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

Summary of 26th Meeting
January 26-27, 2012
Washington, DC

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children was convened for its 26th meeting at 8:30 a.m. on Thursday, January 26, 2012, at the Park Hyatt Hotel in Washington, DC. The meeting was adjourned at 2:40 p.m. on Friday, January 27, 2012. In accordance with the provisions of Public Law 92-463, the meeting was open for public comments.

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Thursday, January 26, 2012

I. Orientation to SACHDNC and HHS

Joseph Bocchini, Jr., M.D.
(Committee Chairperson)
Professor and Chairman, Department of Pediatrics
Louisiana State University
Shreveport, Louisiana

Dr. Bocchini opened the meeting by introducing three presentations that provide foundational information about SACHDNC's work.

A. Ethics for Special Government Employees

Dheeraj Agarwal
HRSA Office of Management/Division of Workforce Management

Mr. Dheeraj Agarwal showed a video on ethics for special government employees. The material in the video covers financial conflicts of interest; misuse of position; appearance of bias or loss of impartiality; teaching, speaking, and writing; and how to get an exception. Mr. Agarwal requested Advisory Committee members contact his office if they think there may be an ethics problem. Office staff members will research the issue to determine whether there is a concern and work with the individual to remedy it. Remedies include waivers, authorizations, divestitures, resignations, etc.

B. Overview: Health Resources and Services Administration and the Maternal and Child Health Bureau

Mary Wakefield, Ph.D., R.N.
Health Resources and Services Administration

Dr. Mary Wakefield, welcomed Dr. Michael Lu, the MCHB's new associate administrator and representative on this committee.

- Dr. Wakefield explained that this committee provides a vehicle through which interested parties bring expertise on reducing morbidity and mortality associated with genetic disorders to the MCHB. She highlighted the importance of the Advisory Committee's systematic reviews, its introduction of modified and new conditions for newborn screening, and its role as a link between genetics and public health. The work of this committee has leveled the playing field for newborn screening across the nation, providing a robust and standardized approach that ensures infants do not miss the opportunity for life saving and life altering screenings for 29 conditions. The CDC recognizes that standardized screening, in conjunction with new technology, has led to life saving treatment and intervention for an additional 3,400 newborns each year. In addition to work with the recommended uniform screening panel (RUSP), the Advisory Committee recognizes that long-term follow-up and the involvement of primary care professionals and other care providers are an integral part of care. These have been important contributions to HHS and HRSA.

- Noting that infant mortality rates in the United States are a reminder that we have unfinished business, Dr. Wakefield outlined the key areas of the Advisory Committee's future work. Closing the gaps in our ability to provide care to our infants and children is very important to the

current administration, and it has committed resources accordingly. For example, the Affordable Care Act (ACA) has increased insurance coverage from 7 million low-income children to 11 million, providing them access to screenings for illness prevention and wellness promotion. The new focus of HHS and HRSA is on expanding access to care and improving its quality. Other provisions of the ACA that have implications for families affected by heritable disorders include (1) the ban on copayments for basic health services and screenings, (2) ending the practice of denying coverage for pre-existing conditions, (3) establishment of high-risk insurance pools for persons with pre-existing conditions, (4) ability to keep young adults on the parents' health insurance policy, (5) elimination of lifetime caps on benefits, (6) reauthorization of family-to-family information centers, (7) deployment of a home visiting program for expectant mothers in high-risk communities, and (8) investment in the community health center system. In another initiative, HRSA works with a public-private partnership that sends expectant and new mothers time-sensitive text messages that lay the foundation for good health practices. These messages include reminders of the importance of screenings.

- Dr. Wakefield thanked committee members for their commitment to finding solutions that provide our nation's infants the best start in life possible. She asked that, in light of the upcoming 2013 reauthorization of SACHDNC, they closely examine committee structures and scrutinize their use of resources so that this important work can continue.

    - In the ensuing discussion, Dr. Frederick Chen pointed out some other parallels between the work of the Advisory Committee and the ACA. The ACA supports the Advisory Committee's focus on applying evidence-based medicine to its analysis. The Advisory Committee has also addressed the need for an interprofessional care team for infants and children with heritable disorders, a service delivery model supported by the ACA. Acknowledging that the Advisory Committee was one of the first groups to address the importance of a broader team approach to health care delivery, Dr. Wakefield added that, as the new agenda is pushed forward, it is important to consider both the delivery models and the individuals receiving care within those models.

    - Dr. Christopher Kus commented that, in the same way that this committee helped get states to screen children no matter where they live, it is also important that they should have access to treatment regardless of where they are. This is a critical part of this committee's work for the essential benefits package.

C. Overview of SACHDNC Legislation

Beverly Dart, J.D.
HRSA Office of the General Counsel

Dr. Beverly Dart, senior attorney with the HHS Office of the General Counsel (OGC), provided an overview of the SACHDNC legislation in order to provide a structural foundation for talking about the Advisory Committee's work.

- The OGC provides legal advice and assistance to HHS, HRSA, MCHB, other operating divisions, and program officials who are charged with specific programs. The 1972 Federal Advisory Committee Act (FACA, public law 92-463) sets the legal framework for advisory groups that advise federal agencies but include persons who are not federal employees. FACA was enacted to ensure that advice offered is objective and accessible to the public. The act defines what an advisory committee is, provides the statutory purpose for such a committee (to provide advice, not execution), and lays out statutory responsibilities for HHS's relationship with the committee (HRSA/MCHB performs most of these with SACHDNC).

- Section 1111 of the Public Health Service Act lays out the authorizing legislation for SACHDNC. It explains that the committee's role is to provide advice, information, and recommendations to the Secretary on newborn and childhood screening, development of policies to enhance the abilities of state and local health agencies, and the 42 U.S.C. grant program.

- The ACA added section 2713, on preventive care and screenings, to the Public Health Service Act, affecting one aspect of the committee's work. This means recommendations for the RUSP adopted by the Secretary now must be covered by non-grandfathered health plans. Once they are added to the RUSP, a further legal and public health effects result.

- This committee has a clear path to move forward in three areas: (1) providing recommendations for the addition of conditions to the RUSP, (2) providing advice to certain HHS agencies, and (3) offering direction on the Newborn Screening Saves Lives Act grant.

- The Advisory Committee needs to exercise caution and consult closely with the program manager when it wants to make recommendations that fall outside the parameters noted above.

    - Dr. Carol Greene asked for clarification on the Advisory Committee's areas of authorization. The presentation addressed only newborn screening, but she believes it originally covered anything to do with the reduction of and death and disability from hereditary disease. Dr. Sara Copeland explained that while the Advisory Committee's work has focused on newborn screening, it is in fact much broader.

    - Dr. Chen asked for clarification about insurance coverage for newborn screening procedures. Dr. Copeland explained that screening is rolled into the newborn screening fees, but occasionally screens need to be completed outside of the birth environment and those are often billed to the insurance company. Because of this, in some states, the insurers express strong interest in additions to the panel. It is important to note that if a screen is on the RUSP, whether or not the state has adopted it to the panel, the insurance companies must cover it if requested.

II. Committee Business

Joseph Bocchini, Jr., M.D.
(Committee Chair)
Professor and Chairman, Department of Pediatrics
Louisiana State University
Shreveport, Louisiana

By way of roll call, Dr. Joseph Bocchini asked committee members to introduce themselves and identify any conflicts of interest each may have.

- The following voting members were present: Don Bailey, Joseph Bocchini, Jeffrey Botkin, Coleen Boyle (CDC), Sara Copeland (HRSA/MCHB), Denise Dougherty (AHRQ), Charlie Homer (via phone), Kellie Kelm (FDA), Fred Lorey (via phone), Michael Lu (HRSA/MCHB), Stephen McDonough, Dietrich Matern, Alexis Thompson, Catherine Wicklund, and Andrea Williams. Carla Cuthbert arrived following the roll call.

    - The following liaison members were present: Natasha Bonhomme, Frederick Chen, Jane Getchell, Carol Greene, Theresa Hart, Allen Hogge, Chris Kus, Joe Leigh Simpson, Beth Tarini, and Michael Watson.

- Also responding to the roll call was Beverly Dart (OGC).

- Dr. Bocchini asked if there were any corrections to the September 2011 minutes. The following corrections were noted.

  - Page 9: The opening statement of the penultimate paragraph, "At the time of the Advisory Committee's inception, the majority of states were not screening newborns," is incorrect.

  - Page 33: In the third line of the third paragraph, "a log of progress" should be changed to "a lot of progress."

  - Page 36: In the fifth paragraph, it is unlikely Dr. Howell said "catarcin immuno type 1." Most likely, he meant "tyrosinemia type 1."

  - Page 38: In the sixth paragraph, the reference to the "American Congress on Obstetricians and Gynecologists" should be "American College of Obstetricians and Gynecologists."

MOTION (APPROVED): To approve the minutes with the indicated corrections. Dr. Stephen McDonough so moved and Dr. Dieter Matern seconded the motion. The motion was approved with 14 ayes and 0 nays. One member was absent (NIH—Dr. Alan Guttmacher).

- There was no Advisory Committee correspondence to report.

III. Orientation to SACHDNC Current Charter, Processes, and Procedures

Sara Copeland, M.D.
(Designated Federal Official)
Health Resources and Services Administration
Maternal and Child Health Bureau
Rockville, Maryland

As the structure and visibility of this committee grows and as we approach the 2013 reauthorization of SACHDNC, we are introducing five structural changes to our processes and procedures to improve the way we work and to ensure that we meet the Advisory Committee's legislated requirements. These changes were presented for discussion and assent.

- Dr. Copeland proposed adding a step to the algorithm of the Advisory Committee's evidence review process—a determination of the public health impact of the screening. This step will change the process from an evidence review to a condition review. The rationale for the change is that it is in SACHDNC's legislative charge to evaluate the public health impact of disorders added to the RUSP. Dr. Copeland noted that a workgroup is currently reviewing the evidence review process used by federal agencies with the intent to facilitate collaboration. The Advisory Committee will see a model of the revised process at the May meeting. Dr. Copeland emphasized that, without an assessment of the public health impact of a screening, the model decision matrix provisions for newborn screening expansion updates to the RUSP are not fulfilled.

  - Dr. Jeffrey Botkin opined that this change would help states incorporate the recommendations into their policies and procedures.

  - Dr. Denise Dougherty asked for clarification regarding the correlation between adding the public health impact consideration and alignment with the U.S. Preventive Services Task

Force (USPSTF) and the Community Guide. Dr. Copeland explained that this is a way of streamlining the groups' efforts.

  - Dr. Don Bailey asked what types of data would be needed to assess the public health impact and who would be responsible for gathering them. This could be challenging because it could require implementation, cost effectiveness, and process studies, thus delaying decisions. Dr. Copeland responded that the workgroup will consider these concerns as it develops a model. A draft consideration of how to include this in our process will be presented at the Advisory Committee's next meeting.

- Dr. Copeland proposed changing the process of discussing and voting on conditions by adding two Advisory Committee members to the evidence review workgroups. These two members would actively listen to the evidence review while in progress. They would then analyze it and present their findings to the larger committee. This process would help frame a perspective for the full committee's discussion and recommendation.

  - Dr. Dougherty expressed concern, based on experience in the Advisory Committee, with the selection of committee members serving in this role. She recommended having a trial period with this process prior to implementing it as a final recommendation. Dr. Bocchini explained that ACIP uses this process successfully. The two Advisory Committee members would serve as the voice of the committee. They would be up-to-date on the data as it becomes available, so they would have the background and rationale needed to make preliminary recommendations for the Advisory Committee's vote. Choosing the committee members would need to be done carefully to ensure objectivity. Tomorrow's presentation on the evidence for hyperbilirubinemia is modeled on this recommendation, so the Advisory Committee can consider its appropriateness. Dr. Bailey concurred that careful thought should go into the selection for this role, ensuring multiple perspectives. Dr. Boyle recommended that the Advisory Committee make some explicit determinations that subject matter experts, and others who have invested years of work into a particular condition, not serve as these representatives.

  - Dr. Copeland noted that since the matter of who works with the evidence review is a policies and procedures matter, it does not need to be decided today.

  - Dr. Botkin asked whether the two representatives would make a single unified or individual recommendations and whether the recommendation(s) would be available prior to the meeting.

  - Dr. Bocchini suggested it would be best to distribute the recommendations prior to the meeting with other evidence review materials so members have time to review and consider it carefully prior to voting.

- Dr. Copeland recommended developing a formal process for reports and products. She suggested each report or product be reviewed by the appropriate subcommittee to deem its appropriateness for further presentation to the Advisory Committee. She also recommended delineating the following four levels of support for material brought before the committee: (1) official support (forwarded to the Secretary for consideration), (2) affirmation of value (forwarded to the Secretary for information only), (3) acknowledgement that it was presented (not forwarded to the Secretary), and (4) no support. The rationale is that the Advisory Committee wants to ensure that it appropriately supports materials that will benefit the heritable disorders community.

- Dr. Dougherty recommended clarifying level 2 support as "important but not actionable." Dr. Botkin would like us to refer the categories as "nature of support" instead of "level of support." Dr. Boyle would like to see the gray area between the action element and levels 1 and 2 clarified. Dr. Copeland noted that the wording for the support levels needs fine tuning, but asked the Advisory Committee to weigh the benefits of the concept of this change.

- Dr. Joe Leigh Simpson asked where the serendipitous findings of soon-to-come whole genome sequence screening fit into this codification. Dr. Copeland replied that anything that is not a clear-cut newborn screening product is presented to legal counsel to determine whether it falls within the legislative scope of our committee.

- Dr. Kus asked if this system might create added work for the Advisory Committee by encouraging requests for action. Dr. Copeland offered an example of how this could be useful, explaining that instead of re-creating work that is being done outside the committee, this would allow the outside work to be submitted for Advisory Committee consideration. It would be submitted to a subcommittee and then, if valuable, forwarded to the main committee. This reduces the need for the Advisory Committee to do all the work.

- Dr. Copeland recommended imposing term limits for nonvoting Advisory Committee members, just as there are for voting members. The recommendation is to have HRSA and ex-officio members develop categories of liaisons with a set number of representatives who would either roll off or be reappointed every 4 years. The rationale is that this system allows a more equitable distribution of influence with the Advisory Committee and provides a rolling influx of ideas.

  - Dr. Alexis Thompson asked if the term limits would be applied at the organizational or personal level. Dr. Copeland responded that it would be at the organizational level. The organizations would select their representatives, but the Advisory Committee determines which organizations are to be represented.

- Per advice from legal counsel, Dr. Copeland recommended separating the by-laws from the policies and procedures. Changes to the by-laws require a formal vote from the Advisory Committee. By separating them, the Advisory Committee will not have to vote every time there is a change to the policies and procedures. This aligns with FACA legislation.

MOTION (APPROVED): To accept the changes to the by-laws. Dr. Stephen McDonough so moved and Dr. Jeffrey Botkin seconded the motion. The motion was approved with 14 ayes and 0 nays. One member was absent (NIH—Dr. Alan Guttmacher).

IV. Public Comments

A. Group from Wisconsin

Donna McDonald-McGinn; Anne Bassett, M.D.; Stuart Berger, M.D.; Julie Wootton; Sheila Kambin, M.D.; Michelle Breedlove-Sells; Jack Routes, M.D.

Ms. Donna McDonald-McGinn

Good afternoon and thank you for allowing us to present to you today. So why should the 22q11.2 deletion syndrome be added to the suggested list of newborn screening studies? To address this, we would like to present historical background, prevalence, key features, genetics, natural history and preventable morbidity and mortality, efficacy of screening, patient and family support for this endeavor, and illustrative case presentations, in rapid fire.

Historically, the 22q11.2 deletion has been identified in the majority of patients with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome, and in some patients with the autosomal dominant Opitz-G/BBB syndrome and Caylor cardiofacial syndrome.

However, once FISH was introduced in the early 1990s as the standard diagnostic test, we realized that they were really all the same diagnosis.

Since then, we have found it to be the most common microdeletion syndrome with an estimated prevalence of 1 in 2,000–4,000 live births. It is present in 1 of 68 children born with congenital heart disease. It is the most common cause of syndromic palatal anomalies, and it is the leading cause of developmental disabilities.

Most patients have the same size deletion, A to D, which includes about 50 genes with TBX1, thought to be responsible for many of the phenotypic features. Most deletions occur as de novo events, but even when inherited, it is often a surprise to the parents, with the resultant 50% recurrence risk.

Both sexes and all races and ethnic groups are affected, but African Americans with the 22q deletion may be underdiagnosed due to a paucity of typical facial characteristics, even with high prevalence conditions and in university-based medical centers.

The 22q deletion is a multisystem disorder with the most common significant medical problems, including immune and autoimmune disease, congenital heart disease, and palatal anomalies in three-quarters; hypocalcemia in 50%–65%; renal abnormalities and feeding and swallowing difficulties in a third; hypothyroidism in a fifth; intellectual deficits in greater than 95%; and psychiatric illness in a large proportion.

It is important to note that ascertainment bias affects prevalence estimates of all features.

Less common issues that contribute to significant morbidity include diverse anomalies as listed on your slide and in your packet.

To illustrate these points, we would like to share the story of one child, 13-year-old Louis Cavana, whose mother, Carol Cavana (founding board member of the International 22q Foundation), is here with us today.

Louis was featured in the recent *Journal of Pediatric Guidelines* paper, which you have in your packet, because he has exhibited so many of these features. Born with tetralogy of Fallot, a pink tet, he was discharged on day 3 of life. At home, he had twitching and jerking. His doctors were not concerned, but Carol insisted the pediatrician observe the twitching. Louis was ultimately hospitalized with seizures and a question of stroke. A calcium of 4.7 eventually explained the findings. Then a diagnosis of 22q.

Now a middle school student, Louis is unable to read. Newborn screening could have ensured monitoring and treatment to prevent his hypocalcemic seizures, especially now that guidelines are established.

Dr. Anne Bassett

What are the highlights of anticipatory care? Monitoring for new onset and adequate treatment of hypocalcemia and thyroid dysfunction is extremely important throughout life, especially at times of biological stress, for example, the surgery readily treated with calcium and vitamin D supplements.

We have provocative results indicating that neonatal hypocalcemia without ongoing treatment may be associated with moderate to severe intellectual deficits.

Standard treatments, however, for all the multisystem conditions are readily available, and specialist referrals as necessary. Clearly, early diagnosis and effective treatment improve outcomes, both physical and cognitive, and we have a key example.

Dr. Stuart Berger

I am a pediatric cardiologist at the Children's Hospital of Wisconsin, and I would like to tell you the tale of two patients, both of whom have 22q interrupted aortic arch.

Patient A, diagnosed by echo prenatally, came to our hospital and was started on prostaglandin, had surgery soon after birth, which included a complete heart repair, and was discharged from the hospital.

Patient B, a late diagnosed patient, was discharged from the hospital on day 2 of life without a diagnosis. The patient presented in the emergency room at 9 days of age, had a very complicated resuscitation and suffered a stroke, was transferred to us where the diagnosis of 22q interrupted aortic arch was made, had multiple additional surgeries, had a hospital bill that was $750,000 greater than patient A for the first year of life, and more importantly went home with a stroke and severe neurodevelopmental delay.

This allowed us to go forward and look at some other data. We did a study at our institution of 180 patients with serious congenital heart disease that was ductal dependent. We wanted to look at the impact of early versus late prenatal diagnosis—looking at cardiogenic shock presentation versus no shock, ICU length of stay, amount of time needing drugs to support the heart, amount of time on the ventilator, and hospital charges.

From that study, of the 65 patients who presented early, not a single one of them, zero, presented with shock, whereas of the patients who presented late, 38 out of about 105 presented with shock and all the attendant problems.

Those attendant problems included a longer length of stay in the ICU, a longer duration of needing drugs to support the heart, a longer period of time on the ventilator, and, on the average, of the babies who presented with shock, their hospital charges were greater than $350,000 more than the hospital charges of the babies who did not present with shock. I want to point out that one early diagnosis of this entity would pay for 1 year of screening in Wisconsin.

So I would conclude by telling you that early diagnosis of congenital heart disease markedly reduces morbidity and mortality, early diagnosis of congenital heart disease markedly reduces overall costs. Pulse oximetry is not set up nor is it able to pick up all forms of life-threatening diseases, and I would tell you that, collectively, these data strongly support newborn screening for 22q.

I'd like to move over to talking about a subject beyond cardiac disease, and we would like to introduce Max Wootton. Max is represented here by his mother, Julie, founder of the British children's charity Max Appeal.

Ms. Julie Wootton

Max was born with undiagnosed complex heart defects, which became totally overshadowed by his other problems—necrotising enterocolitis fueled a fatal spiral of events, including idiopathic thrombocytopenia and massive acidosis—that led to his death of septicemia at the age of 4 months.

Anticipation of potential issues rather than continually reacting to crises would, I feel, have improved his chances of survival and, for other children, their chances of achieving their potential.

This makes sound economic and social sense. For this to happen here in the U.S.A. would impact the diagnostic protocols within National Health Service of the U.K.

Now onto the diagnostic odyssey of Aidan, whose mother, Sheila Kambin, an obstetrician, spent 5 years searching for an answer.

Dr. Sheila Kambin

My son Aidan's diagnostic odyssey incorporated 27 specialists over a 5-year period at major medical centers. Despite having 18 findings associated with 22q, Aidan remained undiagnosed. The cost was upward of $500,000, but what cannot be measured in dollars is Aidan's lost chance for early intervention—interventions that I believe could have substantially improved his prognosis.

What would Aidan's IQ and speech be like today if he had come to attention in infancy? We will never know.

I am a parent. I am also an obstetrician physician who has coped with her son's medical diagnosis by medicalizing every aspect of it. I can recite every anomaly associated with this syndrome. I also work on a special delivery unit, which was built to deliver babies with congenital anomalies, specifically with babies with congenital heart disease. I came here to tell you today that I could not reliably make this diagnosis in the delivery room.

Newborn screening is the only solution to this complex problem. Please do right by these wonderful children and recommend adding newborn screening for 22q.

In contrast to Aidan, we will now present Riley Dempster.

Ms. Michelle Breedlove-Sells

At birth, Riley could not handle her secretions, breath, or feed properly, resulting in a tracheostomy and G-tube placement. Her heart was normal but hypocalcemia was present. Riley's father is a celebrity, a baseball player, whose name brought every specialist in the hospital to help with this diagnosis. An astute geneticist made the diagnosis, and Riley's treatment began immediately. The Dempsters, too, have established a foundation, because they want this type of immediate care for all newborns with 22q.

So back to newborn screening. Can it be done accurately, logistically, cheaply? The group from Children's Hospital of Wisconsin has developed a newborn screening test and Jack will share his data.

Dr. Jack Routes

What would be the optimal test for newborn screening for 22q? Well, it must reliably detect haploinsufficiency in the gene TBX1. It should use existing newborn screening cards. It should use technology that the states have in use, which would be amenable to high throughput screening, and it must be sensitive, specific, and inexpensive.

We propose that we have a test in hand that meets all of these qualifications. As you are aware, in 22q there is a deletion in TBX1. Our assay actually picks up the haploinsufficiency in TBX1 by real-time quantitative PCR.

As a proof of concept, we studied 382 infants with congenital heart disease. We were blinded to those infants who had 22q, and we performed a multiplex PCR to determine if our assay can pick up 22q.

As you can see in the red dots, in every single case, we were able to identify children with 22q. The test was 100% sensitive and 100% specific.

So, that's great with congenital heart disease when you have blood. What about with newborn screening using pre-existing newborn screening cards? In conjunction with the Wisconsin State Lab of Hygiene, we used 80 newborn screening cards, extracted DNA from those cards, put it in a 96-well format, and then randomly included DNA from 22q. We were completely blinded to the results on which well was spiked with 22q. As you can see, in the real world we can identify infants with 22q by haploinsufficiency of TBX1.

In summary, we believe we have developed a test that is sensitive and specific for 22q. Our group was in part responsible for initiating a newborn screening for trek, the same technology, approximately the same cost, about $6 per assay, and it is a technology that state labs are familiar with.

So the next question, do people want newborn screening for 22q? The answer is yes.

B. Kristine McCormick, Mother of CHD Baby Cora

Dr. Bocchini and ladies and gentlemen of the committee, my name is Kristine McCormick. I am mom to Cora. It is an honor to stand in front of you today and personally thank you for your diligence, thoroughness, and swiftness in recommending screening for critical congenital heart defects to the universal newborn panel. I would especially like to thank Dr. Rodney Howell for his leadership.

I gave birth to Cora in November 2009 after an extremely healthy and happy pregnancy. She was the picture of good health—or so we thought. A few days after bringing her home, I was feeding her. I looked up for a split second to tell my husband that I loved him. I looked back down and she wasn't breathing. She was grey. She was pale. We jumped into action, called 911, got to the hospital within 5 minutes in our small community, but it was too late. Cora was dead.

We found out from the coroner and later the autopsy report that she had CHD problems with her pulmonary veins. I didn't even know what CHD was, had never heard the phrase. Now a week doesn't go by that I am not contacted by another mom, dad, or friend of a newborn that died at home suddenly and unexpectedly from undetected CHD, babies like Veronica, Max, Sadie, Luke, Nora, Harlow, and, sadly, I could stand here all day and read names.

I commend this committee for its work so far and look forward to the day that every baby is screened for CCHD with pulse oximetry before leaving the hospital. I am impressed by the efforts of individual states, like my home state of Indiana, where every baby is free, but I am not impressed by the e-mails that I get, and the list grows of babies each day, that we aren't screening every single baby. Thank you.

V. Nomination and Prioritization Workgroup Report

Dietrich Matern, M.D.
(Committee Member)
Department of Laboratory Medicine and Pathology

Mayo Clinic
Rochester, Minnesota

The 22q11.2 deletion syndrome (DiGeorge syndrome) was submitted as a nomination for the RUSP. The workgroup reviewed the nomination, and Dr. Matern presented their findings. The proponents for the nomination include Dr. John Routes, Dr. James Verbsky, Dr. Kathleen Sullivan, Dr. Donna McDonald-McGinn, the Jeffrey Modell Foundation, the Immune Deficiency Foundation, the International 22q11.2DS Foundation, and the Dempster Family Foundation. The proponents provided the information presented here on the disease, concerns, and treatment.

- Also known as DiGeorge and velocardiofacial syndromes, the 22q11.2 deletion syndrome is now known to have an identifiable genetic defect. Unlike other conditions in newborn screening, 22q11.2 DS is an autosomal dominant condition, with more than 90% de novo deletion and less than 10% inherited from a parent. Contrary to other newborn screening conditions, this is an autosomal dominant condition. Prevalence of the condition is high at 1 in 4,000 live births. It is pan-ethnic, and the phenotype is highly variable. Major phenotype features include cardiac anomalies, immune deficiencies, palatal defects typically not easily detected, and developmental and mental issues not identified in the newborn period. Treatment is symptomatic, and many patients are born symptomatic.

- Concerns in early infancy for this disorder include feeding, the heart, and hypocalcemia. Later in life, developmental, palate, and infectious concerns are added. Some patients have milder phenotypes, and some patients are undetected until they have a child of their own with the mutation.

- Due to the varied presentations and phenotypes, each patient requires a unique management strategy once diagnosed. The nomination proponents believe coordinated care and comprehensive approaches across the country are possible, but Dr. Matern feels there may be areas where a comprehensive work-up could not be provided. Early interventions for neuropsychiatric needs could lead to enhanced adult function.

- The newborn screening proposed for the disorder is a molecular genetic method using multiplex quantitative RT-PCR for TBX-1 copy number with a 3.2 mm punch per test.

    - There is overlap of screening for 22q11.2 DS and newborn screens already on the uniform panel. Approximately 50% of patients with 22q11.2 DS would be identified through the CCHD pulse oximetry screen. Based on early findings from the SCID collaborative project, we can estimate that the SCID screen will identify the 67% of 22q11.2 DS patients who have T-cell lymphopenia.

- Dr. Matern reviewed the risks and benefits of the screen as outlined in a 2010 article in *Genetics in Medicine*, "Newborn screening programs: Should 22q11 deletion syndrome be added?" He expressed concern about the lack of a prospective study, the limited number of comprehensive treatment centers across the country, and the need for another dried blood spot punch. He suggested consideration of the fact that a significant number of cases will likely be identified through SCID and CCHD newborn screens.

- The workgroup's recommendation is to not yet initiate an external evidence review. The workgroup suggested that the screening proponents encourage a prospective newborn screening study for 22q11.2 DS that tests performance metrics, explores the adequacy of using SCID and CCHD screens to detect 22q11.2 DS, and explores multiplexing the screen with other assays already in use. The workgroup also recommended developing ACT sheets (Dr. Matern noted his

bias as a member of the ACMG workgroup, which works on the ACT sheets) and participation in the Region 4 SCID project.

- Dr. Bocchini invited discussion of the recommendation.
    - Dr. Fred Lorey reinforced Dr. Matern's comments with his own experiences. He encouraged people to enter data for the SCID test and commented that the immunologists agreed that only DiGeorge immunodeficiency would be entered. That means the actual numbers are quite a bit higher. He noted that 700,000 children have now been screened and approximately 10 were picked up with DiGeorge, with 6 of those having immune deficiency. Without exception, physicians had already diagnosed DiGeorge by the time they got to the test. This implies that adding it to the newborn screen will not accomplish much. One of our requirements for adding a test to the RUSP is that the test detect the disorder before symptoms occur. To date no immunodeficient DiGeorge patients have been reported to us.
    - Dr. Bailey emphasized the importance of considering that if this condition were passed forward to the evidence review committee it would probably not pass muster with that group. Dr. Matern added that in the past conditions without a completed large-scale screening study never were approved, so it may be pointless to put it before the group with that missing piece.
    - Dr. Botkin asked if the hypocalcemia manifestations are a critically neonatal phenomenon where the infants need support prior to the neonatal screening results or can it be a chronic, episodic phenomenon that would benefit from newborn screening. Dr. McDonough has five young patients with DiGeorge and said that if they have CCHD it usually is picked up in a timely fashion, but otherwise developmental delays or chronic hypocalcemia or mild to moderate immunodeficiencies develop. Dr. McDonough asked if the Advisory Committee could advise the funding agencies to expedite the larger population research. Dr. Copeland replied that the Advisory Committee can provide the advice but that does not mean it will result in action.
    - Dr. Michael Watson expressed confusion about Dr. Lorey's restriction to DiGeorge syndrome. Many affected children have both T-cell lymphopenia and congenital heart disease that falls out in both screenings, but the papers you reviewed did not address this. Since both phenotypes may occur in the same patient, it may not be an additional 50%.
    - Dr. Greene made several comments for the record. First, she pointed out that "not diagnosed" does not mean "not symptomatic." Second, because most children with 22q11.2 DS do not have autoimmune deficiency, the trek testing will not pick up a substantial proportion of children who will need treatment. Third, the heart defects of many of these patients are not cyanotic, so they will not by picked up by the CCHD screen. Fourth, this is a condition that clinical geneticists know how to deal with in concert with pediatricians across the country.
    - Dr. Matern reiterated that the problem with the existing statistics is that no prospective studies have been conducted and that we do not have enough information yet from the SCID testing states on how many cases are being picked up.
    - Both Drs. Botkin and Lorey encouraged finding ways to improve data collection from the SCID screening. One of the reasons it may be poor at this point is that a lot of information is requested, making it very time consuming to enter it. However, it has the potential to be an extremely valuable resource.

- Dr. Stuart Berger asked to be on record supporting pulse oximetry screening. He added, however, that there are forms of 22q and CHD that will not be picked up by this screening.
- Dr. John Routes, lead author on the *JAMA* article for SCID newborn screening, is very familiar with the Wisconsin data. Babies who were not diagnosed have been picked up with 22q11.2, but it is not a test suitable for picking up 22q11.2 nor was it designed to be suitable for this. The majority will be missed, and only those with "complete DiGeorge" will be picked up by the trek assay. The real-time assay is both sensitive and specific, with a positive predictive value of about 50% and a very low false positive incidence.
- Dr. Anne Bassett reiterated that a marked minority of patients with 22q11.2 DS have severe immune deficiency or serious genetic heart defects. Yet, with better screening and earlier intervention, multiple associated conditions could have been treated or prevented. Most important, neurocognitive deficits can be ameliorated with early intervention. Hypocalcemia cannot be picked up with any of the existing screenings.

- Dr. Bocchini summarized the intention of this discussion—to determine whether the 22q11.2 DS condition meets the criteria to go forward to the evidence review committee.

MOTION (APPROVED): To not initiate the evidence review of 22q11.2 deletion syndrome at this time. Dr. Dietrich Matern so moved and Dr. Fred Lorey seconded the motion. The motion was approved with 14 ayes and 0 nays. One member was absent (NIH—Dr. Alan Guttmacher).

- During discussion of the motion, prior to the vote, Dr. McDonough offered a modification to the motion with a request to encourage additional research and a prospective study on the benefits of early detection with special consideration for the neurocalcium and developmental issues. After committee discussion, this modification was withdrawn.

Friday, January 27, 2012

Dr. Bocchini requested a roll call.

- The following voting members were present at roll call: Don Bailey, Joseph Bocchini, Jeffrey Botkin, Coleen Boyle (CDC), Sara Copeland (HRSA/MCHB), Denise Dougherty (AHRQ), Alan Guttmacher (NIH), Kellie Kelm (FDA), Stephen McDonough, Dietrich Matern, Catherine Wicklund, and Andrea Williams.
- The following members joined the meeting following the roll call: Charlie Homer (via phone), Fred Lorey (via phone), Michael Lu (HRSA/MCHB), and Alexis Thompson.

VI. Subcommittee Reports

A. Subcommittee on Laboratory Standards and Procedures

Sara Copeland, M.D., Committee Member

- The subcommittee had a lengthy and excellent discussion about Dr. Stuart Shapira's preliminary data from a retrospective study on second screens. The study's findings show a higher incidence of congenital thyroidism (CH) in the two-screen states, a two-to-one female-to-male incidence for CH, and a birth weight and feeding method difference in CH incidence. The purpose of the

second screen study is to look at how thyroid and congenital adrenal hyperplasia are picked up and what the differences are. A point of interest is that a higher proportion of Hispanics are picked up on the second screen. The status of the second screen study is that they are cleaning up the data, modeling the cases, and evaluating the clinical significance of those detected on the second screen. It is a retrospective study so there are limitations due to long-term follow-up and missing data. Dr. Shapira plans to present an update to the subcommittee in May and to the full committee in September.

- The subcommittee members discussed several standing items. The National Library of Medicine is ordering the standardized list of LOINC codes (116 mutations) for cystic fibrosis. They are developing codes for hemoglobinopathy reporting in conjunction with newborn screening programs, with accommodation for diagnosis confirmation. CSLI guidelines are being used to develop results reporting terminology as well as to look at reasons for lab tests. They are working hard on developing robust datasets.

B. Subcommittee on Education and Training

Don Bailey, Ph.D., Committee Member

Dr. Bailey reviewed the charge of the subcommittee and the goals of their meeting, which were to (1) review current activities, (2) review their charter and discuss possible links with other subcommittees, and (3) discuss future education and training needs.

- Current activities of the subcommittee include the following:
    - The phase 1 media scan of HRSA's newborn screening awareness campaign, which came out of a recommendation of this subcommittee, has been completed. The next step is a strategy planning session, to be held in March or April. The subcommittee has two questions about the campaign: (1) What problem are we trying to solve with this campaign? Dr. Bailey thinks the campaign is trying to raise public awareness of the newborn screening enterprise, but the issues of storage and use of dried blood spots cannot be ignored and require a careful approach. (2) How can we sustain momentum and convert campaign activities into enduring day-to-day practices?
    - The plans for the upcoming 50th anniversary of PKU screening provide a national opportunity to highlight newborn screening. CDC is leading the planning, and APHL has a leading role in the implementation of the activities. Activities planned for the next 18 months include media campaigns and webinars, with a culminating anniversary celebration in 2013 at a joint meeting of APHL and the International Society of Newborn Screening in Atlanta. Dr. Bailey encouraged everyone to attend.
    - In their second round, the Genetic Alliance's Challenge Awards have double the number of applicants, and they come from a diverse set of constituencies. Awards will be announced formally in February, and Dr. Bailey asked Ms. Natasha Bonhomme to disseminate the list of awardees to committee members at that time.

- In terms of health professionals, the Genetics in Primary Care Initiative (GPCI) has been funded for 3 years by HRSA and MCHB, with Drs. Beth Tarini and Robert Saul as co-principal investigators. The vision of GPCI is to increase the knowledge and skills of primary care physicians when providing genetic-based services. To meet its first goal, GPCI will mobilize a community of learners through change packets on key topics. To meet its second goal of accelerating the provision of genetic medicine through a technical assistance center, a website will house key information about genetics for primary care physicians. The third goal is to embed genetics training in residency programs.

- NCHPEG is developing a questionnaire that will help primary care providers develop and evaluate family history and genetic screening. A database is being developed to evaluate the effectiveness of the survey.

- Because parents, the public, and health care professionals constitute a very large audience, the subcommittee will carefully review their activities and strategies to ensure they are not missing other important big picture initiatives. To provide a broader perspective, the subcommittee would like to add a representative of the parent and public community as a member.

- The subcommittee recommended the Advisory Committee develop advocate-friendly materials for groups that bring their conditions to SACHDNC for review. The materials should provide a clear understanding of the Advisory Committee's process to help advocates maximize their efforts.

- Next steps for the subcommittee include the following.

  - The subcommittee is pleased to note that several health professional projects underway have an evaluation component.

  - In addition to working on the core competencies for residents, it will be key to include the faculty members who implement information in residency training programs as a target audience when preparing or making changes in those areas.

  - The subcommittee would like a nursing professional added to its roster. Ideally, the Advisory Committee will add a nursing liaison to its ranks and assign that person to the education subcommittee.

  - There is some appeal in having the subcommittee endorse particular products that promote education and training in the field, but there are many groups developing materials and the quantity could become problematic.

- Dr. Bailey invited comments and questions.

  - Dr. Dougherty asked whether, in the cooperative agreement with the APA, the GPCI has a relationship with American Board of Pediatrics Foundation. The foundation has the maintenance of certification responsibility, and they encourage pediatricians to do a lot of quality improvement and measurements. She suggested developing a project to encourage primary care physicians to talk about newborn screening results during the first visit. Dr. Tarini commented that this would be a good link because the most recent large QuIIN project was about newborn screening with a focus on communicating normal results to parents.

- Dr. Cindy Hinton noted that CDC funded the American Academy of Pediatrics (AAP) to develop an EQuIP training module on newborn screening. Designed to develop quality improvement protocols using the ACT sheets, it focuses on closing the loop for all newborn screening results. Now, as part of the MOC, pediatricians can use it to develop practice protocols that ensure every newborn coming into their practice has been screened and every result has been discussed with the families.

- Dr. Boyle reminded the group that the original intent of the awareness campaign was to desensitize the issue of newborn screening so that families would expect it, want it, and considered it an essential benefit.

- Dr. Lorey raised a looming concern. In response to public concern, government agencies have been assuring the population that all DNA is destroyed at the end of the test, not stored. However, GWAS now wants researchers who are providing data to upload it to dbGaP for anybody to use, which means we lose complete control of what others are doing with it. Dr. Alan Guttmacher explained that some, but not all, studies funded by NIH require data deposition. Part of the equation is the broader principle that the data does not belong to the principal investigator and needs to be shared with the research community for the public good. Yet there is recognition of issues of compromising confidentiality. Issues of the balance of safeguards and availability continue to be studied.

- Dr. Copeland advised the subcommittee to wait until the larger committee has developed an organizational process for adding new members, such as a nursing liaison.

C. Subcommittee on Follow-up and Treatment

Coleen Boyle, Ph.D., Committee Member

The subcommittee's focus is on newborn screening implementation beyond short-term follow-up, making sure children who are identified through newborn screening are provided the appropriate services and that those services are equitably distributed. The subcommittee sees its role as that of staying abreast of implementation and how it is carried out. Committee members are concerned about the disconnect between having a fair and equitable mandate for screening but having no mandate for follow-up and treatment.

- One area of considerable activity has been providing guidance in the area of medical foods.

  - In presenting NIH-related activities around medical foods to the subcommittee, Ms. Kathy Camp noted that a December stakeholder's workshop focused on identifying gaps in the safety and efficacy regarding inborn errors of metabolism. In February, an NIH meeting will be held to update the NIH consensus statement around PKU.

  - Ms. Christine Brown updated the group on the issue of reimbursement for medical foods, an issue that the Advisory Committee has brought to the attention of the secretary numerous times. There is concern, in context of the Affordable Care Act and the essential benefit package, that medical foods may not be adopted at the state level. States will have the flexibility to choose from four options; given the choices, states that currently have coverage will most likely continue to have coverage, and those that do not probably will not. The subcommittee will continue to watch this issue and try to remain informed about the process.

- Dr. Sue Berry has completed the manuscript of an article that describes the use of medical foods within the context of families receiving services, attempting to identify the limits of insurance coverage. This article will be brought to the Advisory Committee for further discussion.

- Dr. Deborah Badawi of the Maryland health department presented their experience implementing the CCHD screening at the state level to the state legislature in January. It behooves the Advisory Committee to stay in tune with how implementation rolls out for new conditions on the RUSP.

- The panel's recommendations are that hospitals should follow the protocol that Dr. Alex Kemper put forward. They also laid out the roles and responsibilities as follows: the birth hospital is charged with screening and follow-up; all hospitals have capacity for screening but they must establish capacity for follow-up; hospitals are responsible for protocol for follow-up and clinical management; and the health department is responsible for surveillance of screening data and evaluations. No one is identified to take responsibility for the education component. The main cost of the program is staff time to screen and state infrastructure for evaluation. To date, they have not received negative push-back from any of the hospitals.

- In order to show by example how to clarify roles and responsibilities in follow-up and treatment, subcommittee members considered illustrating it with sickle cell disease, where a gap in the disparity of survival needs to be closed. There is a considerable federal investment in sickle cell and it would, be great to help align that investment with filling the gaps.

- On a final note, Dr. Boyle suggested that the subcommittee develop a process and methodology to determine, prioritize, and guide its work. In response, Dr. Copeland suggested that it be the role of the Advisory Committee to charge the subcommittee with its work rather than the subcommittee choosing. There was general agreement on this point.

VII. Hyperbilirubinemia

A. Final Report from Evidence Review Group

James Perrin, M.D., External Evidence Review Workgroup Member
Professor of Pediatrics, Harvard Medical School

By way of review, Dr. James Perrin reported that elevated bilirubin is common in newborns and arises from many etiologies. Hyperbilirubinemia is a detectable risk factor for acute bilirubin encephalopathy (ABE) and chronic bilirubin encephalopathy (kernicterus). The primary concern of screening and treatment is to prevent the neurotoxic effects of hyperbilirubinemia.

- The workgroup reviewed two key publications. Clinical practice guidelines, published by the AAP in 2009, made recommendations for the prevention and management of hyperbilirubinemia. The main recommendations were to promote and support successful breastfeeding, systematically assess the infant before discharge, provide early follow-up based on the risk assessment, and provide phototherapy and exchange transfusion when indicated. The second publication, a 2009 USPSTF report, indicated that evidence to support routine screening for hyperbilirubinemia was lacking.

- The workgroup developed three case definitions, one for neonatal hyperbilirubinemia, one for ABE (limited to advanced manifestations), and one for kernicterus (persistent and permanent brain damage from bilirubin toxicity).

- Since its last presentation to the Advisory Committee, the literature review has been updated (to October 2011). They reviewed 3,075 abstracts and 201 articles; 112 articles met the inclusion criteria. About half of the studies were case series. There were a few more experimental intervention studies for this condition than for other rare conditions this committee has reviewed, but still a very small number.

- The incidence rates of ABE and kernicterus show they are relatively uncommon phenomena. While higher levels of neonatal bilirubin are associated with higher occurrence of ABE and kernicterus, there is no specific level of bilirubin associated with either condition.

- The three current forms of screening for hyperbilirubinemia are visual assessment, TcB, and TSB. TcB is good at detecting high levels of bilirubin, but not at lower levels. A number of studies document that phototherapy effectively lowers levels of bilirubin in neonates, but only indirect evidence indicates that screening and phototherapy decrease kernicterus. Early treatment with phototherapy diminishes the need for exchange transfusion. After exchange transfusion, adverse events remain common.

- As is true in other condition reviews, economic information on conducting the screenings is very limited. The estimated cost of doing TcB testing ranges from less than $1 to $7.80, with most in the lower range. The estimated cost per case for preventing kernicterus using TSB is $5–6 million and using TcB is more than $9 million.

- The harms of universal predischarge screening are relatively minor and limited. The benefits include identification of newborns who are likely to develop high levels of bilirubin and, through early identification, providing phototherapy which may prevent future need for exchange transfusions and hospital readmission.

- When compared with controls, newborns with increased bilirubin levels experience an increase in acute clinical manifestations. There is fair evidence that adding TcB to visual assessment increases screening sensitivity, thus diminishing the need for TSB blood draws. The evidence does not address whether the predischarge prediction assessment decreases the incidence of kernicterus. The workgroup was not able to identify any data that predicted whether screening for neonatal hyperbilirubinemia prevents kernicterus. While early intervention for hyperbilirubinemia is associated with better outcomes, there is no evidence that treatment prevents kernicterus.

- Gaps in evidence include no clear relationship between specific bilirubin levels and kernicterus, no clear evidence that treating neonatal hyperbilirubinemia prevents kernicterus, no evidence regarding the impact of large-scale screening efforts, and no evidence regarding the cost-effectiveness of the screening.

- Dr. Bocchini opened the floor for discussion.

    - In response to a query about the use of EcT, Dr. Perrin noted that it is rarely done now, so the high mortality associated with it is not a critical issue for this discussion.

- Dr. Botkin asked if the literature provides a better description of the children who end up with kernicterus. Dr. Perrin noted that the samples are very small, but that perhaps two-thirds have high bilirubin levels and the others have any of a number of risk factors. Dr. Lisa Prosser noted that the screening will not find all cases of kernicterus.

- Dr. Chen asked about the workgroup's feedback on efforts to harmonize the evidence review process with other agencies such as USPSTF. Dr. Perrin noted that there was considerable collaboration in their efforts with the USPSTF and that their workgroup benefited greatly from their wisdom; however, the evidence procedures differ substantially due to the limited evidence available for extremely rare conditions. Dr. Kus requested a summary of the differences in the evidence review processes of this committee and the USPSTF. There are two main differences: (1) where a number of studies would be withdrawn from review by the USPSTF, this workgroup included them for review, recognizing their substantial limitations; and (2) the workgroup made the grade criteria more lenient, allowing inclusion of case series.

- Dr. Greene recited the evolution of this screen and how it came to this committee. The question is now coming back to the role of public health, but perhaps it should not be framed as part of newborn screening. With the Advisory Committee's new decision matrix, there is room for a different type of recommendation whereby we can recommend that every baby have the test without it being part of newborn screening. Dr. Bocchini concurred, explaining that we now have the option to move this forward for public health impact analysis.

- Dr. Michael Lu asked about evidence of cost savings with this screen. Dr. Prosser explained that this type of analysis was not done with the review group due to the paucity of evidence available. However, with what little evidence there is on this topic, it is likely that universal screening will require an additional investment rather than save money. The question then becomes whether it is worth the investment.

- Dr. Watson recommended the Advisory Committee look into how its recommendations affect state-level infrastructure of nursery-based screening.

B. Discussion

Catherine Wicklund, M.S., C.G.C., Advisory Committee Member
Alexis Thompson, M.D., Advisory Committee Member

Dr. Bocchini asked Ms. Catherine Wicklund and Dr. Thompson to attend the final discussions of the evidence review group, then frame the discussion for us based on the new decision-making template, and then provide some preliminary recommendations.

- Ms. Wicklund explained that she and Dr. Thompson independently reviewed the workgroup's document, giving attention to the key questions. They then discussed it together and made independent conclusions on the recommendation. It so happened that they were in agreement. They reviewed the key questions using kernicterus as the defining outcome in their presentation.

- 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? There was no direct evidence that screening for neonatal hyperbilirubinemia prevents kernicterus.

- Is there a case definition that can be uniformly and reliably applied? There is a clear definition of kernicterus. What are the clinical history and the spectrum of disease of the condition, including

the impact of recognition and treatment? Incidence rates vary due to factors used to characterize ABE and kernicterus. The spectrum of conditions is not well defined. Evidence for long-term outcomes other than kernicterus is limited and inconsistent.

- Is there a screening test or screening test algorithm for the condition with sufficient analytic validity? TcB appears to be a reliable screening tool for detecting significant hyperbilirubinemia, requiring confirmatory follow-up with TSB. Screening has been associated with a lower incidence of hyperbilirubinemia.

- 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? Newborns with increased TSB levels experience an increase in acute clinical manifestations, but evidence of linkage with kernicterus is insufficient.

- What is the clinical utility of the screening test or screening algorithm? The clinical utility is unclear. Earlier treatment with phototherapy decreases the likelihood of EcT, and treatment lowers TSB, but limited evidence exists that treatment actually prevents kernicterus.

- How cost effective is the screening, diagnosis, and treatment for this disorder compared to usual clinical case detection and treatment? The question cannot be answered due to a lack of data.

- Both Ms. Wicklund and Dr. Thompson concluded that the magnitude of net benefit of implementing a policy of universal screening for hyperbilirubinemia was minimal, but they were unable to determine whether it belonged in category 3 or 4 of the decision matrix. The struggle revolved around whether the condition, which clearly needs more research, would come back to the Advisory Committee for review after additional evidence is generated or it is better framed as a practice guideline and thus outside the purview of this committee. This is an important consideration in helping advocacy groups direct their efforts effectively.

- The floor was opened for discussion.

    - While agreeing with the assessment of the data, Dr. Botkin expressed concern about the idea of not allowing the condition to come back to the Advisory Committee for future consideration. For example, if future randomized control trials show definitive benefits and limited harms, he believes the Advisory Committee should reconsider the condition. Similarly, Dr. Matern expressed concern that professional organizations, such as the AAP, might interpret a negative decision from the Advisory Committee as an indication that the condition no longer merits consideration. Dr. Thompson reiterated the opinion that perhaps this is better suited to practice standards than the universal screening panel. The important thing is that it happens somewhere as part of good medical care. Dr. Kus expounded that if future evidence showed that screening prevents kernicterus, it would need to come back to this committee for RUSP consideration. Dr. Anne Comeau (UMass medical school) commented that the decision matrix was put together very thoughtfully and she does not believe level 4 was meant to preclude the condition from review with new evidence.

    - Dr. Lu raised a concern about insurance coverage for the screen. If it were a clinical standard, the screen might not be covered, but if it were a recommendation of the Advisory Committee, it would be covered. Dr. Chen noted that screening for hyperbilirubinemia is a mainstay of clinical practice and he is unaware of any insurer not covering screening and clinical care.

    - Dr. Lorey emphasized the importance of considering public health aspects of the screening.

MOTION (APPROVED): Screening for hyperbilirubinemia to prevent CBE most appropriately should be category 3. Dr. Alexis Thompson so moved and Dr. Denise Dougherty seconded the motion. The motion was approved with 15 ayes and 0 nays.

VIII. Report: Improving Data Quality and Quality Assurance in Newborn Screening by Including the Blood Spot Screening Collection Device Serial Number on Birth Certificates

Brad Therrell, Ph.D.
National Newborn Screening and Genetics Resource Center
Austin, Texas

About 2 years ago, the Subcommittee on Follow-up and Treatment initiated a look at how to link the babies born with the babies screened. After presenting the information, the Advisory Committee asked for a white paper laying out recommended changes to birth certificates that would facilitate such a link.

- All states require newborn screening and birth registration, but the two programs do not necessarily interact. Thus, states frequently cannot report how many of their babies are screened. As electronic health records become prevalent, there is an opportunity to link the records, greatly facilitating reporting.

- Challenges to doing this include spelling variations in the names recorded, lack of timely records completion, and differing tracking systems and infrastructure for each element.

- Record matching can be done manually or electronically. Although difficult, there are some smaller states that currently match the records manually. Electronic matching can be done either deterministically (exact match, the more difficult of the two) or probabilistically (statistical matching of fields, the method most frequently used). The simplest method to match records would be to record the newborn screen dried blood spot serial number on the birth certificate and link the two databases.

- Other benefits of linking the databases include the ability to confirm the specimen collection, linking with other databases, and creating a mechanism for validating patient demographic data.

- Currently, 96% of states have electronic birth registration. Eleven of those states have a field in the birth registration that collects the dried blood spot serial number, and four states plan to add that. Five states use the field to assess compliance with the screening requirement. Thirty-three states are trying to link their databases. There is considerable variation in matching time.

- Originally, the recommendations were fairly stiff, and the subcommittee was asked to modify them based on discussions with the groups that would be affected by them. While most states generally support the idea, it is not always prominent on their radar screens. Were the Secretary to support it, there would be a better chance of it happening.

- The four recommendations are straightforward. Many states have already implemented the reporting at no extra cost, rolling it in when they were making other routine updates to the system. NAPHSIS estimated that adding this in discretely could cost $25,000–30,000.

- The SACHDNC should encourage state newborn screening programs to utilize a unique serial number on each initial newborn screening specimen collection device to aid in electronic tracking and identification. To facilitate national harmonization, the format of this number should follow that recommended by the national standard for collection of dried blood on filter paper, including strong consideration of a checksum character as an aid in assuring the quality of the computerized input of the serial number.

- SACHDNC should work with NAPHSIS toward a goal of including the newborn screening serial number on the birth certificate to facilitate confirming access of all newborns to timely newborn screening and to provide an external mechanism for evaluating certain demographic data recorded on the birth certificate. The use of these data for improving electronic health information and service quality should be emphasized.

- SACHDNC should work with NCHS toward a goal of including a field for the newborn screen serial number in the next revision of the U.S. Standard Certificate of Live Birth to be recommended to the Secretary of Health and Human Services. Inclusion of this field should be required inasmuch as newborn screening is a required activity in all states and comparison of birth certificates to specimen records represents the most efficient way to confirm screening universality.

- State birth registrars and state newborn screening program directors should be encouraged to consider ways in which electronic data validation of the demographic information collected by the two activities can be used for cross validation and data quality improvement.

- The Advisory Committee members were invited to comment.

  - Dr. Bailey inquired about whether these data would reside at the state level or be amalgamated at the national level. Dr. Therrell replied that a national database is highly unlikely due to the logistics of coordinating state-level programs. However, a field in the database that records persons' moves from state to state is in the plan.

  - In response to a question about birth records in this system that are missing numbers, Dr. Therrell explained that a missing number would be a trigger for a health care provider to do the screening immediately. There would need to be a mechanism on the birth certificate to indicate whether parents opt out of the screening.

  - There will always be persons who are concerned about the government having data on their babies. We need to make this an educational goal. These programs are for the benefit of the baby and this is a way to check that each baby is getting the services it is due.

  - Dr. Lorey reported that his state currently matches these records manually and are anxious to implement the electronic system, but they get resistance from the vital statistics department. A formal recommendation would help.

  - Dr. Chen requested that the group bear in mind the implications this might have for undocumented parents and their babies.

  - Dr. Thompson asked whether funding is a significant barrier to states implementing the serial number. Dr. Therrell believes it is not a barrier because most states wait to add the field when they are making other updates; however, depending on the interests of those involved, the cost could be viewed as a barrier.

- Several committee members expressed interest in hearing from the states that have implemented this already.
- An audience member from Massachusetts noted that, as a person extremely concerned with privacy issues, he is not concerned about privacy in this situation because both the electronic birth certificate and the paper filter already exist as government databases. He also noted that the resistance they are getting is based on the workload, not privacy or cost concerns; a recommendation from a higher level would help in this area.
- Dr. Lisa Feuchtbaum, California, expressed the opinion that the format of the number does not need to be universal across states.
- Dr. Bob Bowman, Indiana, says it will affect the vital records program more than the newborn screening program. He has also run into implementation concerns with transfer babies and babies with religious waivers.

- Dr. Bailey reminded the group that the primary problem we are trying to address is finding babies who have not been screened, and the secondary problem is how states will meet an impending requirement to report the number of babies they have screened. The Advisory Committee's recommendation could be less specific and simply state that every state needs to put in place a policy that assures a check between babies born and babies screened.

- Dr. Thompson raised the issue of people coming back in later years and asking about their sickle cell trait status. Linking the newborn screen to the birth certificate provides a lifetime tie and could be useful in clinical management. This could eliminate the need to re-test persons.

- Dr. Copeland suggested Dr. Therrell move ahead with the paper after modifying some of the wording.

Dr. Bocchini delineated two issues for committee attention: (1) the set of four recommendations that require an Advisory Committee vote and (2) crafting language for a letter to the secretary that does not overstep our boundaries as an advisory committee.

MOTION (APPROVED): Regarding product support for bloodspot screening collection device number on birth certificates, Dr. Stephen McDonough moved **level 1 on all four recommendations**. Dr. Jeffrey Botkin seconded the motion. Committee members discussed issues of privacy, linking numbers, and immigration concerns prior to voting. The motion was approved with 9 ayes, 0 nays, and 6 abstentions (Dr. Charles Homer, AHRQ—Dr. Denise Dougherty, FDA —Dr. Kellie Kelm, CDC—Dr. Coleen Boyle, HRSA—Dr. Michael Lu, and NIH—Dr. Alan Guttmacher).

IX. Report: Implementing Point-of-Care Newborn Screening

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Subcommittee on Follow-up and Treatment Member
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Dr. Nancy Green summarized the manuscript on point-of-care newborn screening that was prepared on behalf of the Subcommittee on Follow-up and Treatment. The full article is in the briefing book. The article defines point-of-care screening as screening that takes place at or near the site of patient care. It also provides background about making decisions about whether a condition should be added

to the RUSP. The authors tried to approach this topic from the public health point of view, but also considered issues for the provider, the newborn nursery, and the public.

- Approached as an essential public health activity, the article lays out the criteria for inclusion in point-of-care screening. In addition to the usual considerations for screening, point-of-care screening criteria includes the urgency of recognition and treatment and whether the screening is physiologically based. The overall guiding principle is the ability to provide better outcomes.

- The feasibility of point-of-care screening depends on several considerations, making a single approach difficult. Factors for consideration include the condition itself, potential state legislation, risk of missed cases, complexity of the screening paradigm, extent to which screening is already part of standard care, the challenge of confirmatory diagnosis, and potential for variability in screening and diagnosis.

- For public health, roles and responsibilities include assurance of quality and feasibility of statewide implementation, surveillance, integration of systems, assessment of impact on clinical care, and public communication. It is important to understand that the roles and responsibilities for providers and nurseries are not the same. Infrastructure is needed for both providers in the nursery and pediatricians involved in providing care immediately after diagnosis.

    - Issues of concern include the practicality of adding to an overloaded nursery environment, cost involved in screening and implementation, and assessment of the effects on routine care. Nursery procedures have many stakeholders, so there needs be careful coordination and collaboration amongst them to avoid disparities.

    - The birth hospitals have responsibilities for providing high quality, standardized screening equipment. They also would have to employ personnel to do the screening and provide standardized techniques for performing and recording the screen and for communicating the results.

- These issues likely have implications for screening beyond the newborn nursery.

- The subcommittee seeks Advisory Committee support of the manuscript. In addition to sharing it with the Secretary as an informational document, members would like to submit it to a peer-review publication.

MOTION (APPROVED): To support the point-of-care report under category 2. Dr. Jeffrey Botkin so moved and Dr. Stephen McDonough seconded the motion. The motion was approved with 14 ayes and 0 nays. One member was absent (Dr. Charles Homer).

For future consideration, Dr. Botkin suggested the Advisory Committee draw up formal guidelines that would address whether a particular point-of-care screening should come before this committee or would be better suited to another professional body that makes recommendations on standards of care. Factors to consider could include aspects of the condition, funding, or politics. Dr. Copeland noted that any group may bring a condition forward to this committee; hopefully, the public health impact analysis will be robust enough in the condition review to adequately address this. If we can get a condition review process in place that is closer to that of the Community Guide and the NSPSTF, we will be able to experience more reciprocity between the groups.

X. CCHD

A. Federal Plan of Action for CCHD—Update

Coleen Boyle, Ph.D., Committee Member
Centers for Disease Control and Prevention
Atlanta, Georgia

When the Secretary went forward with the Advisory Committee's recommended CCHD screening, she charged each agency with specific tasks.

- NIH was charged with conducting research to advance the technology for identifying infants with CCHD and to analyze outcomes related to care and treatment. As part of their research network, NHLBI has a tool for coding and classifying congenital cardio malformations. Their pediatric heart network has assessed the current CCHD practices of nine clinical sites and could serve as a venue for evaluation of screenings.

- HRSA was charged with helping state health departments implement screening and education. They are providing 3 years of funding for six demonstration projects for state implementation of CCHD. They are assisting the Newborn Screening Clearinghouse and NHLBI to develop educational materials on the website and providing technical assistance to the National Newborn Screening Genetics Resource Center.

- CDC was charged with ongoing evaluation and surveillance tracking, looking at cost effectiveness, and leveraging electronic records. All the state programs have been surveyed twice to determine their capacity. This week, Epidemilogical Aid in New Jersey started analyzing the data flow and tracking in the hospital and following up on missed screens. In the spring, CDC will host a webinar to provide technical assistance to states. To build capacity to offer economic aid, CDC will assess the cost to the hospital of implementing newborn screening.

B. New Jersey—CCHD Implementation

Lorraine Garg, M.D.
New Jersey Department of Health and Senior Services
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New Jersey was the first state to pass legislation mandating pulse oximetry screening for newborns to detect CCHD. The unfunded legislation was signed in June 2011 and enacted August 31.

- Hospitals were mandated to screen, as they deemed best, every baby born in their facilities. Because it is a point of care test, the New Jersey Department of Health and Senior Services decided not to conduct active follow-up of abnormal results, leaving that task to the hospital. Initially charged with developing best practices guidelines, the newborn screening services division decided that an expanded role was necessary to support and guide implementation.

- The first step the health department took was to convene a workgroup made up of cardiologists, neonatologists, pediatricians, midwives, nurses, parent advocates, etc., and department of health representation. The group's goal was to develop a recommended protocol for hospitals to use.

- The department produced two webinars. The first webinar provided an overview of CCHD, pulse oximetry screening, and the protocol. The second discussed data collection and reporting.

- Initially, a lot of time was spent determining how to collect individual level data on babies, and the data system was not up and running until about 2 months after implementation. New Jersey is on board to implement an electronic birth certificate, and they anticipate collecting individual level data through it in the near future. In the meantime, quarterly aggregate data on the number of births and the number of babies screened are collected from hospitals, and failed screens are captured (with nurse follow-up) from the birth defects registry.

- Prior to implementation, 17% of hospitals did not have access to echocardiograms. Children born in those facilities who failed the screen would need to be transferred to another facility. Two months post implementation, all hospitals reported using the recommended protocol and that the implementation was going smoothly. The biggest difficulty has been developing a mechanism for tracking screened babies—some have incorporated it into existing electronic medical records, but others must use paper and pencil logs.

- One of the biggest challenges has been the 90-day implementation period. While the program did get up and running on time, they now are having to do work that ideally should have been done prior to implementation. The unfunded mandate has put a stress on staff members and has affected the speed with which they can move forward. Other challenges arise from not being able to screen all babies (e.g., NICU babies) in the same quarter they are born in, the need for intensive training and educational materials, and ongoing quality assurance.

- Program strengths include the speed with which the program was up and running. More than 95% of infants were screened in the first quarter and they anticipate this number improving.

C. Indiana—CCHD Implementation

Bob Bowman
Indiana State Department of Health
Indianapolis, Indiana

In June 2011, the Indiana State Department of Health was informed that a bill to include congenital heart defects on Indiana's newborn screening had been added to state law. The health department was to give a report to the legislature on October 31 and be prepared to implement statewide screening effective January 1, 2012. The department would be responsible for developing a tracking and surveillance component as well as for the diagnostic and follow-up activities.

- The health department quickly identified five items it needed: (1) the complete SACHDNC recommendations (difficult because Dr. Kemper's paper had not been released yet); (2) an understanding of the capacity of Indiana's estimated 100 birthing centers to perform the screen; (3) feedback from Indiana's 24 pediatric cardiologists on how this change would affect them; (4) an understanding of how the birthing facilities felt about this screening and an attempt to engender collaboration with them; and (5) an understanding of what data would be collected and how it would be collected. The latter was a task that could not be addressed fully by January 1.

- First, they developed a list of neonatologists, nurses, pediatric cardiologists, and birthing facilities with whom they needed to develop rapport. Then a survey was sent out to determine the status quo and capacity of facilities for pulse oximetry screening. The survey results indicated that, of the facilities that responded (roughly half), capacity existed to do the screening and 58% could perform echocardiograms if needed.

- Once Dr. Kemper's paper was published, the protocol was reviewed with physicians, and there was consensus that it could be implemented statewide. Questions remained about how to handle

NICU and premature baby screening, and ultimately it was determined that each birthing facility would develop its own protocols for these infants. Pediatric cardiologists were concerned about how false positives would be handled, especially in the case of transferring to another facility, and as of yet this is unanswered and left to individual facilities to determine. By October, the protocol had been posted to the health department's website, a sheet of frequently asked questions had been developed, and the monthly submission of the data was being addressed.

- The Indiana Newborn Screening and Tracking Education Program (INSTEP) is an integrated data system that links birth certificates, newborn screening results, and hearing screening results. Because it is a modulized system, the programmers were able to quickly develop a new module for CCHD. Modeled on the hearing screen report, the CCDH report asks for information on the infants who do not pass the screen (e.g., where they are referred to, whether they are transferred to another facility) and infants who do not receive the screening (e.g., parent refusal, religious waiver).

- In the second survey, the health department sought to ascertain whether everybody had been alerted that pulse oximetry screening would go statewide January 1 and to make sure that they had some sort of protocol in place for referrals. As of December 27, 94 birthing facilities had indicated "yes" to both these items. In response to this survey, almost 47% of facilities reported that they would do the echocardiograms in their own facility, which is lower than the first survey. Based on the feedback, the health department updated the religious waiver form, updated the website for professionals with CCHD information, and created a parent education sheet for CCHD screening.

- Indiana's program has encountered a problem in that, although each birthing facility has an individual who can log into the state health department's Web-based application to enter information on the heel stick and hearing screenings, some facilities have designated a different person to report the pulse oximetry screen. Until the health department can get training programs implemented, this requires some distribution of paper forms that are faxed back to the state health department for entry.

- The state's long-term goal is to have all the screening information for each child readily available to pediatricians when the child is in their office. The health department considered adding the pulse oximetry results to the already crowded blood spot card, but have instead contracted with a vendor to obtain the results directly from the screening equipment.

- The health department's dilemma is that the CCHD screening legislation addressed neither diagnosis nor follow-up. In order to follow the outcomes for the newborns, the state considered linking to the birth defects registry, but it is not efficient and timely enough for CCHD problems. The plan now is to use the birth defects registry information to ensure that children who did not pass the screen receive follow-up care, to evaluate the health-related outcomes for those children, and to evaluate and modify state standards of care for children with CCHD.

- Other concerns in Indiana include the lack of recommendations for (1) newborns who are discharged prior to 24 hours or are born at home, (2) asymptomatic newborns who need to be transported for an echocardiogram, and (3) acceptable pulse oximeters and probes (and whether funding will be available to meet equipment recommendations once made). Queries have come up about whether referral sites will be accredited, how the program will be evaluated (especially on cost), and what CBT codes will be developed for this.

- By July 2012, all Indiana facilities are expected to be reporting to the health department electronically.

In closing, Dr. Bocchini reported that the Wisconsin group that made the 22q11 deletion syndrome nomination presentation at this meeting will provide the Advisory Committee additional data on the distribution of severe immunodeficiency and critical congenital heart lesions in the wider spectrum of patients with the disorder. When it is received, the information will be passed along to committee members.