SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Summary of 24th Meeting

May 5–6, 2011

Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 24th meeting at 9:30 a.m. on Thursday, May 5, 2011, at the Renaissance Washington Dupont Circle Hotel in Washington, DC. The meeting was adjourned at noon on Friday, May 6, 2011. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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Contents

I. COMMITTEE BUSINESS

Dr. Howell introduced the three new members of the Committee: Don Bailey, Ph.D., M.Ed, Fred Lorey, Ph.D and Alexis Thompson, M.D., M.P.H

Dr. Melissa Parisi joins us today as an alternate for Dr. Alan Guttmacher.

Dr. Carol Greene has replaced Dr. Barbara Burton on the Committee representing the Society for Inherited Metabolic Disorders.

- Dr. Joseph Bocchini moved to approve the January 2011 Committee meeting minutes and Dr. Jeffrey Botkin seconded the motion. The minutes were approved unanimously with one member absent (Dr. Ned Calonge).

- Recent Committee correspondence (tab 5 of the briefing book and on the thumb drive supplement) includes two responses from the Secretary:

  Residual blood spot recommendations.

  - The Secretary has referred the residual dry blood spot recommendation to the Department of Health and Human Services' newly formed Interagency Coordinating Committee on Newborn and Child Screening (ICC) for further review.

    - The Committee's report, "Consideration and Recommendation for the National Guidance Regarding Retention and Use of Residual Dried Blood Spot Specimens after Newborn Screening," has been accepted for publication the June issue of *Genetics and Medicine*.

  Critical congenital heart disease recommendation

  - The Secretary determined that the Committee's recommendation to add screening for CCHD to the panel is not ready for adoption due to gaps in the evidence and referred it, to the ICC for further review. The ICC must respond to the Secretary within 90 days and the Secretary will keep the Advisory Committee informed

    - The ICC will examine the evidence gaps described by the Advisory Committee and propose a plan of action to address identification of effective screening technologies, development of diagnostic processes and protocols, education of providers and the public, and strengthening service infrastructure needs for follow-up and surveillance.

    - The supplemental thumb drive contains other correspondence showing support for the Committee's recommendation.

    - Dr. Tim Geleske reported that the Advisory Committee's CCHD workgroup prepared a report that addresses implementation of the screening. Various sections and committees of the American Academy of Pediatrics reviewed and endorsed the report. It will be published in *Pediatrics* with an endorsement statement.

- Dr. Howell reported that he expressed his personal concern about the urgency of the CCHD screening to Dr. Mary Wakefield, the HRSA administrator and ICC Co-chair. He emphasized the generous endorsement of the screening by professional groups represented in the workgroup and the fact that delaying this decision directly affects 4–5 infants per day. He also expressed concern about the conference call to discuss this recommendation that took place on April 21, but of which he and other Committee members received only a 1½-hour notice, leaving all appointed Committee members unable to participate. Dr. Wakefield apologized for the situation and explained that the call had been arranged by a contractor and was primarily intended for stakeholders.

- Dr. Gerard Vockley expressed concern that having another group re-review the evidence that this expert committee already reviewed would diminish the relevance of the Committee and its recommendations. Dr. Peter van Dyck explained that the ICC was charged by the Secretary with addressing the gaps around implementation that were mentioned in the Committee's letter of recommendations, not with the scientific and medical criteria. The concern lies in how the responsible agencies will effectively implement the screening. Dr. Melissa Parisi (NIH) echoed Dr. van Dyck's points.

- Dr. Jeffrey Botkin suggested that this is an opportunity to consider how the Committee might handle similar circumstances in future recommendations in such a way as to minimize the potential for ICC re-reviews.

- An email vote to approve the annual report was solicited prior to this meeting. All members returned a vote of approval except the three new members (Drs. Lorey, Bailey, and Thompson) who were not yet eligible to vote and Drs. Denise Dougherty, Coleen Boyle, and Peter Van Dyck; the NIH and the FDA sent in approval votes.

    - Dr. Dougherty stated that she has no objection to the annual report. Dr. Boyle also approved.

    - Confirmation of the vote to approve the annual report: All Committee members approve except for Dr. van Dyck, who abstains. The three new members also abstained.

- Congratulations to Rebecca Buckley for her election to the National Academy of Sciences

II. Public Health Framework and Hospital-Based Newborn Screening and Committee Discussion

Dr. Howell introduced the topic with a review of the Committee charter and legislation, included in the briefing book and on the thumb drive. According to the charter, the Committee provides advice to the Secretary about aspects of newborn and childhood screening and technical information for the development of policies and priorities that will enhance the ability of state and local health agencies to provide newborn and child screening, counseling, and health care services. Committee members are urged to review these documents.

Dr. Howell made two points.

- Does this Committee have a responsibility to consider the cost of implementing its recommendations?
    - Effective May 21, 2011, pursuant to the affordable health care regulations, health plans and issuers are required to provide coverage without cost sharing, for the first plan year, for services on the Recommended Uniform Screening Panel.
    - What are the roles and responsibilities for screening, either as a standard of care or as a universal mandate?
    - Consideration needs to be given to the roles and responsibilities of public health agencies, general responsibilities under a public health framework, and government's traditional role in public health as assessment, policy development, and assurance.
    - Since newborn screening is deemed an essential public health activity, then assessment, policy development, and assurance functions should apply, albeit they may vary among the various levels of government and may be limited by will or lack of resources.
    - Relevant questions include the following: Should non-dried blood spot (DBS) screenings conducted during the newborn period be deemed essential public health services? Should any or all the government functions be delegated to the private sector? What should be the role of the public health department in in-hospital screening programs?
    - Point-of-care testing has been defined by the Subcommittee on Follow-up and Treatment as medical testing at or near the site of patient care.

Dr. Botkin noted that, while a very successful experience, DBS screening did not incur many of the issues that in-hospital screenings, such as CCHD, do. In this new environment, appropriate questions are raised about whose job it is to do various aspects of the screening and who is responsible for quality assurance.

A. Major Issues

Dr. Nancy Green introduced the topic of "questions regarding point-of-service screening for newborns (POSS-N)" as a broad overview and an attempt to generalize the issues, topics, and challenges faced when recommending new POSS-N screenings.

- Point-of-service screening is defined as screening that takes place at or near the site of patient care. In the case of newborn screening, that is the hospital nursery. The driving idea is to bring the test conveniently and immediately to the patient, with the intent that the patient will receive results and appropriate care in a timely manner. In cases such as CCHD, timeliness is a matter of urgency.
- Stakeholders have expressed concerns about jurisdictions, mandates, financing, and reimbursement issues related to point-of-service screenings. To implement a program successfully, it is important that roles and responsibilities be apportioned appropriately.

- While this Advisory Committee has a larger charge than newborn screening, the complexity of the issues surrounding newborn screening makes it a good place to focus as the Committee considers the interface between professional standards of care and public health programs. In light of this interface, the Committee will also need to consider how newborn screening for conditions such as CCHD or hyperbilirubinemia differ from other types of screenings (e.g., vision, lead) that have established professional guidelines in place.

- Clarity around the roles, responsibilities, and resources of departments and personnel needs to be established. A key aspect to bear in mind is that this will vary by condition, diagnostic need, and therapeutic intervention. Hearing screening is the only current example of POSS-N, and there is general agreement that it is not an ideal example to follow given the vicissitudes of uneven reporting and follow-up. Although newborn screening is considered an essential public health activity, the role of public health programs may be limited to surveillance, evaluation, and education, leaving out the implementation.

- Aspects that need to be considered for each screening are: screening focus, child's age, site of the screening, site of analysis, site of follow-up initiation (diagnosis), site of follow-up care, and the role of public health programs (follow-up, surveillance, etc.). Dr. Dougherty developed a matrix for comparing screenings based on these items.

- Another critical variable is the response of states to approved Committee recommendations. For example, in Indiana, the public health department is mandated to comply with the recommendations. The Committee must bear this burden in mind as it moves forward.

- Defined as universally performed tests conducted for a newborn at the birth hospital prior to discharge, POSS-N must be justified on the basis of urgency, equity, and efficiency. Justification for testing and lack of parental permission would parallel the justifications used for traditional DBS. Critical issues in the context of the public health framework for POSS are generalized issues of roles, responsibilities, resources, and liability as well as condition-specific considerations. At a minimum, the public health role is likely to include centralized data reporting and program evaluation.

- A look at the key attributes that distinguish POSS-N begins with the overriding issue that immediate diagnosis and follow-up care is likely to be needed and provided. The attributes fall into three categories: condition, screening, and diagnostic tests.

    - Condition Attributes—An interpretable diagnosis of a serious condition is made prior to nursery discharge for initiating diagnosis.

    - Screening Test Attributes—Easy, reasonable, safe, and acceptable (not taxing for the infant); simple, quick procedure for the staff; manpower and instrumentation available on site; interpretable results promptly obtained on site; screening available at the nursery with reasonable investment; standardized locally and broadly (state, national); and quality assurance available locally.

    - Diagnostic Process Attributes—Available on site or transportable to the site; feasible; definitive, at least for those at imminent risk of harm from the condition; safe for those with false positive screenings and in proportion to potential benefits for true positives; and with a favorable potential benefit-to-cost ratio.

- The sole current model of POSS-N is newborn hearing screening.

- Should we wait and see how the CCHD recommendations are resolved before the SACHDNC recommends more point-of-service screenings?
- State health departments may bear less responsibility if a POSS condition is added to the recommended panel. For some screenings, public health roles could be limited to surveillance of the results and diagnosed condition.
- Non-DBS screenings could be deemed essential public health services. In such a case, should any or all the government functions be delegated to the private sector?

- The Committee should consider whether the current SACHDNC criteria and structure for review could be used to distinguish tiers of recommendations, each requiring different levels of public health involvement. These tiers might include defining which entities are responsible for follow-up, treatment, and tracking; determining if the roles could be distributed elsewhere; and considering whether public health programs could take on limited roles in non-DBS screening.
  - Other considerations include (1) gaps in funding streams that need addressing, should the POSS-N become a universal standard of care and (2) screening criteria used by SACHDNC may be more stringent than that used in clinical practice.
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B. Perspectives from Committee Members and Organization Representatives

Comments from the Committee.

- Dr. Bailey believes that receiving results promptly at the site of screening is the fundamental essence of point of care screening, not a goal to which to aspire. Dr. Green concurs but added that the landscape lacks definition at this time and so she is wary of insisting on "always."
- Dr. Fleischman cautioned Committee members to separate pragmatism from principle and urged holding to principle at the outset and stated that figuring out what the right thing to do for children should come first and the pragmatic issues follow. Otherwise, the Committee will get mired in the details at the pragmatic level, which will not allow for constructive, rapid resolution of the issues.

The Subcommittee on Long-Term Follow-up drafted a list of questions regarding roles and responsibilities to be used in future discussion on newborn screening. The stakeholder presenters in this session were asked to address and refine these questions: What are the right questions to ask? Do we have all the correct stakeholders identified to participate in the discussion as we move forward?

Committee Mandate

Representing the Advisory Committee, Dr. Howell was asked to address the committee mandate.

- Dr. Howell referred to his comments earlier in the day, highlighting that, per the legislation, the key is that the Committee provide such recommendations as may be necessary to enhance, expand, or improve the ability of the Secretary to reduce mortality and morbidity from heritable disorders, which may include recommendations, advice, and information. It is a broad charge of things to be done in the newborn period to reduced mortality and morbidity.

Primary Care

Representing their respective professional organizations, SACHDNC Organizational Representatives Drs. Chen and Geleske were invited to address the interests of primary care.

Frederick Chen, M.D., M.P.H., F.A.A.F.P.

- Primary care physicians are an important part of the newborn screening process and follow-up treatment. Primary care practices have a lot of clinical practice guidelines to follow. The AAFP has long history of working with the U.S. Preventive Services Task Force, which promulgates the majority of the guidelines, supporting their evidence process, taking recommendations to the academy, evaluating them, and recommending them to its members.
    - The AAFP's policy is to balance clinical practice guidelines with individual clinical decisionmaking and the ability of physicians to make clinical decisions within a context. The distinction between mandatory newborn screening and the broader sense of clinical practice is a factor to be considered as we move forward.
    - Evidence-based methodology to make recommendations is strongly supported. In Dr. Chen's experience, very few guidelines are location dependent, so the formulation of point-of-service screening is new and raises questions about changes to the framework.
    - The Preventive Services Task Force has been successful because it has a clear definition of its audience—practicing primary care providers who deliver some type of preventive services. It does not try to recommend to states or to public health laboratories. It is important for this Committee to be precise about its audience.

Timothy Geleske, M.D., F.A.A.P.

- Of the multiple factors that influence what a primary care physician does in practice—family factors, political recommendations, cultural factors—the most important influence are the recommendations of our professional societies. We depend on our leadership for guidance and to know the literature and the evidence base because most of us do not have the resources to evaluate data to make our own evidence-based decisions.
    - *Bright Futures* recommends nine universal screenings as part of our pediatric exams. Some have a stronger evidence base than others. The physical exam, our most common practice, has very little evidence, yet we all carry that forward. Our clinical guidance has a lot of practical and clinical experience built in because there is a lack of supporting evidence, but that does not mean the practices lack usefulness.
    - The factors that would mandate a universal screening are the same as those that have guided all our decisions: accurate valid test to do it, the benefits of doing the test outweigh the risks, treatment modalities exist, and urgency (important to have the result right there). As stated earlier, the principles are important.

Questions and Comments from the Committee.

- Dr. Fleischman asked, rhetorically, what percentage of family physicians would have 100% compliance with all standard of care measures. He also pondered what the standard of accountability is in the clinical frame. When comparing accountability, the importance of the nature of clinical practice guidelines, the Preventive Services Task Force recommendations, and the rarity of disorders under discussion must be understood, thus the need for 100% ascertainment of the screening tests.

- Dr. Chen mentioned that Elizabeth McGlynn did a study several years ago on the delivery of preventive services to adults; it was 50%. There is a lot of room for individual practice variation. The crux of the question is: When is something mandated by law and when does something fall into clinical practice guidelines?

- Dr. Geleske pointed out that the *Bright Futures* guidelines are extensive and it seems highly unlikely that even 50% of pediatricians are able to comply with 100% of the recommendations. It is the critical nature, the urgency, of the condition that should drive the mandate for universal screening.

- Dr. Howell reminded the group that most of what we discuss are recommendations, not legal mandates.

- Dr. Botkin added that the existence of accountability structures is important. In some contexts, recommendations exist but no one is held to those standards.

- Dr. Kus commented that public health has a role to play in the clinical practice part. By reporting on performance measures for Medicaid and state child health care programs, people can be stimulated to improve.

- Since all the Committee's recommendations take place at a specific point in time, Dr. Vockley suggested developing a mechanism to review evolving evidence as the screening program moves forward and allow for the possible removal of a condition from the panel. Standards of care and expert opinions change, as does the evidence over time.

Hospital and Specialty Care

Representing the Advisory Committee, Dr. Bocchini was invited to address the interests of hospitals and specialty care sectors.

- Although variation exists in the evidence bases and the level of support for the recommendations, universally recommended newborn screening tests and good clinical care are the same thing. Roles and responsibility of individuals depend on what is being looked at and the potential outcome. For example, if five children come to the emergency room each day in extremis because of potentially nursery-diagnosable CHD, it is a public health issue. That is something that needs nurseries and physicians to follow a state mandated or recommended set of guidelines rather a stakeholder group guideline.

- A key issues as we look at point of service testing, is which stakeholders need to be involved. At a base level, hospitals, the public health sector, and physician groups must be involved to formulate a set of implementation guidelines to make things work. Principles are important. Implementation issues will follow, and then roles and responsibilities can be divided.

- We can use existing examples of public/private guidelines done together (e.g., lead screening) to develop new programs. Public health has significant role in point-of-care testing. We are asking hospitals, though, to play a new role. With point-of-service screening, the hospital has to train personnel to use equipment, do the screening, and act on the results in an appropriate way. The public health sector could provide the infrastructure to educate, provide information to parents and physicians, and give smaller hospitals the contacts they need to get the patient appropriate care if there is an abnormal test.

Public Health

- Dr. Kus believes that framing this as an issue of point of care or service screening is a red herring. The real issue is universal newborn screening versus clinical screening.
    - The first question on the subcommittee's list is: What do state public health departments view as their responsibilities in state mandated newborn screening, particularly related to screening for conditions utilizing non-dried blood spot methodologies? When we talk about something being a core condition, it often leads to state-mandated programs, which inherently involves public health. This is classic public health and ASTHO has a policy statement on that. When we talk about state-mandated programs, health departments are responsible for population-based data that leads to the evaluation of the program. When this is confused, difficulties such as those seen in hearing screening, where the screening is mixed with the early intervention program and is often not seen in the public health view, arise. With regard to clinical standards and clinical screening, there is a movement for accountability, as seen electronic reporting, outcome measure reporting. In New York, the state health department reports on how plans do relative to the screenings and then discuss quality improvement.
    - The second question on the list is: What are the responsibilities of the state public health department in point-of-care hospital-based screening in terms of short- and long-term follow-up? This question seems out of place because the discussion is about the first question.
- Dr. Lorey raised concerns and issues with definitions. From a public health point of view, there is no question that it needs to be involved. There are various parts of public health, one of which is newborn screening - which is public health laboratory-based screening on blood spots for heritable disorders. Newborn screening has traditionally been defined this way. The way the panel's recommendations came about until CCHD have been interpreted this way by people in newborn screening. We may need to change the definition of newborn screening. The recommendation for CHD screening, while on solid ground in many ways, is not appropriate for public health labs. It is in neither our purview nor in our state statutes.
- It is essential to consider the implementation of these recommendations and the related charge of public health departments. Public health departments do not have the money or staff to expand what they are doing. For example, SCID screening is a great screening and should be in the newborn screening panel, but the California public health department does not have the budget to handle it. In a news analysis of the screening, it was reported that the screening would cost $7 million and save about $1 million per year. Public health officials deal with people whose focus is on monetary decisions, not on details of specific disorders. Another media item in California asked why the state did not screen for Krabbe disease. In other words, in the trenches, the public health sector faces additionally many non-medical aspects of implementation. If the role of this Committee expands to hospital-based screenings, the public health sector is going to be in a position of not having enough money and having to make choices. The practical aspects must be included from the beginning; implementation cannot be ignored.

Comments from the Committee:

- Dr. Jane Getchell agrees that this is in the public health purview and feels we need to identify the role the role of public health. A public health lab can ensure the quality and performance of a particular test. Is the lab then part of the public health role or not? We have many diseases re-

portable to public health, but what we do with those results varies, and newborn screening follow-up is far more time-intensive than most others.

- In disagreement with Dr. Lorey, Dr. Vockley said that this Committee is not constituted to look only at blood-based lab-based newborn tests. Nothing in the law limits the Committee to that and such a limitation would not be appropriate. Dr. Vockley agrees that implementation must be considered. When evidence-based reviews are done and decisions made, there are explicit questions in the decision matrix that focus on availability of testing and, as best as can be divined from the literature and experience, the costs involved. However, the recommendations are made to HHS, and it is impossible to take into consideration the specific implementation challenges and practices that 50 states will use in implementation. Part of what this Committee has done is push the limits, which requires going into a zone that may not be always comfortable for some of the stakeholders. However, the guidelines can be used as leverage with state legislatures to lobby for additional funding. While that may not be reality now, eventually it is the kind of impetus that these guidelines could bring.

- Dr. Howell concurred that there is no question that it is in the purview of this Committee to look at non-DBS newborn screening. The issue is how the state labs will deal with this responsibility. He added that the Committee has never made a recommendation that had more detailed implementation details than did the CCHD recommendation.

- Dr. Lorey asked that, if POSS is in the purview and in the charge of the Committee, the Committee change the definition of newborn screening, because this is not how it is perceived by the public. Public health officials have to deal with the legislators, who are already giving them a hard time about SCID.

State Medicaid

- Dr. James Figge commented on the three fundamental roles of state Medicaid agencies in regards to this Committee: (1) insurance coverage, (2) public health (can use marketplace power to implement key public health objectives on the ground), and (3) regulatory roles. Medicaid agencies are ideally placed at the intersection between traditional public health functions (such as newborn screening) and the traditional medical delivery system. For example, New York Medicaid traverses between the two systems by working closely with the newborn screening program to ensure that infants with positive screens are able to get confirmatory tests. Because it spans both domains and provides continuity, Medicaid needs be at the table for these discussions. Additionally, Medicaid's large newborn and child population makes it a tremendous advantage for operationalization; if Medicaid implements something on the ground in New York, it will be in place for nearly half of the state's newborns.

- In terms of the insurance function, new programs must be incorporated into comprehensive guidelines that will be supported by HHS so they get into the ACA framework. It is important that initiatives be evidence-based because many states are involved in collaboratives of extensive evidence-base work done on coverage policies for Medicaid programs. Almost every Medicaid program has medical directors who working to ensure coverage policies are evidence based.

- The work of the U.S. Preventive Services Task Force is highly regarded for its rigorous methodology throughout the insurance industry. Dr. Figge recommended this group use the task force's model of evidence development, transparency, and publication to get its work into the public domain in order to help with adoption by Medicaid agencies and other insurers. Such

groups (task force and insurers) can help with implementation and Medicaid, which has state regulatory authority, can help with enforcement.

- Dr. Figge also sits on the Office of the National Coordinator's HIT Policy Meaningful Use Workgroup. A definite opportunity for cross pollination exists between this Committee and the ONC, especially in terms of electronic health records. He pointed out a collaborative opportunity in developing electronic standards as electronic health records and point of care practices are adopted. Such tools help clinicians know what the evidence is and help them get a sense of obligation to get these things done.

Comments from the Committee:

- Dr. Howell affirmed that the evidence group working for this Committee follows a highly rigorous evidence pattern that is recognized and published in high quality journals.

- Dr. Michael Watson reported on a request that he engage in a discussion with the Joint Commission. The commission brings fiscal accountability to the table for hospitals. They understand that there is an obligation to act on newborn screening, as it fits into the major mandate and has critical results value. The commission is trying to balance and fit together this Committee's request for newborn screening with a request from the CDC that has to do with infectious disease screening in pregnant women. The commission is interested in pursuing further discussion with the Committee. Dr. Watson feels the Joint Commission has a place at the table of stakeholders because they can ensure that certain actions take place for implementation, thus tightening critical loops.

Dr. Botkin asked that all Committee members ponder whether there are any other stakeholders not yet identified.

C. Committee Discussion

- Dr. Tracy Trotter commented that the idea of mandates versus clinical guidelines is critical for this Committee to get a handle on. He believes that a well-appearing newborn with a time critical issue that has a serious life-threatening illness, is a public health problem and thus a mandated issue. Clinical guidelines are purposely written with wiggle room that allows a physician to determine whether or not to perform a test. The recommended uniform panel raises the level of the test and it is time to think outside the box regarding implementation of some of the new recommendations. DBS-based newborn screening is one of most successful public health programs ever. As expand newborn screening is expanded, though, new tests may not fit the existing mold. That does not mean they are not public health programs, but it might mean they are not public health laboratory programs.

- Dr. Carol Greene suggested consideration of the following question: Is there a need to redefine newborn screening or can the Committee recognize that it does not need to be restricted to newborn screening? If the Committee agrees that the evidence shows a screening should be mandated, by what mechanism? Because of JCAHO's strength, this organization is a mechanism for assisting with implementation that should be explored. Dr. Kus offered his impression that with the inclusion of hearing screening, newborn screening has already been redefined; however, that redefinition has not been marketed.

- Dr. Fleischman would like to see the nursing community at the table as a stakeholder. The wisdom and support of nurses, who are bedside with the infants and mothers, would be helpful with implementation. The Association of Women's Health, Obstetric and Neonatal Nurses generally represents that group.

- Ms. Sharon Terry suggested including the public as a stakeholder—a combination of parents and advocates. As a consideration in policy, the Committee must discuss how to advance health given budget restrictions and economic decisions.

- Dr. Alan Zuckerman suggested the Committee also anticipate the future, adapting current screening methods to new technology as it is developed.

- Dr. Anne Comeau, a public health newborn screener, offered a different perspective. Newborn screening population-based lab testing undergoes stringent adherence to quality assurance to provide valid test results. With point-of-care screening, there will be hundreds of hospitals running hundreds of different instruments with a variety of personnel trained at different levels. This will call for stringent quality assurance to prove the validity of the testing. A lab system is already in place that understands what is needed for population-based screening. Newborn screening programs have a potential role, accepting the fact that different states will want to implement in different ways.

- Dr. Puryear explained that, per the legislation, there are a few types of recommendations that the Committee can make. The Committee's charge is to provide recommendations, advice, and information as may be necessary to enhance, expand, and improve the ability of the Secretary to reduce mortality or morbidity from heritable disorders. Specific to newborns, the Committee can make recommendations for the uniform screening panel. It can make recommendations more generally for children regarding heritable disorders. It can also address conditions not included in the panel that are treatable with FDA products or other safe treatments. This may allow two types of recommendations—one type for the recommended uniform screening panel (which has immediate implications for the ACA) and another type that is highly desirable to screen newborns but is not included in the panel. In this light, the Committee may address lab versus program concerns. Dr. Howell reinforced this with the sense that this Committee would not want to exclude an important condition.

In closing, Dr. Botkin asked that additional comments be sent to Dr. Boyle or him for inclusion in the future considerations of the subcommittee.

III. PUBLIC COMMENTS

Dr. Howell noted that written public comments were received from Assemblyman Jason O'Donnell (New Jersey) and Emil Kakkis of the Kakkis EveryLife Foundation. These are reproduced in appendix A of the minutes. Additional public comments made at the meeting can be found in the transcripts.

A. Ms. Jill Levy-Fisch, Save the Babies Through Screening Foundation

- Ms. Levy-Fish announced that the Save the Babies Through Screening Foundation is in the final production phase of producing an educational newborn screening video. In the video, families who have had their lives changed by newborn screening are interviewed and share their stories. In contrast, interviews with the parents of families whose child's hereditary disorder was not detected will also be shown. An engaging video of healthy children whose lives were saved by newborn screening will effectively illustrate the importance of the program.

- The foundation is also producing a segment for the Newborn Channel, which is an educational film that will be shown in 3,000 hospitals throughout the United States. The channel will also be promoting their video—in their journal and on their website. This includes the distribution of our brochure to 6,000 health care facilities and health care providers in the country.

- A longer version will be available for viewing on their website and on the Newborn Channel website. The video will also be posted to YouTube and available for linking by interested parties. DVDs are going to be distributed without charge to birthing classes, prenatal health care providers, nursing associations, et cetera.

B. Ms. Annamarie Saarinen, Newborn Coalition 1in100

- Ms. Saarinen's voiced that a 90-day delay regarding the CCHD recommendation would lead to. one thousand babies dying from critical congenital heart disease. But in terms of federal process, she realizes that's close to the speed of sound. She stated, as best that this interagency coordinating committee can leverage the work that's been done, they will be in an excellent position to help address some of the Secretary's additional concerns, provided collaboration occurs. Without that level of collaboration, she cannot imagine in 90 days them having an action plan that's going to really measurably move the ball forward.

  Ms. Saarinen, along with the Newborn Coalition and folks, parents, and families of, reached out to key members of Congress, the Senate Health Committee in particular, Congressional Quality Care Coalition, the entire House Ways and Means Committee, in order to ensure folks who dialogue with the Secretary can offer their perspective.

  Ms. Saarinen's also provided a legislative update. Her point is the world is moving forward with implementing CCHD with or without this Committee and with or without the Secretary and thinks the world is a better place with this recommendation because of what's happening now.

IV. Food and Drug Administration Policies and Procedures Relevant to Individuals with Rare Heritable Disorders

A. Overview

Dr. Vockley explained that this session is a result of a general lack of knowledge on the part of those of us in the rare disease arena about the process used by the FDA for investigational new drugs (IND).

- The 442-page IOM report "Rare Diseases and Orphan Products: Accelerating Research and Development," edited by Marilyn Field and Thomas Boat, provides substantial material related to investigational drugs, FDA interaction with the rare disease community, and research and development on those conditions. The publicly-available summary of the article is in the briefing book.

- This presentation focuses on the topic of accelerating research, which is summarized below.
    - Active involvement and collaboration by a wide range of public and private interests
    - Timely application of advances in science and technology
    - Creative strategies for sharing research resources and infrastructure
    - Appropriate use and further development of trial design and analytic methods
    - Reasonable rewards and incentives for private-sector innovation and prudent use of public resources for product development
    - Adequate organizations and resources for public agencies that fund biomedical research and regulate drugs and medical devices
    - Mechanisms for weighing priorities for research and product development, establishing goals, and assessing progress

- Emergencies can develop when limited access to a drug or screening kit is cut off. In such cases, FDA personnel work to get emergency access to an alternative source or approach. The IOM report identifies three areas of concern.
    - Insufficient resources for timely meetings and guidance for sponsors
    - Inconsistency in reviews of applications for orphan drug approvals across divisions
    - Inadequate resources for the orphan products grants program

- A longer list of issues was identified by those in need of INDs. Sponsor issues include delayed toxicology studies; inadequate characterization of chemical compounds; lack of natural history studies to characterize the disease process; poor use of early phase studies to guide the design of phase III studies; inadequate trial design with lack of formal protocol, well-defined question, adequate controls, validated biomarkers, and appropriate surrogate measures; and lack of advance communication with FDA about the adequacy of clinical trial plans.

- The IOM recommendations were that there should be an assessment of staff reviews of applications for the approval of orphan drugs; there needs to be a review on how that is being done and how that information is communicated; that they should evaluate the extent to which studies submitted in support of orphan drugs are consistent with advances in the science of small clinical trials to ensure that NIH-funded product development studies involving rare diseases are designed to fulfill requirements for FDA approval; that the FDA should expand its Critical Path Initiative to define criteria for evaluation of surrogate endpoints for use in trials of products for rare conditions; that the FDA and the NIH should collaborate on an assessment of unmet device needs and priorities relevant to rare diseases; and that the FDA should take steps to reduce the burdens on potential sponsors of humanitarian use devices.

- Three issues seemed to be consistent across many of the discussions: (1) a need for everybody to better understand issues of compassionate use protocols, (2) a need for alternative emergency supplies, and (3) a complete lack of knowledge of the process for approval of new technologies for diagnosing rare diseases.
    - Relative to compassionate use issues, confusion abounds and discomfort boils down to the fact that the risk/benefit ratio is different for are diseases. If all regulations were applied strictly for rare diseases, the patients would be "regulated to death."
    - Relative to emergency supplies, it is important to note that in the United States many medications are single source and patent protected. The concern is what to do if something happens to that source. There may be foreign sources or non-medicinal grade sources available. Emergency needs for rare diseases cannot be anticipated, so it seems prudent to develop a general policy that can be easily referred to for understanding the process.
    - Relative to new device approval, it is important to note that diagnostic kits are defined as devices. This brings up questions about regulations on using existing kits for new purposes, approval of single lab reagents and tests, and the approval process for rare disease applications.
- The challenge for rare diseases in this arena is communication. It is very important that practitioners and investigators know how to approach the FDA on these issues. Three related challenges are (1) the need for uniform recognition that the FDA is allowed to use its discretion when applying regulations to rare diseases, (2) consideration for the risk/benefit ratio when the inevitable outcome is poor, and (3) protection of investigators and patients alike without making treatment impossible.

B. Expanded Access to Investigational Drugs: The Road to Marketing

Tim Coté, M.D., M.P.H.
Immediate Past Director, Office of Orphan Products Development, FDA

- This Committee and the FDA Office of Orphan Products Development (OOPD) should partner because inborn errors of metabolism are a focus of both groups (5% of all OOPD products), new gene therapies for treatment of ill newborns and children are expected soon, and newborn screening is contingent on a decent test and decent therapy.
- From 1973 to 1982, only 10 new drugs were approved for rare diseases. There are about 7,000 rare diseases, and 25 million people have those diseases. Congressmen and senators are routinely petitioned with requests for assistance and research on these diseases.
- How the Orphan Drug Act (ODA) on works:
    - To get a drug designated as an orphan drug it must be shown that it is promising and it treats a disease limited to less than 200,000 patients.
    - Then the clinical trials are conducted and marketing approval is given.
    - Then incentives are extended, including market exclusivity, tax credits, and fee exemptions.

- The drugs must meet normal FDA guidelines for safety and efficacy. People with rare disease deserve drugs that work, and FDA approval guarantees that they do.
- There is an important latency period. Orphan designation is a very early stage evidentiary criteria, whereas full drug approval takes considerable time after that.

- ODA has been a major success: 366 fully-marketed approved drugs, about 2,400 designated orphan drugs, and one-third of all FDA-approved new molecular entities were orphans in 2010. This is an emerging sector.

- In order to secure orphan status designation, it has to show promise. The orphan status grants bragging rights, which pharmaceutical companies use to seek venture capital. In order to receive marketing approval from the review division, by law it must show safety and efficacy. OOPD is an advocate for this process and encourage more product development. At about $16 million exclusively for rare disease clinical trials, the office has the largest grants program at FDA.

- In summary:
  - The FDA needs to be more engaged with SACHDNC not only on diagnostics, but also on therapies.
  - There ought to be a systematic consideration of newborn screening upon emergence or the licensure of new therapies for newborns and children.

Dr. Pariser, Associate Director, CDER Rare Diseases, FDA spoke to the group from the perspective of the review divisions of the FDA on expanded access, which is more commonly referred to as compassionate use.

- Expanded access provides improved access to investigational drugs for patients who have serious or immediately life-threatening conditions. This includes many serious rare diseases. Patients must have a condition for which there is no alternate or satisfactory treatment otherwise available to them. This enables patients to have access to products outside of a clinical trial. Usually these are products that are either still in development, not being developed, or approved elsewhere outside of the U.S. They are not intended to support any kind of an approval.
  - The FDA's main concern is with the safety. The requirement says that any potential benefit to a patient has to justify the potential risks, and that these potential risks should not be unreasonable (which is subject to interpretation).
  - FDA maintains that the best access to any drug for patients is an approved product, meaning a product that is approved under a marketing application and is available for prescription by physicians. The next best choice would be for patients to be enrolled in well-designed clinical trials that are designed to demonstrate efficacy and safety. The expanded access process is available to patients who are unable to access either of those mechanisms.

- There are four types of expanded access, each considered on a case-by-case basis—emergency (no time to go through normal process), single patient (individual patients who do not qualify for a clinical trial), intermediate size (small groups of patients who do not qualify for a clinical trial), and treatment protocol (promising experimental drugs for serious or life-threatening conditions).

- For emergency types, the applicant usually makes the request by phone. After the request is made, IRB notification must follow within 5 days and written submission of request to FDA within 15 days.
- For non-emergency requests, a written request including clinical history, rationale, criteria for selection of patients, proposed treatment and monitoring plan, investigator qualifications, and CMC information, pharmacology and toxicology information, must be submitted.
- There is no one-size-fits-all summary, but there does have to be data that supports the proposed treatment. The amount of information will vary depending on who is being treated and for how long, the proposed dose, etc.

- IND information that also applies to expanded access:
  - The manufacturer must be willing to supply the drug. They cannot be forced to do so.
  - All IND information is confidential and will not be disclosed to the public.
  - Investigational plans vary widely.
  - Independent review by an IRB is required.
  - The FDA has 30 days to review any initial non-emergency IND. Research cannot begin before the review is completed.
  - Core review team composed of the chemistry team, animal pharmacotoxicologist, and a medical officer.
- At all phases, the FDA is concerned with assuring the safety and well-being of the subjects in the studies. They also oversee the quality of scientific evaluation of drugs to ensure it is adequate to permit an evaluation of the drug's safety and effectiveness..
- The two most common clinical hold criteria (protocol not allowed to proceed) are that there is evidence to believe subjects would be exposed to unreasonable risk and that there is inadequate information to assess the risks. Later phase concerns are around safety also.
- A minority of protocols go on hold, and most of them come off hold if the deficiencies are addressed.
- In the regulatory history of expanded access protocol requests in 2010, 434 of the 446 emergency protocols, all 428 of the single patient protocols, and the single intermediate size protocol in 2010 were allowed to proceed. The purpose of expanded access is to allow access to investigational drugs for patients with serious or life-threatening disorders, which is reflected in these figures. The FDA does consider the condition of the patient and does show flexibility in these situations.

C. Critical Drug Shortages for Necessary Medications

Capt. Valerie Jensen, Associate Director, CDER Drug Shortage Program, FDA, addressed trends in and the FDA's role with drug shortages over the past year.

- Drug shortages may occur for a variety of reasons: manufacturing difficulties, corporate decisions to discontinue or limit production, market concentration, API problems, clinical practice changes, emergencies, and hospital- or pharmacy-based issues.

- In the past 6 years, there has been a rise in shortages. Of particular concern has been a sharp increase in the shortage of sterile injectable drugs. In 2010 there were 178 shortages (compared to 157 in 2009). The basic problem is a lack of capacity.

- Reasons for sterile injectable drug shortage

    - Two large firms had quality issues (particulate, microbial contamination, impurities, stability) that affected a large number of products—54%

    - Manufacturing delays and capacity issues—21%

    - Discontinuation (in the past 5 years, several firms have stopped manufacturing the sterile injectable drugs, leaving many of them available from single sources)—11%

    - API problems—5%

    - Increases in demand due to other shortages, loss of manufacturing sites, component problems—9% (combined)

- To handle the shortage problem, the FDA follows 6003.1 in the Manual of Policies and Procedures (MaPP). The first step, verifying that a shortage exists, is accomplished with market share data and conversations with the pertinent manufacturers. The next steps are to determine the medical necessity of the product (if medically necessary, it gets priority), make long- and short-plans for shortage management, and post information on the website for notification.

- Definition of a medically necessary product: A product is considered medically necessary if it is used to treat or prevent a serious disease or medical condition and there is no other adequately available source of that product or alternative product that is judged by medical staff to be an acceptable substitute. "Inconvenience" alone is an insufficient basis to classify a product as a medical necessity.

- When there is a shortage, the FDA takes the following steps:

    - For manufacturing and quality problems, the FDA works with firms to address the issues. Issues of sterility or particulates, which pose a high risk for patients, can take time to resolve. Lower-risk problems (e.g., packaging or labeling) can often be resolved quickly. Regulatory discretion may also be used to address shortages.

    - The FDA can encourage and facilitate remaining manufacturers to ramp up production.

    - The FDA can expedite issues related to addressing shortages, such as approving a new manufacturing line or getting new raw materials sources approved.

    - In a few cases, the FDA will decide to import a drug to address a shortage. The imports must meet FDA standards. Currently six such drugs are being imported.

- The FDA cannot force a manufacturer to produce a product and they cannot penalize a firm for discontinuing manufacture of a product.

- A key issue for the FDA is getting notification from firms for shortage issues and discontinuations. This allows the FDA work on resolving the issue with the manufacturers in a timely fashion (38 product shortages were prevented in 2010 due to firms providing advance notice to the FDA). It also allows the FDA to post helpful information for health care professional and patients on the website.

- Shortages can be prevented by a commitment on the part of firms to quality, early notification to the FDA of anticipated problems, redundancy in manufacturing, and stockpiling.

D. Overview of Device Regulation

Committee Member Kellie Kelm, Ph.D. from FDA's Office of In Vitro Diagnostic Devices Evaluation and Safety provided an overview of devise regulation.

- The law for medical devices was specified in 1976. The Medical Device Amendments classified all existing in vitro diagnostic (IVD) devices. This is when devices began to be classified and a new bar was set requiring all medical devices be manufactured under good practices. Companies were required to register and list with the FDA, as well as report adverse events.

- IVDs are used for diagnosis, screening, epidemiology and screening, and first response.

- When the FDA considers a device, it first looks at its intended use; in other words, the FDA regulates by intended use and the risk of an incorrect result. Device categories are class I (low risk, exempt from premarket FDA review), class II (moderate risk, requires a predicate device and 501(k) clearance), and class III (high risk, requires premarket approval). Most devices fall in class II. Regardless of class, all devices must be produced under good manufacturing practices.

- In the premarket review, IVDs must establish adequate analytical performance (accurate and reliable), clinical performance (reliable measure of the clinical condition), and labeling.

- In addition to intended use, elements of a submission include a device description, analytical and clinical validation, instrument and software validation, labeling, and manufacturing, design control and quality system requirements.

    - Analytical performance takes reproducibility and repeatability into account, as well as accuracy and limit of detection.

    - Clinical performance can be established with existing data, a review of the literature, and current clinical knowledge. New clinical trial data may need to be evaluated. The population samples should represent the intended use population and ideally be collected prospectively with clearly defined inclusion and exclusion criteria from a minimum of three sites.

- Challenges frequently encountered
    - It is difficult for manufacturers to get true positive patient results. A professional relationship with the state health laboratories can help.
    - Special circumstances, such as interference from drugs, cross-reactivity during evaluation, and sample collection problems sometimes exist.
- Examples of class II devices cleared by the FDA for neonatal screening include devices for inborn errors of amino acid, free carnitine and acylcarnitine metabolism, TSH, 17 α-Hydroxyprogesterone, immunoreactive trypsin, and biotinidase deficiency.
- Other pathways that can be used as new technologies come into play include a de novo petition for classification, a reclassification petition, investigational devices, humanitarian device exemption, emergency use authorization, and compassionate use.
    - Uncleared devices should be reviewed by the FDA for exemption on investigational devices.
- The FDA has several helpful guidance documents:
    - Points to Consider for Portable Blood Glucose Monitoring Devices Intended for Bedside Use in the Neonate Nursery
    - Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable
    - In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions
    - Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
    - Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
    - In addition, the office posts summaries of the data used to clear a device on the website: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

Dr. Vockley opened the floor to questions and comments.

- Dr. Lorey explained that they are working on a SCID test with Perkin Elmer. The four or five states currently screening use a TREC assay that is not FDA-approved. There is no kit, and some states are prohibited from doing screening without kit. They have been told by the FDA that all negative children have to have a flow cytometry screen; that is a diagnostic test, but they are looking at a screening test. The four to five states have successfully screening over 800,000 children for SCID with no false negatives. Why can't the existing test which they're running now be used as the standard?
    - Dr. Kelm affirmed that there is no approved kit. In terms of the study design, she encouraged Dr. Lorey to talk to her office director. She cannot directly comment on the case. Because these are new assays their safety and effectiveness needs to be established and it needs to be confirmed that they measure what is being claimed.
    - Tim Coté noted that the FDA cannot divulge its side of a story, so the audience should be aware that when sponsor shares information, only part of the story is being heard.

V. SUBCOMMITTEE REPORTS

A. Subcommittee on Laboratory Standards and Procedures

- The subcommittee heard from the Massachusetts program on attempts to refine MS:MS interpretation, which is funded thru HRSA. The goal of the project was to improve the predictive ability of data that comes out of newborn screening and, thus, better communicate risks related to it. The metrics they identified look promising. They project has expanded to pick up state labs from New York, Wisconsin, and Connecticut. They are looking at two programs that use derivatized samples and two that use un-derivatized samples for screening purposes.

- Steve Dobrowolski from the Utah group updated the subcommittee on the work that they are doing on spinal muscular atrophy screening (SMA). This NICHD-funded effort was designed to develop better screening for this disorder. Steve showed data on a multiplex PCR-based DNA melting technique not only to identify the SMN1 status, but also in the same screening reaction to define the SMN2 status. They had a nice multiplex assay that still had room to pick up one or two other disorders. This is a nice advancement, which may prove to be the best screening technique.

- Jelili Ojodu from APHL discussed a new effort to build some definitions for quality measures going forward for database capture. The APHL has ongoing interest in identifying key quality measures that are followed by state screening programs. They been asked to develop, by July, an expanded group of quality measures to capture lab systems for long-term follow-up.

- Swapna Abhyanka from the National Library of Medicine explained an ongoing effort to better define the language that is used to exchange information, in particular the language used for reporting newborn screening. The session focused on the questions and answers they should capture relative to newborn screening interpretation.

    - A specific request was made to the subcommittee to help develop the structure and standard of names for new codes for new conditions and tests going forward.

    - Because of the overlap with screening tests and diagnostic tests, they would like to include the reporting language of the diagnostic test as well. This is an official request from the NLM.

    - Dr. Vockley noted that the group is already doing this informally, so formalizing it seems reasonable, but he welcomes concerns and comments from the larger Committee.

    - Dr. Howell noted that the Advisory Committee's Health Information Technology Workgroup has disbanded. Dr. Sharon Terry is expected to comment on that later.

B. Subcommittee on Education and Training

- Dr. Trotter reported that the subcommittee received a number of project and program updates.

- Ms. Natasha Bonhomme reported that the HRSA Genetic Alliance's newborn screening clearinghouse beta website (nbsclearinghouse.org) will go live as babysfirsttest.org in September 2011. User guides, condition-specific information linked to databases, and blog posts from the Immune Deficiency Foundation to bring SCID screening information up to date have been added to the site. In the past 3 months, the beta site has had 1,808 visits, 65% of which were unique users. Thus far, there has been no publicity of the site. Blenderbox is helping with the site development. Both the Materials Workgroup and the Public Education Workgroup have met by telephone several times, and that will continue through the summer.

- The Challenge Awards, designed to engage the community and bridge the clearinghouse with existing programs, announced four awardees on April 1. There were several excellent applications. Those received awards for 6-month projects are: March of Dimes, NYMAC, Hawaii Department of Health, and APHL. In September, we expect to hear updates on their work.

- The Genetic Alliance, APHL, CDC, and HRSA are working together to determine how to identify those in the area of newborn screening and determine how to quantify quality improvement. They expect to have a report in September.

- Other updates came from the following:

  - Family History for Prenatal Providers (Ms. Alaina Harris): Hopefully the tablet-based computer-based family history program will be in testing mode by September.

  - Regional Genetics and Newborn Screening Service Collaboratives (Mr. Brian Pike): There are some interesting educational and training programs, especially in the area of nutrition for metabolic diseases, taking place in the southeastern region.

  - Genetics in Primary Care Institute (Dr. Tracy Trotter): An RFP went out in January, and it has been reviewed. At this point, there is no identified funding, and thus there is no awardee announcement.

  - NNSGRC (Ms. Colleen Buechner)

  - ACMGF Summer Genetics Scholar Program (Mr. Barry Thompson): The foundation's summer genetics scholar program is an exciting program for medical students who have completed their first year of medical school. The scholars spend focused time in a genetic situation. It serves two purposes: (1) it hopefully increases the number of medical geneticists and (2) it introduces young medical students to this exciting field early on so that, as they go on to do other things, they will be generally literate in genetics information.

  - Preserving the Future of Newborn Screening (Ms. Kelly Leight): Ms. Leight provided an update on the development of the organization's educational materials.

  - Saving Babies Through Screening Foundation (Ms. Jill Levy-Fisch, Ms. Cate Walsh-Vockley): The organization is producing an educational video which we look forward to viewing at our next meeting.

  - Updates were also given from the American Academy of Pediatrics (Dr. Timothy Geleske), the American Academy of Family Physicians (Dr. Frederick Chen), and the

American College of Obstetricians and Gynecologists (Dr. William Hogge). They have numerous educational efforts going on.

- The national newborn screening awareness campaign, approved by this Committee, is moving forward and launching into phase 1, which was delayed due to threats of a government shutdown in the spring. In phase 1, the subcommittee is looking at the lay of the land to determine what is out there now, what needs to be identified, what gaps need to be filled, and what it is that audiences want to hear. At the end of the first phase, the subcommittee will meet with the appropriate stakeholders to create a plan, which will be brought to the Committee for consideration.

C. Subcommittee on Follow-Up and Treatment

Dr. Botkin reported that the subcommittee welcomed Dr. Robert Ostrander as a new member of the subcommittee. He explained that the subcommittee focused most of its discussion on hospital-based newborn screening.

- Significant new issues need addressing with screens that go beyond dried blood spot screening. In an effort to not bite off more than it can chew, the subcommittee wants to maintain a focus on newborns as the population of interest for this discussion, leaving discussion of older infants and children for the future.

- The subcommittee's initial plan is to prepare a white paper, tentatively titled "Reframing Newborn Screening." (Organizing a conference had been discussed, but the idea was tabled.) The paper will address reframing the term newborn screening to refer to a broader set of activities beyond dried blood spot screening, addressing issues that make hospital-based screening different. Standards for screening would be identified and outlined in terms of nature of the test, urgency of the intervention, equity issues, and roles and responsibilities of stakeholders with a set of recommendations.

    - Stakeholders are essential to this process. They include public health, hospitals, third-party payers (including Medicaid), primary care providers and their professional organizations, nurses, the public, U.S. Preventive Services Task Force, and the Joint Commission.

    - The subcommittee has identified a core writing group that will be responsible for the initial drafts and for engaging the stakeholders.

    - The group discussed, but was inconclusive about, the benefits of hosting a webinar as a mechanism to gain input from the larger community.

    - The subcommittee did not set a schedule for this project. Dr. Howell asked if the subcommittee could present a draft by the next Committee meeting. Dr. Boyle suggested that the draft be ready for the subcommittee but not the full Committee at the September meeting. Dr. Howell took the silence in the room as assent on the part of the Committee to move forward with the white paper and said a vote was not necessary.

- Dr. Amy Brower updated the subcommittee on the National Coordinating Center uniform dataset efforts in public health measures for long-term follow-up. Good progress has been made in developing data collection uniformity to enhance follow-up on the full range of conditions identified through newborn screening.

- Dr. Susan Berry updated the subcommittee on the draft paper, a regional collaborative survey effort, about medical foods. Ms. Christine Brown discussed federal legislation, which is pending in both the Senate and the House, regarding medical foods.

    - Dr. Howell reported that the Committee sent a letter of support for medical foods to the Secretary. While a good idea, she said the issue is not in her purview. Dr. Howell believes the legislation has recently garnered additional sponsors and asked if it is moving along. He urged Committee members to do individually what they could to push this along.

    - Ms. Brown reported that the medical foods legislation may get attached as an amendment to a Senate bill. She and others will meet with Senator Kerry's staff in two weeks and will know more then. In addition, advocates are looking at other ways to include medical foods as essential health care benefits under the ACA. Geneticists and dieticians have been testifying and commenting at IOM meetings nationwide. The Department of Labor survey, which looked at health care plans and what they cover, was disappointing. The survey found that only 27% of health plans cover diabetic care management, so it seems even less likely that they would cover lab fees, dietetic visits, etc., for inborn errors of metabolism. A coalition of 40–45 organizations is working together on the legislation.

- Dr. Alan Zuckerman provided a thorough update on ongoing HIT activities relevant to newborn screening.

- Dr. Boyle commented that the NAPSIS board and executive director were very supportive of Dr. Brad Therrell's white paper that discusses linking newborn screening-related results to vital record information to facilitate follow-up and evaluation.

D. Report from the EEM Workgroup Meeting

Dr. Ned Calonge reported, on the April meeting, that was attended by Drs. Bocchini, Dougherty, Puryear, Copeland, Perrin, Green, Kimber, and Crofter as well as a number of experts in evidence-based medicine.

- Presentations were made on the EGAPP process (Dr. Steve Toish), the Third Sector Research Centre (Dr. Schuneman)), community guide process (Dr. Jonathan Fielding), the U.S. Preventive Services Task Force (Dr. David Grossman), and the use of modeling to inform decisions and policy (Dr. Diane Petey). Dr. David Atkins (QUERI and USPSTF) helped string everything together.

- The workgroup hopes to translate the following suggestions they heard into additional recommendations for the Committee to consider.

    - The workgroup was urged to consider the place of other types of studies apart from randomized control trials in its evidence-based methodology. The group was advised on how to use observational study designs and case theory to move information forward. It is important to understand the directionality of the bias of other studies and determine whether the bias overcomes the utility of the data in making decisions. Encouragement was given to cast a broader net to gather information.

- Based on local decision making and policy setting, some states launch into screening for new conditions before others do. That offers ongoing information in the form of a natural experiment that can inform the Committee about the utility of the screening approaches. Tracking and developing registries that allow for longitudinal assessment is critical to using these data to fill in the evidence gaps. The Committee is urged to figure out how to make registries come alive and contain sufficient information to provide case theories and comparative data. This is an unusual opportunity to gather data on rare conditions.

- With models, data can be reframed or reconstituted in ways that can help us wrestle with the decision making issues around newborn screening. When data is insufficient, there is uncertainty. Modeling helps define the limits of those uncertainties. It can also help determine the cost benefit of conditions. Sensitivity analysis is important in developing a model. It is important to understand that a model will not answer the question; it will simply provide a way to view the question.

- If evidence is insufficient regarding the benefits of newborn screening for a specific condition, how that uncertainty is communicated to the stakeholders (clinicians, parents, advocates scientists, and researchers) is critical to the success and reception of future Committee recommendations.

- The subcommittee discussed two modifications for consideration.

  - The group revisited an earlier idea to create a provisional category where a condition could be added with the understanding that specific evaluative data would be collected. As the evidence gaps are filled, the condition would be re-reviewed to determine whether to keep it as a permanent condition in the core panel.

  - The group suggested that not all conditions reviewed need to be restricted to a yes or no recommendation for the uniform screening test panel for all births. Some conditions could be recommended as a best practice for hospitals or clinicians. Conditions in this category include those that we feel are beneficial, but do not have enough evidence to say with certainty that they must be done to every birth.

Dr. Calonge invited others to comment.

- Dr. Bocchini, agreed that there were good suggestions made on how to best use limited data and then, in reference to the severity of the problem under evaluation, how to modify the approach (with the limited data available) based on a potential outcome for the individuals. The modeling recommendation provides this Committee a mechanism to look forward and make decisions more rationally.

- Dr. Boyle commented on the idea of acceptance with provision for the core panel. When considering the CCHD screening for the core panel, the group tried to take advantage of the "natural experiments" Dr. Calonge described in his second point. In such situations, the Committee needs a deliberative way to get additional information as it moves forward.

- At the meeting, the discussion did not get this specific, but Dr. Calonge reported that there was a palpable sense that this is something we need to figure out. There are groups of ethical experts looking into the use of information to support public health issues that are also wrestling with information in comparative effectiveness and in genetic testing. They are trying to figure out if exemptions for public health that are associated with HIPAA can translate to broader areas of informed consent and linkage of information. There are ethical groups that have decided that if it's a public health issue it fits under section 5(k) exemptions and do not require informed consent; however, there is a difference between the legal interpretation and public acceptability.

- Dr. Bocchini added that the proposed provisional category would be one that should be used only rarely. The Committee needs to be certain that the recommendation is right before going provisional because taking it out is difficult. Dr. Howell concurred that stopping something is extremely difficult.

- Dr. Botkin supported the provisional approach because it seems that a negative vote significantly inhibits the development of a test for many years, while a positive vote suggests the data is firm. A provisional category could help leverage the larger research world to fill in the gaps in a timely way on promising conditions.

- Dr. Vockley cautioned against providing this option as a back door into automatically getting more funding for a nominated condition.

- In response to Dr. Howell's question about the workgroup's recommendations for moving forward, Dr. James Perrin interjected that the workgroup wants to develop a manual of procedures related to how evidence reviews are done. Dr. Boyle was satisfied that this would address the methodological issues, but is does not address the issue of a Committee decision. Dr. Howell assumes that the workgroup recommendations would come to the Committee for decision.

    - Dr. Calonge restated Dr. Boyle's concern as that of being several fronts to move forward on. One is evidence modeling, which is in the purview of Dr. Perrin's group. The issue of other Committee products is not clearly in the purview of the evidence group. Previously the Committee had a recommendation process committee that published a paper and adopted the process. Traditionally, this would be Committee members working specifically on that process and decision making and then going forward. He recommended thinking about how the Committee should consider other issues, such as modeling and presenting information, that have less to do with evidence review.

- Dr. Kus asked for expansion on the pros and cons of using pilot programs in light of the discussion about a provisional recommendation being difficult to stop. Dr. Calonge noted that the pilot program is a superior approach in part because it allows us to see how it is implemented in a variable environment. The Committee can figure out how, in a structured way, to take advantage of early adopters to incite other states to implement programs.

- Dr. Howell said the Committee looks forward to seeing the material generated by the evidence group and asked Dr. Puryear to consider reassembling the recommendation process committee to look at the way the Committee handles evidence once it comes back.

VI. Evidence Review Workgroup Report: Final Report on the Candidate Nomination Hyperbilirubinemia and Committee Discussion

Dr. John Co presented the Evidence Review Workgroup's report on the candidate nomination of hyperbilirubinemia. The Committee heard the preliminary evidence review of hyperbilirubinemia in January. Today's report provided an interim review.

- The workgroup has a proposed decision tree model that it would like to further develop with the notable health outcomes of ABE, kernicterus phototherapy cases, and false-positive or false-negative cases at the next review committee meeting.

- Dr. Puryear verified that the workgroup wanted to go forward with the decision tree analysis rather than present a final report. Dr. Perrin noted that based on the report Dr. Calonge gave the evidence review group several weeks ago, this group believes it can work further with the decision tree model to provide more advice to the Advisory Committee.

- **MOTION #1 PASSED: To develop the decision tree model before asking for a vote on a recommendation for hyperbilirubinemia screening. Dr. Coleen Boyle moved and Dr. Ned Calonge seconded the motion. The motion was approved unanimously with 15 yes votes, no abstentions, and no absences.**

Dr. Vockley's presentation provided a detailed review of each of the key questions.

- Key question 1: Is there direct evidence that screening for the condition at birth leads to improved outcomes for the infant or child to be screened, or for the child's family? This is the overarching question for the evidence review. If the answer to it is affirmative, the recommendation should go directly to approval. (The rest of the questions are designed to help us get to our decision if the first one is answered equivocally.)

- Key question 2: Is there a case definition that can be uniformly and reliably applied? What are the clinical history and spectrum of disease of the condition, including the impact of recognition and treatment?

- Key question 3: Is there a screening test or screening test algorithm for the condition with sufficient analytic validity?

- Key question 4: Has the clinical validity of the screening test or screening algorithm, in combination with the diagnostic test or test algorithm, been determined and is that validity adequate?

- Key question 5: (a) What is the clinical utility of the screening test or screening algorithm? (b) What are the benefits associated with use of the screening test? (c) What are the harms associated with screening, diagnosis, and treatment?

- Key question 6: How cost effective is the screening, diagnosis, and treatment for this disorder compared to usual clinical case detection and treatment?

- In summary, the answer was no to all questions except question 3, which pushes us away from recommending this screening for the universal panel.

- Compared to other discussions, we have big gaps to fill.
- The screening methodology seems robust, but there are no population studies.
- The evidence that screening will prevent chronic bilirubin encephalopathy is missing.
- The cost-benefit ratio is very high.

- Because we do not have the data to give a positive recommendation, this screening falls under number 3 in the decision matrix. This is not because we think there is no benefit to the screen, nor because we thing that there is a harm to the screen, but because we simply do not have enough data to support a positive benefit conclusion.

- **MOTION #2 PASSED: To see the hyperbilirubinemia evidence review again at the next meeting with a decision tree embedded in the materials. Dr. Gerard Vockley moved and Dr. Tracy Trotter seconded the motion. The motion was approved unanimously with 15 yes votes, no abstentions, and no absences.**

VII. SCID Report to the Secretary and Committee Discussion

Dr. Howell reminded Committee members that when they approved the addition of SCID to the core panel, he sent a letter on behalf of the Committee to Secretary Sebelius with three bullets at the end. It read, "The addition of SCID to the uniform panel is done with the understanding that the following activities will take place in a timely manner:

- The National Institutes of Health will fund surveillance activities to determine health outcome of affected newborns.
- The Health Research and Services Administrations will fund development of appropriate education and training materials.
- And the CDC will develop and distribute to performing laboratories suitable dried blood spot specimens for quality control and quality assurance purposes."

Dr. Amy Brower reminded Committee members that they have a draft report in their briefing binders that summarizes the status of state-based SCID screening programs. The Secretary requested this report in May 2010. Her presentation provided an overview of report.

- Initial SCID newborn screening pilots began in Wisconsin (2008) and Massachusetts (2009). A multi-state project was undertaken in the Navajo Nation (2009). These studies generated screening and follow-up algorithms, created educational materials for families and health care providers, hosted multiple state programs for training in the assay, and developed proficiency materials that are now available to other screening programs. These pilots documented the feasibility of testing for SCID. The findings of these three pilots were presented to this Committee in January 2010.
    - A partnership between Wisconsin Laboratory of Hygiene, Children's Hospital of Wisconsin, and the Jeffrey Modell Foundation led to the first pilot study screening all births in the state. This will conclude in 2011

- CDC funding was then made available to continue the pilot study in Wisconsin and to initiate a second statewide pilot in Massachusetts. This will conclude in 2011.
- The Navajo Nation pilot study began at the University of California, San Francisco and took place in two hospitals in Arizona and New Mexico.

- By January 2010, no classic SCID had been identified in the pilot studies. (The first classic SCID case was identified in April 2010.) New pilot programs were initiated and funded in New York, California, Louisiana, and Puerto Rico by NICHD/NIH, with support from by the Jeffrey Modell Foundation and Perkin Elmer.

- Highlights of project's other key features:
  - Pilots in high number birth states (New York, California)
  - High capacity assay development (New York, California)
  - Regionalization model for samples: Puerto Rico → Massachusetts; Louisiana → Wisconsin
  - CDC quality assurance program developed in the earlier pilot and carried through in this pilot to ensure that each assay was independently developed and validated in the laboratories.
  - A SCID data portal was created. The goal of the portal is to collect, aggregate, and analyze the de-identified screening data generated during the pilot. The subcontract for the portal was administered through the NIH Eunice Kennedy Shriver National Institute of Health and Child and Human Development's Newborn Screening Translational Research Network.
  - Monthly conference calls to share expertise were fostered.

- The workgroup is working with experts in the field to come up with disease categories and to call out the cases identified by the screen. Classic SCID presentation is caused by a complete lack of an immune system, due to deleterious mutation in one or more genes. SCID variants, or partial failure of the immune system due to variation in DNA, are called "leaky SCID," combined immunodeficiency, or Omenn syndrome. There is also a category of non-SCID that represents a loss or gain of a large section of DNA on one or several genes that results in significant impairment in immune function. All these cases would be missed if not for newborn screening.

- As of March 31, 2011, SCID screening has been piloted in seven locations and, as a whole there have been 119 months of continuous screening. Over 914,000 newborns have been screened, and 12 cases of classic SCID, 7 cases of SCID variant, and 55 cases of non-SCID have been identified, diagnosed, and treated. Thus far, it seems that no child has been missed by screening and no child received inadequate treatment.
  - Incidence of SCID as a whole: classic SCID is 1 in 76,000; SCID variant is 1 in 130,000; and non-SCID is 1 in 126,000.

- The findings that are emerging show that the incidence is generally higher than previously reported.

- Incidence rate differences by population are also emerging. In California, there is a higher rate of incidence amongst Hispanics. (It is important to note that the confidence intervals are quite wide due to it still being in the early days of screening.)

- Other emerging findings include, a zero TREC with normal copy numbers for genomic PCR control consistently means the infant is at risk for profound T-cell lymphocyte deficiency. The majority of classic SCID cases have zero TREC. The molecular etiology of low TREC cases is varied. There is a relatively low number of X-linked SCID in California.

- Incidence caveats: (1) Definitions are still being refined by experts, (2) there is a large phenotypic variability within SCID and SCID variant cases, (3) cases are sometimes not finally diagnosed for many months, and (4) the pilots are still in progress.

- Tools and resources developed through the pilots

  - To support the quality assurance measures required by CLIA, CDC provided dried blood spot reference materials for within and between laboratory proficiency testing. These tests are performing very well across all the laboratories.

  - The data portal is providing real-time clinical validation, which was one of the major weaknesses pointed out in the first evidence review. It's available to any interested stakeholder. Novel disease categories that will improve the field and help inform immunologists are being worked on.

  - The laboratory protocols are widely available to any laboratory interested in adopting SCID newborn screening. There are now four independently validated laboratory-developed tests, and the laboratories are available to train and assist others as they implement SCID.

  - A considerable amount of resource sharing has taken place. Monthly conference calls to discuss the challenges and opportunities of implementing SCID allow screening programs to share expertise, troubleshoot, find resources for states that considering implementing SCID, and help with advisory board presentations. Tapping into the expertise of the four laboratories once a month helps with implementation. Clinicians and foundations join those calls and help in the efforts as well.

- The six pilots cover about 25% of U.S. births. According to a survey done by the NBSTRN and the Immune Deficiency Foundation, all states are considering SCID newborn screening implementation based on the recommendations of this Committee. In addition to the pilot projects, Pennsylvania has a partial program, and Texas has a targeted population screening. Colorado, Minnesota, Iowa, Illinois, Michigan, New Jersey, Delaware, Rhode Island, North Caroline, and Florida have approval to implement screening as soon as feasible. All other states are at various stages of consideration.

- Status of State implementation

  - All states surveyed have actively considered SCID newborn screening; 20 have presented SCID newborn screening to their state advisory boards and all have recommended implementation.

  - Over 35% of states participate in a monthly conference call to share expertise. Those calls will continue after the pilot has ended.

- Pilot states have played a key role in educating interested states and stakeholders.
- Nine states rely on regional partners to adopt SCID newborn screening.
- Three states report a requirement for an FDA cleared or approved kit.

- Many educational activities have been developed and delivered.
  - In addition to the data portal, protocol development, and laboratory workshops, the six pilot state newborn screening programs have created and distributed educational materials for parents of newborns with a positive screen or with a confirmed diagnosis.
  - In October 2010, with HRSA funding, the CDC, Association of Public Health Laboratories, the National Newborn Screening and Genetics Resource Center hosted a meeting devoted to SCID newborn screening. The meeting was attended by 192 laboratory specialists, follow-up professionals, and immunologists representing 48 states and 3 countries. A supplementary laboratory workshop was attended by scientists from 28 U.S. newborn screening programs.
  - ACMG developed and HRSA funded SCID clinical decision support materials (ACT sheets) through its National Coordinating Center for the Regional Genetic and Newborn Screening Collaboratives.
  - The Immune Deficiency Foundation launched a Web page for parents, a SCID newborn screening advocate toolkit for use by families to educate their policymakers, and a brochure to warn providers about the danger of administering live rotavirus vaccine to infants with SCID.
  - The CDC, APHL, and Jeffrey Modell Foundation have a 2-year fellowship for postdoctoral candidates during which the candidates focus on newborn screening research, including research into immune deficiencies.

- Seventeen months after this Committee's SCID screening recommendation, one-fourth of births are being screened through pilot programs funded by federal and state agencies and private foundations. Lessons that have been learned include the following:
  - The recommendation triggered 100% of states to act.
  - The biomarker identifies two different clinically relevant populations—"No TRECs" and "Low TRECs."
  - Development, validation, and piloting of novel screening technologies are possible in state newborn screening laboratories.
  - The initiation of newborn screening for a new disorder contributes to clinical and scientific understanding, and it facilitates new research questions.
  - Issues that delay implementation include the following: lack of cost benefit information, lack of financial resources, lack of personnel and expertise, prior commitment of state resources to legislative mandate to screen other disorders, and lack of an FDA-approved kit affects some states.

- The next steps are to conclude the pilots (June and October 2011), continue to support implementation, and take on new efforts.
    - The ongoing efforts of NIH, CDC, and HRSA will continue to support adoption of the screening. The monthly calls will continue and all interested stakeholders will be invited to participate. The SCID data portal will continue to admit cases and analyze results.
    - New efforts include the creation of long-term follow-up datasets; an expert workgroup to refine the screening, diagnosis, and treatment protocols; and two new funding opportunities from the CDC (applications due in early summer 2011).
    - The Primary Immune Deficiency Treatment Consortium, funded by the NIH, works to identify factors that influence outcome, including newborn screening. They seek to determine optimal treatments by natural history studies and multicenter clinical trials. Work is beginning on a joint prospective and retrospective analysis of the SCID cases.
- The activities recommended by this Committee fostered collaboration across HHS agencies and enabled each agency to focus on their expertise. Quality control and improvement materials to ensure test accuracy were distributed by the CDC to pilot states. HRSA funded ACT sheets to guide providers. NIH NICHD expanded the pilots and provided infrastructure for databases to enable diagnosis, treatment, and long-term follow-up.
- This update affirms this Committee's system of evidence-based review of conditions nominated for addition to the uniform panel and subsequent recommendations to begin newborn screening for nominated conditions.

VIII. Committee Discussion

- Dr. Buckley reported that yesterday she was informed of two new cases of SCID, one in New York and one in Wisconsin that had just been discovered. She is sure more will be found as screening efforts continue. In response to a question asked earlier by Dr. Dougherty regarding what happens to patients discovered through screening, Dr. Buckley reported that she attended a meeting in San Francisco in April where this topic was discussed. She is confident that those patients are receiving appropriate treatment, and she has not heard of any deaths for those being treated. The patients have been mainly bone marrow transplanted, but some have also been treated with enzyme replacement therapy for adrenosine diaminase deficiency in anticipation of getting gene therapy.
- Dr. Fleischman asked if Committee members might consider the chair's cover letter that will go along with this report. Are there recommendations the Committee could make to the Secretary that might speed up implementation? Perhaps funding efforts and regional efforts could be used to enhance the programs that are already up and running. There are serious funding questions in several states that affect implementation, which causes concern beyond our immediate successes.
- Dr. Dougherty agrees with the concluding report statement that this is a model for future activities of the Advisory Committee; however, as became evident with the CCHD recommendation, it is not quite a model for what the Committee does yet. She proposed that, for the next meeting, Committee members review the existing framework for making recommendations and determine how to include future research.

- Dr. Buckley added there is now a law that all newly diagnosed SCID patients have to be reported to the International Bone Marrow Transplant Registry. So, each of these babies is reported to the registry. That means that they are getting long-term follow-up. Additionally, the Primary Immune Deficiency Research Treatment Consortium has a 5-year grant to do the long-term follow-up of the babies being treated.

- Dr. Howell said the letter the Committee sent originally to the Secretary had three specific recommendations that were virtually identical to those that went forward on the CHD recommendation thing. He thinks the idea of talking about the way we format things at the next meeting is worthwhile.

- Dr. Parisi asked for clarification about what the state programs labeled targeted screening are doing. Dr. Brower responded that Texas is doing a pilot with Massachusetts to try it out in a few hospitals. New Mexico and Arizona are part of the Navajo Nation program, so they are only screening at particular hospitals. The Navajo incidence rate is 1 in 2,000, but of the 1,200 babies screened so far, none have been found to have SCID.

- Dr. Botkin is uncertain why the report has no outcome data verifying that these children are, in fact, getting appropriate treatment and are benefiting from that treatment in the report. That seems like a huge hole. He also thinks the report would benefit from more information about cost as well as strategies commenting on the identified challenges that have been identified in the lessons learned. He would like to see the report expanded to cover this.

    - Understanding that some of those data will need to come as the programs continue, Dr. Howell asked Dr. Brower to include that in the report. Dr. Brower noted that it has been a year since the first infant was diagnosed, so it should be possible to report on that.

    - Dr. Howell added that it would be nice to have as much outcome data as possible. It will be interesting to see the economic data because the missed infants not only die, but before they die they also run up enormous costs.

    - Dr. Brower related that currently there is no national resource to follow children who were not part of the newborn screening program (since the pilot started) but did get a transplant. The screening programs will work with the PIDTC to get those cases and begin to compare the cost benefit.

- **MOTION #3 PASSED: To send the SCID report forward to the Secretary with the modifications mentioned. Dr. Rebecca Buckley moved and Dr. Fred Lorey seconded the motion. The motion was approved unanimously with 15 yes votes, no abstentions, and no absences.**

- Regarding the variability in rates, Dr. Anne Comeau said that not only has no one found any false-negatives but also about 30 specimens not known to be SCID have been sent to the lab and identified. Between that and the CDC proficiency testing, it is fair to say with confidence that the different tests are working very well to identify all SCID infants.

- Dr. Mei Baker contributed several comments. The first SCID was found in her state. The baby had a bone marrow transplant, and after 5 or 6 months the dried blood spots came back with normal TREC. Regarding population variability, she noted that of the eight cases in California, six are in the Hispanic population group. Her final point was to note that Europe also has a lot of activity around SCID screening in newborns. Several countries have visited the lab to learn the assays.

- For discussion at the next Committee meeting, Dr. Botkin suggested addressing the ethical and regulatory issues with pilot newborn screening programs. The standard informed consent approach is a serious challenge to get effective recruitment for those studies. IDBS would benefit from some commentary at the national level about what is and is not appropriate for the conduct of these studies. He would like to foster additional analysis and discussion about those issues and garner support for certain models of approaching this at the national level in order to help local IDBS in reviewing these protocols. Dr. Bailey volunteered to work with Dr. Botkin on this topic.

IX. ADJOURNMENT

The next meeting of the Committee will be held September 22–23, 2011.

- **MOTION #4 PASSED: To adjourn the meeting.**
Dr. Jeffrey Botkin moved and Dr. Melissa Parisi seconded the motion. The motion was approved unanimously with 15 yes votes, no abstentions, and no absences.

- The meeting was adjourned at 2:30 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/ for

R. Rodney Howell, M.D.
SACHDNC Chair

Sara Copeland, M.D.
SACHDNC, Acting Executive Secretary

The committee at its next meeting will formally consider these minutes, and any corrections or notations will be incorporated in the minutes of that meeting.

1. Assemblyman Jason O'Donnell, New Jersey, Pulse Oximetry

Testimony Submitted to the

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

By

Assemblyman Jason O'Donnell

Member, New Jersey State Assembly, 31st Legislative District

At the

Twenty Fourth Meeting
Renaissance Washington, DC
Washington, DC
May 5-6, 2011

My name is Jason O'Donnell, and I serve as an Assemblyman for the 31st Legislative District in the Great State of New Jersey. I have the privilege of submitting these comments to you today not only as a legislator who has proposed a bill to mandate pulse oximetry testing in the state of New Jersey, but also as a father of a son who survived Congenital Heart Disease. As you can tell, this issue is near and dear to my heart. But more importantly – it just makes sense. In 2011, in the greatest nation on earth, there is simply no excuse for newborn children dying because a small, non-invasive test that costs less than $10.00 has not been utilized to check for heart defects. Thank you, in advance, for considering my comments.

*

In the Fall of 2010 I was fortunate enough to be selected to fill a vacancy in the General Assembly, and subsequently won the special election for that office. I am a career firefighter – I hadn't considered running for public office. Before running for office, my wife and I discussed what this would mean for our family, and the time it would take away from her and our three children, Caroline, 8, Jack, 6, and Patrick, 4. WE decided that I should accept the opportunity and do my best to make a difference.

New Jersey's Pulse Oximetry Bill, A-3744

One of the first pieces of legislation I introduced was Bill A-3744, requiring that a pulse oximetry test be performed on every newborn in New Jersey who is at least 24 hours of age. I am happy to report that

this bill passed unanimously in both the General Assembly and the State Senate, and is now awaiting our Governor's signature.

Understand, please, that in the state of New Jersey, we conduct 54 tests on newborns. None of those tests screen for heart defects. We have a mandatory check for hearing on newborns, yet we don't have a mandatory check for life-threatening heart defects. We lose at least3-4 children a month due to undetected CHD. That's four children a month, four mothers a month, four families a month whose lives will never be the same. With all due respect, a child who has a hearing problem still can live a healthy life. A child who has a heart defect could die within days or years – and too many children certainly have met this fate.

Concerns

Most people were supportive of my bill, but there are those who expressed their doubts.

Accuracy of the pulse ox test was brought into question. Studies have shown that when pulse ox is done at least 24 hours after birth, the false positive rate falls drastically. No test is perfect, so there may still be an occasional false positive. So what does this trigger? Another simple test to ensure that the child's heart is healthy. At the end of the day, a few more hours of testing – and perhaps even a few more hours of parental worrying – is well worth the resolution that those parents will feel knowing their baby does not have congenital heart disease.

Some expressed concerns over cost. The cost of a pulse ox test is less than $10.00. A hospital diaper change costs more than a pulse ox test. Additionally, the precaution from performing the test will prevent the costs of emergency services should the baby have gone home and gone into heart failure. It will help prevent potential organ damage , potential neurological impairment and developmental delay because of an undetected heart defect. In reality, it will also prevent malpractice lawsuits against doctors and hospitals.

Still, others expressed concerns over not knowing enough about the test, asking for more research and more time to consider the matter. There have been studies conducted for the more than a decade, with several just published in the past two years.. The Secretary's Advisory Committee on Heritable Disorders (SACHDNC) in Newborns and Children working with the American Academy of Pediatrics, the American College of Cardiology, the American Heart Association, and other stakeholders to establish standardized federal recommendations for screening and diagnostic follow-up of Critical Congenital Heart Disease (CCHD) is the solution.. We do not need more studies, we need action – our children's lives depend upon it.

Personal Experience

My third child was a particularly hard labor for my wife. The pediatrician examined Patrick when he was born, and heard a heart murmur – something extremely common in newborn babies. To our pediatrician's credit, he decided to be extra cautious, and he asked my wife and I if he could bring in a

pediatric cardiologist. The pediatric cardiologist arrived, examined Patrick, and told us our son needed to have surgery immediately.

We were fortunate. We had a very good pediatrician, and a very good cardiologist. My wife and I had decent health insurance plans. We also live in a major metropolitan area, which afforded us many healthcare options for our son's surgery.

In Summation

Will my bill in New Jersey solve all heart issues for all newborns? Of course not. There are still many issues to confront, such as access to health care in rural areas and disparities in quality care and health insurance in lower socio-economic areas. However, this should not deter us from moving forward with actions that will save lives. Pulse Ox is a first step, not a final solution. There is more work to be done.

I hope and pray that New Jersey can help lead the way to saving the lives of newborns with CHD. Our children deserve nothing less than the best healthcare we can afford them. We can afford them this simple, non-invasive, low-cost test. Thank you.

2. Emil Kakkis, Kakkis EveryLife Foundation, Proposed Revision to FDA Policy on Emergency Drugs for Rare Diseases

KAKKIS EVERYLIFE
FOUNDATION
No Disease is Too Rare to Deserve Treatment

May 5, 2012

R. Rodney Howell, M.D., Chairperson
Secretary's Advisory Committee on Heritable
Disorders in Newborns and Children (SACHDNC)
Dept. of Health & Human Services

24th Meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

Dear Dr. Howell:

Please accept my comments on: **The Food and Drug Administration Policies and Procedures Relevant to Individuals with Rare Heritable Disorders; Critical Drug Shortages for Necessary Medications**

I would like to propose a reasonable solution for at least one type of product based on existing regulations that could be implemented by FDA as a policy for emergency drugs for rare diseases.

Background:
In rare diseases and especially metabolic diseases, there are often single source suppliers for a number of metabolic intermediates. In addition, special vitamins, simple compounds and related small molecule compounds that play a critical role in the management of severe decompensation are also often supplied by a single small commercial supplier. This supply chain is thin and not robust, leading to times at which critical shortages can occur. Given that doctors and hospitals rarely store supplies of these compounds, there is little flexibility in the system when the supplier cannot deliver. In many cases, there may be another supplier, approved in other countries in the European Union (EU) or in Japan, who makes a similar though not identical product that has the same active ingredient. These other similar products are approved for human use in competent regulatory jurisdictions and have passed testing that assures its purity and appropriateness for use in the indications. These alternative sources should be made available in a prudent and thoughtful way during emergency shortages to allow temporary use in the US, without too large a regulatory burden and without delay. We believe this situation exists for arginine and has occurred for many other emergency small molecule drugs in the metabolic space.

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Proposal for Drugs Subject to the new Emergent Metabolic Drug Policy:
As a reasonable regulatory solution for at least one type of limited access situation, we would like to propose that for drugs in the specific situation described below, the review of emergency drug access would be subject to an improved FDA policy.

1) **Product Type is Small Molecule**: The product is a well characterized small molecule drug with typical Generally Recognized As Safe (GRAS) excipients.
2) **Prior Regulatory Approval:** The product is approved in a formulation appropriate for use in a rigorous regulatory jurisdiction (EU main 5 countries or in Japan).
3) **GMP Compliant Production**: The product is produced, tested and released in accordance with Good Manufacturing Practice (GMP) regulations as implied by the regulatory approval. A GMP inspection would not be required but certification accepted.
4) **Active Ingredient is NOT an NCE in the US**: The product contains an active ingredient that has also received approval in a similar though not identical formulation and container/closure in the US; i.e., the active ingredient is not a New Chemical Entity (NCE) by the FDA's criterion and is not covered by NCE exclusivity in the US.
5) **A Physician IND Request is Made to FDA for Use**: The Investigational New Drug (IND) request would be made under the new expanded access regulations governing a "medium" size type program, stating the emergent need, and the basic information as to the current supply in the EU or Japan.

Proposed FDA Policy:
FDA would review the case as an Expanded Access Request for a drug consistent with the above criteria, and assist in the completion of any information required for review, since the physicians submitting the request may have limited knowledge about regulatory matters and limited access to required information. This might involve contact with the regulatory authorities in the jurisdiction under which the product was approved. The FDA would approve the import of the compound for emergency use under a temporary authorization of six months that is renewable if no supply solution is found. Other physicians could obtain the drug via letters requesting use through the same IND. Reimbursement for the drug's price translated to US price plus cost of shipping/distribution would be allowed.

This proposed policy would not apply when the active ingredient is not an approved NCE in the US, which is a more complex situation relating to safety controls. Whether this policy in some form could be applicable to unapproved compounds in the US that are approved elsewhere is up for discussion. With regard to proteins or other biologics, the policy would become too complex

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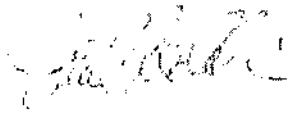
to implement. We believe a focus on the easier small molecules that are already approved NCE's is a clearer and more tractable situation that could be acted on immediately by FDA within existing regulations. If the proposed solution were in place, the situation with arginine for example would not have created as large a crisis as it did in the US among metabolic physicians and patients. Other solutions for complex situations for non-approved NCE's or biologics would require more work and thought.

Thank you for your consideration on this proposal. The Kakkis EveryLife Foundation is dedicated to improving the regulatory and clinical development process for rare diseases. I am ready and able to assist with any questions you may have, please feel free to contact me at ekakkis@kakkis.org or 415-884-0223.

Best Regards,



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