

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

Summary of 15th Meeting  
October 1-2, 2008  
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 15<sup>th</sup> meeting at 1:30 p.m. on Wednesday, Oct. 1, 2008, at the Capital Hilton Hotel in Washington, D.C. The meeting was adjourned at 2:40 p.m. on Thursday, Oct. 2, 2008. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments on Oct. 1, 2008.

## **Committee Members Present**

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# CONTENTS

<b>I. WELCOME, OPENING REMARKS .....</b>	<b>6</b>
<b>II. PROPOSED CONSTRUCT FOR THE ADVISORY COMMITTEE’S RECOMMENDATIONS: REPORT FROM THE DECISION CRITERIA &amp; PROCESS WORKGROUP .....</b>	<b>7</b>
<b>III. POMPE DISEASE NOMINATION: EVIDENCE REVIEW AND COMMITTEE ACTION .....</b>	<b>12</b>
A. External Evidence Review Workgroup’s Draft Report on Pompe Disease .....	12
B. Brief Summary of the Evidence on Pompe Disease by the Committee’s Decision-Making Workgroup .....	14
C. Committee’s Discussion and Decisions Regarding the Pompe Disease Nomination .....	15
<b>IV. PUBLIC COMMENT SESSION .....</b>	<b>18</b>
<b>V. INSURANCE COVERAGE AND REIMBURSEMENT FOR MEDICAL FOODS AND NUTRICEUTICALS .....</b>	<b>19</b>
A. Medical Foods and Nutraceuticals—Report from the Followup & Treatment Subcommittee’s Medical Foods Workgroup .....	19
B. State Policies on Payment for Dietary Treatment of Disorders Identified Through Newborn Screening: A Report Commissioned by the National Coordinating Center (NCC) for the Regional Collaboratives .....	21
<b>VI. UPDATE ON THE NEWBORN SCREENING USE CASE AND RESOURCE GUIDE FROM AHIC’S PERSONALIZED HEALTH CARE WORKGROUP .....</b>	<b>23</b>
<b>VII. CONTINGENCY PLANNING AND EMERGENCY PREPAREDNESS FOR NEWBORN SCREENING AND GENETIC SERVICES .....</b>	<b>26</b>
A. Development of the National Newborn Screening Contingency Plan .....	27
B. APHL’s Newborn Screening Preparedness/Contingency Planning Framework .....	28
C. Report on Emergency Preparedness for Newborn Screening and Genetic Services from the National Coordinating Center for the Regional Collaboratives .....	29
<b>VIII. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS &amp; DISCUSSION.....</b>	<b>30</b>
A. Laboratory Standards & Procedures Subcommittee Report .....	30
B. Education & Training Subcommittee Report .....	32
C. Followup & Treatment Subcommittee Report .....	33
<b>IX. COMMITTEE BUSINESS .....</b>	<b>34</b>
<b>APPENDIX A: WRITTEN PUBLIC COMMENTS .....</b>	<b>37</b>

## I. WELCOME, OPENING REMARKS

**Rodney Howell, M.D.**

**Chair, Secretary's Advisory Committee on Heritable Disorders  
in Newborns and Children**

**Professor, Department of Pediatrics**

**Leonard M. Miller School of Medicine**

**University of Miami**

Dr. Howell opened the meeting by welcoming several new organizational representatives to the Advisory Committee: Dr. Thomas Musci, representing the American College of Obstetricians and Gynecologists (ACOG); Dr. Frederick Chen, representing the American Academy of Family Physicians (AAFP); and Dr. Jane Getchell, representing the Association of Public Health Laboratories (APHL).

Later during the meeting, Stephen Smith, who serves as senior advisor to Elizabeth M. Duke, Ph.D., Administrator of the Health Resources and Services Administration (HRSA), expressed appreciation to the Committee for its work and noted that HRSA's leadership is working hard to give the Secretary of Health and Human Services (HHS) the materials he needs to make the decisions required by the Newborn Screening Saves Lives Act (Public Law 110-204) by October 21, 2008.

**Agenda for the Meeting.** The agenda for the meeting was as follows:

- **Report from the Committee's Decision Criteria & Process Workgroup on a decision and recommendation process for the Committee.** Dr. Nancy Green, on behalf of Dr. Calonge, presented the Decision Criteria & Process Workgroup's proposed process for the Advisory Committee to use in developing recommendations after receiving an evidence review on a condition nominated for inclusion in the uniform newborn screening panel.
- **Evidence review on Pompe disease.** Dr. James Perrin, chair of the Advisory Committee's external Evidence Review Workgroup, gave a report on the evidence for Pompe disease. In addition, Dr. Watson gave a summary of this report prepared by Dr. Rinaldo and Dr. Calonge.
- **Public comments.** A period was provided during which members of the public were invited to offer comments to the Advisory Committee.
- **Update from Followup & Treatment Subcommittee's Medical Foods Workgroup.** Dr. Susan Berry and Alissa Johnson reported on the Medical Foods Workgroup's activities pertaining to financial reimbursement and insurance coverage for medical foods.
- **Subcommittee meetings and reports.** The Advisory Committee's Laboratory Standards & Procedures Subcommittee, Education & Training Subcommittee, and Followup & Treatment Subcommittee held meetings open to the public, and the subcommittee chairs gave reports on what had transpired to the full Committee.
- **Report on the Newborn Screening Use Case from the Personalized Healthcare Workgroup (PHC) of the American Health Information Community (AHIC).** Dr. Stephen Downs, the co-chair of the Subgroup on Newborn Screening of AHIC's Personalized Health Care Workgroup, and Dr. Alan Zuckerman gave an update on the AHIC newborn screening use case and a companion resource guide being developed by the

Office of the National Coordinator for Health Information Technology. They also requested the Advisory Committee's support for these endeavors.

- **Emergency preparedness and contingency planning for newborn screening and genetic services.** Three people made presentations on initiatives related to emergency preparedness and contingency planning for newborn screening and genetic services.
- **Committee business.** The Committee wrapped up its business for the day and discussed agenda items for the Committee's upcoming Web conference on November 24, 2008, and subsequent meetings.

**Approval of Minutes.** The minutes of the meeting from August 7, 2008 (under Tab #5 in the materials distributed to Committee members in their briefing books) were approved unanimously.

## **II. PROPOSED CONSTRUCT FOR THE ADVISORY COMMITTEE'S RECOMMENDATIONS: REPORT FROM THE DECISION CRITERIA & PROCESS WORKGROUP**

**Nancy S. Green, M.D.**

**Associate Dean for Clinical Research Operations**

**Associate Professor of Clinical Pediatrics, Division of Hematology**

**Associate Director, Irving Institute for Clinical Translational Research**

**Columbia University Medical Center**

**Bruce Nedrow (Ned) Calonge, M.D., M.P.H.**

**Chief Medical Officer and State Epidemiologist**

**Colorado Department of Public Health and**

**Environment [via phone]**

**Committee Member**

Dr. Green presented a proposal from the Advisory Committee's Decision Criteria & Process Workgroup headed by Dr. Calonge for a construct that the Committee could use in making recommendations to the Secretary of Health and Human Services (HHS) after receiving an evidence report on a condition nominated for inclusion on the uniform newborn screening panel. The Decision Criteria & Process Workgroup's report dated 9/25/08 ("the Calonge report") was included under Tab #6 of materials distributed to Committee members in their briefing books. The members of the workgroup other than Dr. Calonge are Dr. Dougherty, Dr. Rinaldo, Dr. Boyle, Dr. Trotter, and Ms. Terry. Dr. Green is the liaison member from the external Evidence Review Workgroup.

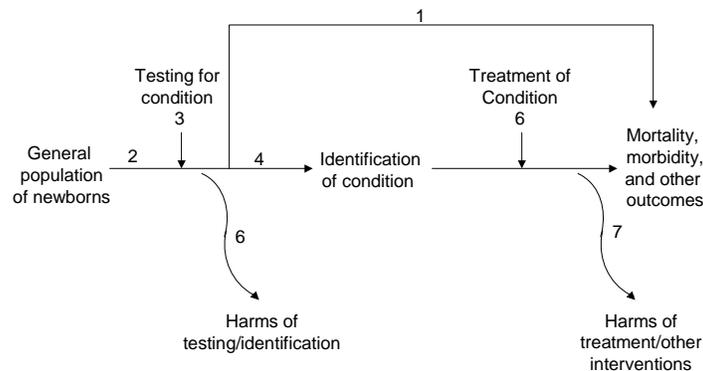
In this report, the Decision Criteria & Process Workgroup noted that the overarching question the Committee must address when considering whether to include a condition in the uniform newborn screening panel is whether screening for the condition at birth will improve health outcomes. The report recommended that the Committee base its recommendations to include a condition on the *certainty of net benefit*.

In many cases, it is unlikely that there will be evidence from peer-reviewed, large-scale, replicated intervention studies or randomized controlled trials involving screen-detected infants that screening for conditions nominated for the uniform panel will improve health outcomes. In such cases, the

Committee will have to consider evidence such as that from population-based observational studies in making its recommendations.

**Analytic Framework and Chain of Evidence.** In cases where evidence of benefit is lacking, the Decision Criteria & Process Workgroup recommends that the Advisory Committee create a chain of evidence to support its recommendations. The chain of evidence is put together with a set of key questions. Figure 1 is a generic analytic framework for use by the Advisory Committee. The numbers in the figures correspond to the eight key questions used to put together the chain of evidence that are discussed below.

Figure 1. Analytic Framework



- **Key question 1 (overarching question): Is there direct evidence that screening for the condition at birth leads to improved health outcomes?** The best evidence would be randomized trials involving screen-detected infants, but for many conditions considered by the Advisory Committee, such evidence is not likely to be available. Questions 2 through 8 below allow for the development of a chain of evidence that, if adequately addressed by research, can be used to support an Advisory Committee’s recommendation regarding the inclusion of a condition on the uniform newborn screening panel.
- **Key question 2: What is known about the condition?** Is the condition well defined and important? What is the incidence of the condition in the U.S. population? What is the spectrum of disease for the condition? What is the natural history of the condition, including the impact of recognition and treatment?
- **Key question 3: Is there a test for the condition with sufficient analytic utility and validity?** *Analytic utility* involves the choice of testing target or targets, the choice of testing platform, the availability of an access to testing reagents, considering whether these are commercially available, custom synthesized, “home brewed,” and/or part of current research, and whether they have right to use clearance. *Analytic validity* refers to the technical, laboratory accuracy of the test in measuring what it is intended to measure. It is key to the dissemination of the test. The goal would be to have very high analytic sensitivity and specificity and a high level of certainty that testing programs across the country would be able to implement use of a test with the same level of analytic validity. Types of evidence would need to address pre-analytic, analytic, and post-analytic issues. A detailed description of evaluating analytic validity, which was developed in part by the EGAPP (Evaluating Genomic Applications in Practice and Prevention) Working Group of

the Centers for Disease Control and Prevention (CDC) and can serve as a starting point for discussion, is presented in Appendix A of the Decision Criteria & Process Workgroup's draft report.

- **Key question 4: Does the test accurately and reliably detect the condition and clinical disease?** There are two parts to this question: First, is the evidence sufficient to conclude that we know what the clinical validity (ability to accurately predict the development of symptomatic or clinical disease) is? This involves only a consideration of the strength and quality (taken together as adequacy) of the evidence in the systematic review of the evidence to determine that we know the sensitivity and specificity of the test. Second, is this level of clinical validity sufficient to justify testing, given the test performance and the incidence/prevalence of the condition, which affect the ability of the test to detect a reasonable number of affected individuals who would be expected to manifest clinical disease, the tradeoff of risks of false positives, and the benefits of early detection of true positives. Issues of tradeoffs between false positives, false negatives, and identification of nonclinical conditions all affect clinical *utility*. A detailed description of evaluating clinical validity, modified from the in-press article on the Evidence Review Workgroup's methods, is presented in Appendix B of the Decision Criteria & Process Workgroup's draft report.
- **Key question 5: Are there available treatments for the condition that improve important health outcomes?** Does treatment of the condition detected through newborn screening improve important health outcomes when compared with waiting until clinical detection? Are there subsets of affected children more likely to benefit from treatment that can be identified through testing or clinical findings? Are the treatments for affected children standardized, widely available, and if appropriate, approved by the Food and Drug Administration (FDA)? This question refers to clinical utility, or the ability of testing for the condition to translate to improvements in important health outcomes, and to whether the potential benefits of testing, diagnosis and treatment exceed the potential harms. To address this question, the Advisory Committee will need to determine the value of proposed health outcomes considered. The EGAPP (Evaluating Genomic Applications in Practice and Prevention) Working Group is in the process of publishing a paper on health outcomes for consideration in evidence-based recommendations for genomic tests. This list is referenced in the Secretary's Advisory Committee on Genetics, Health, and Society's report *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*.
- **Key questions 6 and 7: Are there harms or risks identified for the identification and/or treatment of affected children?** Risks and harms often incompletely addressed in medical research are key to allowing the Advisory Committee to balance the potential benefits and risks when making a recommendation regarding a condition. Included in harms and risks are direct harms to physical health as well as other issues including labeling, anxiety, adverse impacts on parent and family relationships, and other ethical, legal, and social implications.
- **Key question 8: What is the estimated cost-effectiveness of testing for the condition?** This question does not appear in the analytic framework diagram but is a consideration that the Advisory Committee is specifically interested in.

**Approach to Translating Evidence into Advisory Committee Recommendations.** The Advisory Committee will make recommendations regarding whether conditions should be included in the uniform newborn screening panel after hearing a report from the external Evidence Review Workgroup, assessing the strength and quality of the available evidence, and considering other

clinical and social contextual issues. In making its recommendations, the Committee will have to make judgments regarding the following:

- Magnitude of net benefit
- Overall adequacy of evidence
- Certainty of net benefit/harm (critical appraisal questions across the chain of evidence)

Additional details regarding these issues are presented in the report and appendices of the Decision Criteria & Process Workgroup’s draft report.

**Proposed Decision Matrix for Advisory Committee Recommendations.** Finally, the Decision Criteria & Process Workgroup proposed in its draft report that the following matrix be used to structure the Advisory Committee’s recommendations regarding which conditions should be included in the uniform newborn screening panel.

**Table 1: Proposed Decision Matrix for the Advisory Committee’s Recommendations**

<u>RECOMMENDATION</u>	<u>LEVEL OF CERTAINTY</u>	<u>MAGNITUDE OF NET BENEFIT</u>
Recommend adding the test to the core set	Sufficient	Significant
Recommend not adding the test to the core set	Sufficient	Zero or net harm
Recommend adding the test with “provisional” status	Insufficient, but the potential for net benefit is compelling enough to add the test now, with a commitment to evaluate the experience with the test over time	Potentially significant, supported by contextual considerations
Recommend not adding the test now, but instead recommend pilot studies	Insufficient, and additional evidence is needed to make a conclusion about net benefit	Potentially significant or unknown

**Questions & Comments**

Following the presentation, Dr. Howell asked Committee members to discuss the proposed decision matrix for the recommendations in the Decision Criteria & Process Workgroup’s draft report. He noted that the Committee might use the decision matrix to structure its upcoming recommendation with respect to whether Pompe disease should be added to the uniform newborn screening panel.

Dr. Vockley proposed changing the matrix by eliminating the recommendation for adding a condition with “provisional status” and changing the third recommendation to “Recommend not adding the condition now but encourage additional specific studies” (this would be saying that there is almost enough information to support a recommendation but not quite). In addition, he

proposed changing the words in the Level of Certainty column of the third recommendation to read: “Insufficient but potential net benefit is compelling.”

Dr. Vockley also proposed changing the fourth recommendation to “Recommend not adding the condition now” (this would be saying that the information to support the recommendation at present is insufficient). The fourth recommendation is different from the second recommendation (“Recommend not adding the condition to the core set”), because the latter says the condition should NOT be added at all because there is sufficient evidence that there would zero benefit or net harm.

After some discussion, the Advisory Committee voted unanimously to approve Dr. Vockley’s proposed changes to the decision matrix for the Advisory Committee’s recommendations:

- **MOTION #1 (APPROVED):** *In the report by the Decision Criteria & Process Workgroup dated 9/25/08, make the following changes in the decision matrix for the Advisory Committee’s recommendations:*
  - *Recommendation #3: Change to read: “Recommend not adding the condition now but encourage additional specific studies.” Change “Level of Certainty” column for this recommendation to read: “Insufficient, but potential net benefit is compelling.”*
  - *Recommendation #4: Change to read: “Recommend not adding the condition now.”*

On the second day of the meeting, after the summary presentation by Dr. Perrin of the external Evidence Review Workgroup’s draft report on the evidence for Pompe disease, Dr. Trotter moved that the Advisory Committee adopt the decision matrix with the Vockley revisions. During the discussion of the motion, Dr. Howell indicated that there could be modifications to the decision matrix for recommendations in the future. The Advisory Committee voted to approve Dr. Trotter’s motion to adopt the decision matrix with the Dr. Vockley’s changes (5 votes for, 4 votes against).

- **MOTION #2 (APPROVED):** *The Advisory Committee adopts the decision matrix for the Advisory Committee’s recommendations proposed in the report by the Decision Criteria & Process Workgroup dated 9/25/08 with the Vockley changes approved in the previous motion.*

Some Committee members wanted more time to review and make comments on the Decision Criteria & Process Workgroup’s report dated 9/25/08 (“the Calonge report”). Dr. Boyle indicated that between key questions #4 and #5, a question that proved important in the case of Pompe disease and should be added is: Is there a confirmatory test? She recommended that the full Committee be given additional time to look at the report and submit comments, so that a vote on the report could be taken at the Committee’s November 24, 2008, Web conference. Dr. Howell agreed. Dr. Lloyd-Puryear urged Committee members to send their comments on the report to Dr. Calonge as soon as possible, so that the Committee would be able to vote on a revised document at the upcoming Webcast on November 24<sup>th</sup>.

- **DECISION #1:** *The Advisory Committee will vote on whether to approve the Decision Criteria & Process Workgroup’s report (“the Calonge report”) at its November 24, 2008, Webcast. Advisory Committee members should send any comments on the report to Dr. Calonge as soon as possible, so that the Decision Criteria & Process Workgroup can incorporate them prior to that conference call.*

### **III. POMPE DISEASE NOMINATION: EVIDENCE REVIEW AND COMMITTEE ACTION**

In this session, there were two presentations on the evidence for the inclusion of Pompe disease on the uniform newborn screening panel. First, Dr. Perrin presented the external Evidence Review Workgroup's 25-page draft report on the evidence for Pompe disease. This draft report (V. 09 16 08) was included under Tab #7 in materials provided to Committee members prior to the meeting. Second, Dr. Watson outlined the Advisory Committee's Decision-Making Workgroup 2-page summary of the evidence review on behalf of Dr. Rinaldo. This 2-page summary (dated September 26, 2008) was also included under Tab #7. Following the presentations on the evidence, the Advisory Committee made a decision to respect its recommendation regarding the nomination of Pompe disease to the uniform newborn screening panel.

#### **A. External Evidence Review Workgroup's Draft Report on Pompe Disease**

**James Perrin, M.D.**

**Professor of Pediatrics, Harvard Medical School**

**Director, Division of General Pediatrics, MassGeneral Hospital for Children**

**Director, Center for Child and Adolescent Health Policy, Harvard Medical School**

Pompe disease is the first disease to be considered by the Evidence Review Workgroup at the request of the full Advisory Committee. The workgroup's review of the evidence on Pompe disease entailed a literature search, as well as interviews with subject matter experts. The key authors of the draft summary of the evidence on Pompe disease were Dr. Marsha Browning and Dr. Alex Kemper, plus staff (Dr. Anne Comeau, Dr. Nancy Green, Alix Knapp, Dr. Ellen Lipstein, Dr. Lisa Prosser, and Denise Queally). The draft summary includes evidence tables, a list of interviewees, and a bibliography of identified articles. It also lists experts who were contacted. The review provides almost no information about quality, but the workgroup hopes to provide more systematic information about quality moving forward.

**Key Questions Addressed in the Review of the Evidence on Pompe Disease.** Four key questions were addressed in Evidence Review Workgroup's review of the evidence on Pompe disease:

1. Do current screening tests effectively and efficiently identify cases of Pompe disease that may benefit from early identification?
2. Does intervention in newborns or infants with pre-symptomatic or early symptomatic Pompe disease improve health outcomes?
3. What is the cost-effectiveness of newborn screening for Pompe disease?
4. What critical information is missing that is needed to inform screening recommendations for Pompe disease?

In the context of addressing these overarching questions, the Evidence Review Workgroup also considered the following specific questions: What is the natural history of Pompe disease? What is the prevalence of Pompe disease? What are the methods of screening and diagnosis? How accurate are the screening tests? What are the benefits of treatment? What is the relationship

between treatment outcomes and the timing of treatment intervention? What are the potential harms of screening, diagnosis, and treatment?

**Evidence Review Workgroup's Report on the Evidence for Pompe Disease.** The Evidence Review Workgroup found that Pompe disease affects about 1 in 30,000 to 1 in 50,000 individuals but may be influenced by the underestimation of the true prevalence of the infantile form of Pompe, due to increased mortality in the first 15 months and/or the lack of capture of accurate diagnosis prior to death. The ratio of infantile Pompe disease to late-onset Pompe disease in newborns is unknown. Infantile Pompe disease is fatal, often within the first 15 months of life, and treatment with enzyme replacement therapy can be lifesaving. Indirect evidence suggests that earlier treatment for infantile Pompe disease improves health outcomes. Late-onset Pompe disease can also be fatal, but this form of Pompe disease is variable in both age of onset and rate of progression. It is unknown whether presymptomatic or prophylactic treatment leads to better health outcomes for late-onset Pompe disease.

In terms of the key questions identified above, the Evidence Review Workgroup's findings were as follows:

1. **What is the effectiveness and efficiency of current screening tests for Pompe disease?** A large, population-based, pilot study of newborn screening for Pompe disease that relied on a highly sensitive enzyme assay using dried blood spots in Taiwan identified four cases of infantile Pompe disease in a population of 132,528 newborns. There were a high number of false positives. Eight newborns of the 132,528 were referred for diagnostic testing after the first blood spot (0.006%); 1,093 required a second blood spot (0.82%); and 113 (10.3%) were referred for diagnostic testing. No cases of late-onset Pompe disease were detected. The reasons for the lack of identification of late-onset cases are unclear. Other potential screening strategies for Pompe disease are available (e.g., tandem mass spectrometry) but have not undergone population-based pilot testing.
2. **What are the effects of treating Pompe disease on health outcomes?** Treatment of infantile-onset Pompe disease is lifesaving. Without treatment, most children with infantile-onset Pompe disease would die between the ages of 12 months and 24 months. Long-term treatment studies of treating infantile-onset Pompe disease have not been conducted. The optimal time to begin treatment (e.g., presymptomatic vs. after the development of symptoms) for late-onset Pompe disease is not known.
3. **What is the cost-effectiveness of newborn screening for Pompe disease?** No cost-effectiveness data were identified by the Evidence Review Workgroup. Charge data are available for rhGAA. Other costs (e.g., costs of screening, treatment) are not available, and the Evidence Review Workgroup is unaware of any data that quantify the costs or utilities (quality-of-life measure) associated with untreated Pompe disease, treated Pompe disease, the harms of false positives, and positives, and the relative benefits vs. harms of diagnosing late-onset Pompe disease during early infancy.
4. **What critical missing information is needed to inform screening recommendations for Pompe disease?** Several critical pieces of information are needed.
  - a. *Screening*
    - Standardized case definition for infantile Pompe (A first attempt at a definition is included in the Evidence Review Workgroup's report, but it needs to be vetted.)
    - Accuracy of screening for infantile-onset in population studies beyond Taiwan

- Utility of various methods, especially, comparison of activity-based vs. quantity-based
- Feasibility of screening using current laboratory infrastructure
- Demonstration in multiple newborn screening laboratories

***b. Diagnosis***

- Standardized case definition for infantile Pompe
- Differentiation between classic and non-classic during presymptomatic period – Is differentiation possible?

***c. Treatment***

- Is treatment for Infantile Pompe effective? Extent and effect of selection bias?
- Is treatment reproducible in other treatment centers?
- What is effect of development of antibodies to rhGAA

***d. Other***

- Improved strategies for determining prevalence thru systematic case finding, including clarity of early vs. late onset rates
- Are there benefits to identification of late onset Pompe in newborns?
- Acceptability of screening (esp., related to late onset disease)
- Studies of harms of screening and diagnosis
- Cost-effectiveness studies

## **B. Brief Summary of the Evidence on Pompe Disease by the Committee’s Decision-Making Workgroup**

**Michael S. Watson, Ph.D., FACMG**  
**Executive Director**  
**American College of Medical Genetics (ACMG)**  
**Representative to the Committee**

**On behalf of Piero Rinaldo, M.D., Ph.D.**  
**Chair, Decision-Making Workgroup**  
**Committee Member**

Dr. Watson summarized the Evidence Review Workgroup’s findings with regard to the evidence on Pompe disease on behalf of the Decision-Making Workgroup headed by Dr. Rinaldo, who was not able to attend the meeting. When Dr. Dougherty noted that she had not had an opportunity to review the material in its current form, it was explained that the 2-page summary entitled “Decision-Making Workgroup Evidence Review” dated September 26, 2008, which was included in Committee members’ briefing books (Tab #7), had been prepared primarily by Dr. Rinaldo and Dr. Watson.

The summary presented by Dr. Watson used the analytic framework of eight questions proposed in the Decision Criteria & Process Workgroup draft report (“the Calonge report”):

- Key question 1 (overarching question): Is there direct evidence that screening for the condition at birth leads to improved health outcomes?
- Key question 2: What is known about the condition?
- Key question 3: Is there a test for the condition with sufficient analytic utility and validity?
- Key question 4: Does the test accurately and reliably detect the condition and clinical disease?
- Key question 5: Are there available treatments for the condition that improve important health outcomes?
- Key questions 6 and 7: Are there harms or risks identified for the identification and/or treatment of affected children?
- Key question 8: What is the estimated cost-effectiveness of testing for the condition?

On the basis of the report by the external Evidence Review Workgroup, the Committee’s Decision-Making Workgroup arrived at the following conclusions with respect to the evidence on Pompe disease:

1. There are significant concerns with testing specificity and the comparative effectiveness of alternative testing algorithms (repeat specimens vs. second-tier tests) and the potential applicability of prognostic tools.
2. The dramatic effectiveness of available treatment in infantile Pompe disease cases has been noted.
3. Better evidence is needed regarding the ability for screening to distinguish between infantile and late-onset Pompe disease and regarding the efficacy of treatment in either presymptomatic or symptomatic cases.

## **C. Committee’s Discussion and Decisions Regarding the Pompe Disease Nomination**

**Committee’s Discussion of the Evidence for Pompe Disease.** At Dr. Howell’s request, Dr. Perrin and Dr. Watson summarized the evidence with respect to Pompe disease on the second day of the meeting, so that the Committee could discuss it.

- **Condition.** Dr. Perrin noted that concerns included difficulties in distinguishing infantile Pompe disease and late-onset Pompe disease, as well as the lack of a clear case definition of early infantile Pompe disease. Dr. Vockley suggested simply focusing on infantile Pompe. The point was made that because early-onset Pompe disease is very bad, there is a compelling reason to screen.
- **Screening test.** The very high false positive rate found in the pilot study of screening for Pompe disease in Taiwan was a primary concern among Committee members. In addition, the reason for lack of identification of late-onset Pompe disease in the published report was unclear. Dr. Skeels, noting that the recall rate for confirmatory testing in the study in Taiwan was prohibitively high (0.82%), asked if the cutoff could be changed to eliminate false positives without getting rid of true positives. Speaking from the audience, Dr. Alex Kemper said that lowering the cutoff was possible. He explained that the Taiwan

investigators initially used a threshold they knew would produce a high number of false positives to ensure that they would not miss any true positives; when they lowered the threshold; the number of newborns who had to be recalled for a second blood spot was smaller. Those numbers, though not included in the published report, are shown in Table 5 of the Evidence Review Workgroup's report. Dr. Vockley, speaking as a clinician, said that using the numbers generated in the Taiwan study, if he had to follow up on all the patients who initially screened positive for Pompe disease, he would be overwhelmed. He urged the Advisory Committee to consider what happens to clinicians downstream if a condition is added to the uniform screening panel. Dr. Vockley also made two suggestions related to the Evidence Review Workgroup's process: (1) interview as experts not just people on the front line working with a condition and therapy but other individuals who do not have such a vested interest in getting something screened for (e.g., people taking care of patients); and (2) include all of the authors' names of articles in the bibliographies it prepares to facilitate the identification of conflicts of interest. Dr. Perrin took Dr. Vockley's comments under advisement and said he would appreciate the Committee's advice in developing questions to ask experts who are not researchers. Dr. Chen said he is concerned about the substantial false positive rate and noted that there may be another future technique like tandem mass spectrometry (MS/MS) to reduce that. Referring to Key question #6 about harms, Dr. Chen also said that even though there are no specific data on harms for Pompe disease, there is lots of literature on harms of false positives for other diseases like cystic fibrosis, and those harms should be taken into account. Dr. Watson said it remains to be determined what the best screening algorithm for Pompe disease is and whether things can be done to reduce false positives.

- **Acceptability of pilot tests of screening done outside the United States.** Dr. Howell asked Committee members to give their views on whether the Committee should accept pilot studies of screening done outside the United States. Some people, including Dr. Getchell, Dr. Trotter, Dr. Vockley, thought that U.S. pilot studies should generally be required. Other people, including Dr. Boyle and Ms. Terry, suggested that because many conditions under consideration for inclusion in newborn screening programs are rare, the Committee should accept non U.S. studies of screening, or at least consider whether to use them on a case-by-case basis. Dr. Watson said he thought that different things could be piloted in different ways. Finally, Dr. Alexander said that the Newborn Screening Translational Research Network (NBSTRN) currently under development by the National Institutes of Health (NIH) would provide an infrastructure for research that facilitates the development of new screening methods, clinical trials for new therapeutic interventions and support longitudinal research to study the long-term health of children identified through newborn screening. NIH is funding a coordinating center to put the NBSTRN together and to follow up on outcomes (as announced on the Website [FedBizOpps.gov](http://www.FedBizOpps.gov): [www.fbo.gov](http://www.fbo.gov)). Dr. Alexander suggested that Pompe disease would be a perfect pilot for using the NBSTRN. It would also be possible to try screening for Pompe disease using MS/MS to see if that approach could reduce the false positive rate.
- **Treatment and management.** Treatment of infantile Pompe disease may be lifesaving. There are no studies of treatment of screen-positive newborns; however, there is indirect evidence that earlier treatment has better outcomes. Questions about longer term outcomes for treatment and when to begin treatment for adult-onset Pompe disease remain. The only way to find out the answer is through a carefully controlled study in a research environment.

- **Cost-effectiveness studies.** Cost-effectiveness studies of Pompe disease have not been done. Dr. Watson said they should be done. Dr. Howell noted that treatment for Pompe diseases is expensive, but the condition is rare, and without treatment, children die.

**Committee’s Decisions Regarding the Pompe Disease Nomination.** Given some of the questions remaining about Pompe disease, Dr. Skeels moved that the Advisory Committee vote to endorse recommendation #3 for Pompe disease: “Recommend not adding the condition now but encourage additional specific studies.”

Dr. Burton raised process issues, saying that she did not think the Committee should vote on the Pompe disease nomination for two reasons: (1) the nominator was not explicitly notified that this vote would be taken (although it was a matter of public record); and (2) Dr. Dougherty indicated that she and others on the Decision-Making Workgroup had not seen or signed off on the summary slides prepared by Dr. Rinaldo. Ms. Terry agreed that the Committee should not move forward so quickly, especially given that Pompe disease is the first condition the Committee has considered adding to the uniform newborn screening panel.

Dr. Howell asked the Advisory Committee what it wanted to do and polled individual members. Dr. Vockley, Ms. Monaco, Dr. Dougherty, Dr. Geleske, Dr. Chen, Dr. Musci, Dr. Getchell, Dr. Louder, Dr. Telfair, Dr. Buckley, and Dr. Skeels voted to move forward, with the understanding that in the future, a decision point would be put on the agenda and nominators would be notified that a condition was being considered.

The Advisory Committee unanimously approved the following motion offered by Dr. Skeels.

- **MOTION #3 (APPROVED):** *The Advisory Committee’s recommendation with regard to the nomination of Pompe disease to the uniform newborn screening panel is recommendation #3: “Recommend not adding the condition now but encourage additional specific studies.”*

Dr. Howell asked Committee members what they wanted to tell the nominators of Pompe disease they needed to do. Dr. Perrin suggested that the external Evidence Review Workgroup come up with a list of things that the nominators should do and let the Advisory Committee review and vote on that list and a letter to the nominators of Pompe disease. Dr. Lloyd-Puryear stated that if the Advisory Committee approved a letter to the nominators of Pompe disease, no vote on the external Evidence Review Workgroup’s 25-page draft report on the evidence or the 2-page summary of the evidence prepared by the Advisory Committee’s Decision-Making Workgroup would be needed. Dr. Howell agreed with Dr. Lloyd-Puryear. He indicated that members of the Advisory Committee would be asked to approve a letter to the nominators of Pompe disease electronically.

Dr. Burton raised substantive issues with the the Decision-Making Workgroup’s 2-page summary entitled “Decision-Making Workgroup Evidence Review” dated September 26, 2008. Dr. Dougherty asked whether the Evidence Review Workgroup’s report on Pompe disease would accompany the letter to the nominator. Dr. Howell replied that the evidence review would be posted on the Advisory Committee’s Website. Noting that the Evidence Review Workgroup’s report presented to the Committee at this meeting is still a draft, Dr. Perrin said the workgroup would have its final report ready for posting in a couple of weeks. Dr. Howell said that the letter to the nominators of Pompe disease from the Committee could refer the nominators to the Evidence Review Workgroup’s final report on the Advisory Committee’s Website.

Dr. Howell made the following decisions:

- **DECISION #2:** *The Evidence Review Workgroup will draft a list of additional information that is needed on Pompe disease for inclusion in a letter to the nominators of that condition. A letter from the Advisory Committee to the nominators of Pompe disease that includes the list of additional information needed on Pompe disease will be drafted and e-mailed to members of the Advisory Committee for review. The Advisory Committee will vote on whether to approve the letter to the nominators of Pompe disease electronically.*
- **DECISION #3:** *The final report of the Evidence Review Workgroup's report on Pompe disease will be posted on the Advisory Committee's Website (<http://www.hrsa.gov/heritabledisorderscommittee/>), and the nominators will be referred to that report.*

## **IV. PUBLIC COMMENT SESSION**

Two people made public statements to the Advisory Committee on Heritable Disorders in Newborns and Children on the afternoon of Oct. 1, 2008. The text of their written statements appears in Appendix A.

**1. Ronald J. Bartek**  
**Friedreich's Ataxia Research Alliance (FARA)**  
**Springfield, VA**  
**[www.cureFA.org](http://www.cureFA.org)**  
**[fara@cureFA.org](mailto:fara@cureFA.org)**

Mr. Bartek described his 22-year-old stepson Keith's history with the neurodegenerative disease Friedreich's ataxia, which is the most common form of inherited ataxia, affecting about 1 in 50,000 people in the United States. Since developing symptoms and being diagnosed with Friedreich's ataxia in 1997 at age 11, Keith has suffered progressive loss of strength and coordination (ataxia) and developed life-shortening cardiomyopathy, severe scoliosis, and Type 1 diabetes. He now requires a wheelchair and is dependent on others for most activities of daily living.

Fortunately, the gene and mutation for Friedreich's ataxia were identified in 1996. With the support and encouragement of doctors at the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health, Mr. Bartek and his wife founded the Friedreich's Ataxia Research Alliance (FARA) to support education and research for the condition. Since then there has been tremendous progress in understanding the pathophysiology of the disease the protein deficiency involved. Currently, a number of promising therapeutics for Friedreich's ataxia are in clinical trials or in development, including two ongoing Phase III clinical trials that will be completed in 2009. FARA has also started working with a team of investigators at the Mayo Clinic to develop a dried blood test for Friedreich's ataxia. The goal is to validate the test analytically and clinically with a pilot study beginning in 2009 of approximately 70,000 newborns to develop the information needed to nominate Friedreich's ataxia for inclusion on the uniform newborn screening panel.

**2. John Adams**  
**Parent and Volunteer with the Canadian Organization for Rare Disorders**

Mr. Adams, the father of a son with phenylketonuria (PKU) who volunteers with the Canadian Organization for Rare Disorders, gave an update on his son's remarkable response to early drug therapy with Kuvan™, a product developed under the Orphan Drug Act. His son now has a 2-year

supply of formula that he no longer needs and is a guest of the Biotechnology Industry Association. Mr. Adams noted that this month is the 25<sup>th</sup> anniversary of President Ronald Reagan signing into law the Orphan Drug Act, which created market and regulatory incentives for investors and drug developers to pay attention to unmet needs of patients with rare disorders. He noted that his son is one of many who are the direct beneficiaries of this initiative.

## **V. INSURANCE COVERAGE AND REIMBURSEMENT FOR MEDICAL FOODS AND NUTRICEUTICALS**

The Medical Foods Workgroup of the Advisory Committee's Followup & Treatment Subcommittee is seeking to ensure families of children with inborn errors of metabolism have coverage for medical foods, nutraceuticals, and other medically necessary treatments. As a start, the workgroup has been trying to define the scope of the problem in three ways: (1) developing and implementing a family survey regarding coverage of medical foods, nutraceuticals, and feeding supplies; (2) examining federal mandates and regulations governing public and private insurance coverage of these products; and (3) documenting mandates and regulations in place in each state. In this session, Dr. Susan Berry, who chairs the Medical Foods Workgroup, and Alisa Johnson provided further details about these efforts.

### **A. Medical Foods and Nutraceuticals—Report from the Followup & Treatment Subcommittee's Medical Foods Workgroup**

**Susan A. Berry, M.D.**  
**Professor and Director**  
**Division of Genetics and Metabolism**  
**Department of Pediatrics**  
**University of Minnesota**

Individuals with inborn errors of metabolism detected via newborn screening cannot survive without medical foods because they are the treatment. Medical foods are specially compounded formulas that supply a substantial portion of nutrition for the treatment; nutraceuticals are pharmacological doses of cofactors or vitamins, amino acids provided to give substrate or prevent specific amino acid deficiency, other vitamin-like drugs that may provide benefit, and medium chain triglyceride oil). Both classes of agents, medical foods and nutraceuticals, require physician supervision. In addition, there are low protein foods that do not require a prescription but are important adjunctive aid in the treatment of affected individuals.

The problem is that many people cannot afford to buy medical foods and nutraceuticals. These products are often excluded from coverage by insurers because they are not drugs. The Food and Drug Administration (FDA) defines a medical food as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" (<http://www.cfsan.fda.gov/~dms/medfguid.html>).

There are many barriers to insurance coverage of medical foods, many of which are not under anyone's control. First, private insurers have their own practices, and the practices of public insurers vary from state to state. Second, each policy, even with the same insurance company, may have differing coverage. Third, each state has different laws and regulations covering the provision

of medical foods (see <http://www.ncsl.org/programs/health/lawsfoodsformula.htm> for a list of the state laws). Finally, even when laws/guidelines exist, they are subject to interpretation by insurers and the states.

As a result of these barriers, insurers often initially deny coverage for medical food and nutraceutical prescriptions. In Minnesota and other states, it takes repeated appeals to insurers to get them to cover medical foods and nutraceuticals. In the meantime, some patients go without treatment, some change their insurer or obtain Medicaid, and some find charity groups that paid for a month of formula or medicine while appeals are under way. And because coverage is granted for 12-month time periods, the process of obtaining insurance coverage for medical foods and nutraceuticals has to be repeated every year.

The Medical Foods Workgroup has been working on the development and implementation of a survey of families regarding their experiences in obtaining coverage and reimbursement for medical foods, nutraceuticals, and feeding supplies. This survey is now undergoing pilot testing in three regions (Region 2–NYMAC; Region 3– Southeast Region; Region 4–Great Lakes). Following the pilot testing, there are plans for full implementation of 200 surveys in each region in the spring of 2009. The information from the surveys will be used to develop a manuscript and identify potential actions. It is also reviewing mandates and regulations governing public and private coverage of medical foods.

The Medical Foods Workgroup held a meeting on June 2, 2008, to shed light on federal mandates and regulations governing public and private coverage of medical foods and nutraceuticals. In the first part of the June 2<sup>nd</sup> meeting, invited experts gave presentations regarding insurance coverage of medical foods from various perspectives—the private insurance perspective, the public insurance perspective, and the perspective of the federal Centers for Medicare and Medicaid Services (CMS). In addition, experts from the U.S. Department of Labor and U.S. Department of the Treasury discussed the issues pertinent to the coverage of medical foods by employment-based health plans governed by the federal Employee Retirement Income Security Act (ERISA), which preempts state insurance laws. These presentations made it clear that, given the complexity of the insurance structure in the United States, getting broad insurance coverage for medical foods and nutraceuticals would be challenging. The workgroup is now seeking to develop recommendations to impact financing of medical foods for the Advisory Committee’s action. Possible actions to impact the financing of medical foods include the following:

- Medicaid: (1) Broaden the federal statute to cover medical foods; (2) Develop a model state policy for medical food for Medicaid (might be easier).
- Private insurers: (1) Develop a model state insurance law to minimize variation from state to state; (2) Work with the American Medical Association’s editorial board to develop reimbursement codes (CPT) that facilitate billing; (3) Work with insurers to recognize and reimburse for appropriate CPT codes; (4) Work with insurers to improve knowledge base of staff regarding medical foods.
- Other (employer-based health plans covered by ERISA and therefore exempt from state statutes): (1) Explore options to influence employer-based health plans, including federal mandates under ERISA (ERISA plans cover 60 percent of people with private insurance); (2) Seek advice from the FDA about updating the definition of medical foods.

## **B. State Policies on Payment for Dietary Treatment of Disorders Identified Through Newborn Screening: A Report Commissioned by the National Coordinating Center (NCC) for the Regional Collaboratives**

**Alissa L. Johnson, M.A.**  
**Principal Consultant**  
**Johnson Policy Consulting**

Work on documenting mandates and regulations for medical food in place in each state has been done by Ms. Johnson, formerly with the National Conference of State Legislatures. Ms. Johnson performed a study of state policies on payment for dietary treatment of disorders identified through newborn screening for the Regional Genetics and Newborn Screening Collaboratives' National Coordinating Center (NCC).

The method of the study was a search of online statutes and regulations for the 50 states and the District of Columbia beginning in July 2008 using forms of the word newborn, metabolic, inherited, PKU, and genetic. From this search, Ms. Johnson analyzed results that addressed payment or services that allowed individuals to obtain free dietary treatment. Statutory or regulatory provisions requiring referral or counseling only were not included.

This study revealed that states vary widely in their policies that allow individuals to obtain free dietary treatment and therefore avoid bearing the cost of medical foods. At time of the search, 43 states and the District of Columbia had a statute that addressed payment for dietary treatment, and 31 states had a regulation that did so. Some states had both a statute and a regulation. Four states (Mississippi, Oklahoma, South Carolina, and West Virginia) had neither.

The definitions of disorders in these statutes and regulations are widely inconsistent. Many states (26) use different definitions of disorders and treatment within the state. In six states (Arkansas, California, Minnesota, South Dakota, Tennessee, and Washington), insurance mandates pertain only to PKU. In 31 states and the District of Columbia, disorders are defined as disorders screened for under the state's newborn screening program, so they potentially could include all of the metabolic disorders on the American College of Medical Genetics (ACMG) uniform newborn screening panel. Other definitions list specific disorders or are open to interpretation.

The definitions of treatment in the state statutes and regulations are also widely inconsistent and sometimes open to interpretation. Commonly, treatment is defined as medically necessary low-protein food product formulated to have  $\leq 1$  gram of protein. Terms such as treatment services, dietary treatment, therapy, formula, reimbursable treatment costs are not defined in 20 instances.

Legislative and regulatory tools that allowed individuals to obtain free dietary treatment in the states include the following:

- *Insurance requirements for payment.* These exist in 33 states (8 states cover food; 25 states cover food and formula). Some states have caps (ranging from \$200 per month in Louisiana to \$25,000 for formulas and \$4,000 for low-protein modified foods in Kentucky) or age limits (ranging from age 6 in Missouri to age 35 for women in Colorado).
- *State services.* State services include (1) authorization to supply medical foods (40 states); (2) medical foods and formula paid for using Children's Health Insurance, Medicaid, WIC, newborn screening program fees, birth record fees, CSHCN/Title V (Georgia, Michigan,

Nebraska, North Dakota, and Texas); (3) reimbursement to providers (Alaska, Arkansas, Massachusetts); and (4) reimbursement to individuals (Kansas and Arizona).

The ACMG/NCC performed a followup survey that identified 16 states using Title V maternal and child health services block grant funds to provide medical foods or formula for a subset of population (Connecticut, Florida, Idaho, Michigan, Montana, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Tennessee, Texas, Vermont, Virginia, West Virginia)—11 more than in the original study. The followup survey also identified one additional state statute. In several cases where the statute or regulation is unclear, the state is providing assistance. Some states (e.g., Arkansas) have a statute or regulation authorizing treatment assistance, but such assistance is not being provided. The reason is unknown. Some states have clarified the disorders/treatment covered. Twelve states reported legislation introduced or being considered.

### **Questions & Comments**

Dr. Howell asked what immediate steps Dr. Berry and Ms. Johnson would recommend in view of the Medical Foods Workgroup's finding. Dr. Berry said one possibility is developing a model state law and trying to make the reimbursement process for medical foods more uniform across states. Ms. Johnson suggested that the Followup & Treatment Subcommittee work with the National Conference of Commissioners on Uniform State Laws (NCCUSL) in developing a model statute. NCCUSL drafts and proposes specific statutes in areas of the law where uniformity between the states is desirable.

Dr. Louder, speaking as a neonatologist, asked whether the state laws made provision for nutritional products that were not available in regular grocery stores but were not for inherited diseases. Dr. Berry said although many children require specialized diets, including average preemies, the workgroup was not trying to get reimbursement for medical foods for anyone but children with inborn errors of metabolism. Insurers have great misgivings about opening the door to reimbursement of a broad set of products for a wide range of disorders instead of for a set of products for a narrow range disorders. Dr. Howell noted that one way to cope with this problem would be to specify that reimbursement was only for products intended to treat conditions detected via newborn screening that had been approved by the Advisory Committee on Heritable Disorders in Newborns and Children.

Dr. Telfair asked whether Ms. Johnson got any idea in her research how long it took to get legislation enacted. Ms. Johnson said her research did not address this, but her past experiences suggests that a constituent probably initiated the idea of a specific law, and they often do not figure out how to get the money. Dr. Telfair suggested that Dr. Berry add a discussion with those responsible for decisionmaking at the state level and include orientation/training for the people asking the questions to help with consistency. He offered to help with this.

Dr. Alexander urged the Medical Foods Workgroup not to dismiss the idea of federal legislation. Dr. Berry agreed that federal legislation should be considered. It would be more difficult to get federal legislation but federal legislation would be more complete. Dr. Boyle explained that although self-insured plans offered by employers are governed by the Employee Retirement Income Security Act (ERISA) and completely exempt from state laws, federal statutes setting a federal floor for certain services provided ERISA plans that have been enacted in only four instances (i.e., maternity coverage after childbirth, mental health parity, post-mastectomy benefits for breast cancer patients, prohibiting employment discrimination based on genetic information). For that reason, the Followup and Treatment Subcommittee thought amending ERISA would be an uphill battle. Another possibility might be using Title V maternal and child health services block grant funds. Dr. Howell said Title V would impact a large number of kids. Dr. van Dyck said Title

V cannot be used to force states to do anything specific. Dr. Watson emphasized the importance of pursuing multiple approaches to address the problems with medical foods, adding that for ERISA plans, just raising public awareness of the issue might help.

Ms. Monaco asked whether Dr. Berry had found that when insurance companies don't cover medical foods that they might be willing to cover them. Dr. Berry said two things were at work in insurers' decisions not to cover medical foods. In some cases, it is just a matter of education or getting codes. In other cases, the problem is that insurance companies negotiate individually with clients, and if a client does not want something covered, the insurer will not cover it. Dr. Rani Singh, speaking from the audience, noted that many insurance companies are looking for Current Procedural Terminology (CPT) codes, too. Dr. Watson said it would be a good idea to think about developing specific codes pertaining to newborn screening in the Healthcare Common Procedure Coding System (HCPCS) and CPT-4 system. Dr. Howell thanked Dr. Watson for offering to spearhead that effort.

## **VI. UPDATE ON THE NEWBORN SCREENING USE CASE AND RESOURCE GUIDE FROM AHIC'S PERSONALIZED HEALTH CARE WORKGROUP**

**Stephen M. Downs, M.D., M.S.**  
**Co-Chair, Subgroup on Newborn Screening**  
**Personalized Health Care (PHC) Workgroup**  
**American Health Information Community (AHIC)**  
**Associate Professor and Director**  
**Children's Health Services Research**  
**Indiana University School of Medicine**

**Alan E. Zuckerman, M.D.**  
**Consultant, AHIC Personalized Healthcare Workgroup**  
**Co-Chair CCHIT Interoperability Workgroup**  
**Primary Care Informatics Program Director**  
**Georgetown University School of Medicine**

In this session, Dr. Stephen Downs, the co-chair of the Subgroup on Newborn Screening of the American Health Information Community's (AHIC) Personalized Health Care Workgroup, and Dr. Alan Zuckerman gave an update on the newborn screening use case that was approved by AHIC in June 2008 and is being developed by the Office of the National Coordinator for Health Information Technology within the U.S. Department of Health and Human Services. They also described a companion resource guide that is being developed and asked for the Advisory Committee's advice and support for their efforts. When the use case is complete, it will be made available to software developers who can use it as a guide to develop software systems that will meet the specifications of the use case.

As explained at previous meetings, AHIC is a public-private advisory body that has been making recommendations to the HHS Secretary on how to accelerate the development and adoption of health information technology for an interoperable nationwide health information system. A "use case" is a software development strategy to aid in the design of interoperable electronic health information systems.

**Background on the Role of Health Information Technology in Newborn Screening.** Dr. Downs provided background information on the role of health information technology in newborn screening and some of the technical challenges in developing harmonized standards that support the exchange of electronic information. He noted that the HRSA-funded Regional Genetics and Newborn Screening Collaboratives provide an institutional structure for collaboration related to newborn screening and followup care and research, but an infrastructure to enable the electronic exchange of information between different systems, sites, and settings of care is lacking. The objective of the newborn screening use case is to develop LOINC (Logical Observation Identifiers Names and Codes) codes that permit the exchange of newborn screening information between testing laboratories, clinicians, patients and family caregivers, public health authorities, and other entities in a standardized manner.

**Draft Detailed Newborn Screening Use Case.** Dr. Zuckerman gave an update on the “Newborn Screening Draft Detailed Use Case,” dated September 19, 2008, which was included under Tab #12 in materials provided to Committee members in their briefing books. He explained that when AHIC approved the development of a newborn screening use case to describe the high level needs of many systems, stakeholders, and individuals for information exchange in June 2008, it requested that the use case do the following:

- Integrate results from screening in all six clinical domains (metabolic, hearing, endocrine, hemoglobin, pulmonary/genetic, and congenital infections, and other) into a single comprehensive report of newborn screening results.
- Complete a newborn screening consultation and referral document that includes all of the initial screening results, adds and tracks confirmatory testing and referrals, and identifies all providers and all relevant encounters.
- Report deidentified newborn screening, consultation, and referral information to public health authorities, as well as report on individual cases to registries and local service providers.
- Address consumers’ need for educational material regarding the screening and/or suspected or confirmed condition and provide additional information and/or specimens

A draft detailed newborn screening use case dated September 19, 2008, is now available. This has two scenarios. “Scenario 1: Ordering and Resulting” covers initial screening testing, both for dried blood spot and early hearing detection and intervention, and ends with the reporting of results, either within normal limits, or notification of the need for confirmatory testing if results are outside normal limits. “Scenario 2: Abnormal and Out-of-Range Results” covers diagnostic workup for an out-of-range (or abnormal) screening test. Public feedback on the draft detailed newborn screening use case will be accepted through Friday, October 17, 2008. Instructions for providing feedback are provided online at the Website of the Office of the National Coordinator for Health Information Technology (<http://www.hhs.gov/healthit/usecases>).

A final detailed newborn screening use case will be completed in December 2008. Once the use case is complete, it will go to the Health Information Technology Standards Panel (HITSP) for the development of interoperability standards for newborn screening. HL7 is developing an implementation guide for newborn screening laboratory results reporting that will be essential to the work of HITSP. The “Resource Guide for the Newborn Screening Use Case” will provide terminology and codes. After the standards are accepted and recognized by the HHS Secretary, they must be implemented by newborn screening programs. Thus, the newborn screening use case is just the beginning of a long process, and it is important to begin generating interest in implementing the newborn screening use case nationwide.

**Resource Guide for Newborn Screening Draft Detailed Use Case.** Dr. Downs described and gave a Web demonstration of the “Resource Guide for Newborn Screening Draft Detailed Use Case” dated September 19, 2008, which was included under Tab #12 of materials provided to Committee members. This guide is a work in progress that includes condition and analyte terminology, codes, and mapping that may be required for rare genetic disorders and provides LOINC codes to assist in identifying results. The resource guide will be revised to accompany the final detailed newborn screening use case that will be published in December 2008. As new tests and new methods of newborn screening and new codes are added, they need to be added to the resource guide, as do links to other genetic resources. The AHIC workgroups are concluding their work, so AHIC is looking for a home for the resource guide such as the National Library of Medicine. In addition, Dr. Downs hopes that the Advisory Committee on Heritable Disorders in Newborns and Children will continue to advise on the content of the guide.

**Request for the Advisory Committee’s Support.** Dr. Downs concluded by asking the Advisory Committee for the following:

1. An affirmation of the need for new roles for health information technology in newborn screening
2. Comments on the “Newborn Screening Draft Detailed Use Case,” dated September 19, 2008 (under Tab #12 in materials provided to Committee members)
3. Comments on the “Resource Guide for Newborn Screening Draft Detailed Use Case” dated September 19, 2008 (under Tab #12) and other dataset issues
4. Support in implementation of the “Newborn Screening Detailed Use Case” once it is completed
5. Support in maintaining and distributing the “Resource Guide for Newborn Screening Detailed Use Case” once the first version is completed

### **Questions & Comments**

**Comments on the Newborn Screening Use Case and Resource Guide.** Dr. Boyle encouraged individuals on the Laboratory Standards & Procedures Subcommittee to send comments on the “Newborn Screening Draft Detailed Use Case” and the “Resource Guide for Newborn Screening Draft Detailed Use Case” to Dr. Downs. Dr. Howell suggested that individuals on Dr. Boyle’s Followup & Treatment Subcommittee and Dr. Watson’s Research Workgroup provide comments, as well. Ms. Terry recommended changing the name of the resource guide so as not to confuse consumers. Dr. Zuckerman noted that there would be many comment cycles in the future.

**Support in Implementing the Newborn Screening Use Case.** Dr. Howell asked Committee members for comments on the implementation of the detailed newborn screening use case. Dr. Dougherty questioned how the use case could be implemented without some resources. Dr. Downs explained that the concept behind the use cases and the whole AHIC process is to establish a standard set of communication protocols and thereby create incentives for the private sector to produce software that adheres to these standards (like 110 v electricity, or cell phones).

Dr. Alan Hinman, speaking from the audience, explained that the process is leading to an enforceable set of standards. In the case of electronic health records (EHRs), for example, once interoperability standards are developed by HITSP, they are presented to the Certification Commission for Healthcare Information Technology (CCHIT) to use in certifying EHR products. HITSP could complete its process in 2009. Once CCHIT develops its certification process, federal funds will not be used to support health information technology systems that do not follow these

standards. Thus, the process will have a substantial impact on what health information technology systems look like. Dr. Zuckerman said for public health, Medicaid, the Public Health Informatics Task Force, and other entities will be involved in certification efforts.

Dr. Getchell reported that the Association of Public Health Laboratories (APHL) has been working on the Public Health Laboratory Interoperability Project to develop standards for electronic laboratory reporting at the urging of the Centers for Disease Control and Prevention (CDC). Dr. Downs said he and Dr. Zuckerman know about this and will be talking to APHL in San Antonio.

Finally, Dr. Dougherty asked who the contact point for implementation would be now that AHIC's responsibilities are being transferred to its successor in the private sector (AHIC 2.0). Dr. Downs said the contact point is Dr. Zuckerman, but that may evolve after the use case comes out. Dr. Zuckerman said a number of people are working on implementation and the Health Resources and Services Administration (HRSA) will be involved.

**Support in Maintaining and Distributing the Newborn Screening Resource Guide.** At Dr. Down's request, Dr. Howell agreed that the Committee could discuss its role with respect to maintaining the "Resource Guide for Newborn Screening Detailed Use Case" at its meeting in February 2009.

**Committee's Formal Endorsement of the Efforts.** Finally, the Committee voted unanimously to formally endorse the efforts of the Subgroup on Newborn Screening of the AHIC Personalized Health Care Workgroup.

- **MOTION #4 (APPROVED):** *The Advisory Committee recognizes the need for new roles for health information technology in newborn screening and formally endorses the efforts of the Subgroup on Newborn Screening of the AHIC Personalized Health Care Workgroup to develop a newborn screening use case and resource guide for the use case.*

## **VII. CONTINGENCY PLANNING AND EMERGENCY PREPAREDNESS FOR NEWBORN SCREENING AND GENETIC SERVICES**

In this session, three presenters described initiatives related to contingency planning and emergency preparedness for newborn screening and genetic services: (1) the development of a national contingency plan for newborn screening by the U.S. Department of Health and Human Services' (HHS) and other entities; (2) the Association of Public Health Laboratories' (APHL) white paper on a newborn screening preparedness/contingency planning framework; and (3) a 2007 meeting held by the National Coordinating Center (NCC) for the Regional Genetics and Newborn Screening Collaboratives on emergency preparedness for newborn screening.

## **A. Development of the National Newborn Screening Contingency Plan**

**Susan McClure**

**Associate Director for Program and Partnership**

**Development**

**Division of Laboratory Sciences**

**National Center for Environmental Health**

**Centers for Disease Control and Prevention**

**Mark E. Austin**

**Plans Section Lead**

**Division of Laboratory Sciences**

**National Center for Environmental Health**

**Centers for Disease Control and Prevention**

Ms. McClure and Mr. Austin described progress to date on developing the national newborn screening contingency plan that was authorized by the Newborn Screening Saves Lives Act (Public Law 110-204) in 2008. A contingency plan is an operational plan drawn up in advance to address specific situations when things go wrong. Section 1115 of the Newborn Screening Saves Lives Act specifies that the national newborn contingency plan is to cover (1) the collection and transport of newborn screening specimens; (2) the shipment of specimens to state newborn screening laboratories; (3) the processing of specimens; (4) the reporting of screening results to physicians and families; (5) the diagnostic confirmation of positive screening results; (6) ensuring the availability of treatment and management resources; (7) educating families about newborn screening; and (8) carrying out other activities deemed appropriate by the Secretary of Health and Human Services (HHS). It includes plans for use by a state, region, or consortium of states in the event of a public health emergency.

Although national contingency plans are usually created at the department level, Congress directed Centers for Disease Control and Prevention (CDC) to work with the Health Resources and Services Administration (HRSA) and state health departments to develop the national newborn screening contingency plan. Thus, the parties collaborating in the development of the plan include CDC, HRSA, the American Public Health Association, the American College of Medical Genetics, the Association of Maternal and Child Health Programs, the American Academy of Pediatrics, and the Association of State and Territorial Health Officials, as well as the National Association of City and County Health Officials, the Centers for Medicare and Medicaid Services, state public health departments, and state laboratories.

At a CDC/HRSA Workshop in Atlanta on September 24-26, 2008, representatives of federal agencies, state public health programs, state emergency preparedness programs, and clinicians used the eight elements identified in Section 1115 of the Newborn Screening Saves Lives Act as the framework for developing a national newborn screening contingency plan. Making each of the eight elements a strategic objective in the contingency plan, workshop participants used the "SOARS" method to identify operational objectives for each strategic objective, activities for each operational objective, the responsible party for each activity, and standard operating procedures for each activity. One thing that came out of this workshop is the importance of having emergency preparedness plans at every level. Since the CDC/HRSA workshop, a workshop with the three centers of CDC and HRSA has been held. The next steps will be to share the framework with additional partners to get additional input on the plan, to revise the plan and share it with congressional staffers, then share it more broadly. The hope is to complete the newborn screening contingency plan by October 21, 2008.

## Questions & Comments

Dr. Boyle asked for clarification of the difference between an emergency preparedness plan and an emergency response plan. Mr. Austin said that emergency preparedness means planning and taking action to be ready for emergencies before they happen. Emergency response refers to actions taken in response to an actual, ongoing event. Dr. Watson said that more emergency preparedness is needed to get an adequate emergency response so that less mitigation is needed after the fact.

## B. APHL's Newborn Screening Preparedness/Contingency Planning Framework

### Jane Getchell, Dr.PH

#### Association of Public Health Laboratories (APHL) Organization Representative to the Committee

Dr. Getchell reported on the Association of Public Health Laboratories' (APHL) framework for newborn screening preparedness/contingency planning by public health laboratories, which was developed this framework in the wake of recent natural disasters such as Hurricane Katrina and other incidents that interrupted newborn screening services. APHL served as a central point of contact during these incidents and helped newborn screening programs to maintain services by connecting states with other states, federal partners, and companies.

In 2004, a subcommittee of the APHL Newborn Screening and Genetics in Public Health Committee was established to develop a framework to help public health laboratories prepare for and respond to disasters caused by nature, terrorism, and interruptions of testing materials and supplies. APHL recommends that public health laboratories use the emergency preparedness and contingency planning framework to prepare newborn screening contingency plans and that they modify the framework for other laboratory testing programs.

APHL's newborn screening preparedness/contingency planning framework includes the following elements:

- *Partners.* The newborn screening program should forge relationships with partners that can help them prepare for and respond to disasters. Such partners include local entities (hospitals, clinics, physicians, medical associations, case managers, homeland security agency, city and state emergency response centers and press offices) and national entities (APHL, CDC, HRSA, the National Newborn Screening and Genetics Resource Center (NNSGRC), the Association of State and Territorial Health Officials (ASTHO), parent advocacy groups, manufacturers, regional disaster organizations).
- *Emergency laboratory testing.* The newborn screening program should have an emergency checklist to ensure: (1) short-term onsite operation (e.g., availability of emergency electrical power, plan for getting specimens to lab if roads are shut down, plans for getting in touch with case managers, ensuring availability of laboratory instruments, duplication of the information management system, plans for keeping test kits and supplies refrigerated and the lab cool or hot, three month supply of testing materials on hand, and identification of alternate pure water sources); (2) long-term onsite operation (e.g., prioritization of certain tests, identification of other states that use the same screening methods that might be called upon in an emergency); and (3) offsite operation (e.g., a contact list, memoranda of understanding established with other states, plans established for compensation, specimen transport, reporting test results, onsite entry of offsite data, plans for temporary

relocation of staff, and plans for access, retrieval, and entry of all data into local information system after local operation is reestablished).

- *Testing materials procurement.* The newborn screening laboratory should obtain documentation from the supplier of testing materials that it has adequate forward stocking and transportation plans, as well as a plan to provide equipment to an alternative site in a specified period of time.
- *Emergency communications.* The newborn screening program should have an incident command system with a single person in charge, a record keeper, contacts identified (suppliers, APHL, other states), a call back system for in-house staff, annual testing of the communications system, review and updating of the system semi-annually. Communication modes that can be used include the following: telephone (landline, cell, satellite), courier, computer-controlled system (e.g., e-mail), and alternate systems (e.g., radio).
- *Memoranda of understanding for newborn screening emergencies.* A two-page model memorandum of understanding to formalize mutual assistance agreements between state health departments has been developed by APHL. This model includes contact persons, liability (a challenging problem), terms and termination, signatories, services, funding, specimen transport, chain of custody.

Dr. Getchell noted that APHL has a CD with guidelines to assist state public health laboratories in developing a continuity of operations plan to ensure continuation of their essential public health activities during events that may disrupt normal operations. This material is also available on the APHL's Website ([http://www.aphl.org/aphlprograms/Documents/PHL\\_COOP\\_Guidelines.pdf](http://www.aphl.org/aphlprograms/Documents/PHL_COOP_Guidelines.pdf)).

### **C. Report on Emergency Preparedness for Newborn Screening and Genetic Services from the National Coordinating Center for the Regional Collaboratives**

**Michael S. Watson, Ph.D., FACMG**  
**Executive Director**  
**American College of Medical Genetics (ACMG)**  
**Representative to the Committee**

Dr. Watson, speaking on behalf of the National Coordinating Center (NCC) for the Regional Genetics and Newborn Screening Collaboratives, discussed emergency preparedness for newborn screening and genetic services more broadly, focusing not only on what happens at the level of the newborn screening lab but also what happens to the children in chronic disease management who need medical foods and formulas. In addition to having the usual needs of other individuals when mass disasters occur, individuals with genetic/metabolic conditions also need special foods, special medications, special laboratories, specialist physicians, and specialized information. Because these individuals are the “canaries in the coal mine,” getting emergency preparedness right for them would make it much easier to get it right for other individuals with chronic conditions. Unfortunately, there is not much emergency preparedness for these individuals in place.

In 2007, NCC held an Emergency Preparedness for Newborn Screening Meeting to identify needs of metabolic disease patients from newborn screening and genetics programs during emergencies; define the role of patients and providers in such emergencies; provide guidance to local institutions on issues to be addressed and who is responsible (including local, state, and federal entities);

provide guidance to patients and families; and provide recommendations to Regional Genetics and Newborn Screening Collaboratives for disseminating plans within regions. Participants at the meeting assessed all newborn screening components: education of parents and professionals; screening (specimen collection, submission, and testing); followup of screen-positive and unsatisfactory cases; confirmatory testing and diagnosis; medical management and periodic outcome evaluation; and system quality assurance, validity of testing systems, efficiency of followup and intervention, assessments of long-term benefits to individuals, families, and society. They also reviewed newborn screening emergency preparedness at various levels.

In September 2008, Regional Genetics and Newborn Screening Collaboratives conducted a survey of states to learn about their emergency preparedness plans for newborn screening. The survey found that all states but New Jersey and South Dakota had a plan or were developing one. Among 44 states, 38 states' emergency preparedness plans address newborn screening lab functions; 12 address diagnostic confirmation and/or availability of treatments; and 23 have developed contingency plans that empower patients. Many states have generic emergency preparedness plans; not all have plans specific to newborn screening. Much more preparedness is needed to ensure an adequate emergency response so that there is less need for mitigation after the fact.

## **VIII. COMMITTEE BUSINESS—SUBCOMMITTEE REPORTS & DISCUSSION**

The Advisory Committee's Laboratory Standards & Procedures Subcommittee, Education & Training Subcommittee, and Followup & Treatment Subcommittee held meetings that were open to the public during the morning of October 2, 2008. In the afternoon, the subcommittee chairs for gave a report to the full Committee, as discussed below.

### **A. Laboratory Standards & Procedures Subcommittee Report**

**Gerard Vockley, M.D., Ph.D.**  
**Chief of Medical Genetics**  
**Children's Hospital of Pittsburgh of UPMC**  
**Professor of Human Genetics and Pediatrics**  
**University of Pittsburgh**  
**Committee Member**

Dr. Vockley, the chair of the Laboratory Standards & Procedures Subcommittee, summarized what had transpired at the subcommittee's meeting earlier in the day.

**Update on the Subcommittee's Study of Routine Second Specimens.** The study of routine second screens for congenital hypothyroidism (CH) and congenital adrenal hyperplasia (CAH) that was begun by the National Newborn Screening and Genetic Resource Center and APHL on behalf of the subcommittee months ago continues to be stymied by problems in getting state-specific institutional review board (IRB) approvals. The study has both retrospective and prospective components, and would cover approximately 25 percent of births in the United States if all the identified states are able to participate. To date, only 4 states have received IRB approval for the retrospective component of the study, while 3 states have IRB approval for the prospective component.

The Laboratory Standards & Procedures Subcommittee hopes that it can use some of the infrastructure being developed for newborn screening research to address issues that have arisen in this study, including obtaining IRB approval, adequate funding, and public health agencies' capacity to participate in these types of studies. Dr. Vockley asked if there was some way that the Advisory Committee could help get any existing (or soon to exist) entities to help with these issues.

**Assessing Technical Feasibility Before the Committee Considers Nominations to the Uniform Newborn Screening Panel.** In the case of Pompe disease, the first condition nominated for inclusion on the uniform newborn screening panel that the Advisory Committee considered, major technical questions arose. The Laboratory Standards & Procedures Subcommittee discussed the possibility of performing a technical feasibility analysis earlier in the process to save time and effort. Beyond considering the screening technology, the technical feasibility analysis should consider the technology involved in confirmatory testing, the availability of products, and the existence of standards for quality assurance.

**Future Directions for the Laboratory Standards & Procedures Subcommittee.** Dr. Vockley said that future directions for the subcommittee include the following:

- Promote standards development and availability.
- Clarify the role of the Food and Drug Administration (FDA) in approving analyte-specific reagents in newborn screening and confirmatory testing. Suggest to the full Advisory Committee that a representative of FDA be invited to give a presentation on FDA's evolving role in dealing with genetic testing, newborn screening, reagents, etc.
- Review optimum mechanisms to assure that technical aspects of candidate diseases for standard panel are adequate.
- Identify opportunities to provide technical advice to growing clinical trials/screening infrastructure.
- Interact with the Advisory Committee's Research Workgroup headed by Dr. Watson.

### **Questions & Comments**

Dr. Howell noted that he and the rest of the Advisory Committee are concerned about the problem with the IRBs. There will be something on informed consent at the Advisory Committee's meeting in February 2009, and perhaps that would help illuminate the issue.

With regard to the technical feasibility analysis of nominated conditions, Dr. Howell suggested that perhaps the Decision-Making Workgroup headed by Dr. Rinaldo that reviews nominations before they come to the Advisory Committee could look more at technical issues before a nomination comes to the Advisory Committee. Dr. Howell said could it would be possible to bring more people on to the Decision-Making Workgroup to deal with the issue. Dr. Howell also noted that the Newborn Screening Saves Lives Act requires that the Advisory Committee have a full voting member from FDA, so the FDA member will be added soon.

## B. Education & Training Subcommittee Report

**Tracy L. Trotter, M.D., F.A.A.P.**  
**Senior Partner**  
**Pediatric and Adolescent Medicine**  
**San Ramon Valley Primary Care Medical Group**  
**Committee Member**

Dr. Trotter, who chairs the Education & Training Subcommittee with Jana Monaco, reported that the subcommittee's meeting on October 2, 2008, had discussed the following topics.

- **National newborn screening repository.** Discussions with Dr. Brad Therrell and his colleagues at National Newborn Screening and Genetics Resource Center (NNSGRC) had led to an agreement that a specific section of the NNSGRC Website would serve as a repository for materials on newborn screening in various languages and formats. The information will be accessible to the subcommittee's five target audiences—namely, health care providers, affected families, hospitals/birthing centers, screening program staff, and the general public.
- **Protocol for translating educational materials into languages other than English.** The standard protocol used by California newborn screening program will be formalized for generic use and forwarded to the subcommittee for approval as a “gold standard” for the national newborn screening repository. Materials in various languages and formats submitted to the repository may not meet all the criteria and requirements used by the California program, but their adherence or lack of adherence to these will be transparent to users.
- **Educating primary care physicians about genetics and newborn screening.** Because advances in newborn screening pose new challenges to primary care physicians, both educationally and in the management of affected infants (*Pediatrics* 2008: 121; 192-217), the Education & Training Subcommittee wants to continue its partnership with the American Academy of Pediatrics (AAP), the American Academy of Family Physicians (AAFP), and the American College of Obstetricians and Gynecologists (ACOG) in efforts to educate primary care physicians about genetics and newborn screening. The focus will include education regarding primary care physicians' response to an out of range screening result (ACT sheets/State newborn screening programs), their coordination of a complete evaluation of an affected infant, their provision of a medical home and coordination of care for affected children, and their role in educating families and health care workers. It will also include improving the genetic literacy of the primary care physicians, so that they can better interpret genetic test results. The AAP has agreed to consider genetics as a “mega” issue for its members. This means that AAP will make genetics (including newborn screening) a focus for continuing medical education for the next 3 to 5 years.
- **Collaboration in education.** The Education & Training Subcommittee plans to serve in an advisory capacity to current groups involved in educating primary care physicians and public/family education: NNSGRC, Genetic Alliance, National Coordinating Center (NCC) for the Regional Genetics and Newborn Screening Collaborative Groups, the National Coalition for Health Professional Education in Genetics, professional medical associations, and others.
- **Newborn Screening Save Lives Act of 2008 (Public Law No. 110-204).** Section 1112 of the Newborn Screening Saves Lives Act authorizes the HHS Secretary, with HRSA as the lead agency, to establish and maintain a central clearinghouse of current information,

materials, resources, and data on newborn screening, and the Education & Training Subcommittee is thinking about how it can help make this work. The clearinghouse authorized by the Newborn Screening Saves Lives Act must (1) be available on the Internet; (2) include an interactive forum; (3) be updated at least quarterly; and (4) provide links to Websites and information about newborn conditions, screening services available in each state, current research on conditions for which newborn screening tests are available, and the availability of federal funding for newborn and child screening for heritable disorders.

### **Questions & Comments**

Dr. Howell asked how HRSA is responding to the Newborn Screening Saves Lives Act. Dr. van Dyck replied that HRSA is developing a comprehensive implementation plan and doing a lot of things behind the scenes. He promised that as the plans developed, they would be shared with the Advisory Committee.

## **C. Followup & Treatment Subcommittee Report**

**Colleen Boyle, Ph.D., M.S.**

**Director, Division of Birth Defects and Developmental Disabilities  
National Center on Birth Defects and Developmental Disabilities  
Centers for Disease Control and Prevention (CDC)**

Dr. Boyle, the chair of the Followup & Treatment Subcommittee, reported that at its meeting on October 2, 2008, the subcommittee was continuing to focus on two major activities: (1) examining issues related to insurance coverage of medical foods; and (2) defining and characterizing long-term followup after newborn screening (including the components and parties involved in followup).

- **Insurance coverage of medical foods.** Dr. Sue Berry and Alissa Johnson gave the subcommittee an overview of medical foods issues. The subcommittee is conducting a survey of parents in three of the HRSA-funded Regional Genetics and Newborn Screening Collaboratives to get an idea of the burden on parents of current insurance coverage and reimbursement for medical foods and hopes to be able to have a report for the full Committee in the spring of 2009. In addition, as Dr. Berry reported to the full Committee, the subcommittee had a very productive meeting in June 2008 to discuss reimbursement issues. Now the subcommittee is working through some of the ideas that emerged at that meeting (e.g., developing specific codes for reimbursement of medical foods, developing a model state Medicaid policy and model state insurance legislation) and hopes to be able to have a report for the full Committee at the next meeting.
- **Long-term followup following newborn screening.** The Followup & Treatment Subcommittee had a publication in *Genetics in Medicine* with components of long-term followup in 2008 by Dr. Alex Kemper. At a meeting in January 2008, Dr. Alan Hinman walked subcommittee members through players in long-term followup (namely, affected individuals/families, primary care providers, specialty and subspecialty providers, and public health agencies). The subcommittee is now trying to figure where to go next. It was agreed that an effort would be made at the February 2009 meeting to highlight major roles for participants in a paper. Finally, the subcommittee talked about providing input and guidance to other mechanisms that might affect long-term followup, including the use case for newborn screening. Although the subcommittee cannot provide input to the use case as a subcommittee, individual members can provide input.

## IX. COMMITTEE BUSINESS

**Rodney Howell, M.D.**

**Chair, Secretary's Advisory Committee on Heritable Disorders  
in Newborns and Children**

**Professor, Department of Pediatrics**

**Leonard M. Miller School of Medicine**

**University of Miami**

In the final session of the meeting, Dr. Howell reported that Dr. Telfair's term on the Committee was coming to an end and thanked him for contributions. The Committee then finished remaining business for the day and discussed plans for the Committee's upcoming meetings.

**Letters from the Advisory Committee to the HHS Secretary.** Dr. Howell asked that two letters from the Advisory Committee be prepared for the HHS Secretary: (1) one apprising him of the Advisory Committee's formal recommendation about Pompe disease; and (2) one apprising him that the Advisory Committee formally endorsed the American Health Information Community's (AHIC) newborn screening use case and accompanying resource guide.

**Committee Action on Nomination of Niemann-Pick Disease as a Candidate for Inclusion on the Uniform Newborn Screening Panel.** Niemann-Pick disease was nominated for inclusion on the uniform newborn screening panel by Ms. Barbara Vorpahl, who chairs the National Niemann-Pick Disease Foundation. The nomination of Niemann-Pick disease was reviewed by the Advisory Committee's Internal Review Workgroup. This workgroup, formerly known as the Nomination Review & Prioritization Workgroup, is chaired by Dr. Rinaldo and also includes Dr. Buckley, Dr. Howell, Dr. Ohene-Frempong, and Dr. Skeels.

The Internal Review Workgroup recommended that the Advisory Committee not send the nomination of Niemann-Pick disease for a review of the evidence by the external Evidence Review Workgroup. The workgroup based its recommendation on two factors: (1) the lack of population-based pilot studies of the newborn screening test for the condition; and (2) the lack of defined treatment protocols for the condition. The workgroup recommended that the condition be resubmitted for the Committee's review when pilot studies of the newborn screening test and treatment protocols are available.

Dr. Trotter moved that the Committee accept the Internal Review Workgroup's recommendation. Dr. Vockley recused himself from the vote on this motion because his wife works as a counselor for Niemann-Pick. It was a unanimous vote except for the one stated abstention.

- **MOTION #5 (APPROVED):** *The Advisory Committee accepts the Internal Review Workgroup's recommendation not to send the nomination of Niemann-Pick disease to the external Evidence Review Group. It recommends that the condition be nominated again when population-based pilot studies of the newborn screening test and defined treatment protocols are available.*

**Plans for Upcoming Advisory Committee Meetings.** The dates for the Advisory Committee's next meetings are as follows:

- November 24, 2008 (1 p.m. Webcast open to the public)
- February 26-27, 2009

Dr. Lloyd-Puryear asked that Committee members let her know of their availability for meetings in May 2009 as soon as possible. She also explained that Committee members would not get briefing books for the November 24, 2008, Webcast; materials for the meeting will be posted for downloading on the Committee's meeting Website (<http://www.events.SignUp4.com/ACHDNC1124>).

Dr. Howell stated that one item on the agenda for the November 24<sup>th</sup> Webcast would be a vote by the Advisory Committee on whether to adopt the process recommended by the Advisory Committee's Decision Criteria & Process Workgroup headed by Dr. Calonge for developing the Committee's recommendations on conditions nominated for inclusion in the uniform newborn screening panel. Dr. Howell urged Committee members to send their comments on the draft report presented at this meeting to Dr. Calonge as soon as possible, so that the Decision Criteria & Process Workgroup can incorporate them into a revised report that the Committee will vote on in November.

Another item on the agenda for the November 24<sup>th</sup> Webcast will be a report from the external Evidence Review Workgroup headed by Dr. Perrin on the evidence for severe combined immunodeficiency disorder (SCID). Dr. Howell indicated that as a matter of courtesy, the Committee would advise the people who nominated SCID that it was being considered by the Committee and that a decision could be made. Committee members requested that the Evidence Review Workgroup make its criteria more parallel to the outline in the Decision Criteria & Process Workgroup's report. Dr. Alex Kemper said that was the workgroup's plan.

Dr. Howell also asked Dr. Lloyd-Puryear to send the documents on the evidence for Pompe disease to Committee members again and to provide the documents in a form so Advisory Committee members could see any changes that had been made. Dr. Howell said that Advisory Committee members could expect to receive the materials on Pompe disease in the coming weeks and asked for their prompt response.

Other topics suggested for upcoming meetings included the following:

- Report on the storage and use of residual newborn screening specimens
- Discussion of the Committee's role with respect to the "Newborn Screening Detailed Use Case" and companion resource guide
- Report from Dr. Watson on translational research networks
- Presentation on informed consent
- Presentation from the Food and Drug Administration (FDA) on FDA's evolving role in dealing with genetic testing, newborn screening, reagents, etc.

Finally, with no other business at hand, Dr. Howell adjourned the meeting at 2:40 p.m.

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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 in Newborns and Children are accurate and correct.

/s/ \_\_\_\_\_

/s/ \_\_\_\_\_

R. Rodney Howell, M.D.  
ACHDNC, Chair

Michele A. Lloyd-Puryear, M.D., Ph.D.  
ACHDNC, 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**

1. Ronald J. Bartek, Parent and Founder of Friedreich's Ataxia Research Alliance (FARA)
2. John Adams, Parent and Volunteer with the Canadian Organization for Rare Disorders

**1. Ronald J. Bartek**  
**Friedreich's Ataxia Research Alliance (FARA)**  
**Springfield, VA**  
**www.cureFA.org**  
**fara@cureFA.org**  
**Statement to the HHS Advisory Committee**  
**on Heritable Disorders in Newborns and Children**  
**October 1, 2008**



Dr. Howell, Ladies and Gentlemen of the Committee,

Thank you for the opportunity to address you today. My name is Ron Bartek. My 22-year-old stepson Keith has a neurodegenerative disorder—Friedreich's Ataxia. Keith was a beautiful, apparently healthy child at birth and until about age 9, at which time he was doing well in school and was typically active. He was enjoying karate lessons and riding his bike with his brothers and friends. Keith's world began to change rapidly and drastically at that point, though, and by age 11, he was diagnosed with Friedreich's ataxia as his coordination, cardiomyopathy, and scoliosis became apparent. By age 16 he was unable to walk and his scoliosis required surgical implantation of metal rods along the length of his spine. Now, at 22, Keith has developed diabetes, is full time in his wheelchair, and is dependent on others for most activities of daily living. Although his intellectual capabilities remain intact, he has significant communication difficulties due to vision and hearing loss as well as slurred speech. He had to terminate his college education as a freshman due to difficulty overcoming all these challenges. We estimate that there are 5000-6000 individuals like Keith living in the United States.

On the day in 1997 that my wife Raychel and I received Keith's diagnosis, we learned three things: first – Friedreich's ataxia has a horrific prognosis; second – there was no organization focused entirely on supporting research and education in Friedreich's ataxia, although there were other organizations such as the Muscular Dystrophy Association for which Friedreich's ataxia was one of many disorders in their portfolio, but third – the disease gene and molecular defect had just been identified in the previous year. With the support and encouragement of Drs. Giovanna Spinella and Audrey Penn of the NIH's Neurological Institute, we decided to form an organization to support research and education in this disease. I am co-founder and President of that organization—the Friedreich's Ataxia Research Alliance (FARA)—and on behalf of FARA and the patient and research community it represents, I would like to express our gratitude for the important service you provide in helping the most vulnerable members of our society.

Friedreich's ataxia is the most common form of inherited ataxia. About one in 50,000 people in the United States are born with this disease. Symptoms of Friedreich's ataxia include: progressive loss of strength and coordination (ataxia) in all four extremities leading to loss of ambulation within 6-10 years of onset, life-shortening cardiomyopathy, severe scoliosis often requiring surgical intervention, and type 1 diabetes. Onset of symptoms can vary from childhood to adulthood.

Childhood onset of Friedreich's ataxia is usually between the ages of 5 and 15 and tends to be associated with a more rapid progression and premature death.

Since the identification of the disease-associated gene and mutation in 1996, our scientific community has made tremendous progress in understanding the pathophysiology of the disease and function of the protein, frataxin, which is dramatically reduced in our patients. Frataxin functions in the mitochondria and is critical for iron metabolism, antioxidant protection, and overall energy production. A number of promising therapeutics are in clinical trials or in development. At present, in the United States and Europe, there are two ongoing Phase III clinical trials of the antioxidant Idebenone. A Phase II study of the iron chelator Deferiprone is also underway in Europe. These trials will be completed in 2009. Data from previous studies of both drugs suggest improvements in cardiac and neurological function that would, at a minimum, slow the progression of the disease significantly. This past July, Canada granted conditional approval for use of Idebenone in Friedreich's ataxia and FDA filing for approval is anticipated late in 2009. In addition, there is a Phase I clinical trial now underway in the United States of another novel antioxidant in Friedreich's ataxia. This and a number of other drugs now in development with our pharmaceutical partners hold promise for substantially greater benefit.

Due to the progressive nature of this disease and the strong likelihood that damage begins long before symptom onset, we believe that the earliest intervention with these treatments will be critical in reducing and preventing morbidity and mortality. Our organization is clearly not alone in this conviction. For example, at our 3rd International Scientific Conference on Friedreich's Ataxia, in November 2006, Dr. Story Landis, Director of the NIH's Neurological Institute, told FARA that her Institute was so encouraged by our progress and confident that we would achieve effective treatment soon, that we should begin working with NIH colleagues and others on the development of a newborn screening test. Since then, we have been working with a team of investigators at the Mayo Clinic in Minnesota led by Drs. Devin Oglesbee and Grazia Isaya to develop, using dried blood spots, a newborn screening test that is protein-based and multiplexable. The goal is to validate this test analytically and clinically with a pilot study beginning in 2009 of approximately 70,000 newborns so as to meet the nomination standards set by this committee. We would welcome in this development process the involvement of other academic groups and industry as appropriate.

We understand the role of this committee in ensuring that suitable screening tests are developed and safe, effective treatments are available for implementation in the newborn period. We also recognize the social, emotional, and ethical challenges of diagnosing pre-symptomatic individuals.

We look forward to the opportunity to keep you informed as we achieve critical milestones in test development and treatment outcomes. On behalf of Friedreich's ataxia patient families and our research community, thank you for your commitment to the health of newborns and children, for your attention and for allowing me to make this presentation to you today.

**2. John Adams**  
**Canadian Organization for Rare Disorders**  
**Statement to the HHS Advisory Committee**  
**on Heritable Disorders in Newborns and Children**  
**October 1, 2008**

My name is John Adams. I'm from Toronto, Canada, and I happen to be a PKU dad. And I just wanted to take a moment to say thank you very much for everything you do and to share, from a personal basis, a case study of PKU treatment and long-term follow-up.

This Friday, two days from now, will be the one-year anniversary of my 21-year-old son being on the first-ever drug therapy for PKU. He is not a responder. He has turned out to be a super responder. He says he has two side effects. He's sharper and he's more clear-headed. He has been on it for an academic year and his marks have improved. He's now, in a very carefully and measured and thoughtful way, gradually increasing the whole protein load to the point where, since June, he has been on all whole protein and completely off formula.

So my real purpose of coming here today is thanks to the generosity of the taxpayers of the Province of Ontario, I have in my basement a two-year supply of Maximum XP amino acid formula for PKU therapy. If you know any American or any other person in the world who needs that, I'd be happy to donate that.

Thank you so much. My son has also had the pleasure of being an all-expense-paid guest of the Biotechnology Industry Association. He was the non-American case study, patient example, of the successes here of the 25 years of the Orphan Drug Act. So thank you for that. Although I was glad to hear from the previous speaker that we do get a few things right in Canada, the new drug therapy for PKU has not yet been applied for, is not yet available. My son is the first named patient to have access to it in Canada. I just want to work with people who want to work with me to make sure that when there is a breakthrough in treatment for whatever rare condition, the patients get to be early adopters and not late adopters of the new therapy. Thank you very much.