committee meeting.)

As background, Dr. Kemper noted that 2006 had been a very exciting year for Pompe disease. In April 2006, the U.S. Food and Drug Administration approved licensure for Myozyme, the first effective treatment for Pompe disease. Screening for Pompe disease is possible with dried blood spots; however, such screening will identify individuals with late-onset Pompe disease, as well as infantile Pompe disease. Pilot screening has begun in Taiwan, and as of a few weeks ago, they had identified three children with Pompe disease.

Reviews of the evidence, Dr. Kemper explained, fall into two broad categories.

- *Traditional reviews* are narrative reviews, often written by an expert in the condition, that appear in textbooks, and there is much concern that such reviews could be biased.
- *Systematic reviews*, in contrast, have explicit inclusion and exclusion criteria and explicit methods for synthesizing those data qualitatively or quantitatively (a meta-analysis).

The report "Newborn Screening for Pompe Disease: A Synthesis of the Evidence" was a systematic review. Dr. Kemper noted that conducting a systematic review of the evidence poses several challenges. One is synthesizing studies of different designs, study populations interventions, measures, and quality. Another is dealing with publication bias—that is, likelihood that published results are biased in favor or results that are positive (they found something) and underrepresent results that are negative (found that something did *not* happen) or inconclusive. Yet another challenge for systematic reviews, in the case of conditions affecting children and rare conditions such as those for which newborns might be screened, is a lack of studies.

In their evidence review for Pompe disease, Dr. Kemper and Dr. Kishnani decided to focus on infantile Pompe's disease and not late-onset Pompe's disease. The evidence review team used separate methodological and content experts: Dr. Kemper was the methodological expert, and Dr. Kishnani was the content expert. The team cast a broad net for available data and included both published and unpublished data (e.g., from the Taiwan pilot screening project) but excluded animal data. Methodological issues arose in the synthesis of the evidence for Pompe disease that are common to all the rare conditions. First, many important data about the disease are not published in the peer-reviewed literature. One of the chief challenges in using unpublished data is evaluating quality. Second, randomized trials in human subjects (children) are unlikely to be done. Third, quality scores do not easily apply to small studies of rare conditions. Fourth, long-term outcomes are often not available. And fifth, meta-analysis is not possible if studies are heterogeneous. Most of the instruments that have been developed to evaluate study quality are not

designed for the very small studies such as one would expect to find for treatment of Pompe disease. For that reason, Dr. Kemper and Dr. Kishnani qualitatively evaluated the quality of various studies of Pompe disease rather than using standard study quality assessment instruments.

Dr. Kemper stressed that any recommendations or evaluation processes for newborn screening should be linked to a decision analytic model such as the one Dr. Downs would present at this Committee meeting (see next session). Recommendations that come from syntheses of the evidence do not have to be simple "thumbs up" or "thumbs down" recommendations, but Dr. Kemper believes they should be both explicit and actionable. One challenge for the Advisory Committee will be to decide what approach should be use to classify recommendations

The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

- A—USPSTF strongly recommends (good evidence—e.g., colorectal cancer screening for those over age 50)
- B—USPSTF recommends (fair evidence—e.g., amblyopia, strabismus, and visual acuity in children less than 5, and adult depression)
- C—USPSTF makes no recommendation for or against (fair evidence out there, but the balance of benefits and harms is to close to justify a general recommendation—e.g., screening for lipid disorders in younger adults in the absence of risk factors for heart disease)
- D—USPSTF recommends against (fair evidence against—e.g., screening for testicular cancer)
- I—USPSTF concludes the evidence is insufficient to make a decision for or against routinely providing the service (evidence of effectiveness is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined—e.g., developmental dysplasia of the hip)

For newborn screening, where the evidence base is likely to be much scantier than it is in the case of interventions considered by the USPSTF, Dr. Kemper suggested a set of recommendations to State newborn screening programs such as the following:

- Universal screening recommended (all programs should screen once the followup infrastructure is in place)
- Targeted screening recommended (all programs with a high prevalence should screen once the infrastructure is in place)
- Pilot study recommended
- Pivotal studies required (e.g., where screening would be likely to be recommended if we knew this one particular thing)
- No general recommendation (it is up to individual newborn screening programs to decide whether to screen)
- Recommended against (it is recommended that programs not screen, because screening might produce more harm than benefit)

Dr. Kemper and Dr. Kishnani's report "Newborn Screening for Pompe Disease: A Synthesis of the Evidence" includes further elaboration of each of these recommendations and the recommendation of a pilot study of screening in the case of Pompe disease.

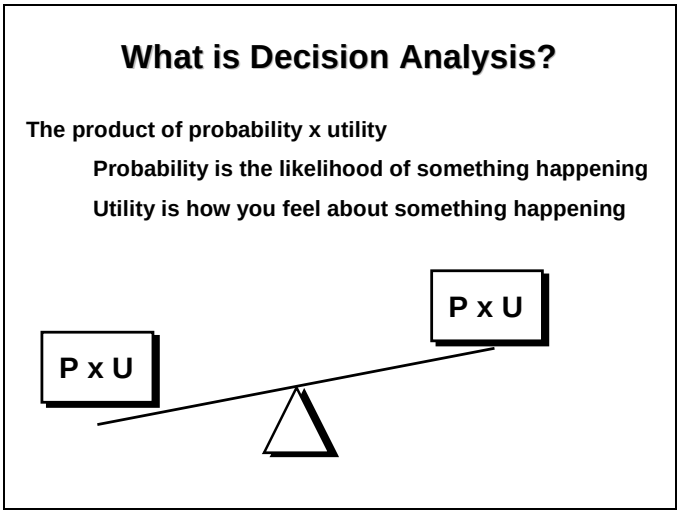
D. Decision Analytic Evaluation of Newborn Screening Tests

Stephen M. Downs, M.D., M.S.
Associate Professor and Director
Children's Health Services Research
Indiana University School of Medicine

Dr. Downs gave a tutorial on using decision analytic approaches to newborn screening, noting that a decision analytic framework comparing benefits and harms that makes tradeoffs explicit is a mechanism for exploring potential value in a situation, such as there is in the case of newborn screening, where there is scant evidence.

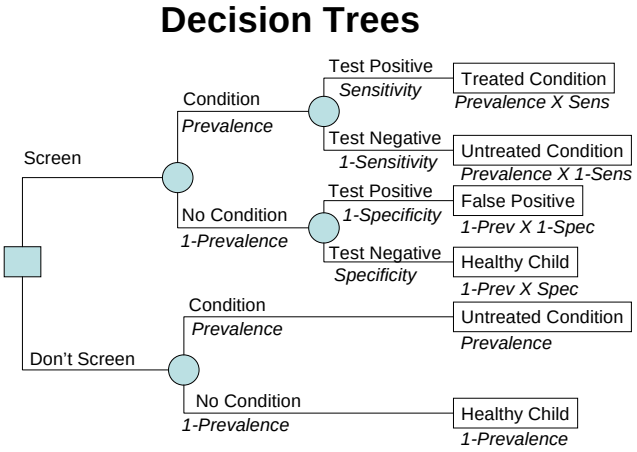
In order to make a decision about including a condition in a newborn screening panel, Dr. Downs said, one needs to consider a number of different variables besides the quality of the evidence, for example: (a) the prevalence of the condition under consideration; (b) the severity of the condition; (c) the quality of the test (sensitivity and specificity); (d) the benefits of treatment (e.g., decreased mortality and morbidity); and (e) the harms of treatment (e.g., false positives). The question is: How does one combine all these variables?

One approach, Dr. Downs explained, is decision analysis. Basically, decision analysis can be thought of as a way of weighing alternatives based on the product of the probability (P) times the utility (U). The probability is a measure of the likelihood that something is going to happen if you follow one course of action. If one sums up the products of the probabilities times the utilities for two different courses of action and then weighs the two results, one is using a decision analytic approach to weighing alternative courses of action (see below).



Decision analysis is generally done with decision trees. A decision tree describes the decision problem being faced (see below). It generally starts with a square decision node. The branches coming off of a square decision node are under the decisionmaker's control (e.g., one is either

going to screen for a particular condition or not going to screen for that condition). The circular nodes in the decision tree are chance nodes. The branches coming off of chance nodes are associated with probabilities. The structure of this tree—that is, the events that can happen and the probabilities that are associated with each of those branches—is informed by the kinds of information that can come from an evidence review such as Dr. Kemper and Dr. Kishnani's report "Newborn Screening for Pompe Disease: A Synthesis of the Evidence" discussed previously.



The probability that one is going to see a particular condition, for example, is simply the prevalence of that condition in the population to be screened. And the probability of not having the condition—assuming that one either has the condition or does not have it—is 1 minus the prevalence. The probability that one is going to see a positive test, given that the condition is present, is by definition the sensitivity of the test. So the probability of getting a negative test is 1 minus the sensitivity or the probability of a false negative. If an infant does not have the condition, the probability of having a negative test is simply the specificity by definition again. And likewise, the probability of having a false positive is 1 minus the specificity. One can do more detailed outcomes than illustrated in the tree above and have each path come to an endpoint by applying a similar mathematical formula.

Each of the paths in the decision tree comes to an endpoint. The endpoint, should a decision be made to screen and should a given child have the condition, Dr. Down said, is that the child's condition will be detected and treated early. If the child's condition is not detected because of inadequate sensitivity of the test, then there will be an untreated condition. If the condition is not present in the child but there is a false positive test, the result will be the need for further evaluation and the attendant stresses attached to that. And if the condition is absent and the test is negative, the result is a healthy child who had a reassuring newborn screening test. On the other hand, should a decision be made not to screen for the condition and should the child have the condition, the result will be untreated or late-treated condition. If there is a decision not to screen and the condition is not present in a child, no harm will result.

Once the results for any given child is determined, one can multiply the figures by 100,000 to compare the estimated number of treated and untreated cases, false positives, healthy children, etc., for 100,000 babies and compare the results with screening vs. no screening. Decision

analysis can also be used to perform sensitivity analysis (i.e., varying the values of particular variables one at time to see what the result on the final results would be if all other variables remained constant). What this does is make tradeoffs between benefits and harms associated with different courses of action explicit.

Dr. Downs showed an example in which he used a decision analytic approach, and built in costs as well as utility outcomes for homocystinuria. The decision tree had basically the same structure as that shown above but was much more complicated.

Questions & Comments

Dr. Gregg asked Dr. Downs how positive predictive value (PPV) fits into the model that Dr. Downs presented. He noted patients are more concerned about knowing if they get a positive test, what the likelihood they actually have the condition is, than about knowing the sensitivity or specificity of a test. Dr. Downs replied that the PPV is determined by the combination of the prevalence, the sensitivity, and the specificity. Knowing the PPV is important when dealing with an individual patient who has a particular test result, but it is not as important in making the a priori public policy decision to screen or not to screen. Speaking from the audience, Dr. Alan Hinman, noted that one way PPV has relevance in public policy is in deciding whether to retest or not. Dr. Rinaldo added that accepting a test with a very low PPV has the potential of creating a very negative attitude toward screening. He would like to see models that are fine-tuned to be in the 20 to 30 percent range of PPV.

Dr. Rinaldo asked how, in the node about whether a test is "positive" or "negative," one would factor in the same numeric result when some programs call it normal and others call it abnormal. Dr. Downs said there is a way to incorporate that in decision analysis, but the better approach would be to fix this problem. A decision analytic approach could be used to identify what the optimal cutoff point of sensitivity and specificity for a test should be, given the available ROC characteristics of the test being considered. The Advisory Committee might then consider recommending that this cutoff point be used.

Dr. Dougherty asked how one might incorporate the quality of the evidence in a sensitivity analysis. Dr. Downs said there are two ways to do it. First, one could build in an additional node around, for example, the prevalence of the condition—create a "chance node" around the uncertainty. Alternatively, one could consider the level of the evidence in a sensitivity analysis.

Dr. Rinaldo asked for a copy of Dr. Downs' slides. There were some small arithmetic errors in the original slides, and Dr. Downs agreed to make revised copies of his slides available to Committee members.

III. REGIONAL GENETICS AND NEWBORN SCREENING COLLABORATIVES: AN UPDATE

Michael S. Watson, Ph.D., FACMG
Executive Director
American College of Medical Genetics (ACMG)

Dr. Watson gave an update on the seven Regional Genetics and Newborn Screening Collaboratives and the National Coordinating Center (NCC) established with support from HRSA's Maternal and Child Health Bureau, Genetic Services Branch to strengthen and support the genetics and newborn screening capacity of the States and the Nation.

Dr. Watson, who is the project director for the NCC, explained that the NCC was established as a partnership with HRSA and the American College of Medical Genetics (ACMG) in Bethesda, Maryland. The NCC differs from another HRSA-funded resource center, the National Newborn Screening and Genetics Resource Center, which deals primarily with the newborn screening programs themselves. The NCC deals primarily with things after newborns are screened and begin to flow out into the system. The NCC's advisory committee is headed by Dr. Jon Zonana.

The NCC hopes to accomplish its mission by doing the following: (a) addressing the maldistribution of genetics service providers, mostly found in academic medical centers in urban centers, in the country to improve access; and (b) bridging the gaps between primary care, public health, and medical specialties and using new technologies (e.g., telehealth) to extend the capacity to deliver genetics services to local communities.

To improve internal communications between the NCC and regional collaboratives, the NCC has developed a Website embedded within the ACMG Website (www.nccrcg.org). It also has a quarterly e-newsletter featuring activities of the NCC, regional collaboratives, and partner organizations. The NCC holds regular conference calls and meetings with the principal investigators in the seven regions and also offers technical assistance to the regions. In addition, the NCC has been working with the National Conference of State Legislatures, which has funding through the NCC grant. Currently, the NCC is in the process of developing tools to evaluate whether access to genetic services improves.

Dr. Watson said he had made a presentation on the regional collaboratives to the Advisory Committee at a previous meeting (January 2005), so his focus in this presentation would be on some of the projects that are spinning out now that the regional collaboratives are in their second and third year of development and work. Current project activities include the following:

- **Telegenetics capacity development**. The NCC and several regional collaboratives are working on telehealth and are about to conduct a survey in the regions to get a sense of what kinds of tools are available to them through their States or within their own institutions. The NCC is going to think about telehealth reimbursement and various legal issues that may affect the ability to fit telehealth rules to genetics.
- **Emergency preparedness.** The NCC and regional collaboratives are undertaking a few newborn screening projects related to emergency preparedness. The Region 2: New York-Mid-Atlantic Consortium (NYMAC) for Genetics and Newborn Screening is focusing on getting backup and protection of newborn screening dried blood spots and the ability to test those spots during a disaster such as the events of 9/11 in New York City. The Region 3: Southeastern Regional Genetics Group, spurred by Hurricanes Katrina and Rita in the Gulf States, is focusing on how to reconnect different providers and how to reconnect providers and patients.
- **Management guidelines.** The ACMG has begun developing intermediate management guidelines that are directed at groups of providers who may not have a strong background in genetics. A HRSA-funded ACMG workgroup has developed (a) an ACTion (ACT) sheet for each condition in the ACMG uniform newborn screening panel, which describes the short-term actions a health professional should follow in communicating with the family and determining the appropriate steps in the followup of a newborn who has screened positive for a specified condition; and (b) an algorithm that presents an overview of the basic steps involved in determining the final diagnosis in the infant for each condition. These materials are posted on the ACMG Website (http://www.acmg.net/resources/policies/ACT/condition-analyte-links.htm), and many

other Websites (e.g., Genetics Home Reference, National Newborn Screening and Genetics Resource Center) link to them. The ACT sheets and algorithms are being distributed to newborn screening labs and programs and to the Regional Genetics and Newborn Screening Collaboratives, and a survey of the utility of these materials is being planned. All of the materials are being developed for manual use, but also to be compatible with use in electronic health records and health information systems, which will enable health care providers to cope with the massive amount of genetics information. The ACMG will maintain the ACT sheets and algorithms, revising them as necessary every 3 years, and developing adding guidelines over time.

- **Educational program development.** The NCC received a supplement to begin looking at the core educational programs in newborn screening and genetics. It has performed a couple of reviews at the National Board of Medical Examiners and has been reasonably successful at improving the genetics content in the U.S. medical licensing examination process.

- **Genetic services delivery infrastructure development.** The NCC is considering means for developing a system whereby it can map all of the genetics service providers in the country and kinds of services they provide (laboratory services, clinical services, services for special populations, etc.) and then overlay this information with patient populations. A number of the regional collaboratives, including the Region 1: New England Regional Genetics Group, have already begun to map the distances between provider and patient groups so that they can work to improve access.

- **Data collection and long-term followup projects**. There are huge gaps in the evidence for conditions that are, or might be included in the ACMG uniform newborn screening panel. To address this problem, the NCC and regional collaboratives are trying to develop a system whereby all patients identified in newborn screening are set up in a patient registry. That way, it will be possible to establish prospective cohorts with a minimal data set for research and clinical trials. Three of the regional collaboratives, including the Region 6: Mountain States Genetic Network, have made their first ventures into this area of investigation. Oregon has a project related to tandem mass spectrometry. In the central part of the country, the Region 4: Great Lakes Genetics Collaborative has a data collection project on MCAD (Medium-chain Acyl-CoA Dehydrogenase) deficiency. The NCC plans to move to the development of national databases as soon as possible.

- **Quality assurance and improvement activities.** The Region 4: Great Lakes Genetics Collaborative, as reported by Dr. Rinaldo at the February 2006 Advisory Committee meeting, has undertaken a laboratory improvement project. In conjunction with that, Dr. Rinaldo is studying State practices and cutoff ranges in tandem mass spectrometry (MS/MS) testing for specific conditions in the uniform newborn screening panel. In addition, there are efforts to develop performance indicators for use in evaluating genetic services and data collection activities.

- **Additional activities. A**dditional activities include (a) a grant to examine national collaborative research projects, which are a mechanism to bring various agencies and experts together to talk about how to develop and organize national data collection activities; (b) a November 2006 conference in Morocco to be discussed by Dr. Howell; (c) a review of genetic carrier screening in certain subpopulations (e.g., Ashkenazi Jews, hemoglobinopathy); (d) the transition from pediatric to adult medicine; (e) metabolic disease nutrition (some States provide fee; others more difficult); (f) telecommunications capacities between regions and within and with the NCC; and (g) how to address reimbursement issues related to family health history, etc.

Questions & Comments

Dr. Gregg asked whether any efforts were being made to draw genetics counselors more aggressively into newborn screening. Dr. Watson said historically genetics counselors have not had a large role in newborn screening, but he expects their role will increase as newborn screening expands.

Dr. Boyle asked if any evaluations of the ACT sheets were being planned. Dr. Watson replied that surveys had been sent out. In the first 6 months, they have asked the States utilizing the sheets to attach a survey of their utility and some very specific questions of the people who received them. He noted that Ms. Anne Gramiak from the American Academy of Pediatrics would be talking about that in her presentation to the Advisory Committee

IV. FEDERAL LEGISLATION: AN UPDATE

Cindy Pellegrini
Assistant Director
Department of Federal Affairs
American Academy of Pediatrics (AAP)

Ms. Pellegrini gave an overview of the current political landscape and legislation in the U.S. Congress, in the wake of the November 2006 elections.

Major changes have occurred in the congressional committees that might interest the Advisory Committee.

- *Senate Health Committee.* This committee is undergoing a significant philosophical shift. The new chair is Sen. Edward Kennedy of Massachusetts. The committee has two new Democrats (Sen. Barack Obama of Illinois and Sen. Sherrod Brown of Ohio), one new independent who caucuses with the Democrats (Sen. Bernie Sanders of Vermont); and two new Republicans, Sen. Tom Coburn of Oklahoma and Sen. Bob Allard of Colorado.
- *House Energy and Commerce Committee.* This committee also has undergone a significant philosophical shift. The new chair is Rep. John Dingell of Michigan. The ranking member from the minority party is Rep. Joe Barton of Texas. The chairmanship of the subcommittees remains to be determined, but it is expected that Sen. Frank Pallone from New Jersey will chair House Energy and Commerce Committee's Subcommittee on Health.
- *Appropriations Committees*. In the Senate Appropriations Committee, the new chair is Sen. Bob Byrd of West Virginia. Sen. Thad Cochrane from Mississippi is the ranking member. Sen. Tom Harkin may chair the Health Subcommittee of the Senate Appropriations Committee. In the House Appropriations Committee, the new chair is Rep. David Obey, who is reorganizing the committee. The new ranking member is Rep. Jerry Lewis from California.

As a result of these changes, Ms. Pellegrini said, priority issues may change. Bills of particular interest to the Advisory Committee include the following:

- *Newborn Screening Saves Lives Act.* This bill would provide grants for education and training related to newborn screening, help States that want to expand newborn screening

do so, and improve the regulation of labs doing newborn screening. Sen. Christopher Dodd of Connecticut and Sen. Mike DeWine of Ohio had introduced this bill for the past few years. Senator Dodd chairs the subcommittee of the Senate Committee on Health, Education, Labor, and Pensions with jurisdiction over the bill. A corresponding House bill is sponsored by Rep. Lucille Roybal-Allard of California and Rep. Mike Simpson of Idaho.

- *Screening for Health of Infants and Newborns (SHINE) Act*. This bill would establish recommended guidelines for States to use in newborn screening. Sen. Hillary Rodham Clinton of New York will reintroduce this in next Congress. Her cosponsor Sen. George Allen was defeated. This bill will be referred to same subcommittee as Sen. Dodd's bill, the subcommittee that he chairs.
- *Genomics and Personalized Medicine Act.* This bill, introduced by Sen. Barack Obama, would establish an interagency working group to foster research and the translation of that research into personalize medicine. It would authorize $150 million for pharmacogenomics research and translation of results into the clinical setting. It also would provide a 100 percent tax credit for the development of these tests—in effort to drive development quickly. The bill has workforce provisions to train people in genetics and genomics. It also has provisions related to the regulation of genomics and genetic tests.

Ms. Pellegrini concluded by saying that a prevailing theme over the past several weeks, as Democrats have started developing their agenda for the 110th Congress, is that difficult budget choices are going to have to be made. The Democrats are reinstituting "pay-as-you-go" rules, known as PAYGO, which will require Congress to pay for any further tax cuts with offsetting tax increases or spending cuts. Thus, anyone seeking funding is going to have to propose offsetting cuts in other places in the budget.

Questions & Comments

Dr. Louder asked whether any of the bills Ms. Pellegrini discussed would be signed in the next 2 years. Ms. Pellegrini replied that if the model of the mid-1990s is any guide, the potential of a veto threat made the Congress work together more to get signable bills. Dr. Brower asked whether Sen. Kennedy's Laboratory Test Improvement Act would be introduced. Ms. Pellegrini said she thought it would, but said she was not an expert on this.

Dr. Rinaldo asked what was happening with the National Institutes of Health budget. Ms. Pellegrini said the NIH budget would be a tremendous challenge. Many small programs have been flat funded—amounting to a functional decrease—for 4 to 8 years and are significantly below their previous power to do things like fund new grants. The real challenge is that the NIH budget is already so large that to give them a small increase draws all the funding that would be available to give increases to dozens of other programs. Congress is aware of NIH problems, but not sure how to address it. HRSA has had huge cuts in the last several cycles.

Dr. Telfair asked for comments on bills related to funding for hemoglobinopathy. Ms. Pellegrini said there is a lot of energy. Over last few years, few reauthorizations of rare disease have passed, because Rep. Joe Barton refused to act on them until the NIH reauthorization was passed. Now that the NIH reauthorization has passed, the smaller bills may move ahead.

V. INTERNATIONAL NEWBORN SCREENING MEETINGS

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

Dr. Howell reported on two international newborn screening programs that occurred in the fall of 2006:

- 2006 Meeting of the International Society for Neonatal Screening (ISNS), held on Awaji island, Japan, September 16-19, 2006 (which Dr. Howell attended)
- A conference entitled "Strengthening Newborn Screening in the Middle East and North Africa," held in Marrakech, Morocco, November 13-15, 2006 (http://www.newbornscreening-mena.org/) (which Dr. Howell did not attend)

He said both meetings were extremely successful and showed that there is a lot of interest in newborn screening internationally, which provides an opportunity for collaborations. He also noted that some other members of the Advisory Committee were present at these meetings. For example, Dr. Rinaldo was in Japan; Dr. Lloyd-Puryear and Dr. van Dyck were in Morocco.

International Society for Neonatal Screening Meeting in Japan. The 3-day ISNS meeting held in Japan, September 16-19, 2006, was a very large meeting, with several hundred participants from all over the world. There were many specific workshops and papers. They dealt with all aspects of newborn screening issues facing the international community, which are similar to issues in the United States. A major theme at the meeting was new technologies in newborn screening. There were presentations related to multiplex technologies, the value of second-tier testing, screening for lysosomal storage diseases, and tandem mass spectrometry. A plenary lecture by Dr. Ellen Clayton addressed ethical issues related to new technologies. The use and handling of dried blood spots was the basis of a research symposium. There also was a considerable discussion about newborn screening in the developing world. There is increasing interest in newborn screening in the developing world as certain of the infectious diseases improve, and there are certain simple technologies that can make a very big impact even in a country with very few resources.

Conference on Strengthening Newborn Screening in the Middle East and North Africa. North Africa and the Middle East are characterized by a high degree of consanguinity, so the rare conditions such as those in the newborn screening panel can be expected to be vastly higher in this region of the world. Last year National Institutes of Health (NIH) Director Dr. Elias A. Zerhouni (a native of Algeria), Dr. Howell, and some U.S. State Department representatives went to Morocco to discuss strengthening newborn screening in North Africa and the Middle East.

The November 13-15, 2006, conference "Strengthening Newborn Screening in the Middle East and North Africa," in Marrakech, Morocco, was an outgrowth of those discussions. The conference was sponsored by the Kingdom of Morocco's Ministry of Health, the National Institute of Child Health & Human Development (NICHD) within NIH, and a plethora of other organizations, including INSERM, the Centers for Disease Control and Prevention (CDC), HRSA, the March of Dimes, the National Newborn Screening and Genetics Resources Center, UNICEF, etc. Although Dr. Howell was at the last minute unable to attend this conference, Dr.

James Hanson, Ms. Gillian Engelson, and Ms. Danuta Krotoski from NICHD provided him with information.

The focus of the conference in Morocco was on identifying the research and infrastructure needs of newborn screening in the Middle East and North Africa and assisting in the development of newborn screening programs in the region. The goals were to do the following: (1) determine the research and infrastructure needs; (2) identify areas for research collaboration to strengthen regional newborn screening capacity; (3) examine cultural and social issues surrounding newborn screening; (4) provide opportunities to share informational resources; (5) discuss international technical support and collaborative research opportunities; and (6) identify strategies to coordinate an epidemiological assessment of the incidence/prevalence of conditions within the region.

There were 130 participants at the conference, representing 33 countries, including 18 countries from the Middle East and North Africa. Dr. Howell said the people are well trained in the region; but they are lacking facilities and equipment. The group ended up with what has been termed the "Marrakech Declaration."

- Encourage all countries in the Middle East and North Africa to develop policies and necessary support to establish systematic national newborn screening programs that should screen for at least one condition.
- Establish a collaborative network to facilitate an exchange of information.
- Annual regional meetings and smaller, more focused workshops.
- Development of an advisory committee to oversee collaboration.

The Marrakech group also developed a plan of action for the next year, which includes developing a final draft plan for pilot newborn screening for a single disorder— congenital hypothyroidism—by March 2007. Spontaneously France invited them to come spend a week there, the ISNS agreed to fund 304 people from Morocco to go, and PerkinElmer agreed to donate screening equipment.

Questions & Comments

Dr. van Dyck noted that he had been struck by the energy and interchange between and among people from the different countries at the conference in Morocco, and several people have suggested that there is considerable potential for followup.

Dr. Green, noting that NIH has traditionally been a relatively small funding source for newborn screening, asked whether Dr. Zerhouni's interest in newborn screening forecast some broader interest in newborn screening at NIH. Dr. Howell said he was not sure there would be additional money, although Dr. Zerhouni is clearly aware of the importance of newborn screening. Dr. Alexander said NICHD had primed Dr. Zerhouni for the trip by making newborn screening one of NICHD's primary initiatives for new activities for the fiscal year 2006.

Dr. Telfair asked whether the meeting in Morocco addressed political issues, noting that the whole of Africa does not have a newborn screening system and said that the political realities of making this happen in Africa are difficult. Dr. Howell said the political leadership of Morocco was supportive of this, and the King appoints the prime minister there.

VI. THE AAP'S PROMOTION AND EVALUATION OF NEWBORN SCREENING EDUCATIONAL MATERIALS

Anne Gramiak, M.P.H.
Manager, Screening Programs
American Academy of Pediatrics (AAP)

Ms. Gramiak gave an overview of the AAP's current activities related to newborn screening and genetics:

- The AAP has been promoting the newborn screening parent and provider materials developed by Dr. Terry Davis with funding from HRSA's Maternal and Child Health Bureau.. When these materials became available last year, the AAP did a direct mailing of the materials to all if its members and made additional copies available by request. To date, the AAP has had 185 requests for almost 30,000 copies. The AAP has links to the PDF files on the Medical Home Website (wwwmedicalhomeinfor.org), so people can print the materials at will.
- In May 2006, the AAP published an e-supplement to *Pediatrics* entitled "A Look at Newborn Screening: Today and Tomorrow," (Vol. 117 No. 5 May 2006, pp. S193). This supplement is available to the public free of charge on the *Pediatrics* Website (http://pediatrics.aappublications.org/cgi/content/full/117/5/S1/S193).
- The AAP has been promoting the ACT(ion) sheets for conditions in the uniform newborn screening panel developed by the American College of Medical Genetics (ACMG) for health professionals. The ACT sheets describe the short-term actions a health professional should follow in communicating with the family of a newborn who has screened positive for a specified condition and in determining the appropriate steps in the followup of the newborn. The AAP included a flyer in the August 2006 issue of *AAP News* and also included an article in the "For Your Information" section. There is a link to the ACT sheets on the AAP Website.
- The AAP Committee on Genetics published its own fact sheets on specific conditions detectable via newborn screening in the September 2006 issue of *Pediatrics.* The "Introduction to the Newborn Screening Fact Sheets" and fact sheets consist of five parts: newborn testing, followup of abnormal screening results; diagnostic testing, disease management, and continuous evaluation and improvement of the newborn screening system. They were included in the materials in the briefing books distributed to Advisory Committee members (TAB #9) and are also available online (http://aappolicy.aappublications.or/cgi/content/full/pediatrics118/3e934).
- Ms. Gramiak has been doing some technical assistance with the Regional Genetics and Newborn Screening Collaboratives and National Coordinating Center (NCC). It is hoped that over time, the AAP's participation will increase and help to better link medical homes and AAP chapters with the resources of the regions and vice versa.
- Since January 2007, the AAP has been making plans for the development of a clinical report to give the general pediatricians guidance on what to do in the newborn screening system if a child has a positive result, and then also to discuss the resources available as they would interact with that system. Dr. Edwards is the chair of this committee. The report will probably be published this year, following internal and external review. The project is somewhat unique because it is part of the AAP's Partnership for Policy

Implementation Project, which is intended to make policy statements more granular with decision algorithms.

Ms. Gramiak reported on the results of an AAP survey of users of the ACT sheets for health professionals related to conditions in the uniform newborn screening panel. The AAP survey was conducted in the summer of 2006 using Survey Monkey and a sample of people 60 participants (36 pediatricians, 24 family physicians) who self-selected to participate. The results from the survey were quite positive. Physicians said that they found the ACT sheets to be germane and would use them if they had a patient with a screen-positive result; would recommend that their colleagues would use them, etc. Having a local resource section of the ACT sheets was useful to a majority of respondents. When asked in the survey what format changes should be made to the ACT sheets and what additional information should be added, respondents most commonly said none, although a few people did suggest changes. When asked where to market the ACT sheets, the respondents gave the following answers: professional bulletins; AAP and American Academy of Family Practice Websites and mailings; Listserv announcements; specialty Websites; send directly to primary care physicians; State newborn screening programs; and review articles in key publications.

Questions & Comments

Dr. Lloyd-Puryear reported that AAP was going to do a more formal survey of its members but wanted to coordinate with the Education & Training Subcommittee of the Advisory Committee.

Dr. Boyle asked whether any thought had been given to evaluating the ACT sheets in practice among clinicians, physicians in primary care who are actually managing children, to see whether or not they are helpful and how they could be used. Ms. Gramiak said that the AAP was developing plans for next year and writing a proposal to do an implementation project of the clinical report. The clinical report highly recommends using the ACT sheets. So if the AAP is funded to do the implementation project, it would be looking at the ACT sheets and their use.

VII. HHS SECRETARY'S PRIORITY INITIATIVE ON PERSONALIZED HEALTH CARE

Gregory J. Downing, D.O., Ph.D.
Program Director, Personalized Health Care
Immediate Office of the Secretary
U.S. Department of Health and Human Services (HHS)

Dr. Downing reported on HHS Secretary Michael Leavitt's priority initiative related to personalized health care—one of the Secretary's 10 priority initiatives. Dr. Downing is the program director for this initiative. In that capacity, he coordinates transagency programs for the analysis, planning, and implementation of policies and systems to facilitate the adoption of personalized medicine through the integration of health information technology (HIT) and genomic technologies.

The HHS Secretary's vision for personalized health care is as follows:

> "Health care is tailored to the individual. Prevention is emphasized. Propensities for disease are identified and addressed through preemptive intervention. Discovery and innovation move higher quality and safer medical products to the market faster and more cost effectively."

The key enablers of personalized health care are the following:

- *Advances in genomics*. Rapid advances in the science base—e.g., the Human Genome Project—in disease processes have set the stage to explain and address individual differences in health states.
- *Health information technology*. HIT is transforming the U.S. health care system by establishing the means for patient-centric care. In 2005, the American Health Information Community (AHIC) was chartered as a Federal advisory body chaired by the HHS Secretary to make recommendations to the HHS Secretary on how to accelerate the development and adoption of HIT. There is representation on AHIC from all of the Federal agencies, industry, health plans, and consumer groups. AHIC has several workgroups, including biosurveillance; consumer empowerment; chronic care; electronic health records; confidentiality, privacy, and security; and personalized health care.
- *Belief in the transformative potential of integrating HIT and genetic information.* The integration of HIT and the genetic information is believed by many to be transformative in our health care practices. The goal is to seize the opportunity to anticipate and plan for the future to achieve maximum beneficial impact.

The longer term objective for the HHS Secretary's personalized health care initiative is to take advantage of advances in research that have positioned us to harness new and increasingly affordable medical and scientific technology and to develop clinical tools that are increasingly targeted to the individual, allowing the health care system to give consumers and providers the means to make more informed, individualized, and effective choices. The 2-year objective is focusing on some concepts and priorities that will support health care systems transformation to achieve the longer term objectives.

Planning for the personalized health care initiative began in March/April 2006, with all of the HHS agency heads meeting with the Secretary and discussing their plans with him. One focus has been just gathering information about what is going on across the country in terms of health care delivery systems and their development of biobanks, information systems, and electronic health records. Several emerging opportunities have been identified. Some people say it is too early to consider using genetically based tests in medical management, but practical applications of medical genetic tests exist or are emerging—for example, identifying risk for disease, confirmatory diagnostic tests, and selection of appropriate therapies (pharmacogenomics). Newborn screening tests and tests that determine risk factors (e.g., BRCA 1 in breast and ovarian cancer), risks particularly for familial diseases are examples. A number of the genomic platforms have been utilized and are now commercially available and utilized in making treatment decisions for a variety of diseases.

The goal is to build an interface of HIT, genomics, and the health care delivery system. Bringing these together in some sort of a framework and harmonizing the nomenclature across all of these systems has been challenging, and it has been suggested that one of the key roles for government is to convene organizations to agree on an approach to accomplish this objective.

The personalized health care initiative has the following goals:

- ***Goal #1: Link clinical and genomic information to support personalized health care.*** This is really about establishing an interoperable public/private data network of networks to deliver information on individual medical outcomes and linking findings to genetic laboratory tests. The second aspect of this is really beginning to take shape in the context of establishing a pathway for the data integration from genetic tests into personal e-health

records. AHIC's Personalized Healthcare Workgroup is working to develop recommendations to AHIC on policies for access to publicly funded genomic databases, as well as standards for inclusion of genetic test results into personal e-health records. The Personalized Healthcare Workgroup is chaired by Dr. Doug Henley from the American Association of Family Physicians and Dr. John Glaser from Harvard Partners.

- ***Goal #2: Support the appropriate use of genetic lab tests in medical practice***. This means encouraging regulatory policies and practices that provide sufficient assurances and protections to consumers that genetic test information is used for their medical benefit. Patient confidence about the use of their genetic information is really paramount. We need to do this in the right way so that trust is established with the public, to advance their long-term quality of health care and not just for information-gathering or for purely business perspectives. In addition, there is a need for regulatory oversight of genetic testing to ensure analytical and clinical validity (e.g., regulation of testing platforms and systems, and regulation of proficiencies for performing genetic tests and interpreting laboratory data).

Dr. Downing concluded by emphasizing that the personalized health care initiative is a long-term effort that will involve working with other groups—such as the Secretary's Advisory Committee on Genetics, Health, and Society, the National Institutes of Health, the Food and Drug Administration, the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children—to establish some pathways in which the policies and infrastructure is developed in a way that maximizes the utility of the genetic and HIT capabilities. It will also involve developing an effective communications strategy for the public about how and why we want to utilize individuals' health and genetic information to improve health care.

VIII. THE CONCEPTS OF BENEFIT AND TREATMENT

A. Universal Screening for Metabolic Disorders Historical Context and Adverse Outcomes

Jeffrey P. Brosco, M.D., Ph.D.
Associate Professor of Clinical Pediatrics
Director, Clinical Services, Mailman Center for Child Development
University of Miami
Miller School of Medicine

Dr. Brosco, a developmental pediatrician with a Ph.D. in history, under a contract from HRSA, was asked to produce an accurate document with respect to harms resulting from newborn screening during the early history of universal newborn screening for metabolic disorders, in particular, phenylketonuria (PKU). In this session, Dr. Brosco reported on his study, noting that the questions faced with respect to the expansion of newborn screening to other conditions in the early 1960s are very similar to the questions faced today.

Background. The Advisory Committee asked Dr. Brosco to look at the early history of newborn screening, universal newborn screening for metabolic disorders, in particular PKU, and look to see if there was evidence that substantial numbers of children with false-positive results had medically adverse outcomes. Part of the impetus for examining the evidence was the fact that Dr. Norm Fost and a few others have alleged that in the early years of PKU screening, in galactosemia, and perhaps others, there were many instances of children who were falsely

identified as having the disorder, were treated inappropriately, and ended up dying or having a developmental disability. Dr. Fost says hundreds of children turned out this way.

Methods. Dr. Brosco decided to look at six particular conditions that were the most prominent newborn screening programs in the 1960s and early 1970s: congenital hypothyroidism (CH), PKU, congenital adrenal hyperplasia (CAH), galactosemia, sickle cell disease, and maple syrup urine disease (MSUD). He defined medically adverse outcomes narrowly as death and permanent disability (in particular, mental retardation).

His strategy for the literature review consisted of searching for information using online databases such as PubMed and Ovid, local databases, and Google. In addition, he did a keyword search looking at specific conditions and synonyms, plus all the different things that could go wrong with a child. He did a manual search through textbooks and publications by historians. He also used an organic methodology (which consists of looking at the references of every article you get, and adding any new reference you find, then going to that and looking through those references to find any new references, and so forth to create a single list). He found about 100 articles or so that overall that might be relevant.

For the oral history, Dr. Brosco interviewed prominent researchers and clinicians associated with major newborn screening programs in the 1960s and 1970s: Harvey Levy, Richard Koch, Ed McCabe, Selma Snyderman, Harry Hannon. He used semi-structured interviews, which meant he had a series of 10 questions that were routine, but would pursue those questions in any direction that an interviewee would lead. He also asked each interviewee who else he should interview to be sure to get as many different voices as possible. The interviews were taped and partially transcribed.

Results. According to Dr. Brosco, there are no population-based data or disease registries for newborn screening conditions in the early years of newborn screening programs in the United States. A PKU registry run by the government was politically inconceivable at the time. There are no data, or even informal followup, of false-positive results.

On the basis of his literature review and oral history interviews, Dr. Brosco found that there is *no* evidence of substantial numbers of children with false-positive results who had medically adverse outcomes in the early history of universal newborn screening for metabolic disorders (PKU).

- The *literature review* yielded some case reports in the 1960s of children with PKU suffering adverse medical consequences from malnutrition (seizures, hypoglycemia, failure to thrive) as clinicians struggled to balance children's nutritional needs with the need to keep their phenylalanine levels low. After 1970, there were still reports in the literature of clinicians having difficulty in balancing the nutritional needs of the growing infant with the need to keep phenylalanine levels low. There also were reported problems with metabolic variance, with babies thought to be "heterozygotes" and babies with "transient hyperphenylalanine." These are not typically what one would consider false positives.
- The *oral history interviews* with researchers and clinicians did not yield evidence of substantial numbers of children with false-positive results who had medically adverse outcomes either. The clinicians were not very worried about false positives. Their personal experiences led them to be concerned about children with mental retardation from PKU because of false negatives.

Dr. Brosco said that one thing he learned from his research is that there is definite value in screening for conditions with no current treatment, because once there is a treatment available, it is not ethical to withhold that treatment in order to learn about the natural history of the disease, genetic variants, etc. He emphasized the importance of developing a coordinated plan to carefully study the expansion of newborn screening programs and to follow up all true positives and at least some, if not all, false positives.

According to Dr. Brosco, the questions faced with respect to the expansion of newborn screening to other conditions in the early 1960s are very similar to the questions faced today. In some ways, policymakers do not want to do newborn screening in a very large population until we know everything we need to know, but we cannot know everything we need to know until the studies of the natural history of the conditions, the variance, etc. have been done. Delaying screening is going to mean that some children do not receive the benefit from screening. On the other hand, moving ahead may lead to some harms and wasted effort.

Finally, Dr. Brosco said that the current debate that he sees in newborn screening is about values and experience. Clinicians value their personal experiences of children harmed by failure to prevent mental retardation. They felt very strongly that false negatives were the big problem, and want no child untreated who needs it. Ethicists and epidemiologist tend to be more comfortable with the greatest good for the greatest number. Dr. Brosco cautioned that it is important to avoid the "inward vision/outward glance" problem that very often affects American medicine. This is the idea that when we are focused on a very specific problem, we see things very well; however, we often fail to see how it fits into that broader context.

Questions & Comments

Dr. Green asked Dr. Brosco to clarify how the diagnoses in the case reports from the 1950s and 1960s were being made—from the bacterial inhibition assay, from the early screening, or more careful followup diagnostic tests? Dr. Brosco replied the field was changing and that different tests were used. There was serum level followup for all of the identified cases, typically using 4 milligrams of phenylalanine per deciliter as the cutoff. The clinicians would expect that children with 25 or 30 milligrams were going to fit the classic PKU. They were not sure what to do with the children with 5–6 or 15–20 milligrams. But some of the children had levels as high as 30 or 40 milligrams per deciliter; they would be treated, and then they would start to have failure to thrive, and then they would put them on a regular diet and they would improve. Several different things were going on that were confusing. One was that some children had transient hyperalaninemia; others were among the 400 genetic variants for the various enzymes that can give you what looks like PKU. So it was very hard for clinicians to figure this out, but these were all children who had something different about their phenylalanine metabolism, so they were not false positives in the sense that we usually think about, where the child had nothing wrong. The clinicians were closely following the children's phenylalanine levels in serum, but they were unable to get the treatment right.

Dr. Alexander said that he hoped that Dr. Brosco would publish his findings and share them widely to dispel the urban legend that spreads on basis of hearsay without factual analysis. He asked: How, as we expand the number of conditions in the newborn screening panel, can we avoid the pitfalls of what was done? Dr. Brosco said first, ensure that there is adequate followup of kids that who screen positive, including false positives, so that time is not lost. Use outcome measures at outset. Second, begin newborn screening before there is a treatment, so you can learn about the natural history of the condition and avoid the ethical problem of withholding an available treatment. Third, decide whether it is better to move forward with screening for a

particular condition regionally or nationally. Dr. Brosco said he is uncertain about which way is best because he has not done the sensitivity analysis, but he thinks that when we look back at the PKU case, probably we will find that a regional implementation did mean that thousands of infants did not get a benefit that they could have early on. But before he can say that with any confidence, he wants to redo the numbers.

Dr. Kus asked: If you screen for conditions with no known treatment, how do you decide which conditions to screen for? Dr. Brosco said he said he was no expert on this, but he would think that one might use criteria such as the prevalence of the condition, the natural history, and so forth. His main point was that the availability of an effective treatment should not necessarily be the first and most important reason for deciding whether to include a condition in a screening program.

Speaking from the audience Dr. Rani Singh noted that there is a tremendous amount of variation in the diet for PKU, which has evolved greatly from what it was in 1950, and she suggested that data be collected about the treatment as well as the condition. Dr. Brosco noted that Diane Paul is writing a history of PKU and will probably include that.

Dr. Dougherty asked about the risks of identifying somebody and then giving them a treatment—say, for example, a bone marrow transplant—that has not been shown to work or the benefits do not outweigh the risks. Dr. Brosco said when people were trying to figure out what to do about PKU in 1966, they did not have good data on the natural history of PKU. They recognized that aggressive treatment for PKU carried some dangers, either of general malnutrition or restricting phenylalanine in a child for whom it should not be restricted; the problem was that they did not feel it was ethical to withhold treatment from any infant who might benefit. What this history suggests is that there is benefit to a widespread screening program that maps out what variants are, what the natural history of a condition is, and then that yields data from which it is possible to evaluate the risks and benefits of allowing the condition to run its course or to try some treatment.

B. Changing Perspectives on the Concept of Benefits of Newborn Screening

Don Bailey, Ph.D.
Distinguished Fellow
RTI International

Dr. Bailey, the former director of the Frank Porter Graham Child Development Institute and the W.R. Kenan, Jr. Distinguished Professor of Education at the University of North Carolina, who has written very widely about family dynamics when dealing with Fragile X, noted that he is a special educator by training rather than a physician and comes at the issue of benefits of newborn screening more from an intervention perspective than from a medical perspective.

A fundamental tenet of newborn screening is that the screening should produce a proven benefit to the child. Dr. Bailey emphasized that it is possible that advances in technology will lead to a scenario in which hundreds of things could be screened simultaneously at very low cost and with great accuracy. It is also possible that advocacy efforts and competition from the private market will push for a rapid and significant expansion of the public health newborn screening program, perhaps much more quickly than the public health infrastructure would like to see. Thus, Dr.

Bailey said it is important for the Committee and policymakers to consider a key question: Does the fact that we *can* screen for something mean that we *should* screen for it?

Dr. Bailey stated that he would like to see research and a research infrastructure that thinks systemically and holistically about all of the benefits and all of the harms that could occur from expanded newborn screening, and then tests to learn under what conditions benefits would be maximized and under what conditions harms would be minimized. He and his colleagues have written two articles about the concept of benefit in newborn screening, and Dr. Bailey reviewed them for the Committee: a 2005 article entitled "Newborn Screening for Developmental Disabilities: Reframing Presumptive Benefit,"[*] and a forthcoming article entitled "Changing Perspectives on the Benefits of Newborn Screening."[†]

"Newborn Screening for Developmental Disabilities: Reframing Presumptive Benefit." In this 2005 article, Dr. Bailey and his colleagues suggested that the concept of benefit should be expanded to include more than a significant medical benefit to the child.

The authors write that early identification of some conditions—even if there is no medical treatment—could provide the opportunity to optimize the infant's environment to maximize the potential effect of environment on phenotype. The early years are a foundational period in the effectiveness of early intervention. Newborn screening can provide access to family support services and information that can have positive benefits for families and prevent costs to families and society of the "diagnostic odyssey."

For many conditions, newborn screening provides earlier access to an existing program of services (e.g., the Part C Early Intervention Program through the Individuals with Disabilities Education Act) that families endorse as both positive and effective. Expanding newborn screening is consistent with research on consumer preferences for information.

In addition, there is a trend of consumers holding professionals accountable, and there are some cases about the "duty to warn." One could envision a situation where a technology might pick up 100 conditions, but if a professional chose to disclose only a few of them and a parent realized that, this legal duty might come into play.

Furthermore, newborn screening could have other benefits to science and society—for example, yielding data that could be used to determine the true incidence rate of a condition and identifying the full range of genotypic and phenotypic expression.

"Changing Perspectives on the Benefits of Newborn Screening." In this forthcoming article, Dr. Bailey and his colleagues review the concept of benefit from newborn screening as construed historically in major reports and policy statements in the past several decades. The authors found that almost all historical reports reach the same general conclusion that screening should be limited to those conditions for which there is a proven benefit; however, the reports differ in their conceptions of what constitutes benefit.

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[*] Donald Bailey et al., Newborn Screening for Developmental Disabilities: Reframing Presumptive Benefit, *American Journal of Public Health* 95(11):1889-1893, 2005.

[†] Donald Bailey et al., Changing Perspectives on the Benefits of Newborn Screening, *Mental Retardation and Developmental Disabilities Research Reviews*, published.

- *Early reports.* Two of the early reports—a 1968 World Health Organization (WHO) report (Wilson & Junger) and a 1975 National Academy of Sciences (NAS) report (Committee for the Study of Inborn Errors of Metabolism)—said that screening should be undertaken only when the prospects for treating the condition are at least reasonable. But both reports proposed a very broad conception of treatment. The 1968 WHO report included medical or dietary interventions; drug therapy; the management of the patient in relation to his total social situation, his immediate family, and social group; and special social, medical, or educational services. The 1975 NAS report discussed three forms of benefit: (a) benefit to infant (direct treatment or ameliorative procedures or advice or procedures in adjusting to the condition); (b) benefit to family (informed reproductive decisions); and (c) benefit to society (monitoring and surveillance so true range of condition can be known; also to assess natural history without therapy).
- *The 1994 Institute of Medicine (IOM) report*. The 1994 IOM report (Andrews et al.) came out with a very different perspective. It recommended that screening occur only when there is strong evidence of benefit to the newborn at the earliest stage possible. The general ethical principle that a person should not be used as a means for the benefit of others was endorsed, leading the IOM to conclude that screening is not justified solely on the basis that it could inform parents of reproductive risk. The IOM report also raised significant concern about the identification of untreatable conditions, arguing that it could provide information that might be stigmatizing and cause individuals to be uninsurable, unemployable, and unmarriageable.
- *Reports after the 1994 IOM report, including the 2005 American College of Medical Genetics (ACMG) report.* The subsequent reports—the 1995 American Society of Human Genetics/ACMG report; 1997 National Institutes of Health-Department of Energy Task Force on Genetic Testing (Holtzman & Wilson); 2000 American Academy of Pediatrics Newborn Screening Task Force; 2004 CDC/Foundation for Blood Research ACCE Model Process for Evaluating Data on Emerging Genetic Tests; and the 2005 ACMG report *Newborn Screening: Toward a Uniform Screening Panel and System*—take a tack similar to that of the 1994 IOM report, focusing on medical benefits to infant alone.

Dr. Bailey and his colleagues arrived at the following nine reflections pertaining to the concept of benefit in newborn screening:

1. *Benefit has been and remains a core consideration for screening decisions.* In discriminating among candidate conditions for newborn screening, the question is not whether benefit occurs but (a) the nature of the benefit; (b) the magnitude of the benefit; and (c) the level of benefit relative to costs or possibility of harm.
2. *Benefit has focused on improved physical health for the infant via medical treatment.* Most historical reports focus on this benefit, although "treatment" and "benefit" are often used interchangeably.
3. *Newborn screening rarely prevents all negative consequences of a condition.*
4. *Screening for all conditions has perceived benefits for family and society.* Most reports consider these as additive to infant benefits rather than a standalone justification for screening. Only two reports (WHO, 1969; NAS, 1975) considered these as legitimate bases for policy decisions.
5. *There is no agreed-upon threshold for meaningful benefit.* There are several important questions, among them: What level or kind of improvement in well-being should be considered sufficient? How do we weigh direct benefits to the infant in

relation to benefits for families or society? These issues are complex, value laden, and difficult to quantify.

6. *Stakeholders differ in their perceptions of benefit.* Professionals tend to endorse a more conservative stance, insisting upon improved health outcomes. Parents and advocacy groups generally take a broader view of benefit; in fact many would argue that information about a condition would constitute sufficient benefit, regardless of treatment potential. For many parents, there is no such thing as an "untreatable" condition.
7. *"Secondary conditions" complicate discussions of benefit.* If in the process of screening for one condition, another known genetic, chromosomal, or metabolic abnormality is detected, it is the duty of the clinician to inform. This means that two hypothetical conditions of equal severity and equally low ratings of benefit would be differentially included in screening by virtue of the technology used to identify a third condition. Does this circumstance obviate the relevance of benefit?
8. *Benefit is only a part of decisionmaking.* A powerful benefit could be undermined if there was inconsistent followup or access to treatment; extraordinary cost; or risk for substantial harm. Conversely, if no harm were likely and costs were reasonable, it is possible that a broader definition of benefit might be acceptable.
9. *Research is needed to inform policy.* What are the real costs to families and society of the diagnostic odyssey? Does parent knowledge about a condition in their child constitute sufficient benefit? What would be the impacts of a two-part screening program, one set of conditions mandated and the other set screened voluntarily with informed consent? What does informed consent or informed decisionmaking mean if we envision the possibility of screening for literally hundreds of conditions—something that may become a reality in the near future? Dr. Bailey said that he would like to see research and a research infrastructure that thinks systemically and holistically about all of the benefits and all of the harms that could occur from expanded screening, and then tests to see whether benefits and harms actually occur.

Questions & Comments

Ms. Monaco agreed with Dr. Bailey that parents have a different view of the benefits of newborn screening and asked why there were no reports from the family organizations cited in Dr. Bailey's forthcoming article. Dr. Bailey replied that the reports cited in the article were all issued by task forces appointed by major national organizations. As far as he knows, families have never issued a report of this nature. Ms. Monaco said it was frustrating to families to have organizations speak for them instead of letting families speak for themselves. She also suggested that this issue would be important to consider in the future.

Dr. Green raised the possibility that the recommendations in some of the early reports cited by Dr. Bailey might have been made in the context of newborn genetic testing, which requires parental consent, rather than in the context of newborn screening. She added that the issue is whether certain tests should be performed in the context of newborn screening or in the context of pediatric care. Dr. Bailey replied that his view was that decisions about mandated screening should be fairly conservative but that the question of whether voluntary screening should be put in the public sector would have to be addressed in the next few years. Dr. Brad Therrell from the National Newborn Screening Resource Center noted that a few States currently do voluntary screening for some disorders in the expanded panel.

Speaking from the audience, Ms. Kerry Silvey from the Region 7: Western States Genetic Services Collaborative stated that there is a big difference between “treatable” and “curable.” There are many conditions that are not "curable," and yet in our medical system we provide “treatment” for those conditions. She also noted that requiring uniformity could hurt good newborn screening programs. Finally, she said that she thinks the issue in the case of PKU currently is not that there is something wrong with the diet but that it is not easy for people to stay on that diet.

Dr. Louder asked for comments about how payers would view the concept of benefit. Dr. Bailey said he believes that payers would probably be interested in a wider consideration of both the costs and the benefits of newborn screening.

C. The Concepts of Benefit and Treatment: History and Current Practices

Ellen Wright Clayton, M.D., J.D.
Professor of Pediatrics
Professor of Law
Co-Director, Center for Biomedical Ethics and Society
Vanderbilt University

Dr. Clayton is the Rosalind E. Franklin Professor of Genetics and Health Policy, a professor of pediatrics, and practices general pediatrics at the Vanderbilt University School of Medicine. She noted that she is currently investigating the effects on families of expanded newborn screening in Tennessee, with funding provided by the National March of Dimes and that work would inform at least some of her comments.

Dr. Clayton noted that there are significant pressures to expand the concept of benefit in newborn screening beyond medical benefit to the child and stressed that it was important to figure out how to allocate decisionmaking between parents and providers, both individually and in a public health system. She concurred with Dr. Bailey about the need to consider a broad range of tradeoffs in making decisions about what disorders to screen for and to conduct additional research. Dr. Clayton strongly cautioned Advisory Committee members to avoid being captured by notion that because some newborn screening technology (e.g., gene chip technology capable of monitoring the whole genome) is available, it must be used to its full capacity.

Pressure for Expanding the Concept of Benefit in Newborn Screening. Dr. Clayton said that pressures to expand the definitions of benefit and treatment in newborn screening are mounting. Some parents argue that they have a “right to know” what their condition their child has. Some parents point to the benefits of avoiding a diagnostic odyssey to find out what condition their child has. Others cite the benefits of early intervention. As Dr. Bailey pointed out, some parents believe that all disorders are treatable.

Some people suggest that a benefit of newborn screening is to provide information for reproductive decisionmaking. This issue, Dr. Clayton said, is actually quite complicated. In the State of Tennessee, where half the women who are pregnant are covered by the State’s Medicaid program, it is illegal to offer any kind of prenatal diagnostic testing, carrier screening, amniocentesis, anything that might lead a woman to choose to terminate a pregnancy. The public policy of the United States is not consistent on this issue.

Finally, some people suggest that a benefit of newborn screening is ascertaining the true incidence of the disorder and identifying children for further study. There is enormous value in case ascertainment, Dr. Clayton said, but there are also enormous ethical and regulatory complications raised by this argument.

Starting Points. Dr. Clayton outlined the following as starting points for her presentation:

- Resources are limited and there are many problems to be address. An article in the *New York Times* last week, for example, said a third of the world's population suffers developmental disability as a result of iodine deficiency.
- Most pediatricians do not know enough about newborn screening.
- Many (most) parents do not know much or anything about newborn screening. Far fewer actually make an informed decision about this. As a result, the debate is really about the parents "duty to know," not the parents' "right to know."
- Most parents of affected children detected by newborn screening say they are glad they know. The majority of new true positives from the expanded newborn screening program in Tennessee are 3-methylcrotonyl carboxylase (3-MCC) deficiency Dr. Clayton wonders whether physicians are always doing the right thing to pass all the information they have on to families. A new study from Germany suggests that the penetrance of 3-MCC deficiency is actually about 10 percent, and that 90 percent of kids who have that abnormality in fact aren't sick and have no symptoms. So Dr. Clayton questions that parents say they are glad to know, but what do they know?
- False-positive results are inevitable, and there is abundant evidence that false-positives cause distress in families and increase health care utilization (e.g., a review by Susan Waisbren).
- Most commentators agree that genetic testing of children is not appropriate if no treatment is needed during childhood, although this sentiment is increasingly contested.
- Finally, reporting everything that is detectable makes things more complicated. Dr. Clayton firmly believes that the availability of technology—for example, the gene chip—should not end the discussion about what to test for and report. She does not believe that everything that can be known using a technology has to be known and has to be disclosed.

Defining Benefit in Newborn Screening. Dr. Clayton said that she believes that parents' views are important. For children to thrive, parents have to do well too, and the family and pediatrician all have to work together. She agreed with Ms. Monaco that the voice of consumers had not been particularly well heard in newborn screening.

On the other hand, Dr. Clayton noted, what parents want has never been the sole determinant of what the health care system or public health care systems do. The health care system and public health care systems are increasingly relying on evidence that, admittedly, does not assess all the potentially relevant variables, including the psychosocial impacts of various interventions. But health care providers, health care systems, and public health care systems do—and should—pay attention to risks, costs, and competing demands.

What should be done when parents and providers/policymakers disagree? This is the fundamental question that underlies the clinician-parent relationship in care of children. Even the most liberal commentators would say there is a role for the clinician to a parent that something is

not a good idea. Dr. Clayton urged the Committee to recognize that there is some room at the level of both the individual clinician encounter and the public policy encounter to talk about variables that need to be taken into account other than what parents want.

Proposed Minimal Criteria for Inclusion in State Newborn Screening. Dr. Clayton proposed the following as minimal criteria for inclusion of a condition in a newborn screening program:

- The disorder must be symptomatic during early childhood. A recent *Journal of the American Medical Association* article focused on preimplantation genetic diagnosis of cancer predisposition syndromes. Such predispositions that would not be symptomatic during early childhood should not be included in newborn screening.
- The disorder must be highly penetrant (unlike 3-MCC, which has only 10 percent penetrance).
- The disorder must be reasonably amenable to early intervention.
- There must be evidence that the "diagnostic odyssey" would cause the child physical or developmental harm.
- It should not make sense to do the screening sometime after birth. It is easy to screen in the hospital at birth, but for some things it may make sense to screen more proximate to the time of intervention.
- Evidence of reproductive benefits for the family or having a diagnosis, while supporting inclusion of a condition in a newborn screening program, are not sufficient criteria by themselves.

Newborn Screening for Case Ascertainment: Research or Public Health Surveillance? Dr. Clayton said there is no doubt about the value of learning about natural history of a genetic, chromosomal, or metabolic condition and doing research, but the question that arises is: Is newborn screening for ascertainment public health surveillance or is it research? If we are doing research, we have to comply with Federal regulations governing "human research subjects" and to get the parent's permission. If we say we are doing public health surveillance, then once we get the data we have to figure out what we are going to do with the data.

Dr. Clayton concluded her presentation by saying that the Advisory Committee's work is very important and urging the Committee not only to focus on the problem before it, but to be mindful of the system beyond and be mindful of the way things actually work in the real world as it talks about how we are going to decide what to screen newborn infants for—and not to be captured by the notion that because technology is available necessarily means that we can or ought to be using it.

Questions & Comments

Dr. Telfair asked Dr. Clayton to give guidelines to the Committee and others who have to consider the other variables that ought to be considered in the process of making decisions about the inclusion of conditions in newborn screening programs. He also asked if she had any suggestions related to her comment about whether case ascertainment through newborn screening is research or public health surveillance. Dr. Clayton replied as follows:

- Newborn screening for purposes of ascertainment makes her nervous. She believes that parents need to be able to enroll their children in research protocols. This is not just a legal but a moral imperative.

- The Committee and other policymakers need to ask whether a diagnosis should be given just because it is possible to detect something—especially for disorders such as 3-MCC that are not very penetrant. Dr. Clayton believes that if the new data indicating that 3-MCC is only 10 percent penetrant are valid, there will a very real question about whether we ought to be screening for this disorder and what we ought to be telling parents about it, because it certainly is different from what parents are being told now. If a diagnosis is going to be given, research on the overall psychosocial impacts should be conducted.
- The Committee ought to think about developing criteria for when to take things *off* the newborn screening panel. Some States have removed disorders (e.g., histidinemia and severe combined immune deficiency).
- The Committee should pay attention to benefits to families, but focus on the benefits to the child, with secondary benefits to the parent because they affect the child and are important.

Dr. Hawkins noted that Dr. Clayton's presentation was very good, but also very controversial. He said that the notion of requiring informed consent for newborn screening from parents opens a black box, but if all parents had to sign for informed consent, it would be a great opportunity to educate the parents about newborn screening and what was getting ready to happen and opportunities for child to be treated. Dr. Clayton thanked Dr. Hawkins for making that point, noting that it is the job of child health care providers to educate and empower parents about newborn screening before the birth occurs, so that they can provide the best possible care for their children.

Dr. Skeels asked Dr. Clayton to say more about the minimal criterion for inclusion that a disorder should be highly penetrant. Should a clinical disorder, the phenotype, be highly incident in the population, or should the genotype that places the child at risk for that disorder be highly penetrant? And how would Dr. Clayton recommend one go about determining or ascertaining how high is high enough? Dr. Clayton replied that what she meant was, what is the likelihood that the child is actually going to develop symptoms if a child has a true metabolic variant? She thinks it is really troubling, if true, that 90 percent of children who have 3-MCC actually never get sick. The appropriate cutoff point for the penetrance level would depend on what the outcome of the disorder was (e.g., developmental delay, mental retardation, death, metabolic instability). If the outcome you are trying to avert is death, then maybe a 10 percent penetrance level would be acceptable. If the outcome is something more benign, the penetrance level should be higher.

Dr. Skeels said that Oregon's newborn screening program has already come to the conclusion that it needs to shift parent education about newborn screening to the prenatal period and away from the perinatal period, but they are grappling with how to make the shift. Dr. Clayton said the American College of Obstetricians and Gynecologists (ACOG) last year endorsed the idea that obstetricians should be doing the education of parents, and she agrees.

Dr. Alexander stated that many people would argue that newborn screening for reproductive decisionmaking or obtaining a diagnosis are beneficial to the child. In the case of reproductive decisionmaking, if parents can use information from newborn screening to avoid the birth of a second or even a third affected child, one could argue that the index child would benefit by not having resources, attention, whatever else distracted from them and focused onto others. In the case of the diagnosis, one could argue very strongly that there is a significant benefit to the child from newborn screening that allows the child to avoid the diagnostic odyssey. Dr. Alexander asked Dr. Clayton to comment. In response to Dr. Alexander's question about reproductive issues, Dr. Clayton referred back to her comments about the State of Tennessee and the country's

public policy about reproductive genetic testing. In response to his question about the value of having a diagnosis for a child, Dr. Clayton said that if she were confident that a disorder would be symptomatic in early childhood, she would be willing to consider that as a benefit to the child. Otherwise, why not screen for Huntington's disease or mutations in BRAC 1, which parents who have these conditions in their family want to know about in their children?

Dr. Kus said that the question about what should we do when parents and providers/policymakers disagree is actually broader: What should we do when parents, providers, policymakers, and other interested parties disagree? In addition, Dr. Kus asked: What is the answer to that question? Dr. Clayton replied that she does not have a satisfactory answer and has come to considerable more humility to that question than when she started. In the early 1990s, she saw a scientist who had a slide with a disk in his hand saying "we can do newborn screening and learn everything about every child." The challenge is to come up with criteria that we think we can possibly defend. Dr. Clayton thinks it is important to look at opportunity costs, impacts on a variety of people, make public policy levels that are more transparent, and involve consumers on policy panels. It is also important to think about giving a label to someone who is not affected; complicated issues of false positives; issues of false negatives; and issues of all other competing demands on our time. We have to make tradeoffs as best we can, recognizing we live in a world of incomplete information.

IX. COMMITTEE BUSINESS—SUBCOMMITTEE MEETINGS and REPORTS

The Followup and Treatment Subcommittee, the Laboratory Standards and Procedures Subcommittee, and the Education and Training Subcommittee of the Advisory Committee held meetings that were open to the public from 2:30 p.m. to 5 p.m. on Monday, December 18, 2006. On the second day of the meeting, December 19, 2006, each subcommittee made a report back to the full Committee, as discussed below.

A. Followup and Treatment Subcommittee Report

Denise Dougherty, Ph.D.
Senior Advisor, Child Health
Agency for Healthcare Research and Quality (AHRQ)

Dr. Dougherty gave an overview of the Followup and Treatment Subcommittee's planning for a 1-day meeting, previously approved by the Advisory Committee, to develop a logic model for long-term followup and treatment in newborn screening. She then described some of the exciting presentations the Followup and Treatment Subcommittee heard at its meeting the previous day.

Plans for Meeting on Long-Term Followup and Treatment in Newborn Screening. The Followup and Treatment Subcommittee has been working on when and how to have a 1-day meeting to identify all the elements of long-term followup and treatment in newborn screening. The subcommittee hopes to have the meeting in the spring of 2007.

Dr. Stephen Downs from Indiana University School of Medicine, who knows newborn screening programs as they exist now and also has a good big picture of the child health services delivery system, has agreed to help with the 1-day meeting on long-term followup and treatment in newborn screening. He will be sending a concept proposal to HRSA, so he can be reimbursed. Dr. Downs has proposed drafting a white paper for discussion at the 1-day meeting. He and others

will help identify potential participants for the meeting, who will be asked to comment on the draft paper. After the meeting, the paper will be revised and submitted to the full Advisory Committee, and possibly published. The idea is to come out with something that says what the critical elements of long-term followup are—right now things are too granular and piecemeal.

The issue of who is responsible for long-term followup and treatment is a much harder question, given the fragmentation of the U.S. health care system, and it is not likely that the meeting will address that question.

Summary of Presentations to the Subcommittee. The Followup and Treatment Subcommittee heard three presentations at its meeting on December 18, 2006. These presentations showed how complicated it is to provide long-term followup and treatment for life to a child identified as a newborn but also identified some solutions:

- Dr. Richard Antonelli, Associate Professor of Pediatrics, University of Connecticut School of Medicine, and Chief Division of Primary Care, Connecticut Children's Medical Center, gave a presentation on the medical home and its evolving definitions and concepts. Rather than thinking about the medical home as just the primary care provider, he described more of a systems approach to thinking about health care delivery for children, especially children with special health care needs.
- Dr. Jim Figge, Medical Director of the New York State Department of Health's Office of Medicaid Management, identified some of the policy issues in trying to have a rational, comprehensive, effective system. He has worked through a lot of these issues in New York, and they have developed regulations and guidance on what needs to be paid for in the Medicaid program in New York.
- Ms. Jill Levy-Fisch presented on the medical food and formula issue and really walked us through the difficulty a parent has in trying to get the appropriate medically necessary food formulas for children.

The Followup and Treatment Subcommittee is planning to discuss with Dr. Lloyd-Puryear and Dr. Downs the possibility of having the medical food and formula issue done as a case study, with a white paper following up on it. The subcommittee believes that the medical food and formula issue probably has similarities with occupational therapy, physical therapy, social work, mental health, and other kinds of services that children with special health care needs require.

Questions & Comments

Dr. Telfair said that Dr. Antonelli covered a lot of information in his presentation to the subcommittee, and one of the things in addition to what was mentioned that he covered was the idea of looking at care coordination as also being broader than just the medical home.

Speaking from the audience, Dr. Alan Hinman said that one of the exciting things about Dr. Figge's presentation was that it included a description of how the Medicaid program in New York is setting a standard that other carriers may need to follow, because Medicaid is typically viewed as sort of the minimum necessary to be done. The Medicaid program has laid out for Krabbe disease what Medicaid must cover or what Medicaid plans must cover. This seems to be a new approach and one that could be considered in other States as a means of encouraging insurance coverage.

Dr. Kus added that the model in New York that Dr. Figge discussed is one in which the Medicaid, the Maternal and Child Health Program, and the newborn screening program are all at the table

discussing benefits for children with Krabbe disease. The goal is for the process to yield a good benefit package for children with special health care needs, which would then influence other providers within the State.

Dr. Howell asked Dr. Dougherty to write a summary of the Followup & Treatment Subcommittee's meeting and to include in the summary the slides from the presentations. She agreed to do this. Dr. Howell also underscored the importance of research on followup and treatment issues.

- ***DECISION #2: Dr. Dougherty will write a summary of the Followup and Treatment Subcommittee's December 18, 2006, meeting and decisions. The summary will include copies of the slides and other materials used in the presentations to the subcommittee.***

B. Laboratory Standards and Procedures Subcommittee Report

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

Dr. Brower reported that both of the Advisory Committee's new members, Dr. Skeels and Ms. Monaco, are now members of the Laboratory Standards and Procedures Subcommittee. She then summarized what had transpired at the subcommittee's meeting on December 18, 2006. The meeting had the following agenda items: (a) an update on the routine second specimen study from Dr. Harry Hannon and Dr. Stuart Shapira from the Centers for Disease Control and Prevention (CDC); (b) an update from Dr. Rinaldo on the collaborative study in Region 4: Great Lakes Genetics Collaborative of State practices and cutoff ranges in tandem mass spectrometry (MS/MS) testing for specific conditions in the uniform newborn screening panel; (c) consideration of the effect of environmental factors (e.g., temperature) on enzymatic assays; and (d) a brief discussion of proposed guidance, regulations, and Federal legislation that may affect laboratory testing.

Update on the Study of Routine Second Specimens. One of the Laboratory Standards and Procedures Subcommittee's first priorities for the short term is a study to assess the utility of the routine second newborn screen. The goals and draft protocol for the study of the utility of routine second screens of newborns for CH (congenital hypothyroidism) and CAH (congenital adrenal hyperplasia) have been approved by the full Advisory Committee. In addition, a workgroup of stakeholders primarily from States involved in routine second screens was convened in December 2006. Stakeholders at the meeting—including parents, laboratorians, the follow-up individuals for each participating State, and clinicians—agreed to participate in the study of routine second specimens.

The next steps for the workgroup are to finalize the protocol for the routine second specimen study, seek institutional review board clearance of the study, work with the APHL Association of Public Health Laboratories to create a data storing and gathering mechanism, and begin the first phase of the study, which involves a retrospective study. The retrospective study, expected to begin in February 2007 and last about 6 months, will be focused on collecting as much data as possible from States that routinely do a second screen from the past 2 to 5 years, with the understanding that some of the data may be incomplete. Following the retrospective study, the

protocol for the prospective study will be refined on the basis of the retrospective study's results and the prospective study or Phase 2 will begin.

Update from the Region IV MS/MS Collaborative Project. Dr. Rinaldo provided an update on the newborn screening project of the Region 4: Great Lakes Genetics Collaborative, which is trying to get data on at least 50 true-positive cases for each of the 42 MS/MS primary and secondary conditions in the uniform newborn screening panel. Because of the small number of true positives for these conditions, data are being collected collaboratively. As of December 14, 2006, there were 30 U.S. States and 28 countries in the study, and the number of participants was expected to grow. The data for the study are being collected much faster than had been anticipated. So far, a total of 2,950 true-positive cases have been reported, including at least 50 true-positive cases for 14 of 20 conditions in the uniform panel and 50 true-positive cases for 3 of 22 secondary targets in the uniform panel. Dr. Rinaldo has now begun to analyze the data. Dr. Brower said that she would make a copy of Dr. Rinaldo's full presentation available for the minutes of the subcommittee's meeting.

Investigating the Effect of Environmental Factors on Enzymatic Assays. One of the newborn listservs raised a question about biotinidase deficiency and how the newborn blood spots are handled and the impact of temperature, storage, etc. Dr. Harry Hannon from CDC offered to do a literature search and to provide an update of this issue to the Laboratory Standards & Procedures Subcommittee at its next teleconference. The subcommittee hopes to have a good baseline from the retrospective study of routine second specimens, at least in some States, to start to understand some of those factors.

Proposed Federal Regulations and Legislation That May Affect Laboratory Testing. The Laboratory Standards and Procedures Subcommittee asked Mr. Jelili Ojodu from APHL, who agreed to talk to his committees at APHL, to report back to the subcommittee on draft guidance and legislation on public health labs. The subcommittee will discuss this at its next teleconference.

Questions & Comments

Several Committee members asked for additional information about the study of routine second samples being conducted by the Laboratory Standards and Procedures Subcommittee. Dr. Green asked whether the study was also assessing what is happening with States that only do a single sample. Dr. Therrell replied that nine States require a second sample, but the study also includes some States that just recommend a second sample and some States that do not do a second sample. The focus of the study is on finding out whether there is a benefit to doing a second screen, finding out if there is a difference in those cases that are detected on second versus those detected on first.

Dr. Howell made several comments. First, he said the study of a routine second sample is also very important. About 25 percent of the babies in the country get a second screen, and this practice represents a significant commitment of resources. Either nobody should be getting a second screen or probably everybody should be getting one. Dr. Skeels disagreed that the policy should be "all" or "none," noting that Oregon's data, presented at the last National Symposium on Newborn Screening, indicates that they pick up some disorders on the second sample that they do not pick up on the first sample. Dr. Skeels said he believes the Committee should give States data and national guidelines, but allow States to make their own decisions about what their screening practices should be.

Dr. Howell also said he believed that Dr. Rinaldo's study of cutoffs for patients with documented disease (true positives) was also going to be very valuable. Historically, we have said that the upper 5 percent of values is abnormal. This study, by looking at what the values were in a large number of cases that were later proven to be true positives, is providing a different paradigm for determining what constitutes abnormal.

Finally, Dr. Howell said that work done by the late Nestor Shamoles in Argentina might be helpful in considering the effect of environmental factors on enzymatic assays. He has done an extensive look at mailing blood samples when he was working on the Pompe's assay. Brazil's climate is very hot and humid, and he mailed samples all around the country in the heat of the summer.

C. Education and Training Subcommittee Report

Gregory A. Hawkins, Ph.D.
Assistant Professor
Section on Pulmonary, Critical Care, Allergy, and Immunologic Diseases
Department of Internal Medicine
Wake Forest University School of Medicine

Dr. Hawkins, the new chair of the Education and Training Subcommittee now that Dr. William Becker has completed his term of service on the Advisory Committee, reminded everyone that subcommittee's approved charges are as follows:

- Review existing educational and training resources for health professionals, parents, screening program staff, hospital/birthing facility staff, and the public.
- Identify deficiencies and make recommendations for action regarding the five groups.

In recent months, Dr. Haskins noted, the Education and Training Subcommittee has focused to a great extent on how to create an effective communications strategy to increase public awareness of the importance of newborn screening. But during a conference call on December 6, 2006, subcommittee members agreed that before planning to mount a large-scale communication effort, the subcommittee should evaluate adequacy and effectiveness of the newborn screening educational resources for health care providers and parents that currently exist.

Existing resources include the ACT sheets developed for health care providers by the ACMG, the newborn screening materials developed for parents and health care providers by Dr. Terry Davis, and newborn screening materials from the AAP, American College of Obstetricians and Gynecologists (ACOG), and American Academy of Family Physicians (AAFP). Key questions to be answered are these: (a) Were the materials received? (b) If so, how were they used? (c) What was the response of health care providers and parents to the newborn screening materials? (d) Are the materials sufficient to reinforce education between the health care providers and parents? (e) What improvements are needed?

Not only the questions above, but the question of the timing and form of newborn screening educational materials needs to be addressed before the development of a newborn screening communication plan. When (and in what form) are newborn screening educational materials most effective?

- ***"Front end."*** During the prenatal/pretest period (materials for obstetricians, family practitioners, and parents)?

- ***"Back-end."*** During the postnatal/post-test period (materials for obstetricians, pediatricians and family physicians, parents)?

At the Education and Training Subcommittee's meeting the previous day (December 18th), there was a consensus that the subcommittee's immediate focus should be on assessing the prenatal ("front-end") newborn screening educational process. Subcommittee members noted that there is already considerable research about the newborn screening education during the postnatal ("back-end") period. For example, Dr. Alex Kemper did a survey of pediatricians and family physicians in 2006 that showed that these providers involved in the postnatal period are not doing a very good job in managing the followup care of children with positive newborn screening tests.[*] In addition, professional organizations such the AAP have been conducting or are proposing to conduct surveys of their members with respect to the use and utility of newborn screening materials.

Thus, the Education and Training Subcommittee voted unanimously to make the following recommendations to the full Advisory Committee.

Education and Training Subcommittee's
Recommendations to the Advisory Committee—December 19, 2006

1. Recommendation re Education and Training Subcommittee's Emphasis on Prenatal Education:

That the full ACHDGDNC endorse the Education and Training Subcommittee's emphasis on prenatal education by creating a mechanism to assess the healthcare provider-parent prenatal education process.

2. Recommendation re Mechanism to Study Prenatal Newborn Screening Educational Materials in the Context of the Clinician-Patient Relationship:

Preamble

- The ACHDGDNC Education and Training Subcommittee recommends that the ACHDGDNC formally endorse prenatal education for parents, with an emphasis on prenatal education that occurs within the health care provider-patient relationship, and by the professional organizations and entities most frequently involved in prenatal education, such as ACOG, AAP, AAFP, hospitals, birthing centers, clinics, and midwives.
- The fundamental message communicated should be consistent with existing newborn screening educational materials (e.g., those developed by HRSA, the March of Dimes video) such that no new educational materials need to be created.

Formal Recommendation:

That the full ACHDGDNC endorse the following proposal:

That the U.S. Department of Health and Human Services develop and fund a mechanism to study the distribution of existing newborn screening educational material and acquisition of knowledge about newborn screening by expectant parents in the context of the clinician-patient relationship.

[*] Alex Kemper et al., Primary Care Physicians' Attitudes Regarding Followup Care for Children with Positive Newborn Screening Results, *Pediatrics* 118:1836-1841, 2006.

According to Dr. Hawkins, the Education and Training Subcommittee believes the proposed study should focus on prenatal newborn screening education, with a target of education in the third trimester of pregnancy. The study should be hypothesis driven and be completed within 1 year. The study should center around the evaluation of currently available material; no new material should be created for the study. The study should assess different methods of learning by parents. The study should assess different methods of information transfer between clinicians and parents (e.g., showing a newborn screening video in the clinician's office, one on one contact with the clinician, just handing out newborn screening literature in the clinician's office) to see which has the best results in terms of learning by parents. Finally, the subcommittee suggests that the study might be implemented by selecting a representative city such as Winston-Salem, North Carolina, which has about a quarter million people but primarily one hospital that does all the prenatal and obstetric care in the city. Another possibility might be involving one of the Regional Genetics and Newborn Screening Collaboratives in the study.

Questions & Comments

Dr. Howell asked for comments from other Committee members about Dr. Hawkins' presentation. Members of the Education and Training Subcommittee echoed their support for the subcommittee's recommendations to the full Committee. Dr. Gregg said obstetricians have no real indication that what they tell patients about newborn screening makes any difference; if obstetricians knew they were making a difference, they might be more willing to educate parents about newborn screening during the prenatal period.

Dr. Green agreed that prenatal education related to newborn screening seems to be the area needing the most attention at this time. She added that the March of Dimes would donate copies of the video "A Parent's Guide to Newborn Screening" (shown to the Committee on Tuesday, December 19, 2006) for use in the study.

Dr. Edwards stated that the December 6th conference call focused mostly on the ACT(ion) sheets and the relationship with parents and communication between the pediatrician and the parent. But he noted a shift in the subcommittee's thinking at its meeting the previous day (December 18th). Subcommittee members recognized that the obstetric community agreed to recommend last year that obstetricians be involved in educating parents about newborn screening, so it is important to get a better understanding of how they can best communicate newborn screening information to their patients as a first priority. That does not mean that solved the problem of ACT sheets and communication with parents has been fully addressed.

Audience member Dr. Kenneth Pass from the Region 2: New York-Mid-Atlantic Consortium (NYMAC) for Genetics and Newborn Screening gave a brief report to the Committee about the need for newborn screening educational efforts undertaken by New York and NYMAC. Ms. Monaco said she was on the workgroup for education that is working on some of the NYMAC and New York State educational materials and would be happy to be provide the Education and Training Subcommittee with whatever information she could.

Dr. Hawkins confirmed that the Education and Training Subcommittee's future agenda items would include additional consideration of postnatal ("back-end") education about newborn screening for both parents and providers. In addition, he said, the subcommittee would also revisit the idea of a broad communication plan for getting the message out about newborn screening.

Thus, the Committee voted to approve the following motion corresponding to that recommended by the Education and Training Subcommittee:

- ***MOTION #3: The Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children recommends that the U.S. Department of Health and Human Services develop and fund a mechanism to study the distribution of existing newborn screening educational material and acquisition of knowledge about newborn screening by expectant parents in the context of the clinician-patient relationship.***

X. VIEWING OF MARCH OF DIMES VIDEO—*A PARENT'S GUIDE TO NEWBORN SCREENING*

Nancy S. Green, M.D.
Medical Director
March of Dimes Birth Defects Foundation

Dr. Green showed the Committee the March of Dimes' 8-minute video on newborn screening entitled *A Parent's Guide to Newborn Screening*. The video is targeted to pregnant women in the third trimester and their families, explains what newborn screening is, its purpose, the testing procedure, and what parents need to do if retesting is necessary. It shows widely diverse families and is available in Spanish and English. Funding for the project came from the HRSA's Maternal and Child Health Bureau, as well as from the Hastings Center.

XI. PUBLIC COMMENT SESSION

The following individuals made public statements to the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children on the afternoon of Tuesday, December 19, 2006. The written text of their statements appears in Appendix A.

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

Ms. Gartzke expressed her conviction that newborn screening should be offered for all those diseases/disorders that can provide a benefit to the child and or family in the early childhood years. She explained that she is not insensitive to the issue of false positives for parents but thinks that that problem pales in comparison to the loss of her daughter to Krabbe disease following a 6-month diagnostic odyssey. Ms. Gartzke urged the Committee to finalize the nomination form and process for adding conditions to the uniform newborn screening panel as quickly as possible so that more children's lives can be saved. Finally, she said that she hoped to share an update on the Krabbe screening in New York State with the Committee at its next meeting.

2. Jill Levy-Fisch (read by Micki Gartzke)
Parent & President
Save Babies Through Screening Foundation

Ms. Fisch underscored her deep belief that every baby should be screened for every disorder for which there is an available test, regardless of the availability of treatment. She believes that parents have the right to know what to expect with their children and that most families would

prefer false positives to not having available testing done and having an affected child become impaired or die. Furthermore, children suffer when newborn screening is not done. If her son had benefited from early detection, he might not have had to undergo a 2½ -year diagnostic odyssey and might not have ended up developmentally delayed with a gastrointestinal tube.

3. Andrea M. Williams
Executive Director
Children's Sickle Cell Foundation, Inc.

Ms. Williams said her interest in newborn screening arises from her experiences as a parent and from working with the newborn screening sickle cell trait followup program at Children's Hospital of Pittsburgh. Ms. Williams believes that newborn screening is important to identify carriers of genetic conditions who themselves do not require medical intervention, so that they are empowered to take better care of their children and families. When Ms. Williams' youngest child was born with sickle cell disease in 2000, she and her husband were completely unaware that they had a 25 percent risk of having a child with the disease. Ms. Williams was aware that she carried sickle cell trait, but her husband did not know that he was a carrier. Of the couple's two older children, one had been born with sickle cell trait and the other had no sickle cell trait or disease. Ms. Williams has become involved with the newborn screening sickle cell trait followup program at Children's Hospital of Pittsburgh, because she believes that it is important that parents of children with sickle cell trait be contacted and educated about sickle cell disease and trait and be encouraged to seek genetic counseling so that they are empowered to make decisions for themselves and their child.

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

Dr. Sybinsky, on behalf of AMCHP, stressed the importance of a comprehensive and coordinated newborn screening system—clearly a vital public health service. He specifically highlighted the importance of long-term followup (LTFU)—those activities occurring after screening and diagnosis which minimize the health consequences of confirmed disorders. As an underfunded and comparatively neglected component of the newborn screening system, LTFU is a priority issue for AMCHP. The infants that benefit from early detection of treatable disorders are poorly served when the newborn screening system effectively loses track of them after referral for treatment. Moreover, society-at-large forfeits an opportunity to gather valuable data on treatment interventions and disease outcomes. In order to realize the *full* public health benefits of newborn screening, LTFU must be recognized as an integral system component and funded accordingly. The expansion of newborn screening prevents both an opportunity and an obligation to do this. Dr. Sybinsky distributed a December 2006 AMCHP report "Newborn Screening Long-Term Followup: A Framework, Challenges, and Opportunities" as part of his public comments.

5. Barbara Ballard
Parent and Administrator, SCID Network of Families
Board Member, Immune Deficiency Foundation

Ms. Ballard spoke on behalf of families with children with severe combined immune deficiency (SCID). She related her personal experiences as the mother of a boy with X-linked SCID named Ray who did not receive a diagnosis until a series of infections had ravaged his body. At birth Ray seemed perfectly normal. He thrived until he was 10 ½ months old. Then a series of infections, beginning with PCP pneumonia, required him to undergo numerous intrusive medical

procedures (to be on a ventilator, to undergo a bone marrow transplant, to be fed parenterally, etc.) and left him with severe lung and gastrointestinal damage and deaf. His medical costs to date have already maxed out a $2 million insurance policy vs. the estimated $10,000 it would have cost to treat him had he been diagnosed as a newborn. All of his quality-of-life issues are a result of infections contracted during the delayed diagnosis period and are not inherent to SCID. Ms. Ballard said her view is that the current uniform newborn screening panel does not have enough diseases in it. She and other parents of children with SCID urge the Committee to give future children a better chance by screening newborns for additional conditions. Finally, Ms. Ballard emphasized that the effects of false positives from newborn screening would depend on the approach a physician used to convey information to parents.

6. John Adams
Treasurer, Canadian Organization for Rare Disorders

Mr. Adams, a PKU dad from Toronto, Canada, with a 20-year-old son who is now a university student, said he is grateful to the people who helped his son by pushing for newborn screening for PKU years ago and is trying to help others achieve similar happy outcomes. He noted he attended the fourth meeting of the Advisory Committee to obtain both information and inspiration. In many ways, Canada lags behind the United States when it comes to newborn screening. Newborn screening is not covered by Canada's health insurance program, and no professional association has yet taken a public position on newborn screening. More than 400 labs in 50 countries participate in the U.S. Center for Disease Control and Prevention's (CDC) Quality Assurance and Proficiency Testing for Newborn Screening program, but Mr. Adams found that some Canadian labs did not even know about this CDC program. He and his colleagues intend to remedy that situation. Mr. Adams showed several maps showing where different Provinces in Canada stand in terms of screening newborns for specific condition. Mr. Adams said he feels very strongly that when building local capacity, it is important to buy services from the outside for the sake of babies born in the interim.

7. Carol Greene, M.D.
Society for Inherited Metabolic Disorders (SIMD)
Director, Pediatrics Genetics Clinic
University of Maryland School of Medicine

Dr. Green made a formal request on behalf of SIMD to send an organization representative to the Advisory Committee. She said members of the SIMD are scientists and clinicians—including physicians, nutritionists, nurses, and counselors—who have developed or improved the screening, diagnosis, and treatment for inborn errors of metabolism. An SIMD organization representative will bring experience with newborn screening and with treatment and long-term followup of metabolic disorders that is directly relevant to the Committee's charge.

XII. UPDATE ON THE APHL's NEWBORN SCREENING ACTIVITIES

Michael R. Skeels, Ph.D., M.P.H
Director, Oregon State Public Health Laboratory
Association of Public Health Laboratories (APHL)

Dr. Skeels gave a report on the newborn screening activities of the APHL. He noted that the APHL has a Newborn Screening Genetics and Public Health Committee, and Dr. William Becker

has been the chair. Dr. Becker is the newly elected president of APHL, so he will probably be somewhat less directly involved in newborn screening than he has been in the past.

Two APHL position statements/policy statements approved in June will sunset on June 30, 2007, and are currently under review by the APHL Newborn Screening Genetics and Public Health Committee:

- "Parental Consent in Public Health Newborn Screening Programs" (which states that explicit parental consent is not necessary for mandated public health newborn screening)
- "The Role of the Private Laboratory Sector in Public Health Newborn Screening Programs" (which states that the role of private laboratories should be limited to contractually prescribed arrangements)

(Copies of both statements were included under TAB #14 of the binder prepared for Advisory Committee members for the December 2006 meeting. The statements are also available on the APHL's Website: http://www.aphl.org/programs/newborn_screening_and_genetics/policy.cfm.)

A second area of activity for the APHL Newborn Screening Genetics and Public Health Committee is contingency or continuity of operations planning. There is more awareness than ever that there is vulnerability in all of our public health systems, and newborn screening is no exception to that. The APHL committee has been working over the last 15 months or so to try to educate newborn screening programs in the United States about the necessity of developing continuity of operations plans and then working with vendors to make sure that they're aware of the critical needs for emergency planning, and to also discuss other options for providing newborn screening services, surge capacity, regional collaborative projects and so forth, so that in the event of any sort of a shortage or interruption in services or supplies at one program, that the babies in that State are not vulnerable.

A third area of activity for the APHL Newborn Screening Genetics and Public Health Committee is training and education. The centerpiece for the coming year will be the 2007 Newborn Screening and Genetic Testing Symposium, which is scheduled for May 7th–10th, in Minneapolis, and will be cosponsored by the International Society for Neonatal Screening (ISNS). This symposium, as always, addresses the needs of laboratorians, followup managers, nurses, metabolic specialists, and all the other professionals who constitute the newborn screening team in each program. The theme this year will be harmonization of newborn screening systems, an attempt to create more continuity and consistency and to look at newborn screening from a systems approach to the extent possible.

A subcommittee of the APHL Newborn Screening Genetics and Public Health Committee is working on outsourcing of newborn screening activities. It is developing a survey instrument to solicit information from States' experiences with outsourcing or contracting for newborn screening services to develop guidance to programs thinking about outsourcing either all or components of their newborn screening services.

Finally, Dr. Skeels noted, the APHL, with heavy support and participation from the Centers for Disease Control and Prevention and cosponsorship by the Genetics Resource Center, held a workshop on the use of second specimens in newborn screening in December 2006. The meeting was initiated by the Laboratory Standards & Procedures Subcommittee of the Secretary's Advisory Committee on Heritable Disorders and Genetic Disease in Newborns and Children, and the chair of that subcommittee Dr. Brower reported on it earlier. The purpose of the meeting was for people to share experiences and try to get to the bottom, to the extent possible, of how

beneficial second testing is. What really came out from the meeting is the need to gather more information and do more analysis, and then to share that information with everybody who is interested.

XIII. COMMITTEE BUSINESS

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

Schedule Change for 2007 Advisory Committee Meetings. After reviewing Committee members' availability, Dr. Howell announced that the scheduled meetings for 2007 have changed. The new dates are as follows:

- May 14-15, 2007
- September 17-18, 2007

Agenda for the Next Committee Meeting. Dr. Howell asked for agenda items for the Advisory Committee's May 14-15, 2007 meeting. Committee members made the following suggestions:

1. A discussion and/or presentation on the cost analysis issues in the evidence review during the consideration of which conditions to include in the uniform newborn screening panel
2. Another Federal legislative update like the one presented by Ms. Pellegrini from the American Academy of Pediatrics
3. A presentation from Dr. Louder on the U.S. military's activities and initiatives pertaining to newborn screening
4. A report on the Followup & Treatment Subcommittee's planned 1-day meeting to identify elements of long-term followup and treatment in newborn screening
5. An update by Dr. Rinaldo on the Region 4: The Great Lakes Genetics Collaborative's study of State practices and cutoff ranges in tandem mass spectrometry testing for specific conditions in the uniform newborn screening panel
6. A more in-depth report on one or two different activities that the Regional Genetics and Newborn Screening Collaboratives are working on
7. A discussion and vote on the draft policies and procedures for the Advisory Committee prepared by Dr. Lloyd-Puryear (see below)

Dr. Howell asked Committee members to notify Dr. Lloyd-Puryear if they had any additional items they would like to see put on the agenda.

Deadline for Comments on Policies and Procedures for the Advisory Committee. A draft document prepared by Dr. Lloyd-Puryear entitled "Policies and Procedures for Operation and the Development of Recommendations for Screening Newborns and Children for Heritable Disorders and for the Heritable Disorders Program," was included in the materials distributed to Committee members in their briefing books for the December meeting (TAB #15). Dr. Lloyd-Puryear has been seeking comments on this for several months.

Dr. Howell asked Committee members either to send in their comments on the draft or to let Dr. Lloyd-Puryear know that they have no comments by the end of January 2007, noting that the Advisory Committee would vote on the policies and procedures at the May 2007 meeting. It was agreed that Dr. Lloyd-Puryear would e-mail the draft protocols document to Committee members and organization representatives to facilitate their review.

- ***DECISION #3: The Committee will vote on standard operating procedures for the Advisory Committee at the May 2007 meeting. By the end of January 2007, Committee members should either send in their comments on the draft policies and procedures or let Dr. Lloyd-Puryear know that they have no comments on the draft. Dr. Lloyd-Puryear will send the electronic file of the draft policies and procedures for the Advisory Committee document to Committee members for review.***

Conclusion of the Meeting. Dr. Howell closed the meeting by noting that it had been an extremely productive meeting and that he felt considerable progress had been made in terms of moving the nomination process for adding conditions to the uniform newborn panel forward. He thanked Committee members for their hard work, wished them a happy holiday, and said he looked forward to seeing them at the next meeting in May 2007.

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

/s/ _____

R. Rodney Howell, M.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.

APPENDIX A: WRITTEN PUBLIC COMMENTS