SECRETARY'S ADVISORY COMMITTEE ON

HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Thursday, January 26, 2012

Afternoon Session

1:30 p.m.–3:00 pm

Park Hyatt Hotel

Washington, D.C.

CHAIRMAN BOCCHINI: All right, let's go ahead and call the meeting to order.

All right, thank you. We're going to modify the agenda slightly to address the public comments. First, a group from Wisconsin, as I understand it, wanted to provide some information about the nominated condition that we are going to talk about momentarily, so bring all the public comments first. So I guess one thing we're looking for -- we're going to go ahead.

Donna McDonald-McGinn is going to represent the group from Wisconsin. So the other public commenter is not here, so we would like you to step forward. The rules for public comment, we will try to determine how much time is available based on how many individuals or groups wish to make presentations, so in this case we have one group for pulse oximetry and one group for the nominated condition, so it will be 10 minutes per group, so please go forward.

Thank you for coming.

DR. MCDONALD-MCGINN: Good afternoon and

thank you for allowing us to present to you today.

So should why the 22q11.2 Deletion Syndrome be added to the suggested list of newborn screening studies? Well, in order to address this, we would like to present historical background, prevalence, key features, genetics, natural history and preventable morbidity and immortality, 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, velo-cardial facial syndrome, and conotruncal anomaly face syndrome, and in some patients with the autosomal dominant Opitz-G/BBB syndrome and Caylor cardiofacial syndrome.

However, once this was introduced in the early 1990s as the standard diagnostic text, 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 to 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 sized 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 percent recurrence risk.

Both sexes, all races and ethnic groups are affected. But African-Americans with the 22q deletion maybe 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 multi-system 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 to 65 percent. Renal abnormalities and feeding and swallowing difficulties in a third. Hypothyroidism in a fifth hypothyroid. Intellectual deficits in a greater than 95 percent. And psychiatric illness in a large proportion.

But 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 three of life.

At home he had twitching and jerking. His doctors were not concerned, but Carol insisted the pediatrician observe the teaching. 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. BASSETT: What are the highlights of anticipatory care?

CHAIRMAN BOCCHINI: What is your name?

DR. BASSETT: Anne Bassett.

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 maybe 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. BERGER: My name is Stuart Berger. I'm 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 was diagnosed by ECHO prenatally. Came to our hospital and was started on prostaglandin and had surgery soon after birth, which included a complete heart repair and was discharged from the hospital.

Patient B, which was a late diagnosed patient, was discharged from the hospital on day two of life but without any diagnosis. 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, and actually 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 neuro-developmental 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 dependent. We wanted to look at the impact of early vs. late prenatal diagnosis; looking at cardiogenic shock presentation vs. no shock; ICU length of stay; amount of time needing drugs to support the heart; amount of time on the ventilator; and hospital charges.

Very interesting, from that study of the 65 patients that presented on early, not a single one of them, zero, presented with shock, whereas of the patients that presented late, 38 out of about

105 presented with shock and all attendant problems.

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

So I would conclude by telling you the 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 introduced Max Wootton. Max is represented here by his mother Julie, founder of the British children's charity Max Appeal.

MS. WOOTTON: Thank you.

Max was born with undiagnosed complex heart defects, which became totally overshadowed by his other problems, necrotising enterocolitis through a fatal spiral of events, including idiopathic physiopedia and massive acidosis that led to his death 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 USA would impact on the diagnostic protocols within national health service of the U.K.

Now onto the diagnostic odyssey of Aidan Shaw whose mother, Sheila Kambin, an obstetrician,

spent 5 years searching for an answer.

DR. KAMBIN: Hello, my name is Sheila Kambin. My son Aidan's diagnostic odyssey incorporated 27 specialists over a five-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 which 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'm a parent. I'm 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 the 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. And 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. BREEDLOVE-SELLS: At birth, Riley could not handle her secretions, breath or feed properly, resulting in a trach and G2 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.

And astute geneticists 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. ROUTES: My name is Jack Routes, and I'm from Children's Hospital of Wisconsin.

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 used to 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 halpoinsufficiency in TBX1 by real-time quantitative PCR.

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

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

So that's great with congenital heart disease when you have blood. What about with the newborn screening using pre-existing newborn screening cards.

So in conjunction with Wisconsin State Lab of Hygiene -- next slide -- we used 80 newborn screening cards, extracted DNA from those cards, put it in a 96 file format and then randomly included DNA from 22q. We were completely blinded to the results on which was spiked with 22q. And as you can see in the real world we can identify infants with 20q by halpoinsufficiency of TBX1.

So 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 trach, the same technology, approximately the same cost, about six dollars per assay, and it is a technology that state

labs are familiar with.

So the next question, do people want newborn screening for 22q?

DR. COPELAND: I'm sorry, your time is up.

DR. BASSETT: The answer is yes.

DR. MCDONALD-MCGINN: Thank you for your kind attention.

CHAIRMAN BOCCHINI: Thank you for your coming in for your presentation. We appreciate it.

We have an additional public comment on pulse oximetry, Kristine McCormick.

MS. MCCORMICK: 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, never even 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'm impressed by the efforts of individual states, like my home State of Indiana, where my baby is free, but I'm not impressed by the e-mails that I get, and the list growing of babies each day, that we aren't screening every single baby.

Thank you.

CHAIRMAN BOCCHINI: Thank you, Ms. McCormick, for your presentation.

That will close the individuals who asked for an opportunity for public comment.

We will now go to the Nomination Workgroup report.

As you're aware, the 22q11 Deletion Syndrome was submitted and was reviewed by the committee. We'll review the findings and hear the recommendations of the working group.

Deitrich?

DR. MATERN: Thank you for giving me the opportunity to describe what the Nomination and Prioritization Workgroup discussed last December, and this is a summary. Again, the issue was whether 22q11 Deletion Syndrome or DiGeorge Syndrome should

be added to newborn screening.

The proponents are partly here, at least Dr. Routes and Dr. Verbsky from the Medical College of Wisconsin in Milwaukee, Dr. Sullivan and Dr. McDonald-McGinn from the Children's Hospital in Pennsylvania. The supporting organizations of this proposal are the Jeffrey Modell Foundation, the Immuno Deficiency Foundation, the International 22q11.2DS Foundation, the Dempster Family Foundation. And I do think now we have to add the Max Appeal, and DCFF and the 22q11 Foundation.

So you heard now a lot about already 22q11.2DS, which is again also known as the DiGeorge Syndrome, or the Velocardiofacial syndrome. If you are unaware where they names come about, a physician usually makes the diagnosis of a group of patients that have similar symptoms, and because they don't know what the cause of the disease is that they see in front of them, they give it a descriptive name such as velocardiofacial syndrome or later the name is assigned based on the physician who first described it, such as the DiGeorge Syndrome.

So it took some time until it was realized what the actual cause of the disease in these patients is, and apparently now for 22q11.2 Deletion Syndrome, there is a genetic defect that has been identified. Now contrary to most other conditions that we deal with the newborn screening, this is a autosomal dominant condition or chromosomal recessive. However, also contrary to most of the conditions, this is in more than 90 percent of the de novo deletion and less than 10 percent inherited from a parent.

The prevalence, as we already heard, is relatively high, 1 in 4,000 live births. It does not affect a specific ethnic group. It is pan-ethnic, so anybody can be affected.

This phenotype is highly variable, and as you can see in this table that I took from one introduced by the proponents, the various anomalies that can be detected, where cardio anomalies in particular. Critical heart disease is fairly frequent at 77 percent. Immune deficiency is also very frequent with 77 percent. Panels of defects

which are typically not so easily detected when they are not overt, palates to the cleft or cleft lip, which occurred in only up to 13 percent. The velopharyngeal insufficiencies are more difficult to diagnose and certainly something that is not done in the neonatal care unit.

And then you have the developmental and mental issues that affect a large number of patients and they are also, of course, not identified in the newborn period.

The treatment is, at this point, symptomatic, so we have patients apparently they have heart disease or heart defect that needs to be treated by surgery usually so there is nothing causative or cumulative, which again of course nothing for newborn screening, either.

One of the differences maybe to other conditions is that apparently many of the patients are born symptomatic so they have clearly already a problem, such as congenital heart defect that we will not be able to prevent anymore by the newborn screening.

Over time, there are different concerns. Again, this is from the review by the proponents from last year. And you can see in early infancy primarily the heart and the hypocalcemia are the primary issues. Later in life, you have the development, palate and infections being added. So you can also see that over time there are issues with this condition as the patient ages or depending if you have a milder type, it might not be detected until you're older or an adult or maybe because your child wasn't identified as having 22q11DS, and then family studies reveal that actually a parent carries the mutation. So that also tells you that apparently you can have people go through life fairly long and don't show any symptoms until there's a child born and another patient is identified.

The other issue about treatment, and again from the same paper, is states that more significant issues relate to management of patients once a diagnosis is established. The varied presentation and the varied phenotypic constellations mandate

that each patient has a fairly unique management strategy.

We just heard from the proponents that they feel that such management can be accomplished basically across the country. There might be some areas, however, where I think we may not be able to have a really comprehensive workup, at least not very close to where the patient is living.

The promise and the possibility of improved interventions for neuropsychiatric needs could lead to enhanced adult function. Again, this is an assumption, and generally I would agree that if you treat someone prospectively that is always better than later.

So the proposed method as we just heard is a molecular genetic method using RT-PCR. It requires the usual 1/8-inch or 3.2mm punch per test. And the question that comes up is whether there is overlap with existing newborn screening methods.

So if we look back at this table you will notice again that there are anomalies playing a big role and CCHD is apparently a part of this

condition.

So what many of these patients can be identified through pulse oximetry, which is now part of the uniform panel and just waits for implementation across the country.

The other thing that immune deficiency plays a big role. And again, it is currently being implemented across the country, and could patients be identified through a SCID screening?

So pulse oximetry, one would expect that at least 50 percent of the patients here would be identified because they have a cyanotic heart disease, by pulse oximetry.

Through SCID screening. If you look at the collaborative project and those few programs that submit the data as of last Monday, 41 cases that had abnormal SCID screen have a severe combined immune deficiency. Seven of these 41 cases actually were eventually diagnosed with the DiGeorge Syndrome or 22q11.

So I don't know about all of the cases but this is apparently -- at least 7 out of 41 is a good

percentage of all the cases that are identified through a SCID screening.

And again 67 percent of 22q11 DS have T-cell lymphopenia, so you would expect that again another half at least should be picked up by SCID screening.

The next question is, now that you have proposed DNA-based assay and SCID is being implemented, which again is the technology apparently now making its way into every screening laboratory, couldn't you combine those two?

So another paper fairly recent, 2 years ago, in Genetics and Medicine tried to address the issue of whether this condition should be added to the newborn screening panel. We could go through it and this table you see the benefits and the risks, which are really nothing more new from the society perspective. The benefits are that you might have some impetus for development of effective screening. We have that already.

The risk is that we don't yet have a fully tested screening technique. Based on limited

studies that were done -- and I agree they were blinded. They were done on newborn screening blood spots. But again it was not a high throughput population wide screen at this point.

So while apparently the limited study apparently shows very good sensitivity and specificity, whether this will hold true when you start screening thousands of samples I don't think we can answer at this point.

What about the false positives? What will people say when there are false positives? Another question that maybe Dr. Tarini can speak to this later, is how do of physicians who do not have specific training with these conditions talk to the families and are able to help them go through the process of confirming a diagnosis, if there were false negatives possible?

The other issue would be that, the screening tests as proposed, I believe you could also identify cases that have 22q11 duplication syndrome, which is not always considered because most of these patients appear to be just fine. So

you have a risk that you identify something that is clinically irrelevant and puts family through the ringer until that is clarified. And in the end, they may have some kind of genetic abnormality in their medical record that really doesn't have to be there.

But for the individual, of course, as we already heard, there are significant benefits if you have a heart defect and you do not go home before the problem has been addressed. You can address all of the other issues prospectively as opposed to once a patient is already developing symptoms, and that should be of benefit. And the risk, again, is basically the ones I've already mentioned in not being sure whether the early identification is really what is required for every single patient that has a spectrum of syndromes that are possible.

And for the family, the benefit of course is that they know sooner than later what is going on with the child, and the risk is that you have what is called the vulnerable child syndrome that you create by basically causing parents to wonder what

is wrong with her child, thinking about guilt, bonding, all of these issues that may be a negative.

So also again, as kind of alluded to, there's been no prospective study to date, so we think that the assays are working very well in newborn screening.

In the past, we know that the tests are implemented, and we think they work very well because of the limited studies we've done. Once we go into real-life screening, you realize there are a lot of problems that one should really have thought about earlier.

So again, a large study prospectively hasn't been conducted yet. And the question is whether you will identify cases that are not necessarily needed to be identified such as the duplication.

The other issue is, again, that I think a large number of patients should be identified through currently recommended screening for SCID and CCHD. And then the other question would be, to be answered in a prospective study maybe, is must one

really identify all the other cases that do not have immune deficiency, or heart disease be identified that early.

Do we have an issue with the comprehensive treatment centers across the country? Are there really enough? Are they close enough? Those are things that we are not yet sure of, and I also would suggest that one has to consider the blood spot sample. Four or five blood spots are collected on every baby. On the screening card, you're screening for now at least 29 conditions. That doesn't mean we need to take 29 punches, but we take probably five or six punches to screen for all those conditions. Every time you propose a new test that requires its own assay of our blood spot punch, we lose some of that real estate on the card.

So as we go forward, I think that needs to be addressed, and we should particularly consider if you extract DNA already for one test, maybe you can use that same extract to look for the other condition as well. So that would be something to consider going forward, whether we really need an

extra punch to do the screening test.

So the recommendation to this committee from the workgroup are to not yet initiate an external evidence review and to suggest to the proponents and the newborn screening community at large to conduct a prospective newborn screening study for 22q11.2DS to determine the test performance in a high throughput fashion. If current newborn screening for SCCID and CCHD are sufficient to detect clinically significant 22q11.2 DS cases, the testing for this condition could be multiplexed with other DNA-based testing such a SCID and also to suggest developing the ACT Sheets algorithms so that physicians who will eventually get a phone call about an abnormal newborn screen for this condition know what communicate to the families and what to do next.

I have some bias here because I am a member of the workgroup that works on the ACT Sheets, so I would like to make you aware of that.

So also then to recommend to the newborn screening programs that already test for SCID to

please enter your true positive data into the region collaborative website so that people can see how many SCID cases are identified through prospective screening.

Thank you very much.

CHAIRMAN BOCCHINI: Thank you for that presentation.

Dieter has summarized the discussions and recommendations of the Nomination and Prioritization Workgroup in a very nice manner.

And to further discuss this, there is a template within which the Nomination and Prioritization committee works to look at whether the nominated condition has met each of the requirements to potentially go forward to evidence review. And I think he has very nicely summarized those issues that have been met and those issues which have not yet been met, which led to the committee making its decision.

So we will open this now to discussion by the committee.

DR. LOREY: This is Fred. I would like to

make a couple comments. Can you hear me?

CHAIRMAN BOCCHINI: Yes.

DR. LOREY: I wanted to talk a little bit more about the relationship with the SCID tests. The numbers that you put up, I want to second the emotion that we are having trouble with people entering data, so I also want to encourage people to enter data. And also, there was agreement among immunologists that we would only enter the DiGeorge that had an immune deficiency. So the number is actually quite a bit higher.

And just a few observations from our SCID screening. We have now screened about 700,000 kids, and we picked up about 10 DiGeorge and, I'm talking off the top of my head, but I believe that six of them are immune deficiency and the other four are not. And generally the direct values tend to be lower for those that are immune deficiency, but you will still pick up some without and at the higher end of your cutoff, and I assume a lot more above your cutoff that don't involve immune deficiency.

The other thing we observed is that I

believe without exception every result -- positive result we called out, it was a DiGeorge. The physicians had already diagnosed every time we got the test done. So I'm not sure, no matter what test is used, I'm not sure we're going to be accomplishing a lot by adding this to newborn screening.

So it is a syndrome, and I think in our analysis we have to separate the parts because if you remove the immunodeficiency part from it, it really doesn't meet many if any of the criteria for newborn screening, most notable being the requirement that the test detect before symptoms occur. And that is not true, except for immune deficiency, and we're picking those up in the drug assay.

To date, we haven't had any immune deficient DiGeorge patients reported to us. We have had some doctors who now know we're screening diagnose DiGeorge and then ask us for the TREK result, which was always negative. And by negative, I mean either the TREK was negative or it was one we

picked up, sent to the flow and the flow was negative.

So I'm just sort of reiterating what Dieter said, but based on a fair amount of experience.

Thanks.

CHAIRMAN BOCCHINI: Thank you, Fred.

Any other comments, questions, input? I just want to make sure the committee has a good -- I'm sorry. Don?

DR. BAILEY: I don't know much about this condition. I'm moved by the presentation by the advocates. From what I hear you saying is that if we recommended this go for forward to the evidence review committee route, it would probably not pass muster from that group right now. Would that be a fair assumption?

So I think it's important for us to recognize that if it's not going to do well in the evidence review process the way we have it structured right now, that's --

CHAIRMAN BOCCHINI: I think part of the

screening requirement in the past to go forward and also when it went forward, usually if there was not a large-scale screening study done, it never was approved anyway. So I don't see a reason to put it forward to the evidence review when we already know that this piece is missing.

DR. BOTKIN: A quick question about the hypocalcemia manifestations. Is this is critically neonatal phenomena where the kids need support prior to the time of the newborn screening result to come back, or can this be a more chronic or episodic phenomenon that will benefit from newborn screening?

Does anybody know?

DR. MCDONOUGH: It can be both. I think I have five children in my practice with DiGeorge and they have critical heart disease sooner but if they don't have -- or chronic hypocalcemia or mild immune deficiency -- by the way, I can tell you that the ones that I am familiar with, that we have not picked up some of them.

Is there any way that our committee can advise funding agencies to expedite some of the

research that needs to be done in this area for standard testing of a bigger population?

DR. COPELAND: You can do whatever you want. Whether or not it is capable of being done is a different issue. You can.

DR. MCDONOUGH: From my experience, I can see the benefit of picking up on some of these kids earlier, hoping that universal heart disease screening will be done, so there will be some kids who will be missed though, who will have DiGeorge who won't have heart disease and won't have immune deficiencies. And I think there'll be quite a few, because the incidence is 1 of 4,000 SCID screening is not picking up any --

CHAIRMAN BOCCHINI: Coleen?

DR. BOYLE: Just because this will reflect on the suggestions back to the committee in terms of what needs to be done, I guess I would open this up for others. You're adding something about the clinical utility, understanding more about -- since you mentioned that this has a very broad spectrum and perhaps we are all concerned about the severe

end of that, but getting a better sense of that, so really adding a clinical utility piece to this.

DR. MATERN: That's basically what I meant by is it sufficient, clinically sufficient to -- the cases are sufficient to be picked up.

CHAIRMAN BOCCHINI: Cathy?

MS. WICKLUND: So we're talking about the test performance metrics and using real-time PCR. Is it necessary to do this with every single dilution disorder, or can we talk about the technology itself and utilizing that technology the way we utilize it in other disorders and the test performance metrics in that way?

DR. COPELAND: So we are considering the disorder that was submitted to us, which was for sequencing of 22q11.

DR. MATERN: If you wondering whether or not the false positive rate that is occurring in SCID may be translatable to this. I don't know.

CHAIRMAN BOCCHINI: Mike?

DR. WATSON: It's really for a question for Fred. I think because I was confused by the

semantics of his restriction to the DiGeorge Syndrome, which is defined by an interrupted aortic arch type b vs. VCF and CAFC, what may have a much broader range of congenital heart disease associated with them, because I do think it's important to understand how many have both T-Cell lymphopenia and congenital heart disease that would fall out of both of the screening tests that we do. And I don't think that was in the paper we reviewed, as to how many occur in the same patient of both of those. It may not be a 50 percent that fail the lab all the time, but DiGeorge would be restricted to a relatively small proportion of the 22q minus patients, I think.

I just didn't understand the data that Fred presented. This is the biggest data set of 700,000 on the SCID, but when he said restricted to DiGeorge, I got lost because I think T-Cell lymphopenia occurs in 22q independent of DiGeorge, as a narrow subset --

DR. COPELAND: They've been calling it complete DiGeorge, and I think that is where some of

the semantics come in, is a lot of -- I've heard the immunologists calling it complete DiGeorge.

But it's a semantics issue, I do believe. But, Fred, if I'm wrong, please feel free to chime in.

DR. LOREY: I am not the expert but I did hear that term, yes.

DR. GREENE: I should probably say that although I am sitting in the SIMD chair, this is not an SIMD disease, but I am a clinical geneticist. And though I'm experienced with deletion 22 and I thank people for clarifying the semantics issue, but what I heard are several things I think I would like to put on the record.

One is not diagnosed does not mean not symptomatic, so for the families that are also -- apparently don't have a diagnosis but they may be schizophrenic, they may be walking around with a low calcium, they may have all sorts of health problems that they don't know about, that when we start to correct, when we figure out what is going on in the family -- that is also true in older siblings.

Another point that I heard, the incredible data. Of 700,000 kids screened, picked up 10 that were labeled DiGeorge, never mind the semantics. But it sounds like 10 probably deletion 22qs picked up in 70,000. I've heard two numbers. I heard 1 in 2,000; I've heard one of 4,000. If we in the 1 of 4,000, not even the 1 in 2,000, that is picking up 1 in 17 deletion 22 kids. So I don't know, Dieter, with due respect, where you got the number that TREK screening will pick up 50 to 65 percent of kids with deletion 22q. But in my experience, most kids with deletion 22q, and I see a lot of them, don't have immune deficiency.

So counting on TREK screening to pick it up ain't gonna help.

DR. LOREY: This is Fred. I would like to correct that. That is not what I was saying.

What I was saying was the immune deficiency is the one that qualifies for the newborn screening criteria. We do not attempt to pick up the non-immune deficient. We do pick up some. And we are fully aware that way above our cutoff are

probably the majority of DiGeorge cases but they are not immune deficient. And that is why I am saying, when we have this discussion, we have to pull apart the different disorders because we believe we are picking up the immune deficient cases, and by no means are we picking up any substantial percentage of the total cases.

But I can tell you, every one we reported of the 10, whether immune deficient or not, the doctor already knew.

So we are not trying to pick up all DiGeorge by that screen. All I'm saying is we are picking up the immune deficient ones.

DR. GREENE: Thank you. And I believe that we are then in agreement. We are picking up the immune deficient patients with the deletion 22, but of course not the non-immune deficient ones.

DR. METERN: The 67 percent comes basically out of the table where it says 67 percent of patients have low T-cells, so nobody has real data at this point. And that is basically, in my opinion, the most important, that there's no

prospective study that is done. And from the SCID testing states, we do not yet have enough information back as to how many are actually picked up.

DR. GREENE: And I am not in any way, shape, form able to respond to some really important questions that are being raised about the level of some important -- knowledge, but I think it important for nobody to walk away thinking that TREK testing is going to pick up a substantial portion of kids who will need treatment.

With respect to the heart, many of the patients that we see with deletion 22, their heart defects are not -- so lots of actionable heart issues but will not be picked up on the critical cyanotical, congenital heart disease screen.

And absolutely reinforce lots of folks have completely normal calciums. That's why the screening says you keep monitoring the calcium. They can go down and get your ICU after their calciums gradually drop-down and then hit your ICU in coma and seizing when they are 16.

There's also other things that I think that folks who presented hit the highlights. We monitor speech. We monitor hearing. We monitor eyes.

Speaking as a clinical geneticist, somebody hands me a diagnosis of deletion 22. I know what to do. I know what to monitor. I have guidelines. I can talk to the family. I can partner with the pediatrician anywhere in the country. If the family can make it down once, great. If not, I can talk the pediatrician through it. There are genetic counselors all over the place, if the family is having a hard time. Yes, we all get -- both Dr. Tarini and I work on false positive concerns. We know that we can make people anxious. It sounds like this would probably have a low false positive rate, but it ain't gonna be zero. But there are genetic counselors around who partner with pediatricians.

So I am not speaking to some of the data questions or the technical questions, but speaking as a clinical geneticist, hand me this information,

hand me a pediatrician with questions, we can deal with it. We're not going to fix it. It's not going to answer the questions about cost effectiveness or anything else. And speaking as me personally, folks here in the room have heard me argue against plenty of things where "Don't give me this, please. I don't know what to do with it." This is, "Give it to me, please. I know exactly what to do with it."

CHAIRMAN BOCCHINI: Questions? Comments?

DR. BOTKIN: Yes, just one question. I'm not sure I understood or remember exactly how this went, maybe this was Fred. But are there ways to improve SCID screening data collection that would give us better answers in this domain over the next year or so? That would give us additional information about at least the T-cell subgroup of this of this group? And potentially think about it as states ramp up congenital heart disease screening, are there ways to collect some of these data so that we have more information later than we have today?

DR. LOREY: Boy, that is a million-dollar

question.

I think we should, because the limited data entry that we have for our site is really only from the four states that were in the pilot. And we can't even get all four of them to enter their data.

So one of the reasons is because immunologists just want a lot of information in there. Personally, I think it's more than we need, and it's difficult and time-consuming to enter all the CDC information, all the pulse oximetry information, so maybe we could have a discussion about that issue. But I agree.

I mean, this is a valuable resource if we can get people to contribute. And then the other thing, maybe we might want to revisit it. And again, we need to include the immunologists because they are the ones who told us not to record the DiGeorge. And you know, maybe we should. Maybe we should report them all. And then whether they were or were not, that data goes to waste, really.

Although, I agree with the previous speaker that we will find a big chunk of the non-

immune deficient ones.

Maybe we can offer to pay running.

DR. COPELAND: Please keep it very brief.

DR. BERGER: I just wanted to make a brief comment. To remind you, I'm the cardiologist.

I want to go on the record to say that I absolutely am in support of pulse oximetry screening, but I will tell you that there will be forms of 22q and congenital heart disease that will not be picked. Interrupted aortic arch up is actually not a form of cyanotic congenital heart disease. And these babies may well be saturated and not have a difference between upper and lower extremities at the time they go home, until the ductus closes as that date 9, day 10 of life. Similarly, tatralogy of Fallon is a form of cyanotic congenital heart disease and has a relatively high incidence in the 22q syndrome. That may also not be picked up by pulse oximetry for the time that the ductus is open.

So even though pulse ox will pick up some stuff. Many of deletions may not be picked up in

this syndrome.

DR. ROUTES: Again, there seems to be an issue but the immunology. I was the lead author on the JAMA paper for the newborn screening for SCID. I was the one who raised the money and optimized the assay, worked with the states and got things going. I'm very familiar with the data from Wisconsin. We have picked up babies with 22q that were not diagnosed. It is not, as pointed out very nicely, it is not a test that is suitable for picking up 22q. You will miss the vast majority. And in fact, only those with "complete DiGeorge," which is defined by almost no T cells, will be picked up by the TREK assay.

All I do for a living when I see patients is immune deficiency. So that's my livelihood.

The immune deficiency varies from very severe to mild, but the TREK assay was never designed to pick up 22q. It can never be designed to do that.

And then one other thing about technology, I think everyone would agree, and certainly our

experience in Wisconsin was, how amazingly sensitive the assays -- the real-time assay was with a positive predictive value of about 50 percent. I mean, it is amazing. And in comparison to the other test that we do for newborn screening, the real-time assay has had an incredibly low incidence of false positives.

In our first year when we screened 70,000 infants, only 17 went to flow cytometry. I mean, imagine that. And out of those, 50 percent had T-cell lymphopenia. This is the same technology. It may not be exactly as good, but it will be pretty close.

CHAIRMAN BOCCHINI: Okay.

DR. LOREY: I'm not disputing any of those facts. I don't think anyone is trying to say that was screening for DiGeorge -- but the point I was trying to make was if you remove the immune deficiency from the equation, then what is left -- newborn screening. And based on 700,000, we could pool our data and we're probably at 1.5 million. If anybody has missed any immune deficient DiGeorge,

it's -- that's all I'm trying to say. I'm not trying to say to do any more than that, but you have different comparisons, because it is a syndrome.

CHAIRMAN BOCCHINI: If there are no further comments or questions -- yes, one more?

DR. BASSETT: I just want to reiterate the point that the severe immune deficiency is a marked minority of patients with the 22q deletion. In fact, it's a minority that have serious congenital cardiac defects. This does not mean that they don't have an awful lot of morbidity. I have seen over 150 adults with this condition.

It also doesn't mean even if they are a late diagnosis, they haven't had a slew of multiple, treatable, Some preventable associated conditions that could have been better with screening and early intervention.

The most important thing for parents and patients of the neurocognitive deficits and some of these can be ameliorated with early intervention, including treatment for hypocalcemia that you cannot pick up with any of the existing screens.

CHAIRMAN BOCCHINI: Thank you. We certainly appreciate the points that were brought up in this discussion. And I think many of them are clearly very relevant and would be important parts of an evidence-based review of this subject and of the potential for addition of the nominated condition.

I think they key in terms of adding SCIDs and critical congenital heart disease to the schedule to the recommendations recently was what potential impact that either of those would have on identification of patients with this condition.

I think the key thing is whether the test, which clearly has very high performance metrics in the situation that you have created, has been tested in a population-based setting to determine outcome. And I think that's the key issue that the Nomination and Prioritization committee sort of hangs on because that is a criteria for which we must meet to go forward.

So I think those were the major issues that came up to discuss, and I think Dieter did a

really nice job summarizing those for us.

So I think now it comes to the committee for a decision. So the question is, do we have a motion to accept the decision of the --

DR. COPELAND: So if someone moves for it, I'm remembering now you have to move it and second it before you can vote.

The vote is on whether or not to move 22q deletion to the evidence review or not at this point in time.

DR. MATERN: Can I make the motion to not initiate the review at this point?

CHAIRMAN BOCCHINI: Do we have a second?

DR. LOREY: Second.

CHAIRMAN BOCCHINI: Thank you.

So it's been moved and seconded. Is there any further discussion by the committee?

DR. MCDONOUGH: Is it possible to amend the motion to encourage additional research on some of the unanswered questions we have here about a pilot study, a prospective study to screen a population for this and to look at the benefits to

come up with early detection, addressing some of the neuro calcium issues and the developmental issue.

I can just tell you, from my experience, it would be really nice to pick up some of these kids earlier.

So I move that, to clarify that language to make it nicer, to make it a sentence, rather than a rambling paragraph.

CHAIRMAN BOCCHINI: Is there a second to that?

MS. WICKLUND: I second.

CHAIRMAN BOCCHINI: Is that acceptable to the original motion?

DR. MATERN: Yes.

CHAIRMAN BOCCHINI: So we then have the original motion modified by the request to initiate pilot studies.

First we need to determine if there's anybody who will abstain.

DR. HOMER: This is Charlie Homer. This is not abstaining but the request for research, I'm just trying to put that in the context of this

morning's conversation about what we can ask, who we can ask to do what. Is that more for the internal people on the committee who have access to data to do it, or is it actually at the level of a formal recommendation to go to somebody outside the committee? I'm just trying to think of what the level of that second modification is.

CHAIRMAN BOCCHINI: I think in this case, it is going back to the individuals who nominated the condition and that there is support from this committee for that to occur, not that it's a formal --

DR. COPELAND: Dr. McDonough, did you want this to be a recommendation back to nominating, or was this a recommendation to the Secretary?

DR. MCDONOUGH: It would be a recommendation wherever it can assist the process to get funding for the research. I guess a statement of intent from the committee that this is an issue, that we're not just dropping at this point because it doesn't qualify, but hopefully we'll spur it to come back and revisit it in a year.

But I'm new at this, so I don't know.

DR. COPELAND: So looking at those wonderful tables that I sent you, that are not completely clear, but if you look at the table for projects, where would you say your nature of support is?.

DR. MCDONOUGH: I would say number two. It would go to the Secretary who has resources to do research.

DR. COPELAND: So there are two that goes to the Secretary. One includes an action; one includes just an FYI.

DR. McDONOUGH: It would be an FYI.

DR. HOMER: I object to that. I think that's a second go-round to the purpose of the committee. I have no problem with the suggestion, but not to the Secretary. Perhaps we could just issue a statement of the findings of the subcommittee and make that recommendation.

DR. MATERN: I think the committee agrees that this is an important condition, but I think what is missing is that piece of a prospective

studies so that we have a better understanding of identifying all the cases, of not identifying cases that don't need to be identified as indifferent conditions.

So we -- I guess a vote is, are we going to initiate external review vote yet or not? So my motion was to not do this yet, to suggest to the proponents or anybody who wants to do it, to do a prospective study. I don't know if there are any other countries interested in doing this or are doing this already. And then we can suggest to the Secretary that she maybe comes up with a way of funding it or opening a way to funding it to anyone who is interested.

I don't think we want to suggest that the Secretary has to find funding for this to go forward. If the proponents or anybody else finds ways to do this, they should go ahead and do it.

CHAIRMAN BOCCHINI: Alexis?

DR. THOMPSON: I'm wondering -- my sense is there are probably levels of concern with the original motion and -- would it be possible to vote

on them separately?

DR. HOMER: I would agree with that. My only issue is that we're sending something to the Secretary when we already decided to go with a full review, let alone the Secretary. So I think a separate motion that doesn't go to the Secretary or -- I just don't want to confuse our main vote.

CHAIRMAN BOCCHINI: Is that reasonable? Is the committee comfortable separating the two to go forward --

DR. MCDONOUGH: I withdraw my motion then.

CHAIRMAN BOCCHINI: All right.

The motion withdrawn, and then we're back to the original motion to accept the report of the committee that this nominating condition does not go forward to the evidence review committee at the present time.

Yes?

DR. BOTKIN: Yes, I guess I would say, in clarifying what the motion is, is the assumption that this slide is the motion, so this recommendation includes a prompt for additional

research on some very some fairly specific outcome measures? So to a certain extent I think we're picking up on Steve's concern here that the committee wants to make a positive statement to say that there's enough promise to the screening that somebody ought to be collecting additional data, and I think the whole recommendation does that in its totality.

DR. COPELAND: So just to clarify the process, if you vote not to move this forward, the nominators would get a letter back outlining what the committee voted on and what the recommendations were and the suggestions will go, just to clarify.

CHAIRMAN BOCCHINI: All right with that clarification then, any additional questions?

And then we are ready to vote.

No one will abstain, so we will call the roll.

DR. COPELAND: Don Bailey?

DR. BAILEY: Are we always going in alphabetical order?

[Laughter.]

DR. BAILEY: I'm changing my last name.

[Laughter.]

CHAIRMAN BOCCHINI: So a vote yes means a vote to accept the recommendation.

DR. BAILEY: Yes, I tend to feel for children of for families and to want to support their proposal, because I think that there are children who will clearly benefit from this, but I do think that I am swayed by two things. One is that it would not pass muster in our evidence-based review process, so there is no point in sending it to it now. Secondly, especially if we have added this criteria of public health impact that these larger studies, as are suggested here, is what is needed to help determine the impact in a much broader kind of way.

I do think it ultimately raises some question for us as we go forward. How many -- for every condition are we going to have to do large-scale implementation studies? And that will be something for us to discuss.

But that's a long-winded answer to say,

yes, I support this recommendation.

DR. COPELAND: Dr. Bocchini?

CHAIRMAN BOCCHINI: Yes.

DR. COPELAND: Dr. Botkin?

DR. BOTKIN: Yes.

DR. COPELAND: Dr. Homer?

DR. HOMER: Yes.

DR. COPELAND: Fred?

DR. LOREY: Yes.

DR. COPELAND: Dr. McDonough?

DR. MCDONOUGH: Yes. Can I ask a question? If the groups are allowed to reapply after a year or so?

DR. COPELAND: They don't even have to wait for a year. We just outline suggestions and when they feel they have met those criteria, that they can get past that hurdle, then they can --

DR. MCDONOUGH: So, yes. I would like to find some advice from legal counsel about how we can send a message on that we would like to have more research done in this area, if something could be drafted and voted on.

DR. COPELAND: We can't vote on it at this meeting. We only have scheduled votes. But maybe next meeting.

Dr. Matern?

DR. MATERN: Yes.

DR. COPELAND: Dr. Thompson?

DR. THOMPSON: Yes.

DR. COPELAND: Ms. Wicklund?

MS. WICKLUND: Yes.

And I just want to echo what Don said. I think you eloquently discussed the struggle.

DR. COPELAND: Andrea Williams?

MS. WILLIAMS: Yes, I feel the same way.

DR. COPELAND: Agency for Healthcare Research and Quality?

DR. DOUGHERTY: Yes.

DR. COPELAND: Center for Disease Control and Prevention?

DR. BOYLE: Yes

DR. COPELAND: Food and Drug Administration?

DR. KELM: Yes.

DR. COPELAND: Health Resources Services Administration?

DR. LU: Yes.

DR. COPELAND: Okay.

CHAIRMAN BOCCHINI: Thank you all very much. I appreciate the efforts that you have made. We have come a long way in the development of this potential test for implementation. So thank you.

So with that, we're now ready for short break and then the beginning of the subcommittee meetings.

Sara, do you want to reiterate where everybody is?

Okay, so let's reiterate where the subcommittees are going to meet before we close the session.

DR. COPELAND: So Laboratory Standards are in Salon 1 and 2 down the hall to the right next to the bathroom. Follow-Up Treatment stays here. And Education and Training is next door in the Gallery 3 Ballroom.

CHAIRMAN BOCCHINI: And those who are

signed up for dinner, meet in the lobby at 6:15.

And then tomorrow morning, we began again at 8:30 in the morning.

[Whereupon, at 2:55 p.m., the meeting was adjourned.]