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

Summary of 14th Meeting
August 7, 2008
Audio Conference Call

Prepared for:

Genetic Services Branch
Maternal and Child Health Bureau
Health Resources and Services Administration
Rockville, MD

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1. Opening

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children met via audio conference Thursday, August 7, 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 Chairperson R. Rodney Howell, MD, at 1:12 p.m., when Executive Secretary Michele A. Lloyd-Puryear, MD, PhD, determined that a quorum was present.

Dr. Howell welcomed members to the 14th meeting of the Advisory Committee (AC), noting the committee's name had changed ("and Genetic Diseases" having been deleted) and its mission had been expanded. He announced that the American College of Obstetricians and Gynecologists had appointed Thomas Musci, MD, as the new representative to the AC.

The agenda, which was distributed by email in advance of the meeting, was followed.

2. Action: Approval of Minutes of January 14–15, 2008, Meeting

It was moved and seconded to approve the minutes of the January 14–15, 2008 meeting as distributed. Dr. Lloyd-Puryear conducted a roll call vote. The motion was approved unanimously by the 11 voting members present.

3. Remarks from HRSA Deputy Administrator

Dennis P. Williams, PhD, thanked the AC members on behalf of Elizabeth Duke, Administrator. He noted the significance of a virtual meeting in cost savings. The Health Resources and Services Administration (HRSA) hopes to conduct more advisory committee meetings in this manner if it works well. He would appreciate the members' feedback on the effectiveness of the virtual meeting.

The new legislation on newborn screening (NBS), the Newborn Screening Saves Lives Act of 2008, will have an impact on the work of the AC and upon NBS in general. The law was enacted quickly without time for extensive analysis and input from HRSA. Dr. Duke formed a business team within HRSA and is convening weekly meetings in order to implement the law with all due speed. Some interpretation of the law will be required.

4. Nomination and Review Process: A Review

Nancy Green, MD, Division of Pediatric Hematology and Associate Dean for Clinical Research Operations, Columbia University Medical Center, a contractor to HRSA, gave a PowerPoint presentation outlining the process by which the AC reviews a condition for NBS. (See summary of January 2008 meeting for information on the history, charge, and composition of the Nomination Review and Prioritization Workgroup (NRPW). Using the nomination form posted on the HRSA Committee web site, anyone may nominate a condition and complete the form with the required information and references. HRSA staff conducts an administrative review and if it is determined that the nomination merits additional consideration, it is submitted to the AC chair, who then determines when to forward the nomination to the Nomination Review and Prioritization Workgroup (NRPW). The NRPW's tasks have been to list criteria for readiness for evidence-based review and then to make a recommendation to the AC about whether or not to submit a nomination for evidence-based review. The Workgroup examines the evidence to determine whether it is sufficient to justify a review by the Evidence Review Workgroup (ERW).

The ERW is external to the AC, that is, the membership is made up of persons who are not members of the AC. Dr. Green and Marie Mann, HRSA, participate in biweekly meetings. To date, the ERW has

defined (1) terms from the nomination form that required clarity and (2) the criteria for evidence. The Workgroup is expected to submit a formal report to the AC for each of the conditions that it reviews. Neither Workgroup makes decisions. It makes recommendations to the AC, which is the body that makes the final decisions about recommendations to the Secretary.

The NRPW asks six questions to determine if a nominated condition is ready for consideration by the ERW. The nomination form calls for information that describes the following aspects of evidence in order that the Workgroup may make a recommendation.

1. Is the nominated condition(s) a medically serious one?
2. Are there prospective pilot data either from U.S. or international sources available from population-based assessment for this disorder?
3. Is the spectrum of this disorder well described to help predict the phenotypic range of those children who will be identified based on population-based NBS?
4. Is there a screening test that is capable of identifying the condition?
5. If the spectrum of disease is broad, would there be, through testing and evaluation, the ability to identify those children who are most likely to benefit from treatment, especially if the treatment is onerous or risky?
6. Are there defined treatment protocols available, and if applicable, is there Food and Drug Administration (FDA) approval or clearance for those treatments?

The NRPW recommends to the AC that a nominated condition be sent to the ERW or not. If the AC accepts the recommendation for external review, the nomination is then forwarded to the ERW.

Dr. Green explained that in considering a nomination, the ERW can make one of the following recommendations to the AC:

1. Add to the universal NBS panel
2. Targeted screening
3. Pilot study to be undertaken prior to any recommendation
4. More critical studies needed
5. No recommendation
6. Recommend against adding to NBS panel

Q&A

Michael Skeels, PhD, MPH, asked about the role of cost-benefits data in the reviews. Dr. Green responded that the consideration of such data would be within the purview of the external evidence review process. Cost data are infrequently available. When queried about the availability of resources to respond to the lack of information on cost, Dr. Green suggested that collection of cost data could be incorporated into a recommendation for a critical study or a pilot.

Coleen Boyle, PhD, MS, inquired about the directions of the communication lines between the NRPW and the ERW depicted on Slide 3 of Dr. Green's presentation. Dr. Green said that communications might go in both directions insofar as one workgroup would want clarification from the other workgroup. Dr. Howell interjected that the primary communication would be from the NRP W to the ERW. Dr. Green agreed to revise and clarify the diagram. She reiterated that the AC, not one of the workgroups, makes the decisions on recommendations.

Al Berg, MD, MPH, American Academy of Family Physicians, asked about a mechanism for periodic reconsideration or review of conditions that the AC has already considered. The National Guidelines Clearinghouse, for example, requires a review every 4–5 years.

Ned Calonge, MD, MPH, Chief Medical Officer and State Epidemiologist, Colorado Department of Public Health and Environment and AC member, said that although the evidence for conditions should be reviewed over time, no one can say with what frequency. The conditions are rare, and therefore considerable time may be required to acquire a sufficient number of cases for a review.

Dr. Howell remarked that the National Institutes of Health (NIH)-proposed effort with the Translational Research Network to follow in a research mode some of these rare conditions is still in development. That particular group may produce information that would require that the AC conduct another review.

Dr. Calonge suggested establishing a process that periodically looks at and summarizes any new information about a condition that is on the recommended screening panel. For example, the Clinical Task Force uses medical officers and members to scan the literature for landmark articles. The AC could establish a policy whereby every 5 years (or other periodicity) the literature is searched. This would require resources.

Peter van Dyck, MD, MS, MPH, Committee Member and Associate Administrator, HRSA Maternal and Child Health Bureau, suggested that the NRPW consider this issue and make a recommendation to the AC. Reviews should take place when there is sufficient new information. He went on to suggest that Dr. Green's committee take responsibility for drafting guidelines concerning the frequency of reviews.

Tracy L. Trotter, MD, FAAP, reported that the American Academy of Pediatrics policy is to review its policy statements every 3 years, not necessarily a full review but a review to determine if there is sufficient new evidence to conduct a full review. It is important to have a policy on and a structure for reviews.

Dr. Boyle mentioned that it is important not only to review new conditions but also to re-review conditions on the recommended list when enough cases have been accumulated for a new review. It may also be necessary to think about the type and amount of evidence that would be needed to justify removing a condition from the recommended panel.

Noting that the discussion indicated considerable interest in developing a process for periodic follow up reviews, Dr. Howell assigned this topic to Dr. Green's Workgroup and asked that she report back to the Advisory Committee.

Dr. Howell asked Dr. Green to explain slide 5 again: Severe Combined Immunodeficiency (SCID) and Pompe are in the external review process, but what is the current status of Krabbe, Fabry, and Niemann Pick? Dr. Lloyd-Puryear reminded the members that the NRPW is reporting on the Krabbe disease and Fabry disease nominations later in the meeting. This is an action item for the meeting. There was no previous vote on the two nominations. Niemann Pick is still under consideration by the NRPW.

Dr. Calonge said that some of the six questions considered by the NRPW are ones for which there might be evidence available from the literature review. He asked whether that evidence would be presented in the ERW's reports. Dr. Perrin replied that his report (later on the agenda) would include this topic.

Dr. Calonge asked what happens with a review in the absence of evidence on the cost effectiveness of population-based strategies: Do we have the resources to construct an outcomes table based on prevalence, cost of therapy, marginal cost, and other follow-up issues so that we have a ball park understanding about the up sides and down sides of the costs? Dr. Perrin said that Dr. Calonge's question was a very important one. There is little published evidence with respect to cost. The ERW

hopes to provide outcomes tables, at least on a crude level, of these data, but the strength of the evidence is limited.

Dr. Green pointed out that one possibility is for the ERW to recommend to the AC that an assessment of the cost impact be made. She went on to say that the six questions that the NRPW considers are based on the nomination form and the references submitted with that form by the nominator.

5. Decision Criteria and Process Workgroup

Dr. Calonge said that because he did not have Internet access, he was unable to distribute his report to the AC. He noted that later in the meeting members will vote on recommendations from Dr. Perrin's group. To begin with, the Decision Criteria and Process Workgroup (DCPW) was uncomfortable with having only two options: to recommend or not to recommend. Ideally, one would want to have solid evidence from randomized trials to say that screening for a condition improves health outcomes. But with extremely rare conditions, this is an impractical standard for decision making.

DCPW has been considering six questions that are very similar to the list of six questions used by the NRPW. Dr. Calonge described the six questions:

- Is the condition well-defined and important? Documentation will be provided on the nominating form and will be used in determining whether to forward a nomination to the ERW.
- What is known about the natural history of the disease?
- What is known about the treatment history of the disease? Clarifying what is known about the condition, its spectrum, and whether or not there is sufficient evidence or at least sufficiently hopeful evidence that there is an effective treatment available is an important issue.

The next set of questions looks very much like the ACCE questions that are currently used by the Evaluation Genomic Applications in Practice and Prevention Working Group, which is chaired by Dr. Berg.

- Does the test have sufficient analytic validity? This is an important question because for metabolic and genetic tests the laboratory methods might vary from laboratory to laboratory, and for home-based tests. Population-based screening depends on the replicability across testing centers or laboratories. Although this is not a question that the Preventive Services Task Force asks, it is very important in both metabolic and genetic screening. The test must actually measure what it is supposed to measure so that it can be replicated in other laboratories.
- Does the individual fall on the part of the spectrum that requires treatment, or in the case of a genetic test, is it only an increased risk of disease and not a disease at all?
- Does treatment result in improved outcomes?

He went on to say that Piero Rinaldo, MD, Ph.D., Professor of Laboratory Medicine, Mayo Clinic College of Medicine and AC member, had agreed to work on this section of the DCPW's report and then described the distinction between analytic validity and clinical validity. Clinical validity is how the test results translates to the disease and considers penetrance, false positives, false negatives, and overdiagnosing. Clinical validity has different attributes in newborn metabolic screening compared to newborn genetic screening.

Dr. Calonge continued by saying that there may be a consideration of consistent cutoffs for the clinical positive predictive value and negative predictive value or of a level of false positives that we are willing to accept in diagnosing a condition in a newborn. Such discussions are just beginning in the field because the willingness to accept a false positive may be based on how onerous, risky, or expensive the treatment is, as well as the harms associated with making a false diagnosis.

A final issue in clinical utility is the extent to which important health outcomes occur if positives are treated. The draft document the Workgroup is preparing lists the health-related outcomes for genetic screening that are described in the findings and recommendations of the April 2008 Report of the Secretary's Advisory Committee on Genetics, Health, and Society, **U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services** (http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf). Outcomes are categorized into four groups: health information impact, therapeutic choice, patient outcome impact, and familial and societal impact. The Workgroup will attempt to weigh those outcomes in terms of the potential down sides to the testing. When the Workgroup has the information to answer the questions about the importance of the test, the availability of treatment, the analytic and clinical validity of the test, and its clinical utility, the potential benefits and potential harms can be weighed to determine, based on the best evidence or estimates available, whether the benefits are greater than the harms.

Phenylketonuria testing is an example of the benefits greatly outweighing the harms, but in many cases in which the net benefit is extremely small, zero, or even negative, the recommendation should be not to add the test.

He then spoke about level of certainty. Decisions about net benefits should be applied with a level of certainty, for instance, very certain, moderately certain, or uncertain. With moderate certainty or above, a mistake is unlikely. In the uncertain area, however, there is insufficient evidence, and we need to have additional choices for the final outcome in addition to add or not add. The Workgroup discussed situations in which tests may have potentially significant net benefit, but the research is not completed or the evidence is not adequate. Nevertheless, it may be that the potential for net benefit is compelling enough to add the test now with the commitment to evaluate the experience with the test over time. Thus, the recommendation may be to add a test with a provisional status with the express expectation that the AC will review the evidence at a later time and recommend continuing or removing the test. Another situation is one in which little is known about the net benefit. The evidence is not sufficient to recommend provisional status, but a recommendation could be made to conduct pilot studies. In summary, the possible recommendations are as follows:

1. Add the test to the core set because of sufficient certainty of significant net benefit.
2. Do not add the test to the core set because of sufficient evidence of zero benefit or net harm.
3. Add the test with provisional status where the certainty is insufficient but the potential for net benefit is compelling. Evaluate the experience with the test over time.
4. Do not add the test now but instead recommend pilot studies.

The Workgroup is developing a decision matrix, which will soon be distributed for comment. Dr. Calonge spoke about situations in which there is a lack of evidence for making a recommendation. Direct evidence from randomized trials is the preferred standard for evidence. But the rarity of the heritable conditions makes randomization unlikely and an impractical standard. Therefore, the Workgroup attempted to delineate decision criteria for those conditions for which evidence from trials data was not available. A search of the literature was organized around the six key criteria described earlier in the meeting (listed above).

Q&A

Dr. Boyle said that it may be challenging to decide between a recommendation of a pilot study and a recommendation for provisional status. She asked if the two categories could be collapsed into one. Dr. Boyle is a member of the Workgroup but was unable to participate in the discussion about the matrix.

Dr. Calonge reiterated that the Workgroup members wanted to differentiate between these two categories. Granting provisional status does not slow the process in a situation in which the evidence is not yet available and it is believed that the evidence will support the test once it is available. Dr. Boyle

replied that she understood that distinction with regard to EGAPP, but it is a clinical test. A public health screening program is entirely different.

Dr. Trotter, another Workgroup member, reaffirmed the Workgroup's agreement on the four categories, saying that in working on the decision matrix, members believed that their future considerations would likely involve tests for which the evidence was insufficient and they wanted to have more than one possible response.

Dr. Calonge said that one consideration is that once a condition has been given provisional status, it is difficult to remove it from the screening panel although Colorado recently removed a condition because no positives had been found over a 20-year period. Dr. Boyle said that she considered the provisional status as being a public health function, and therefore exempt from informed consent, whereas a pilot study was within the context of informed consent and research. There is an ethical and legal aspect of informing people about the lack of knowledge involved with a test.

Dr. Calonge agreed that the ethics of adding a test in a public health population-based strategy where there is still a level of uncertainty but not to inform patients of the uncertainly is an issue to consider. Another participant raised the question of how many of the conditions currently in the recommended panel would meet the level of certainly now being required for an "add" recommendation.

Dr. Skeels noted that Dr. Boyle's point was an important one, but even if a screening is recommended, each jurisdiction must decide to implement it. Dr. Berg said that many groups are struggling with what kind of and how much evidence to require prior to recommending and implementing a clinical treatment or public health intervention. This question is not unique to the AC. The bar is being raised as to evidence, which raises an interesting question about interventions previously accepted that would not meet current criteria. Saying that he was too new to the AC to make a suggestion, he commented that the general direction of the discussion is at the cutting edge of where these reviews need to be.

Before leaving the conference call, Dr. Calonge indicated that he would rework the explanations contained in the current draft document, but intended to retain the provisional status for some conditions for which the best evidence is lacking. He will distribute another version to the AC next week. He announced that because he will be unable to attend the October meeting, Dr. Green will present the recommendations of the Workgroup. Dr. Green agreed and asked that the document accurately reflects the struggle to take into account gradations of evidence, which is very important. But she expressed concern that the states may interpret the gradations differently. She referred to a pilot on SCID being conducted in Wisconsin that does not require informed consent.

Dr. Howell asked that the forthcoming version of the Workgroup's report take into account today's discussion and Dr. Boyle's comments.

6. Nomination Review and Prioritization Workgroup: Report on Candidate Nominations: Krabbe Disease and Fabry Disease

Dr. Rinaldo reviewed his PowerPoint slides, which included fact sheets for Krabbe disease and Fabry disease, and the scoring included in the American College of Medical Genetics (ACMG) and HRSA report. At the time of the report, the consensus was that there were no sensitive specific population-based screening tests available and validated for Fabry disease and Krabbe disease, but as new studies were completed, there was a need to reevaluate the evidence. He summarized the revised process for the AC's consideration for adding disorders to the NBS, a process that was described by Dr. Green earlier in the meeting, and focused on the role of the NRPW. The NRPW was formed to deal with the possibility of the receipt of a number of nominations simultaneously and the need to establish priorities for consideration by the ERW. The NRPW makes recommendations to the AC on the order of submission of nominations to the ERW.

Dr. Rinaldo went on to explain how the process was applied to the cases of Krabbe disease and Fabry disease. Krabbe disease was nominated by Micki Gratzke on behalf of the Hunter's Hope Foundation. It was submitted in September 2007. The administrative review was concluded in January, and it was reviewed by NRPW in March. The application did not adhere to the page recommendation, something that the AC may want to be stricter about in the future. In contrast, the SCID nomination was only 2 pages and was very well-done. Fabry disease was nominated by Maryam Banikazemi from the Fabry Information and Support Group. The nomination was received December 2007, reviewed in less than a month by HRSA staff, and reviewed by the NPRW in March. The nomination conformed to the 2-page limit.

The Workgroup can handle only a limited number of nominations and must consider them in the order received. It may sometimes be necessary to place some nominations on stand-by status. New findings may trigger reconsideration. He pointed out that the quality of the documentation submitted with the nomination affects the Workgroup's review, saying that the SCID nomination was a good model to follow for its brevity and conciseness.

He then reported on the findings of the Krabble review. It is a medically serious condition. Data are available. The clinical spectrum is well-described. The clinical spectrum helps to predict the phenotype with the range to be determined by another group. Although there is a lack of consensus on the benefits of early identification, the Workgroup recommended that the nomination be sent to the ERW.

NRPW recommendation and subsequent motion: Krabbe disease meets the criteria for evidence-based review. Recommend the clarification of identifying those infants most likely to benefit and the efficacy of treatment.

Dr. Rinaldo then turned to the report on the Fabry disease nomination. The evidence documents that it is a medically serious condition with a well-described clinical spectrum. The prospective studies were conducted in Italy, Austria, and Taiwan. The data from Italy are very provocative and the Workgroup determined that the studies should be replicated in a U.S. population before being acted upon. Although Fabry disease is technically detectable in a screening panel for late stage detection, the following factors limit its appropriateness for inclusion in NBS:

1. The late and variable onset of the disease
2. Uncertainty whether those at highest risk of serious symptoms can be discerned in newborns
3. The lack of published data on preventive treatment early in life
4. The undetermined risk of immunologic response to ERT

On the other hand, and quite differently from Krabbe disease, there is an FDA-approved treatment. Premature treatment may lead to immunological response and could neutralize the effectiveness of treatment at a later time.

Dr. Rinaldo referred to a paper published in 2006 in the ***American Journal of Human Genetics*** by Marco Spada, Alberto Ponzone, and their colleagues, in collaboration with Bob Desnick, describing a pilot study in which 12 cases were identified. Some were clearly at the genotype level, indicating late-onset. He quoted the study: "The incidence will be approximately 1 in 4,600 – 7-to-1 ratio of patients with the later-onset versus classic phenotypes." "Results suggest that the later-onset phenotype for Fabry disease is under diagnosed."

The Workgroup noted that a prospective study in the United States of screening and therapeutic intervention is needed to demonstrate the benefits of screening for this disease. Therefore, the Workgroup determined that the nomination does not yet meet the criteria for submission to the ERW.

A pilot study recommendation may be appropriate. Until additional evidence is available, it is not a good use of resources to submit the nomination to an external review.

NRPW recommendation and subsequent motion: It is not recommended that Fabry disease go forward to the expert review group at this time.

According to Dr. Rinaldo, the consideration of these two diseases shows the progress being made in NBS. But issues related to phenotype and clinical presentation remain. As cited in the article by Spada et al. in the *American Journal of Human Genetics*, the later-onset phenotype of Fabry disease is underdiagnosed among males with cardiac, cerebrovascular, or renal disease. The late onset dilemma is not unique to heritable disorders, an example being the current discussion around LSD screening for children.

Dr. Howell reminded the members that prior to the meeting, they had received by email from HRSA the nomination forms and a summary of the NRPW's report on Krabbe and Fabry. He called for discussion.

Q&A

Members expressed some uncertainty whether a vote on the Krabbe nomination had been taken at a previous meeting. The Executive Secretary searched the minutes and announced that the AC had not previously voted. She referred them to page 40 of the minutes of the January 2008 meeting.

Gerard Vockley, MD, PhD, stated that the Workgroup had presented a very well-reasoned recommendation. He noted the need to reconsider the use of terminology (e.g., "to send forward," "not to send forward," "reject"). The AC should strive for consistency and uniformity in terms. Dr. Skeels said that there should be consistency in the use of terms such as sensitivity, specificity, false positive, false negative, and predictive value throughout all of the different analyses and recommendations. This is something that the AC should work toward.

In response to a question about the importance of a U.S. study, Dr. Rinaldo replied that it would be a dangerous precedent to recommend a screen that no one in the United States is conducting.

7. Action: Recommendation on Krabbe Disease Accepted

Dr. Vockley moved to accept the Workgroup's recommendation and to forward the Krabbe disease nomination to the Evidence Review Workgroup. Dr. Skeels seconded the motion.

The Chairperson called for discussion of the motion.

Dr. Boyle asked if the review had relied primarily on the references cited by the nominator. Dr. Rinaldo responded that Dr. Green devised a form that provided the framework for the Workgroup's conference call to consider the nomination. Each member of the Workgroup had the nomination packet and the opportunity to express his or her opinions during the conference calls. Dr. Rinaldo said that he agreed that the AC should establish a standardized nomenclature.

Dr. Boyle noted that the Krabbe nomination was submitted in September 2007 and the major population-based or the prospective data are based on the New York experience. But there have been new studies since that time.

Dr. Rinaldo responded that the members did benefit from an update on the New York experience and information presented at the ACMG meeting in Phoenix. Dr. Lloyd-Puryear interjected that the NRPW met before the Phoenix meeting. Therefore, the members did not have access to the information presented there.

It was clarified that the motion dealt with forwarding the nomination for an evidence review, which will take into account studies completed since the time of the nomination. Dr. Howell said that had the NRPW considered the later information, the outcome would have been the same.

There being no further discussion, the chairperson called for a roll call vote. The Executive Secretary called the roll. All 10 members present voted in favor of the notion. The motion carried unanimously.

If response to a question from Dr. Boyle, Dr. Howell clarified that the motion included the entire recommendation of the Workgroup, which included to "recommend the clarification of identifying those infants most likely to benefit and the efficacy of treatment."

8. Action: Fabry Recommendation Accepted

Dr. Rinaldo said that the current evidence was not sufficient to justify the use of resources for forwarding to ERW. That may change over time. The data coming out of Italy are so provocative and with such far-reaching consequences, that at a minimum they should be reproduced in the United States.

Duane Alexander, MD, National Institutes of Health, noted that the Workgroup's work was well done and demonstrated the value of the two-staged review process. He moved to accept the Workgroup's recommendation, "It is not recommended that Fabry disease go forward to the expert review group at this time." The motion was seconded by Dr. Skeels.

The Chairperson called for discussion of the motion.

Dr. Skeels said that the wording was important. At this time, we do not recommend that the nomination be sent forward for the review process, but we consider it to be an important issue that is worthy of a pilot basis. We are not shutting the door on the nomination, but we need more information.

Dr. Howell stated that the people who prepared the nomination are knowledgeable and expert in this area and the AC would like to be constructive. We should say that this is our opinion at the current time and ask them to continue their work and resubmit a nomination at a later time.

In response to a question about the importance of a U.S. study, Dr. Rinaldo said that it would create a dangerous precedent to add a test which no one in the United States was using.

Michael S. Watson, PhD, FACMG, Executive Director, ACMG, said that he agreed that there are circumstances in which it is important to have U.S. studies, for example, with diseases such as G6PD. Dietary lifestyles vary considerably between countries. One would have a very different perspective on the disease in Southeast Asia compared to the United States.

Dr. Alexander stated that the AC should encourage the Krabbe mode, which was based on a prospective study in one state and provided very useful evidence. There is value in having the results of a test under U.S. conditions to guide AC actions.

Dr. Howell suggested that members of the AC in one of their many roles may want to work with the Fabry group to carry out pilot studies in their respective regions.

The Chairperson asked the Executive Secretary to call the roll for the vote. All 10 voting members present voted in favor of the motion. The motion carried unanimously.

9. Evidence Review Workgroup: Report On the Candidate Nominations: SCID and Pompe Disease

James Perrin, MD, Professor of Pediatrics, Harvard Medical School Director, Division of General Pediatrics and Director, Center for Child and Adolescent Health Policy, Harvard Medical School and MassGeneral Hospital for Children, a contractor to HRSA, described his PowerPoint slides. He first described the process used by the ERW of which he is one of 10 members, most working in the Boston area and presenting expertise in a range of fields. He began by reiterating that the purpose of the ERW is to provide a systematic, reproducible, thorough, and transparent process for gathering, organizing, and analyzing available data on conditions that have been submitted by the AC for in-depth evidence gathering and evidence review. The ERW works in conjunction with a four-member Evidence (External) Advisory Group, which has reviewed the ERW's process and later will review its conclusions before they are presented to the AC. The external advisors help to identify sources of new information and assist with access. They do not actually analyze the evidence. The ERW focuses on process and timelines as well as evidence. (See minutes of January 2008 AC meeting for a list of members and the charge of the two groups.)

Issues in evidence reviews center around the rarity of the conditions under review and access to evidence. Because the conditions are rare, there is typically a lack of randomized trials research as well as limited information on cost and benefits across all potential outcomes. Gaining access to unpublished investigator findings and proprietary data in addition to published evidence can be challenging.

Dr. Perrin summarized the ERW's Year 1 activities. The members agreed upon a data abstraction form, which is based on forms used by other evidence review groups, and an evidence review outline, making the review process systematic. They also developed a clear conflict of interest policy for participation in reviews. This policy, which is based on Institute of Medicine policies, considers both direct intellectual conflicts and financial conflicts. Anyone involved in the review is asked to declare conflicts of interests. It is necessary to work with investigators who not only have financial interests but often very strong beliefs. The ERW does not ask the investigators for their opinions or recommendations, but rather uses them to identify additional sources of evidence and to determine if the existing evidence has been correctly identified. He went on to summarize the rationale and objectives of the evidence review, which is intended to provide timely information to the AC to guide recommendation decisions for a specific screening program and to be comprehensive, objective, and transparent. As described during the January 2008 meeting, an evidence review (and the subsequent report to the AC) addresses the following areas:

1. Natural history of the condition, including variations in phenotype
2. Incidence relative to genotype, phenotype, and phenotype variations
3. Impact and severity
4. Methods of screening and diagnosis, including screening test utilities, and the feasibility and acceptability of screening
5. Efficacy and effectiveness of treatment
6. Harms or risks of screening, diagnoses, and treatment
7. Costs of screening, diagnosis, treatment, late treatment, and failure to diagnose in newborns (to the extent these data are available)

According to Dr. Perrin, the report to the AC will include a description of the decision model that was used in the development of the evidence questions, which builds upon the work of the NRPW.

Criteria for inclusion in the literature reviews include:

1. Peer reviewed studies in English language publications

2. Published within a 20 year time period
3. Exclusion of case series with fewer than four cases
4. Data quality that meet current standards

Consensus statements will be reviewed as guides, but not abstracted. The gray literature will generally be limited to that provided by pharmaceutical companies and other unpublished studies. Another source of information (although not used in the SCID and Pompe disease reviews) is focus groups of investigators and families.

The ERW presents its results in the order and content of the seven areas listed above, as well as outcomes tables showing the decision analysis model results. This information is then summarized in a table format, which indicates where evidence is absent and what information was considered to be most critical. The report will contain a statement – for example, "The current weight of the evidence suggests that the prevalence or incidence of this condition is X, that the rates of these different phenotypes based on the genotype are Y, and that the weight of the evidence currently regarding the screening test experience has been in population studies and smaller studies…." The ERW presents its findings to the AC without recommendations.

Next, Dr. Perrin described how this process was applied to SCID and Pompe disease. The ERW began the reviews in June after HRSA had awarded a contract. The Pompe disease review is building on earlier work by Alex Kemper, which needed to be updated. Dr. Kemper, Marsha Browning, and Denise Queally are having conversations with investigators and interest groups. The ERW expects to submit the Pompe report to the AC for action at the October 2008 meeting, following a review by the External Advisory Committee. He expects to send the SCID report to the External Advisory Committee in late September. Data abstraction has been completed, and key investigators are being contacted for additional information.

Lessons learned from the Pompe disease review were described by Dr. Perrin. Workgroup members attempted to identify sources of unpublished data through their individual relationships, discussions at meetings, suggestions from advocacy groups, and citations in the literature. Given that the Workgroup members were well-connected and knowledgeable in the field of genetics, it was not difficult to identify sources of evidence.

Prior to any discussions with researchers and informants, the Workgroup obtained conflict of interest declarations. The contacts found the need for declarations difficult to understand and were frequently overwhelmed by such requests. The extent to which the declarations are complete and honest is not known. Researchers were typically willing to provide high-level summaries of their unpublished work and to clarify their summaries in subsequent interviews. However, they were understandably reluctant to provide their data. As a result, the data that were provided to the ERW lack granularity and the level of detail is not sufficient to fully evaluate the evidence, but they do enable the Workgroup members to better understand the direction of on-going research. The efforts to obtain unpublished data did not result in evidence sufficiently strong to be included in the results section of the ERW's report to the AC. Nevertheless, this information can be incorporated into the discussion section if the findings suggest new methods of screening, diagnosis, or treatment, or if unpublished findings differ from published findings.

Q&A

Dr Berg said that using focus groups was a novel addition to the traditional sources of evidence. Insofar as family members have strongly held views, how would focus group data be used? Dr. Perrin replied that the ERW has yet to use this method. Focus group data may perhaps generate 'best estimates" where there is no information in the literature on which to generate estimates.

Ethan D. Hausman, MD, FAAP, FCAP, Medical Officer, Division of Gastroenterology Products, FDA said that the idea of using pharmaceutical data was excellent, but he cautioned against the acceptance of data from them, and said that it is important to assure that the data have not yet been cleaned. Dr. Perrin responded that he agreed, but said that it is very difficult to know what data are being received. Obtaining and evaluating unpublished data is very challenging. He said that he was interested in advice from the AC on the time frame of reviews and the use of unpublished data. It was noted that the contracts necessary to conduct the reviews were delayed due to HRSA's budget cycle and contracting requirements.

Dr. Watson inquired about the application of conflict of interest declarations to the gray literature. Investigators may work in a variety of settings: businesses, foundations, clinical labs. For the ACMG, a big issue in developing guidelines has been the impact of the orphan drug legislation which essentially gives a company a monopoly on the sale of a particular drug, and when approved by FDA, the company often gets a phase IV surveillance band aid of doing long-term follow-up, which brings everybody who treats patients into the clinical trial activity. He asked whether conflicts could be graded or ranked.

Dr. Perrin replied that it was an interesting idea, but that he was not aware of a method for grading conflicts of interest. Most of the researchers have substantial conflicts: They have or are seeking research grants or they are employed by a profit-seeking organization. It is often possible to differentiate a clear financial and a clear intellectual conflict.

Dr. Vockley suggested what he called a heavy-handed approach – make it the responsibility of the nominator(s) to provide the data or table the nomination. Dr. Perrin said that investigators will willingly give up data that will change the level of evidence. But to date, with the Pompe review, the investigators have reported that they have no new data that change the evidence base.

Dr. Vockley asked if the Workgroup was comfortable with investigators saying they have no pertinent data. They should show the data and the Workgroup should decide whether it is pertinent. The Workgroup can ask if the investigator has anything more, and the answer is either yes or no. If the answer is no, then they have been forthcoming. Dr. Perrin replied that this was very good phrasing that the Workgroup could use. The ERW will report to the AC on these efforts.

Dr. Rinaldo pointed out that the order of the reviews described by Dr. Perrin has actually voided the order recommended by the NRPW. Dr. Perrin replied that "voided" was a rather strong word. The ERW could hold the Pompe report until after the submission of the SCID report, but because the Pompe review requires less time, the report would be ready soon. Dr. Trotter said that he would defer to the judgment of the AC chair and executive secretary. Dr. Rinaldo asked whether the timeline referred to the time of the AC action or of the final report. Which is more important? He wondered whether "Prioritization" should be removed from the name of the NPRW. Dr. Perrin said that the Pompe situation was a unique one due to the complications of the budget and contracting. In the future, the ERW expects to follow the recommended order for reviews.

Dr. Howell commented on the order of the reviews, saying that the ERW should be attentive to the order recommended by the NRPW. Nevertheless, data were available on Pompe disease and the review process was able to move on it quickly. Budget constraints prevented moving ahead on all of the nominations simultaneously. The appropriation of the HRSA budget is an important consideration. Future reviews are expected to proceed in a timelier manner.

Dr. van Dyck said that reports and recommendations can be submitted to the chair and a virtual meeting can be convened to act on recommendations. Dr. Howell agreed to convene a call to vote on the SCID report as soon as it was available.

In response to a query from Dr. Boyle, Chairperson Howell said that the forthcoming reports and recommendations will be distributed to the AC well in advance of the October meeting, including not only the ERW report on Pompe disease but the decision matrix from the DCPW. Dr. Tracey reiterated that the DCPW will present information but not make recommendations.

Members commented on the comprehensiveness of the ERW's work.

10. Newborn Screening Saves Lives Act 2008: New Legislation

Dr. van Dyck reported on the implications of the new law for the AC. A copy and summary of the law were distributed to members prior to the meeting. The Act reauthorizes and expands the role of the AC, establishes an Interagency Coordinating Committee, and creates an Internet-based information clearinghouse. It requires the secretary to ensure the quality of laboratories involved in NBS activities, and to develop a national contingency plan for NBS. The law gives NIH the authority to carry out research in NBS, including identifying new screening technologies and researching disease management strategies for conditions that can be detected through screening.

Section 2 authorizes the awarding of grants and states that an application for grant funds must contain assurances that the entity will adopt guidelines and recommendations of the AC that have been adopted by the secretary and are in effect at the time of grant award or renewal. Section 4 expands the role of the AC to include developing a model decision-matrix for NBS expansion (the decision matrix described in Dr. Calonge's report) and considering ways to ensure that all states attain the capacity to screen for the recommended conditions. The law calls for an evaluation of the potential public health impact of expanded screening.

The law expands the membership of the AC to include the FDA commissioner and persons with expertise in ethics and infectious diseases. The clearinghouse called for in Section 5 is the responsibility of HRSA in consultation with the Centers for Disease Control and Prevention (CDC) and NIH. Section 6 states that CDC in consultation with the AC shall provide quality assurance for screening labs and quality control and other performance test materials to evaluate the performance of new screening tools. The Interagency Coordinating Committee on Newborn and Child Screening will be composed of representation from CDC, NIH, AHRQ, and HRSA. Contingency planning is to be conducted through CDC in consultation with HRSA and state health departments to develop a national contingency plan for NBS by states in the event of a public health emergency. This section also authorizes the Hunter Kelly Research Program, with consideration of recommendations by the AC.

Q&A

Chairperson Howell asked Dr. van Dyck to describe what HRSA is doing to implement the new legislation. Dr. van Dyck responded that Dr. Williams spoke about ongoing efforts at the beginning of the meeting. HRSA has formed an internal work group, which meets weekly. Staff is working with CDC to begin contingency planning as well as implementation of the other sections of the law. Staff is focusing on the requirement that the secretary adopt or reject an AC recommendation within 180 days, including those recommendations pending at the time of enactment. The secretary is also required to publicize these determinations. HRSA is also working to establish the relationships required to carry out implementation.

Dr. van Dyck reminded the members that P.L. 110-237 is authorization legislation. The Senate appropriations bill for 2009 is for level funding. The House subcommittee marked up a very slight increase in funding. Both are considerably less than authorized. Section 1109 included earmarked grants.

Dr. Skeels asked about the direct impact on the AC. Dr. van Dyck said that the major changes were putting the evidence based review process, which the AC is already beginning to do, into the law, requiring that the AC report on its work, adding a membership slot for the FDA with no change in size of membership, and adding ethics and infectious disease expertise as current terms expire. There is no change in requirements for consumer participation.

Christopher Kus, MD, MPH, representing the Association of State and Territorial Health Officials, asked about the requirement for demonstration programs to evaluate effectiveness. Dr. van Dyck replied that no ear marks had been appropriated for section 1101 demonstrations.

Dr. Howell opined that NIH may fund follow-up translational networks. Dr. Alexander said that prior to the enactment of the legislation, NIH had set up a grant mechanism to organize the regional networks with some coordination by a national coordinating center in a research context above and beyond the primarily service context in which they currently operate. This mechanism can provide long-term follow-up as new conditions are added to the screening process. The National Coordinating Center for the Genetics and Newborn Screening Regional Collaborative Groups will have a role in research.

11. Committee Discussion and Wrap-Up

The chairperson noted that discussion had been ongoing throughout the meeting.

Dr. Berg stated his appreciation of the background materials distributed to the members. He asked if there would be an opportunity for discussion of the papers. Chairperson Howell responded that such discussion had occurred in the past at face-to-face meetings. Arrangements could be made for discussions in the future if there is sufficient interest. He recommended that members read the articles and also identify and disseminate materials that would be helpful to the AC. Dr. Berg noted that a recent article by Dr. Calonge in ***Health Affairs*** was at variance with some of the AC decision.

Chairperson Howell replied that the staff distributes informative articles without regard to whether they agree or disagree with AC recommendations.

12. Public Comments

Three members of the public had requested an opportunity to provide written comment. Only one member of the public was present to read her comments. Jacque Waggoner, Chief Executive Officer, Hunter's Hope Foundation and a grandmother of Hunter Kelly, applauded the life-saving role of the AC. She cited a report from the ACMG, **Newborn Screening: Toward a Uniform Screening Panel and System**, which recommended that state NBS programs mandate screening for all 29 core panel conditions and all 25 secondary target conditions, and that all clinically significant information discovered through NBS be provided to the relevant health care professionals and family. The Foundation is concerned that assumptions are being made that the 25 secondary conditions will automatically be reported because they are revealed when the core conditions are screened. The Foundation advocates that all states mandate screening for all conditions recommended by the AC and that states implement an ongoing process to ensure their programs are current with AC recommendations. She thanked the AC for its action on the Krabbe disease nomination.

Dr. Howell thanked her for her remarks and reminded her that the Krappe recommendation was approved for an evidence review.

13. Adjournment and Future Meetings

Staff is in the process of scheduling the January and May meetings. Members were reminded to send their calendars to staff as soon as possible.

All items on the agenda having been discussed, it was moved and seconded to adjourn the meeting. Meeting adjourned at 4:40 p.m.