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

Summary of 16th Meeting
November 24, 2008
Audio Conference Call

Audio Meeting Participants
November 24, 2008

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CONTENTS

1. Opening

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children met via audio conference Monday, November 24, 2008. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments and was so announced. The meeting was called to order by Chair R. Rodney Howell, M.D., at 1:10 p.m., when Executive Secretary Michele A. Lloyd-Puryear, M.D., Ph.D., determined that a quorum was present.

Dr. Howell welcomed members to the 16th meeting of the Advisory Committee (AC). The agenda, which was distributed by email in advance of the meeting, was followed.

2. Action: Approval of Minutes of October 1–2, 2008, Meeting

It was moved and seconded to approve the minutes of the October 1–2, 2008, meeting as distributed. The motion carried unanimously by voice vote.

3. Remarks from HRSA Deputy Administrator

Dennis P. Williams, Ph.D., thanked the AC members on behalf of Elizabeth Duke, Administrator, for refining the process of considering nominations and for their leadership and foresight. HRSA is operating under a continuing budget resolution through March 6, 2009. He expected no immediate change in the operations of the AC. He called the members' attention to the October 2008 letter from Dr. Duke on behalf of Secretary Leavitt in response to the Committee's recommendations, which said that the Secretary is considering adopting the conditions recommended in the report of the American College of Medical Genetics as a national standard for newborn screening programs. However, Secretary Leavitt wants input from the President's Council on Bioethics and other groups before making a final decision. Dr. Williams went on to applaud the AC on the progress that it has made toward refining the process for evaluating conditions for newborn screening and for ensuring that the process is systematic, thoughtful, and transparent. He also acknowledged the AC's support for the personalized healthcare use case and advice and endorsement of the newborn screening action sheets and algorithms as clinical resources for health professionals.

Dr. Howell called the members' attention to another letter in the meeting materials. Angela Trepanier of the National Society of Genetic Counselors requested representation on the AC. The number of seats is fixed and no organizational slots are currently available.

4. Internal Review Workgroup: Report on the Candidate Nomination:

Spinal Muscle Atrophy (SMA)

Rebecca Buckley, MD read the summary report of the Internal Review Workgroup in the absence of the chairperson, Piero Rinaldo, M.D., Ph.D. The report, based primarily from the nomination form and also from submitted references and other publicly available materials, was distributed in advance of the meeting. The review was conducted October 20, 2008. SMA, or Werdnig-Hoffman disease in its more severe from, is a very serious condition that is characterized by progressive degenerative motoneuron disease and has an expected lifespan of less than 3 years. Its incidence is approximately 1 per 10,000 births. Prospective pilot data from population-based assessments are available. Analytical and clinical validation has been pursued in a single laboratory. It remains to be seen how effectively the screening method can be implemented in public health laboratories. The proposed screening method is one of the first examples of a primary screening test based on genotyping. Those individuals that could benefit from treatment are easily identifiable. Nutritional support and respiratory care are the only treatments currently available. Drug treatments are being investigated. In summary, Dr. Buckley noted that

critical elements are missing from both the test characteristics, such as reproducibility outside of an academic lab, and treatment efficacy beyond the relatively limited benefits of palliative measures. According to the Internal Review Workgroup, "The nomination of SMA might be premature for evaluation at this time as judged by the evidence…there are critical elements missing for both the test characteristics (reproducibility outside of an academic lab) and treatment efficacy beyond the relatively limited benefits of palliative measures."

"The Internal Nomination and Prioritization Workgroup recommends no evidence review at this time and further recommends a nominator to conduct prospective pilot studies in one or more traditional public health laboratories in order to show reproducibility of the preliminary findings in Dr. Prior's laboratory. The time frame required to collect the analytical evidence mentioned above could also lead to a better assessment of the efficacy of novel treatment modalities under investigation."

Dr. Howell asked if other members of the Workgroup wished to comment. Michael Skeels, Ph.D., stated that the report reflects the consensus of the Internal Review Workgroup. Gerard Vockley, M.D., Ph.D noted that a strong clinical rationale would be required to add a screen for a single disorder for which the only available therapy is only supportive. Dr. Howell remarked that SMA is an important condition that's worthy of addition to the NBS panel but at present it is not ready for evidence review.

Action: Ned Calonge, M.D., M.P.H., moved to accept the recommendation of the Internal Review Workgroup as stated above. Tracy L. Trotter, M.D seconded the motion, which was then approved unanimously by voice vote.

5. Decision Criteria and Process Workgroup

Dr. Calonge described the Decision Criteria and Process Workgroup's report, which was not available via Webcast, and the comments he had received to date, most of which had been distributed to the members. He and Nancy Green, M.D., will revise the report for action at the February meeting. Members had been asked to comment on an earlier version of the report. Discussion ensured. Comments included but were not restricted to the following:

Including a check list and making the document more concise would increase its usefulness. This document should parallel the review outlined by the external Evidence Review Workgroup..

The chain of evidence must be clearly described. Outlining the chain of evidence approach, or body of evidence approach, will be important for others to understand the AC process and how the analytic framework works. It is necessary to acknowledge that some disorders are so rare that the evidence may never be "strong" or "adequate". Dr. Calonge noted that one approach to consider was the one used by GRADE, which was somewhat less rigorous than he preferred. Michael Watson, Ph.D., mentioned the Phase 4 surveillance at FDA, which may not be practical for screening.

To what extent was there strong evidence for the 29 core conditions ? Are we now requiring different standards of evidence?

Key Questions 1 and 3 and the figure illustrating the analytical framework need to be elaborated.

Clinical history and spectrum of disease are better terms than natural history. Because of intervention and treatment, the natural history of a disease is rarely known.

Key Question 3: Analytic validity is critical for standardizing the screening approach across labs.

The decision process should differentiate between analytic validity and clinical validity. The U.S. Preventative Services Task Force, as does EGAPP, assumes that there is analytic and clinical validity. There is variation across labs in testing.

Since there are different usages of the phrase "false positive rate", the document should make clear which definition is being used. . One section of the document refers to the percent of false positives using all samples tested as the denominator. In another section, "false positive" refers to the percent of all positive results that are false (the denominator is the number of positive screens). The solution for this issue is to clarify via footnote what definition is being used.

The integrated aspect of test algorithms should be noted in the paper.

The discussion of Key Question 3 includes a much greater level of detail than do the other questions. Dr. Calonge explained that in a previous version of the document much of the detailed discussion had been placed in an appendix. But the Workgroup members disagreed on the placement of the detailed discussion. Several members of the AC recommended placement in the appendix.

It is important to discuss both analytic validity and analytic utility as well as analytic validity and clinical validity. Analytic validity is the extent to which the test detects what it is supposed to test. Clinical validity asks, "Does the test predict clinical disease?"

Key Questions 4 and 5: It would be helpful to include the concepts of the predictive value of a positive and the predictive value of a negative result; that is, how predictive is the test.

There appears to be an overlap between Key Questions 1 and 5. Dr. Calonge explains that question 1 focuses on whether screening makes a difference while question 5 focuses on what are the clinical outcomes. It was suggested that under the question 5 section, there should be a discussion around diagnosis of clinically important disease, including diagnostic testing attributes.

Key Question 6: Much of the literature on the harmful effects of false positives is not disease specific. There is very little research on the effects of informing families and who informs them of a devastating diagnosis.

Key Question 7: Data on cost will likely be limited. But it may be possible to comment on the cost of an additional screen (minimal), follow-up and diagnosis, and long and short term treatment, as well as the cost of nontreatment. Psychological costs and opportunity costs should be included. The AC members may not have the expertise to address all of the cost-effectiveness issues.

Members discussed dropping the question on cost effectiveness, anticipating that there would rarely be sufficient evidence to answer the question. But other members pointed out that to remain silent would place State screening programs in a quandary. Members agreed that whatever information on cost effectiveness is available should be collected and described, but that recommendations would often be made in the absence of cost-effectiveness data.

Dr. Calonge asked that any additional comment be sent to him soon. He agreed to distribute the next version of the document showing changes so that members would not be required to read the entire report, only the new and revised sections. Action is expected at the next AC meeting in February 2009.

6. Evidence Review Workgroup: Preliminary Report on the Candidate Nomination: Severe Combined Immunodeficiency Disease (SCID)

James Perrin, M.D., Professor of Pediatrics, Harvard Medical School, MassGeneral Hospital for Children, presented slides based on the extensive materials circulated to the members in advance of the meeting. These materials consisted of: the draft review summary (authored primary by Ellen Lipstein, M.D., and Alix Knapp, M.S.), evidence table and abstracted articles, bibliograpy of all identified articles, and a list of interviewees.

Dr. Howell repeated that the report is preliminary. Dr. Perrin referred to the status of the Evidence Review Workgroup's ongoing work in addition to the current work on SCID. The final report on Pompe disease was submitted and the review of Krabbe disease is in progress. He stated that the discussion of the Decision Criteria and Process Workgroup's report would be helpful to the Evidence Review Workgroup. He will assure that relevant issues are incorporated into the Workgroup's forthcoming report.

Dr. Perrin gave a brief overview of SCID and then moved on to desribe the methods of the review, which consisted of a systematic search of the published literature in English that resulted in the selection of 60 articles for indepth review and abstraction, combined with a review of unpublished data obtained from professional contacts. Following these reviews, interviews were conducted with selected genetic experts. Key kindings are summarized below.

At least 1 in 100,000 newborns are affected. Incidence is likely underestimated in the absence of screening. Incidence may be higher among Native American groups (Navajo). Experts reportedly believe that with systematic case finding, the prevalence may be higher due to earlier diagnosis of infants who would otherwise die prior to confirming a diagnosis of SCID. Although several population-based screening trials are underway or planned, to date no population-based screening trial has been completed. Without curative treatment, newborns with SCID develop severe, often opportunistic, infections which lead to early death. Studies indicate that treatment, most commonly with hematopoietic stem cell transplant, is effective in decreasing both the morbidity and mortality associated with SCID. There is some evidence that earlier treatment may lead to better outcomes. Nevertheless, the review led to the conclusion that critical evidence appears to be lacking in the following areas: prevalence, accuracy of screening, feasibility of screening, acceptability of screening, cost effectiveness, and adequacy of screening.

7. Committee Discussion on the Nomination of SCID to the Recommended Uniform Screening Panel

In response to a question from Dr. Calonge, Dr. Perrin said that there's a lack of good evidence about what are the risks of false positives in SCID and very little in the published research literature about the diagnostic workup and confirmatory testing. This is an important consideration in that "bone-marrowing" the false positives would not be good. Dr. Buckley, noting her conflict of interest, replied that confirmatory tests can be done within 3 hours of birth. (Dr. Howell later stated that Dr. Buckley was encouraged to participate in the discussion and respond to direct questions but would be recused from voting on the nomination).

Gerard Vockley, M.D., Ph.D., led the discussion, which he organized around the seven key questions delineated by the Decision Criteria and Process Workgroup. The key points are summarized below:

1. Is there direct evidence that screening at birth leads to improved outcomes?
There is no direct evidence because the results of screening programs are not yet available. Dr. Buckley's studies have primarily involved infants who were tested because of a sibling's diagnosis. It would be useful to compare infants identified as a result of their sibling's diagnosis and those without a

SICD sibling. Dr. Vockley noted that it would be helpful to have the information on the children who were diagnosed strictly on the basis of family history included in the Evidence Review Group's report.

2. Is the condition well-characterized?
There is a characteristic clinical picture in the children that are identified with symptoms. But we do not know if there is a milder variant, which would be identified by universal screening.

3. Is there a test with sufficient analytic validity and utility?
There's a lack of screening data as related to population screening. The ongoing pilot studies may yield findings to answer this question. The currently available evidence is insufficient. There may be other ways to identify infants with SCID, such as a white blood cell count and a manual differential on the cord blood, on which Dr. Buckley reported she had considerable unpublished data.

4 & 5. Has the clinical validity of the test been determined and is that validity adequate? What is the clinical utility of the screening test?

Referring to the graph in Dr. Perrin's PowerPoint presentation, members asked about the difference in outcomes between early and late detection and treatment. According to Dr. Buckley, the differences were "highly statistically significant," and there was no significant difference across race and gender. One confounder may be that the study extended over a period of 26 years, a period during which transplant procedures improved. A greater proportion of the children who received a transplant early are more recent cases, and the technologies and treatments are better compared to the cases with later treatment, thereby introducing a possible bias in terms of survival. Another member asked if the infants with the early transplants were also more likely to have been started earlier on antimicrobial therapy. Dr. Buckley responded that after a diagnosis of SCID, the patient is generally put on prophylactic Septra to prevent PCP, but those treated later may have been treated with antibiotics for various illnesses before the diagnosis was made. The one main difference is that the infants that were transplanted early remained well babies throughout the post-transplant course compared to the late treatment infants who often had a rocky course. Committee members desired more information about the characteristics of the two groups of children, those who were transplanted early and those who were transplanted after a later diagnosis.

Before leaving the meeting, Dr. Calonge mentioned several areas that need additional information, including the testing platform, uniformity of testing, and specificity; threats to internal validity of the separation of the survival curves based on early detection; external validity or the capacity of states to implement screening and to follow up with diagnosis and treatment. He noted that from a public health perspective the identification of a condition in the absence of a curative strategy is not necessarily helpful.

Before it was time to move the agenda, Dr. Vockley concluded that, as with the other conditions that the AC has considered, the lack of data on the results of screening programs makes it very difficult to make recommendations.

Dr. Howell stated that the report and the discussion were excellent and that the SCID recommendation would come before the AC for action at the next meeting, scheduled for February 26–27 2009 in Bethesda, Maryland.

8. Public Comments

Dr. Howell opened the lines for public comment. Six members of the public had pre-registered to comment. They were:
Marcia Boyle, President, The Immune Deficiency Foundation
Micki Gartzke, Vice President, Save Babies Through Screening Foundation
Priva Kishnani, Duke Medical Center
Ronald H. Laessig, Ph.D., Emeritus Director, School of Medicine and Public Health, University of Wisconsin
Jennifer M. Puck, Professor of Pediatrics, University of California San Francisco
Heather Smith, Co-Founder, SCID, Angels for Life Foundation

However, only three members of the public actually commented before the AC.

Dr. Boyle emphasized that babies born with SCID have the most severe of the more than 150 recognized primary immune deficiencies. They die before their first or second birthday if not given immune reconstitution by bone marrow transplantation. If a baby with SCID receives a transplant in the first three months of life, then the survival rate can be as high as 95 percent. However, the rate falls dramatically with later transplants. Many children with SCID who were transplanted had siblings who died from SCID. Newborn screening for SCID would save the lives of babies with SCID and give them more normal lives. The effect of live virus vaccines on these infants is another issue to consider.

Heather Smith, the cofounder of the SCID, Angels for Life Foundation, and the mother of two children with SCID, described her personal experience with her first child, who died from SCID in 1993, although the cause was not determined until months later. The outcomes for the second child, who was diagnosed prenatally and then had a bone marrow transplant in utero, have been much better. That child is now a thriving teenager. Ms. Smith described another case in which a mother of an undiagnosed infant had charges brought against her by child and protective services.

Dr. Jennifer Puck, who nominated SCID for consideration by the AC, said that there are several different transplant protocols to use for SCID. Many institutions have developed their own protocol rather than using a standard one because the disorder is so rare. All of the protocols save lives in contrast to no treatment. Infectious complications are present at diagnosis in SCID cases, except in those with a known family history or a prior death. Insofar as treatment saves lives, Dr. Puck believes it is wrong to delay institution of newborn screening until a single ideal treatment is found. Secondly, although outcomes following successful treatment for SCID are not always complete cures, the overwhelming majorities of children who receive these treatments develop, thrive, attend school, go to college, get jobs, and pay taxes. Their intellectual function is normal or near normal. A recent publication from England confirmed these outcomes, finding that any residual impairment can almost always be attributed to the infections that occurred due to the delayed diagnosis rather than the SCID itself or its treatment. She reported that she is aware of the Wisconsin screening program, which is using the TREC test and has indeterminate rates similar to the ones described in Dr. Perrin's report.

9. Committee Business

Dr. Howell announced that May 12–13 2009 had been confirmed as meeting dates. Queries will soon be sent out by staff concerning a September 2009 meeting, likely after September 10. Dates will be examined to avoid conflict with the meeting of the International Society for Inborn Errors of Metabolism in San Diego and religious holidays. Members asked that staff send out the official invitation to the February 26–27 meeting as soon as possible. Budget constraints are making it more difficult (especially for government employees) to obtain travel approvals.

10. Adjournment

All items on the agenda having been discussed, the meeting was adjourned at 3:40 p.m.

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

These minutes were formally approved by the Committee on February 26, 2009.