THE ADVISORY COMMITTEE ON HERITABLE DISORDERS

IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS

5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Thursday, May 9, 2024

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P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks, and Committee Business

NED CALONGE: Good morning, and welcome to the May 2024 Advisory Committee on Heritable Disorders in Newborns and Children. I welcome everyone, and I'm glad you're able to attend, especially my fellow panel members. As we're gathered here in person at 5600 Fisher's Lane, Rockville, Maryland, I would like to open the meeting by taking a moment to acknowledge the land on which we gather today.

We acknowledge that the land and water on which our meeting is taking place was and still is inhabited and cared for by the Susquehanna and the Piscataway peoples, including the Piscataway Conway Tribe, and the Choptico Band of the Piscataway Indian Nation.

We are grateful for the past and continued stewardship of this land, and we pay our respects to Maryland's indigenous community and their elders, both past and present, as well as future generations. At this point I'm going to turn things over to Leticia Manning, who's going to go over some Federal Advisory Committee Act information, and building information. Thanks Leticia.

LETICIA MANNING: Good morning everyone. So I'm going to start off with roll call. From the Agency for Healthcare Research and Quality, Kamila Mistry.

KAMILA MISTRY: Here.

LETICIA MANNING: Michele Caggana?

MICHELE CAGGANA: Here.

LETICIA MANNING: Ned Calonge?

NED CALONGE: Here.

LETICIA MANNING: From the Centers for Disease Control and Prevention Carla Cuthbert?

CARLA CUTHBERT: I'm here.

LETICIA MANNING: Jannine Cody?

JANNINE CODY: I'm here.

LETICIA MANNING: Christine Dorley?

CHRISTINE DORLEY: Here.

LETICIA MANNING: From the Food and Drug Administration Paula Caposino?

PAULA CAPOSINO: Here.

LETICIA MANNING: From the Health Resources and Services Administration Jeff Brosco.

JEFF BROSCO: I'm here for Dr. Warren.

LETICIA MANNING: Jennifer Kwon?

JENNIFER KWON: I'm here.

LETICIA MANNING: Ash Lal?

ASHUTOSH LAL: Here.

LETICIA MANNING: Shawn McCandless?

SHAWN MCCANDLESS: Here.

LETICIA MANNING: From the National Institute of Health Melissa Parisi?

MELISSA PARISI: Here.

LETICIA MANNING: And Chanika Phornphutkul?

CHANIKA PHORNPHUTKUL: Here.

LETICIA MANNING: Thank you. And for our Organizational Representatives, from the American Academy of Family Physicians Robert Ostrander?

ROBERT OSTRANDER: Here.

LETICIA MANNING: From the American Academy of Pediatrics, Debra Freedenberg?

DEBRA FREEDENBERG: Here.

LETICIA MANNING: From the American College of Medical Genetics, Cindy Powell?

CYNTHIA POWELL: Here.

LETICIA MANNING: From the American College of Obstetricians and Gynecologists Mara Black? From the Association of Public Health Laboratories Susan Tanksley?

SUSAN TANKSLEY: Here.

LETICIA MANNING: From the Association of State and Territorial Health Officials Scott Shone? I believe he is here. From the Association of Women's Health Obstetric and Neonatal Nurses Shakira Henderson? From the Child Neurology Society Margie Ream?

MARGIE REAM: Here.

LETICIA MANNING: From the Department of Defense Jacob Hogue? From the Genetic Alliance Natasha Bonhomme?

NATASHA BONHOMME: Here.

LETICIA MANNING: From the March of Dimes Siobhan

Dolan?

SIOBHAN DOLAN: Here.

LETICIA MANNING: From the National Society of Genetic Counselors Cate Walsh Vockley?

CATE WALSH VOCKLEY: Here.

LETICIA MANNING: And from the Society for Inherited Metabolic Disorders Sue Berry.

SUSAN BERRY: Here.

LETICIA MANNING: Perfect, thank you. So now I'm just going to go over the ethics and conflict of interest reminder. As a reminder, Committee members must recuse themselves from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner. Unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing you to participate.

As in the case today, when a vote is scheduled, or there is a specific activity proposed, and you have a question about a potential conflict of interest, please let me know immediately. For those that are participating virtually, you can email me. For meeting participation, according to FACA, all Committee meetings are open to the public.

If the public wishes to participate in the discussion, the procedures for doing so are published in our Federal Register and/or are announced at the opening of a meeting. For this May meeting, the Federal Register notice, we said that there would be

a public comment period, and there will be a public comment period today and tomorrow.

Only with the advanced approval of the Chair, or myself, the Designated Federal Official, may public participants question Committee members or other presenters. Public participants may also submit written statements that will be shared with the Committee members. As a reminder, it is stated in the Federal Register notice, as well as the registration website that all written public comments are part of the official meeting record, and are shared with the Committee members.

Any further public participation will be solely at the discretion of the Chair or myself. For those that are participating virtually, audio could be found through your speakers, and as a call-in option. For Committee members and organizational representatives that are attending virtually, you can change your name as you would like it to appear in the Zoom display name to ensure the meeting host can find you easily please identify yourself with your first and last name, along with your relevant organization.

If you are having any kind of technical difficulties, please email Emma Kelly at ekelly@lrginc.com. Please note that when you are promoted to a panelist to speak, the system will briefly log you out of the meeting, and you will automatically rejoin within 10 seconds.

There's also a way to enable closed captions. You can do so by selecting the show captions options in the Zoom taskbar

at the bottom of your screen. So that is there. And now, I turn it back over to Ned.

NED CALONGE: Thanks Leticia. You'll remember that during the November 2023 meeting the Committee initiated a pause on accepting new nominations for consideration for addition to the RUSP until May 2024. During this time the Committee Chair, myself, and HRSA Staff assisted the potential nominators on core elements that are needed for nominations.

The Advisory Committee on Heritable Disorders in Newborns and Children will begin accepting new nomination packages May 31st. HRSA Staff and I remain available to assist all potential nominators. Information is available on the ACHDNC website, and we'll also be talking about the nomination process further today.

Next slide. I don't know if they did it or I did it. As many of you are aware, the National Academies on Science Engineering and Medicine is conducting a consensus study examining the current landscape of newborn screening, NBS systems and processes.

As Committee's task is to examine newborn screening systems, processes, and research in the United States, and provide short-term options to strengthen existing NBS programs, and a visionary roadmap for over the next five to 15 years. Committee's report and recommendations are due to HHS in the spring of 2025.

Over the past few months the National Academies of Science Engineering and Medicine held several information

gathering sessions. Currently, the NASEM is looking to hear from people who are impacted by, and interested in, newborn screening programs in the United States, including families with children, the rare disease community, public health professionals, clinical care providers, health care administrators and health care payers.

You can use this QR code to access a survey which will close on May 21st, coming right up. Okay. In our Newborn Screening Saves Lives legislation, there's a mandate to create a clearinghouse of newborn screening information. The Health Resources and Services Administration's Maternal and Child Health Bureau maintains the Newborn Screening Information Center website, which serves as this clearinghouse.

In a future meeting we'll have a presentation that will provide more details about the Newborn Screening Information Center. You can use this QR slide--the QR code on this slide to access the NBSIC. Oh, it doesn't always work. Okay. I want to thank Committee members who reviewed the 2024 meeting summary.

If they have any comments on the summary please share them with Leticia, so we can make further revisions, and we'll share updated versions with the Committee, review them and vote to adopt and accept them tomorrow. Kind of a roadmap for meeting topics today, we're going to start the morning with public comments.

Then we'll have a presentation from the Food and Drug Administration on the regulatory process of the review for drugs for rare diseases. When we return from lunch we'll have an update

on the Duchenne Muscular Dystrophy evidence review, followed by Committee discussion. I'm going to then provide an update on the proposal for changes to the public health assessment for the decision matrix, and we'll end the day with a brief presentation and Committee discussion about the ACHDNC nomination and evidence-based review process.

Then tomorrow, we have a guest speaker from Bangor University in Wales, to talk to the Committee about an approach for qualitative evidence synthesis. We'll then have public comments and end the day with updates on the newborn screening ad hoc topic groups, and some other updates from the Association of Public Health Laboratories.

So, during this meeting we will have two public comment periods. Today we have nine oral public comments, and we'll have additional ones tomorrow. So, what I'd like to do is call people up. We have a podium in the room this morning, which is--looks very formal, but I hope it still carries the informality that we like and the closeness of our public comment period.

I'm going to start by asking for Matthew Ellinwood to please come up and give your public comment.

Public Comments

MATTHEW ELLINWOOD: Greetings, and thanks to the Committee for this opportunity. My topic today is the N-of -1 Rule, which requires that to be eligible for evidence review, a

nomination include a perspective identified pilot study yielding at least one clinically confirmed and treated patient.

I submit that this requirement is neither supported by the science, nor practice of newborn screening. I, and many others implore the Committee to consider including an alternate pathway by which the component elements of this rule can be met using multiple programs or approaches, rather than through a singular pilot study detection.

We filed an alternative pathway to nomination, state newborn screening programs will likely be subject to more legislative mandates to try to meet this requirement, which is a less than rigorous rationale for screening. Given the fact that analytical validity, clinical utility and treatment urgency and efficacy can all be demonstrated by other means, insisting on the N-of-1 Rule, especially for an increasing number of ultra rare conditions will mean delaying RUSP nomination and evidence review for little scientific gain, with attendant degradations of public health.

Michael Gelb, Dieter Matern, Amy Gaviglio and I have shared with the Committee our recently published commentary on this topic, a commentary endorsed by 35 additional experts in the field. During the adoption of this rule, discussion focused on analytical validity, clinical utility, treatment urgency and efficacy, and the evaluation of the system of newborn screening.

We submit that the analytical validity of a screen can be met with a retrospective study. Furthermore, the many relevant

aspects of therapy can be well documented in the literature with, for example, sibling studies and care standards. The rule also contained language describing a population similar to the U.S. population with respect to known prevalence. Two problems are implicit in this statement.

First, without a nationwide screening and reporting system, all prevalence of rare disease is an estimate. Second, based on population diversity, a pilot study in one group may not reflect the population prevalence in another group, or state, or in the country at large, all of which make these suspect criteria for supporting a hard and fast rule, such as the N-of-1 requirement.

The remaining rationale of the N-of-1 Rule is that it tests the system of newborn screening. The fallacy implicit here is that we have a unitary national system to test, which we do not. Likewise, it assumes that the experience of one family will be the experience of any family detected through newborn screening.

As we know, this could not be further from reality. If we take the case of NPS 1, we now have multiple approaches used in screening, with even greater variability in the use, or lack thereof, of second-tier testing. This programmatic variability extends to clinical insurance and support systems. With this level of diversity, no single pilot case detection tests the system, rather it simply assesses how the system worked in that specific circumstance, from which no generalized conclusions can

possibly be made.

Not allowing for an alternative pathway to the N-of-1 Rule sets up a needless hurdle to the consideration of a condition otherwise deserving of a RUSP nomination evaluation. In conclusion, we do not seek a wholesale overturning of the N-of-1 Rule, but merely an alternative road to RUSP nomination eligibility, wherein the component elements of the N-of-1 Rule can be adequately met to consider evidence review. Thank you for your time.

NED CALONGE: Thank you. Next I have Annie Kennedy.

ANNIE KENNEDY: Good morning. My name is Annie Kennedy, and I'm pleased to provide comments here today on behalf of the EveryLife Foundation for Rare Diseases. Of the 38 conditions that have been deemed by this Committee to meet the criteria for addition to the RUSP, the vast majority seek to screen for newborns whose conditions are rare.

The Committee is correct to consider a rare disease community in the context of public health and health equity concerns. Representing just shy of 10 % of the U.S. population, as rare disease patients, we struggle to access providers who have ever even heard of our diagnoses, let alone have access to decision tools, treatment algorithms and clinical care guidelines.

Most rare disease communities are marked by the scarcity of clinical experts, and within the estimated 10,000 rare diseases, fewer than 600 of them have ICD codes, meaning that conducting health economic studies, and tracking outcomes through

electronic medical records and public datasets, in most rare patients is just not possible.

Rare disease patients are in many ways invisible. And in fact, it is the preparation for a condition for the RUSP that often helps solve for many of these disparities within a specific rare disease. An excerpt from the American Public Health Association's code of ethics for public health specifically speaks to the issue of health justice and equity.

"Health justice and equity also extend to ensuring the public health activities do not exacerbate health inequities." As we consider enhancements to the evidence review process, we should be cognizant of requirements that may unintentionally exacerbate existing inequities and rare, such as N1 studies, and cost benefit analyses.

For we believe that no baby is too rare to save. And because of the work of this Committee, together with the stakeholders in this ecosystem, our communities are seeing that the success of newborn screening and the panel, has led to new populations of thriving young people. Communities represented by conditions on the original panel, such as CF and sickle cell, are now young adults in high school.

Members of the Pompe community who were first identified through newborn screening, and who received lifesaving therapy, are entering their tween years. And kiddos with SMA type 1, who were picked up through screening are now entering Kindergarten and first grade. And the truth is that they and

their parents are probably completely unaware that this Committee, or this room full of innovators and advocates even exists.

Some may not even know that had they been born just a few years earlier, prior to the landmark therapy approvals and RUSP nomination packages, that they may not have even have the opportunity to attend preschool. But they are living proof that our newborn screening system works, and that we have rightly prioritized screening for rare and serious conditions, whose outcomes can be significantly improved through timely intervention.

As we look ahead, we know that there are currently life altering therapies approved that are unable to be delivered to babies within the optimal therapeutic window. As we may hear in just a few minutes, there exists extraordinary promise for even more innovative therapies in development to transform the lives of rare patients even further.

We stand ready to support the work of this Committee, as we collectively strive to keep pace with a new generation of transformative diagnostic opportunities, and lifechanging innovative therapies because as a community, as a society, we know that no baby is too rare to save. Thank you.

NED CALONGE: Thank you for your comments. Next I'd like to invite up Christopher Curran.

CHRISTOPHER CURRAN: Hello. My name is Christopher Curran. Thank you for allowing me to testify in support of a federal requirement to add Duchenne newborn screening to the

standard newborn screening panel. My 13-year-old son, Connor, has Duchenne Muscular Dystrophy.

This disease is very difficult to diagnose in the early stages, and in fact, Connor had a delayed diagnosis at four years of age. Duchenne Muscular Dystrophy is a devastating neuromuscular disorder that deprives its patients of function, and ultimately their lives.

This disease slowly robs children of the ability to use their muscles. Walking is the first to go. Then the child loses the ability to feed himself, or even hug his parents, and then fatally ends in heart and lung failure by the time the child reaches his late 20's.

During the first four years of Connor's life, we were concerned that he was not able to meet childhood physical milestones as quickly as his brothers, but our family pediatrician advised us that there are wide variables to when a child reaches certain developmental milestones.

By the age of two, our concern and confusion grew over Connor's apparent muscle weakness. At this point, we decided to enroll Connor in the Connecticut Birth to Three program, which offers comprehensive early intervention for Connecticut residents. The team came up with a plan to try to strengthen his muscles through various exercises.

Unfortunately, these exercises involved the many eccentric contractions, or exercises that require the patient to put on the brakes, like walking down a steep hill. These

exercises are definitely not recommended for patients with Duchenne Muscular Dystrophy. They do more damage than good.

As Connor aged, he fell more often, had low endurance, and had a very difficult time walking up the stairs by himself. It was also a challenging time for us as his parents. We were frustrated that the months of Birth to Three therapy seemed to not help at all, and we were confused and worried about our child. It became increasingly more obvious that he was developmentally outside normal variables, and we were referred to a developmental pediatrician and neurologist, who diagnosed Connor with Duchenne Muscular Dystrophy.

This was a devastating diagnosis for Connor, and a heartbreaking one for all of us in his family. As difficult of a diagnosis that Duchenne is, early diagnosis would have enabled our Connecticut Birth to Three team to come up with a more appropriate exercise and stretching plan for Connor, and he would have been enrolled at birth, enabling him to benefit from the program, from the very beginning of his life.

Also, as parents, we would have had the opportunity to learn more about Duchenne, the fear and confusion that so many DMD parents experience when faced with limited information on why their child is struggling with basic physical abilities is real and traumatic. Knowledge is empowering.

When Connor was diagnosed there were not many available drug treatments except for steroids, however, early intervention with steroids would have benefitted Connor as evidenced by

published studies. In addition, many new drugs have been approved since Connor's diagnosis, which would enable newly diagnosed children to be treated on a proactive and timely basis.

Time matters with Duchenne. With every passing day kids with Duchenne lose strength and ability. Connor's story does not have to be the reality in this nation any longer. Early diagnosis is easy, with a simple blood test costing only $8.00. Right now, there's an opportunity make a historic and positive change in the Duchenne care in the United States. It is vitally important that we act now on a federal level.

Acting now ensures patient parents have every opportunity to address their DMD kids medical and physical therapy needs in an appropriate and timely manner. Acting now ensures that DMD patients are not inadvertently harmed by inappropriate physical therapy exercises. Acting now ensures that DMD parents and kids don't have to experience the confusion and emotional trauma that late diagnosis brings.

We are hopeful that DMD kids born in the United States will have the extraordinary benefit of early diagnosis and have the benefit of appropriate intervention. Thank you for your kind attention to my story.

NED CALONGE: Thank you Mr. Curran. Next we have Jason Dempsey.

JASON DEMPSEY: Good morning Committee members. My name is Jason Dempsey from Mason, Ohio, which is close to Cincinnati. It's very fitting that I followed the previous

testimony as my story is very similar as well. I'm here to talk about my son, Jude. He's nine years old, and he does share his name with a popular Beatles song, Hey Jude. That was on purpose.

It was nice that I got to talk to a lot of you via Zoom back in August. I'm excited to be here today to talk to you in person about the importance of adding Duchenne Muscular Dystrophy to the RUSP, and how it could have helped our journey. Early diagnosis of DMD is significant to us because we were not blessed with an early or easy diagnosis.

In December 2020, in the middle of the pandemic in the week before Christmas Jude was diagnosed with Duchenne Muscular Dystrophy at age six Long before that we had noticed Jude was missing those developmental milestones, crawling, walking, talking, and although he did hit those milestones eventually, we were still noticing some developmental issues such as toe walking.

That started us on a two plus year journey that included leg braces, intense physical therapy. All this was in an effort to try to resolve his toe walking by improving range of motion and strengthening his legs and core. After two years of physical therapy, and not getting the results that we had hoped for, it was suggested that we have the CK blood test to rule out any type of Muscular Dystrophy.

Sadly, the test did not rule out Muscular Dystrophy, and we were sent to the neuromuscular clinic at Cincinnati Children's Hospital where Jude underwent the full evaluation and genetic testing. That brings us back to that week before

Christmas in 2020, where Jude was diagnosed with DMD at age six.

Now Jude is a third grader. He rides a mobility scooter at school because he doesn't have the strength in his legs to walk to the lunchroom, or to go, you know, walk to recess, or walk to the art class that he loves so much. But I've often wondered if his daily life now would have been any different had we known sooner.

What if we had tested him at two and a half when we first noticed the toe walking? Or maybe if we had tested him when he first missed those developmental milestones at a year and a half, or what if we had tested him as a newborn, long before we even noticed any symptoms?

I do know that if Jude was diagnosed at birth we would have started him on Muscular Dystrophy protocols immediately, and wouldn't have spent over two years in physical therapy, which was actually hurting him and damaging his muscles. We would have also had the ability to participate in potentially life altering clinical trials that unfortunately he was aged out of by the time he was diagnosed.

So right now there are many treatments, gene therapies in development for DMD. One of them was approved by the FDA for ages four and five again Jude would have been too old to take that unfortunately. I'm hopeful that with these developments we are getting closer to hopefully seeing this terminal illness potentially turn into just a chronic illness.

I'm very thankful that this Committee is looking into

this topic, so we can take a step closer to testing our newborns, making a quick diagnosis, getting our babies the treatments that they need. In summary, quick call back to the reference I made about the famous song that includes Jude's name.

The lyrics to that song if you're familiar, they go, "Hey Jude, don't make it bad. Take a sad song and make it better." And that is the life lesson that I'm trying to teach my son, and ultimately why I'm here today. We want to take our sad song, and try to make it a little bit better for someone else.

So please strongly consider adding DMD to the RUSP, so that we can ensure that American babies that are in RUSP alignment won't have to endure a long and painful diagnosis like Jude did. Thank you for your time.

NED CALONGE: Thank you. Next is Lauren Stanford.

LAUREN STANFORD: Hi. Thank you for giving me the opportunity to make some comments here. My name is Lauren Stanford, and I'm the Director of Advocacy at Parent Project Muscular Dystrophy. On behalf of the estimated 15,000 individuals living with Duchenne in the United States, who underwent extensive, heartbreaking, and avoidable diagnostic odysseys extending an average of two to five years, I'm here to advocate for the addition of Duchenne to the recommended uniform screening panel, also known as the RUSP.

The addition of Duchenne to the RUSP will not only ensure that future babies born in the U.S. will avoid the irreversible consequences of the diagnosis odyssey, but will also

enable opportunities to introduce timely interventions during optimal therapeutic windows.

Duchenne Muscular Dystrophy is a progressive, genetic disorder. It robs children of their ability to walk and raise their arms. It can also significantly impact developmental endocrine, bone, heart and lung function, and is almost always fatal before age 40, and tragically sometimes even decades sooner.

PPMD has been tirelessly working towards the inclusion of Duchenne in newborn screening for over a decade. Our efforts aim to ensure timely diagnosis and optimal timeframe for interventions, and to enable the best possible outcomes for every baby born with Duchenne Muscular Dystrophy. Today we stand at a critical juncture in our ability to optimize health outcomes and Duchenne.

With deep understanding of the benefits of addressing developmental delays as early as possible, eight recent FDA approved disease altering therapies, and a pipeline of options on the near horizon. Early and equitable diagnosis is paramount. It means timely access to lifechanging therapies, and relieves families of the burden of delayed diagnosis.

Early identification is not just about extending life. It's about improving its quality, and empowering families to navigate the challenging journey with greater resilience. We value our partnership with the ACHDNC and appreciate you considering our community's request to postpone the vote on this matter as new evidence is prepared for your review.

PPMD is currently driving multiple projects that we feel have a direct impact on the current body of evidence. Included in those efforts is an analysis of longitudinal patient data on the impact of early intervention with steroids. We intend to submit our findings of this analysis for publication by late summer.

PPMD is also continuing to invest in the national and Duchenne newborn screening infrastructure. Last week we announced a $250,000.00 award to the University of Rochester to help bolster standardized capture of data from newborns identified at birth.

Through this effort, we are bringing together leading providers from Ohio, Minnesota and New York, where Duchenne has already been added to the state newborn screening panels, as well as other KOLs in Duchenne to establish uniform data collection for all babies that screen positive for Duchenne Muscular Dystrophy through newborn screening efforts.

In addition, we are also convening clinical leaders to further our work on the establishment of evidence based clinical care for newborns identified with Duchenne at birth. The addition of Duchenne to the RUSP would recognize the urgency of timely intervention in Duchenne and the profoundly positive impact we have on children with Duchenne when we introduce clinical and therapeutic resources immediately.

In conclusion, I encourage the Committee to support the addition of Duchenne to the RUSP as you continue your evidence review. We have laid the groundwork. We continue to strengthen

evidence for review, and we are working through solutions for long-term data collection, and care standards now in anticipation of adoption.

Together, we can change the trajectory of this devastating disease, offering hope and a brighter future for those affected by Duchenne Muscular Dystrophy. Thank you.

NED CALONGE: Thank you. Next we have Marit Sivertson.

MARIT SIVERTSON: Good morning. My name is Marit Sivertson. My husband I have three boys, one of whom has Duchenne Muscular Dystrophy. When Brecken was born in 2014, like all Minnesota newborns, he was screened for over 50 disorders. Little did we know then that the only test that mattered for a disorder more common than others on the RUSP was missing.

So like the families you've heard from, we spent two years navigating the health care maze to figure out why Brecken was missing milestones. Our concerns were dismissed by our pediatrician. To be told repeatedly that nothing is wrong with your child when your instincts say otherwise is deeply distressing.

Delayed diagnosis leads parents towards interventions such as physical therapy, which we know cause irreparable harm. By contrast, the FDA approved screening test for Duchenne is safe, effective, and requires just a few extra drops of blood from newborns heels. So why are we here? Arguing for Duchenne's inclusion on the RUSP. Some argue we shouldn't screen for disease without treatments, but that was the Duchenne of yesterday, not

today.

We have eight FDA approved treatments, one of which just made history as the first approved gene therapy. For my family, that milestone hit home. Four years ago Brecken received gene therapy through a clinical trial, and we've seen its EFFICACY. Brecken is thriving at 10 years old. He swims, he runs, he plays soccer.

We thought we'd never see these moments. Doesn't every family with Duchenne deserve them too? Unfortunately, that possibility is stymied by the slow adoption of screening. The FDA's Dr. Peter Marks recently said that a newborn screening we are not the United States, but the 50 states plus territories.

Absent that national newborn screening standard, the average age of Duchenne diagnosis is five years old. Despite decades of initiatives to lower it. Seven approved therapies, gene therapy included, are indicated for children five and under. That means that 28 % of five year olds diagnosed with Duchenne, 120 children per year will not be diagnosed by their sixth birthday, the current cutoff for gene therapy.

120 children each year, ineligible for transformative treatment at the time of diagnosis. Delayed diagnosis also costs money, an estimated $200,000.00 per family. Worse, the delay is even longer for families of color, and lower socioeconomic status. The lack of uniform screening creates inequities and exacerbates disparities even as our health care system strives to reduce them.

That is why now it is the time to provide equity across

all 50 states. Your evidence review must include all new and emerging treatments, whether FDA deems them safe and effective on a traditional, or an accelerated timeline. We have heard from this Committee debate theoretical harms of false positives or early diagnosis.

Fortunately, the readily available confirmatory test for Duchenne eliminates false positives, and the argument against early diagnosis overlooks the power of preparedness. Rather than waste time in a diagnostic odyssey, parents could evaluate treatments and clinical trials, apply for state medical assistance, and work with schools to help their children thrive.

As you deliberate today remember time is muscle. States have proven Duchenne can be added to existing screening for under $10.00 per patient. My home state, Minnesota, will soon follow Ohio and New York in Duchenne screening. As we battle insidious diseases that debilitate our children. Do we want to be the 50 states, or united in progress to save muscle and lives?

The answer is straightforward. This Committee can connect the dots between an existing screening test, an FDA approved disease modifying therapies for Duchenne. Please approve this nomination, seize this new day for Duchenne, and let science, not geography guide patient outcomes. Thank you.

NED CALONGE: Thank you. Next I have Paul Melmeyer.

PAUL MELMEYER: All right. Good morning everybody, and thank you for the opportunity to comment on the ongoing review of Duchenne Muscular Dystrophy for consideration for the recommended

uniformed screening panel. I'm Paul Melmeyer, Executive Vice President of a policy and advocacy at the Muscular Dystrophy Association.

MDA is proud to serve the Duchenne and spinal muscular atrophy in the Pompe disease communities, along with many other rare neuromuscular disease communities. First and foremost, we're very grateful for the Committee's continuing full evidence review for the Duchenne nomination, also particularly grateful for the work of Dr. Kemper and his team as well as the technical expert panel, on which MDA is represented.

We look forward to continuing to contribute to the evaluation during these quarterly ACHDNC Meetings, the TEP, in which we are a member as I said, and then any other appropriate venue. We're also grateful that the Committee is considering our and PPMD's request for a delay in voting on whether to recommend Duchenne for the RUSP.

We've requested this delay because we believe additional evidence that could be instrumental to the Committee's decision making on this nomination should be made public in the coming months. As PPMD already stated, our organizations are putting a particular emphasis on collecting longitudinal data on the early effectiveness of steroid interventions; more conversely, the health cost of delaying access to steroids, as steroids have been used in care for those with Duchenne for decades.

However, we do strongly urge the Committee to not myopically focus on steroids as the only intervention that when

they're administered earlier in childhood, could have positive health outcomes rather than waiting until the standard time of diagnosis.

Also happening this summer, by June 21st to be precise, is the FDA's upcoming decision on whether to expand the label of Elevidys, the only FDA approved gene therapy for Duchenne. While none of us can predict what the FDA will decide, various options include expanding Elevidys' label to all ambulatory boys, or perhaps the boys two years of age or older, and either of these options can be either an accelerated approval, or a full traditional approval.

Regardless, if FDA goes in this direction, hundreds of boys with Duchenne within that label could benefit from this gene therapy, but could go untreated for several years if Duchenne newborn screening is not recommended. Furthermore, these very same boys could access FDA approved exon skipping therapies, which are approved without any age limitations, and it is common knowledge that diagnosis of Duchenne is imperative to understanding when planning and implementing physical and occupational therapy among other physical activities attacks the muscle, as we heard this morning from several families.

Please remember, and I'll reiterate again, one of the conclusions here. Time is muscle, and there is no stage of this disease--no stage, whether clinical symptoms are observed or not, in which muscle is not being damaged by Duchenne. And without the technology to reverse muscle degeneration currently in existence,

this delay is irreversible.

Again, we're very grateful to the Committee for considering delaying the vote on adding Duchenne to the RUSP as we collect and submit additional evidence, and await FDAs decision on Elevidys. But as the Committee continues to deliberate, we further implore other Committee members to consider all interventions that preserve muscle from the moment the child is born, as a reason for why Duchenne newborn screening is appropriate.

I will just close by saying this might be the final meeting of a handful of the Committee members. I just will thank them for their service, and appreciate the time you spent on the ACHDNC. Thank you very much.

NED CALONGE: Thank you. We're now going to turn to folks online, and first I have Craig McDonald. And seeing that we don't have Craig, I wonder about do we have Crystal Proud? Hi Crystal, we can see you.

CRYSTAL PROUD: Hi. Thank you so much. I'd like to thank the Committee for permitting me to share some considerations regarding newborn screening for Duchenne Muscular Dystrophy. I'm Crystal Proud, the pediatric neuromuscular neurologist, and I'm the Director of Neurology and Neuromuscular Medicine at the Children's Hospital of the King's Daughters.

I cared for hundreds of patients with Duchenne Muscular Dystrophy over the past more than ten years, and I witnessed the evolution of therapeutic interventions that are radically changing

the outcomes for our boys impacted by this degenerative and devastating disease.

As you know, DMD is a genetic disease that leads to progressive muscle weakness, and loss of the ability to walk between the ages 10 to 13, and early mortality with death usually by age 28, attributed to cardiopulmonary insufficiency. Natural history has been well characterized, and permitted the capacity for us to detect meaningful change, with interventions including some recent advances in therapeutics, some of which have been described here today.

Prior to now there may not have been significant benefit with early identification of boys with DMD as far as survival goes, due to the lack of disease modifying therapies. However, over the past several years we've been able to see the approval of several disease modifying therapies for Duchenne. Most of these therapies are indicated and approved for patients younger than the average age of diagnosis.

In my region, for example, unfortunately the average age of diagnosis is much higher than what you've heard earlier today. It's around age six or seven years old, because at this point boys are demonstrating sufficient weakness that leads to slowness, or inability to go upstairs, tripping and falling and incoordination that separates them from their peers.

Oftentimes it's their elementary school teachers that bring them to my clinic. We know the path of physiology of disease is present even by the time these boys are born. We have

evidence on muscle biopsy as well as serological biomarkers of muscle destruction, even on the day of their birth.

And thus, it's clear that we're diagnosing patients clinically well after the pathophysiology of disease has progressed to a degree such that the full impact of these therapeutics we've talked about, may not be optimized because they'd be ineligible to receive therapies, or they would have been eligible to receive therapies earlier had they been diagnosed at a younger age.

In addition, they'd be permitted to be supported by comprehensive multidisciplinary care that's been demonstrated to prolong survival. Now, my clinical judgment informs my treatment recommendations to my patients, but I can't offer treatment options to patients who are not yet aware of their diagnosis.

FDA has exercised its scientific judgment and has granted broad labels to enable access for several Duchenne therapies at the earliest possible time the expert treating physician, clinician and families decide. Many of these restore dystrophic expression, and have demonstrated efficacy regarding motor function, pulmonary function and cardiac function.

Now, regarding motor function, we know that once boys lose the ability to ambulate, they have a predictable pulmonary decline which ultimately contributes to their early death, and thus treatments have demonstrated a distinction and a shift from natural history, ultimately will lead to increased survival for our boys with DMD.

I'm hopeful this Committee will accept the FDA's determination that the potential benefits of interventions of treatment, including dystrophic and restoration therapies, like exon skipping and gene transfer therapies will outweigh the potential risk no matter the age, including at the youngest ages, before fibrotic changes have led to irreversible muscle damage.

Understanding that these are guided by discussions with expert clinicians. I myself have treated 26 boys with gene transfer therapy, including boys as young as two years old, and I've seen the impact of these therapies over the past more than four years that have been lifechanging.

Newborn screening for Duchenne should be a straightforward proposition. The screening test is FDA cleared, the sequencing confirmatory tests accurately identifies affected patients with the FDA approved therapies, with more in the pipeline.

It's a new day for patients living with Duchenne, and even more so if we can diagnose them when muscle damage presents, which is at birth. Thank you so much for hearing my comments today.

NED CALONGE: Thank you. That ends our public comment session for today. I want to pause long enough to thank especially the parents for coming today, preparing such thoughtful comments, and I know we all appreciate hearing from you, and the impact of this condition on your children. Thank you for coming.

At this time I'd like to take a ten minute break.

We're a little bit ahead. I think that will get us started at maybe ten minutes early at 11 o'clock, and we'll proceed with the meeting at that time. Thank you.

Break

(Break.)

Regulatory Process for the Review of Drugs for Rare Diseases

NED CALONGE: Thanks. Our first presentation of the meeting will be on the Regulatory Process for the Review of Drugs for Rare Diseases. And we're delighted to welcome Dr. Anita Zaidi, as our speaker. Dr. Zaidi is a team leader in the Division of Rare Diseases and Medical Genetics in the Office of New Drugs at the FDA.

She earned her medical degree at the University of Missouri and Kansas City, and completed her internal medicine residency at Banner University Hospital in Phoenix, Arizona. She joined the FDA as a medical officer in 2017, and has been a team lead since 2021. She serves as a leader on a multi-disciplinary team in the review and evaluation of scientific data to assess safety and effectiveness of new drugs, specifically of those rare genetic diseases. Welcome, Dr. Zaidi.

ANITA ZAIDI: Thank you.

NED CALONGE: And make sure you talk into the mic.

ANITA ZAIDI: Can you hear me? Okay. I do have a PowerPoint. Thank you so much for inviting us. I'm really happy to be here to try to explain our regulatory review process. It can sometimes seem a little bit complicated. So, just this is my general disclosure statement. I don't have any conflicts of interest, and nothing to disclose, and the talk reflects my views, not necessarily those of the FDA.

So, my outline is basically I'm going to talk about the definition of a rare disease, and orphan products. The regulatory framework of drug evaluation, and then the benefit risk framework, and then I'll talk a little bit about the Advisory Committee, and then also the pathways for approval, which it sounds like you might actually know. And then just, you know, my conclusion.

So, and the definition of a rare disease by the Federal Food Drug and Cosmetics Act defines it as a disease or condition that affects less than 200,000 persons in the United States. An orphan drug is a drug or biological product used for the prevention, diagnosis or treatment of a rare disease in the U.S.

And so, the orphan drug is probably not important here, but in general, if you know, if a drug has orphan status, it doesn't have to abide by something that we call PREA, which is the Pediatric Research and Equity Act. If you do not have PREA, or if you do not have orphan status, then you are required to provide a pediatric study plan, meaning that you have to either--you have to basically state that you can come up with a plan for a clinical

trial design for your drug to treat in the pediatric population.

Obviously, most of the rare diseases, probably what we're talking about here, they do have orphan status, so they don't need to abide by this pediatric study plan. So, I think everybody kind of knows a little bit about this, but there's a lot of challenges in the rare disease drug development, and so because of these challenges it's been very difficult to try to have to try to develop drugs for rare diseases because we are having trouble coming up with a good clinical trial design to show that these drugs are safe and effective.

Some of the issues are that there's, the natural history is poorly understood. These diseases are progressive, and serious. There's no adequate, approved therapies, and because of that we don't have any precedents. The small populations, that's one of the biggest issues is that we have these little populations. We don't have the sample size to really be able to show good effect.

And then the Phenotypic and Genotypic diversity within a disorder, so these are your rare diseases, and then on top of that each patient presents differently. And then the development programs themselves will have the lack of solid translational background, meaning we don't even have the nonclinical studies, the animal studies to kind of show the drug effect in these diseases.

And then we just, you know, there's not a lot of research in the outcome measures, and the biomarkers that are

often used in the clinical trial design, the end points. And then of course again, there's lack of precedent. So if we don't have any--if we don't have anything to go off of, and so this is sort of a challenging space. This is an unknown space for a lot of these diseases.

So, we have that. And so, in general, to be able to approve a drug you have to have two adequate and well controlled studies. Each persuasive, meaning that they have to be two completely independent studies. An adequate and well controlled study basically means that you can distinguish the effect of the drug from other influences, right?

Now, the idea of getting two well controlled studies in the rare disease is basically impossible, right? So, it's hard enough to get one trial. To get enough patients enrolled into one trial, so to be able to do that for two is, you know, it's a big ask. So, we do have a new complimentary standard that came out in 1997, which is the one adequate and well controlled trial, plus confirmatory evidence.

And again like confirmatory evidence is that independent evidence that this drug works. And so, this is sort of the route that we go for a lot of rare diseases. And then, of course the adequate well controlled trial has to show that there's benefit of the drug that outweighs the risk of the drug.

So, I won't go into a lot of the detail about the confirmatory evidence, but the important thing to know is that you need the one adequate and well controlled trial. You know, that

shows up, there's no, that--you can see an effect that nothing can compound that.

Plus the confirmatory evidence, which is the independent confirmation of that benefit. There is actually a guidance that came out in 2023, if you want to go you can look at that into more detail. So, when we are looking at the approval for possible approval of a drug, we have to determine that the drug is safe and effective, and you'll hear us say that over and over again at the FDA, is the drug safe and effective.

Effective basically means that there's substantial evidence that the drug will have the effect, or is represented to have under the purported labelling conditions of use. Safe isn't really defined, but it's because we know that all drugs have risks, so it really is just a demonstration that the safety of the like the safety is basically that the benefit of the drug outweighs the risk of the drug.

And so, broadly speaking the benefit risk assessment in FDA's drug regulatory context is how we make the informed judgment whether the benefit with the uncertainties outweighs the risk with its uncertainties, or ways that we can manage those risks under the conditions of use, and it's always--and we'll describe that in the labeling.

And of course, one of the most important things is that we always recognize the input of the patients because it's their experience that helps us inform the benefit risk assessment. They understand the therapeutic context. They understand whether or

not those benefits are actually, are meaningful to them.

They're the ones that can tell us whether or not how much risk they're willing to accept, and how much uncertainty they're willing to accept. And so we have to balance the perspective of the patients with the judgment, with our own judgments and the data to determine the overall benefit risk of a product for the patients.

So, in any drug that's approved, that our review is public, and I have the website so that you can pull it up, but in the very beginning of the review we have a benefit risk framework, which you see here. And this is sort of a synopsis. And the reviews themselves are like 100 pages, but this is sort of a synopsis of that review, and it's how we make our determination for the approval of a drug.

So, the first two rows are basically the therapeutic context, so the condition and then what are the current treatment options. And then the bottom two columns are the benefit and risk management, so that's actually looking--when we're looking at the evidence of the drug, the data that the clinical trials have provided, the confirmatory evidence that the drug has provided.

So, the benefit is the efficacy, and then the risk and risk management is all the safety issues. So what I'm going to do is I'm going to actually go through a case study of a drug that was approved in 2022. This is called olipudase alfa. It was approved in 2022 for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency, ASMD, in

pediatric and adult patients.

It's an autosomal recessive lysosomal disease that , results in a deficient activity, and acid sphingomyelinase, an enzyme that metabolizes sphingomyelin into ceramide and phosphorylcholine, so what we see of course in a lot of these genetic, rare genetic diseases there is multiple kind of subsets. You know, there's a lot of heterogeneity with this.

So this one has three subtypes, which is Type A, which is the most severe form which has profound CNS involvement hepatosplenomegaly, interstitial lung disease, and they barely--they usually don't survive past two to three years.

Type B doesn't have CNS involvement, but it also has hepatosplenomegaly and interstitial lung disease. And then Type A is sort of an intermediate form with some CNS symptoms, but they also have hepatosplenomegaly, and interstitial lung disease. And so I want you to look at basically so the indication right, what you see, is just ASMD.

We did not, you don't see a sub-type, and you also note that it just says pediatric patient, so we don't have an age restriction. And so, I'm going to go into a little bit more detail of how we came to that indication.

So, this is actually me copying and pasting from our review, and it's public, again, so you can look at that. And so, this is the first row, which is the analysis of condition. And when we talk about the condition, we of course talk about the patient perspective. And so, the clinical trials looked at

reduction in spleen volume, and then they looked at DLCO, which is basically improvement in the lung volume.

And so, when we were looking into that one of the questions is does that matter to the patient? Do they care? And especially with the splenomegaly right? So people can have splenomegaly, but it's not something that's you know, something that they notice, right? It's not meaningful to them. And what we did note is that the organ enlargement is actually clinically meaningful to them.

And so, you see that in the red is that they do note that they actually have a lot of issues with pain and vomiting, feeding difficulties, just from the organ enlargement. So we note that saying okay, that so that end point is actually meaningful to them. So then, the other thing is the current treatment option. So until Olipudase was approved, there was no current treatments for it.

That's always something that's always going to be in the back of our mind right, is, are there treatments? Is there anything else there? Right now there is nothing available. And then we look at benefits. So I'm not going to go into the efficacy because it was efficacious. You know, there was improvement in the spleen volume, there's improvement in the lung quality. We know that.

But the big question was that you see in the red box in the left, no patients less than two years of age were treated, and were enrolled into this clinical trial. And also, no patients

with ASMD Type A, the most severe form, it has the CNS manifestations. They were also not in this clinical trial.

So then our question was because these patients were enrolled do they become--do we exclude them from the indication, you know? So that was, it was a big discussion that, you know, that the review teams have to think about right, because we don't have a lot of evidence, right? We have no clinical trial evidence, right?

But, so we had to look back at the disease itself, right? And so one thing we know is that the disease is still similar, even though the ASMD Type A patients had CNS manifestations, which is different, they also still had the hepatosplenomegaly, they still had the ILD, the interstitial lung disease, and that mechanism of that disease is the same in a Type B and Type A, right.

So, we're like okay, even though they may have some different with the CNS, the peripheral symptoms are still the same. The other thing we considered is are the less than two patients different than the greater than two patients? We did— still, it was sort of a, I don't want to say mechanism, but it was a spectrum, right.

So even the less than two patients, they still had the same disease. They still had the same peripheral manifestations. A one-year-old versus a three-year-old, it's no different than what we know from the literature and from the experts. And then the last thing is what does the drug do? So Olipudase is an

enzyme replacement therapy. We don't expect it to work differently in a one-year-old versus a three-year-old.

So in that, when looking at all those, and then of course the last thing is are there any drugs available for these patients, and there's not. So, when we looked at kind of those considerations, you know, we decided to expand that population. But the last thing is what's the risk. We have very minimal safety data.

We have, I think there was an expanded access use, but overall we don't have safety data on those patients, right? So what can we do to make sure that they aren't at an increased risk with taking this drug that, you know, the patients that are over two, or the patients with ASMD Type B.

And so we do have so we did ask them to do a postmarketing requirement, which basically means they have to follow any patient under the age of two, and any patient with ASMD Type A, and they need to follow these patients for safety to check to make sure that they aren't at increased risk for any safety issues.

And something that we kind of also look at is, you know, is there going to be off label use? It's always something that's there, and so this is sort of also a way for us to be able to actually document safety. If there is off label use, we're never going to get any information from those patients, so this would be our way to get information on those patients.

So that's sort of how we kind of came to that

determination of the label, of the indication. So this is just basically the website, so any drugs that are approved are in the public domain. It's the FDA labeling website, but it also contains all the reviews.

And so, and then I think that benefit risk framework that I showed you, it's been there probably for at least the last ten years, so if you don't want to read the full review, you can at least read the beginning part of it, and then if you have questions you know, you can be able to go back down.

I will say that drugs that are not approved, those are still considered proprietary information, so that information on those drugs would not be in the public domain. So the other thing I want to talk about is that something that we do consider. I will say that our division, we have not had an Advisory Committee, but as you guys know, we are developing one.

But for most of the other divisions they do have an Advisory Committee, which is where you can receive input from subject matter experts, patients, academia, and other external stakeholders when we're evaluating the potential benefit and risks of a new therapy. And this is actually, this is when there's a lot of transparency because now the public kind of sees the information that we get.

And this is where the experts can really discuss the sum of information in our analysis, along with you know, the sponsors analysis. And they can provide a public opinion and recommendation. And then of course there's the public hearing too

regarding that product under discussion.

So we are developing one for the rare genetic diseases, and I think we're still looking for people, so if anybody is interested and wants to put their name in the hat feel free, just like you know, diseases are rare, there's not very mean rare disease experts, so of course we're always looking.

But basically this will be a forum, a discussion of experts knowledgeable in the fields of medical genetics and inborn errors, small population trial designs, translational silence, we are looking at a lot of that, especially since we don't have a lot of clinical information. Pediatrics, epidemiology statistics, and of course like the related specialties.

And it's going to have nine voting members, including a Committee chairperson, and we're pretty excited about this because like I said so if we do decide not to approve a drug, it doesn't go--there's no public forum for that, so people are kind of in the dark about why a drug is not approved, but at least with the Advisory Committee's at least the data is out there now, so that there's a little bit more transparency.

So I think I know that some people had already talked about the accelerated approval pathway, and the traditional pathway, but I'll just kind of touch on that too. So, there are the two different pathways that you can use for approval, so I'll just like kind of the biggest difference is that with the traditional approval it's all about the end point.

The approval pathway depends on the end point, so the

traditional approval, it measures how a person survives, how they feel, how they function. Or is it a validated end point that we know predicts clinical benefits, so like blood pressure. Blood pressure itself doesn't really matter, but we know that blood pressure affects cardiovascular outcome, you know, there's a good understanding of that.

There's no postmarketing studies that are required to confirm efficacy, and that's really important because you do want an adequate well controlled trial, right? And so to do that after a drug is approved can be complicated to say the least. So the accelerated approval pathway is basically looking at a marker that reasonably likely to bring clinical benefits, so usually a biomarker, but because it's reasonably likely we still need that post approval confirmatory trial that has to be adequate and well controlled, to look at actually a clinical end point.

And so, that's one of the big differences. And also, for accelerated approval there are different conditions to receive that. Basically, it has to be serious or life-threatening disease, and again it looks at an end point that's reasonably likely to predict clinical benefit, or it could be a clinical benefit that measures something earlier than you know, universal morbidity or mortality, and of course if there's lack of alternative treatments.

Again, saying this again, but serious condition. It can also be something that's meaningful advantage over like the available therapy, so increased compliance, better safety profile,

things like that. And again, the big thing is you still need to have that post approval confirmatory trial to evaluate, so evaluate that clinical end point.

So these are just like two examples of drugs that, in the rare disease space that have received approvals. A traditional approval was Velmanase for--it's an enzyme replacement therapy approved for the treatment of non-CNS manifestations of--I forgot to add it, but it's Alpha-mannosidosis in adult and pediatric patients, and this looks like a clinical end point, so three minutes stair climbing, six minute walking test, forced vital capacity. Those are things that we all consider clinically meaningful to that patient population.

Accelerated approval, Migalastat, which is a pharmacological chaperone, was approved for a treatment of adults with Fabry Disease and an amenable gene variant. So the efficacy of that was based off of the substrate GL3 reduction in the kidney. So that's not, that's sort of a biomarker. We're not really sure what that means, and so they do have to do post approval confirmatory trial to confirm that that's actually that reduction is actually clinically meaningful to the patients in regards to either improvement in renal function, or slowing of renal decline.

So just in conclusion, so approval considerations for drugs and biologics, if that substantial evidence of effectiveness, again like the adequate and well controlled trial, and then demonstration that the benefit outweighs risk, which is

you know, the benefit risk framework that I showed you. And then we do always take into account the scientific opinion of the Advisory Committee if it's applicable at that time.

We do have the different approval pathways, but they still have the same statutory standards for safety and effectiveness, so we still follow the same benefit risk framework regardless of the approval process that we're looking at, so. Any questions?

NED CALONGE: Thanks so much for a wonderful presentation. I hope you're willing to stand up there and have a few questions?

ANITA ZAIDI: Yeah, of course.

Committee Discussion

NED CALONGE: We're going to start the discussion with Committee members first, and then we can move on to organizational representatives. As a reminder, please raise your hand and unmute the microphone in front of you. For those on Zoom, please use the raise hand feature when you would like to make comments or ask questions.

And when speaking, please remember to unmute yourself, speak into the microphone, and state your first and last name each time you ask a question or provide comments to ensure proper recording and attribution in the report. Thank you. So with that, are there any questions? I'm going to start with Christine

Dorley.

CHRISTINE DORLEY: Good morning. Thank you, Dr. Anita for a really good presentation. Just out of my own curiosity regarding the nontraditional approval for drugs. I just wonder how robust is the process for reporting postmarketing, whether there are any safety issues, or other issues that are developed? How quickly is that reported? And what is the frequency that the drug manufacturer has to report to you regarding that follow-up postmarket?

ANITA ZAIDI: Yeah. So actually they have strict requirements, so we do what--you actually, I think you can see it on the--I can't remember if it's actually on the website, but we do require certain dates that they have to be able to make, so when they have the protocol in, when they have the data, and when they have their analysis in, and then the final reports.

And then for safety they do have, we have, so if there's a death it usually has to be within 24 hours. If it's a serious adverse event it has to be within 15 days, so we do have basically different kind of ways for them to follow through with the postmarketing requirements.

CHRISTINE DORLEY: Okay. And then one last question that I have. Do you have any idea of the rate of pulling these nontraditional pathway medications off of the market because of safety issues, or other things that may come up?

ANITA ZAIDI: So when you mean nontraditional, you're talking about the accelerated approval?

CHRISTINE DORLEY: Yes, uh-huh?

ANITA ZAIDI: Yeah, so you know we didn't have the best pathways, but I think after I just forgot the name of the drug, but there was a recent withdrawal of a drug where you did remove a drug from the market. So now, we are developing kind of stricter guidelines about being able to withdraw a drug. But I will say it's actually it used to be very difficult to withdraw a drug from the market under accelerated approval.

But I think there's been an understanding that we do need to have better guidelines for that, so there is, they're still working on it, but I think it's getting better in regards to being able to do that. But I think we usually ask the company to just withdraw the drug themselves, so which a lot of companies have done too.

CHRISTINE DORLEY: So what would be the qualifying, I guess, metric that would say to this drug manufacturer pull this drug? Would it be one person to die, or more deaths, or severe reactions?

ANITA ZAIDI: It really it depends because so, it depends on how, so I guess if you're looking at so within the accelerated approval pathway, we're looking at actually efficacy, right? So we'll pull a drug if their postapproval trial fails, then we have grounds that we can try to pull a drug. For safety it kind of goes through different measures because it depends on if it's a specific patient population, then we can restrict labeling.

So, it kind of depends on what the event is because we may not pull a drug if it's only affecting certain patient populations. We may restrict labeling. We have kind of, we have other ways that we can keep the drug on the market for the people that it may benefit, but restricted for the ones that are actually you know, that may be developing those symptoms, so I think it kind of depends.

NED CALONGE: Thank you. Other questions from panel members? Oh hi, Jennifer.

JENNIFER KWON: Hi. I really appreciated Christine Dorley's, I'm sorry, start over. Jennifer Kwon, Committee member. And thank you for that great talk. Probably it's saying something bad about me that it was so illuminating, and I really appreciated Christine Dorley's questions because I think a lightbulb went off about the accelerated approval process, and maybe a follow-up question would be how long do you give companies to provide you the data to make it an official approval, or is it always under an accelerated approval?

Because and I'll just give you an example, because that's the one thing I need just to be concrete. We prescribe a drug called Eteplirsen, or EXONDYS 51 for Duchenne patients, and I, you know, I'm just involved in the order writing, you know, start forms, letters of medical necessity, all this stuff, all the paperwork to say why it's efficacious in this patient with particular mutations.

And I'm looking at the most recent prescribing

information, and it still says it's approved under accelerated approval in the prescribing information. And so, I'm just kind of because it's been around, of course, a long time, so I was just curious about if there's a limit, if that's still correct, how to think about this.

ANITA ZAIDI: Yeah, there's not really a limit because the postapproval trials, it really depends on what the postapproval trials are. If it's a long trial, then I'm not sure about that drug specifically, so I don't know what their postapproval trial is. Also, sometimes depending on the type of disease if they fail that trial, or it wasn't statistically significant, but we think it might have been a design issue.

We may allow them to try to do another trial. So it's really dependent on what that postapproval trial is, and where they're at with that because they may be doing like a ten year study. I'm not sure, so that might be why it's under the, why it's still considered under accelerated approval, or if their first trial wasn't statistically significant, then we may allow them to do another trial, you know, trying to redesign what their trial is.

So then again that's like, you know, it might be another few years.

NED CALONGE: Melissa?

MELISSA PARISI: Thank you. Thank you for your presentation. My name is Melissa Parisi. I'm from the NIH. And I had a question about the Genetic Metabolic Diseases Advisory

Committee, so I think you mentioned that this is a relatively new committee that is just being stood up.

Although I don't have personal experience, I have heard that the Committee that given drug or entity gets referred to can result in differences in outcomes with regard to the approval process.

So I'm just wondering whether this new Committee is likely to be handling all of the new drugs that are related to conditions that are commonly seen by this Committee inborn errors of metabolism, or whether there's like to still be this differential between new drugs that might end up going to a more neurologically focused Advisory Committee versus one that may be more GI focused for the hepatosplenomegaly type things.

Given the fact that, you know, so many of the conditions have manifestations that are both CNS as well as multi-organ involvement?

ANITA ZAIDI: Yes, so the Advisory Committees are dependent, they're stood up by the Division, and so this one is specifically for my division, which is the Division of Rare Diseases and Medical Genetics. And so, we deal with a lot of ultra-orphan diseases, but for instance, like Duchenne is under the Division of Neurology, so they most like have their own Advisory Committee that might be looking at their drugs.

And same for like if it's mainly a GI focused rare disease, then it's probably going to be under the GI Division, and they have their own panel of experts. I think we do pull from the

other divisions, or the other Advisory Committees, but yeah, it really the Advisory Committee is very dependent on who, which division is actually going to be the one that's managing the review.

NED CALONGE: Sean?

SHAWN MCCANDLESS: Thank you, Shawn McCandless from the University of Colorado. Thank you. That was great. I wonder if you could discuss the thought processes and efforts to develop and assess novel or innovative study designs for rare and ultra rare diseases that are occurring in the Division of Rare Diseases and Medical Genetics at Cedar.

And also, the follow-up question would be could you speak a little bit to your thinking, or the Division's thinking about statistical analysis, and especially how to think about the pre-stated statistical analysis plan when outcome measures are not so clearly well-known or understood for the condition?

ANITA ZAIDI: Yeah. I mean so we're--I feel like our division is all about the novel and new designs. I mean we know that being able to do, you know, the normal, you know, parallel group, randomized control trial, phase one, phase two, three, is incredibly difficult, so we actually are.

And one thing we try to encourage is because it's a rare disease population, there's not a lot of patients. We want to leverage as much data from each patient as we can, so we're always encouraging sort of the seamless trial design so that we can get as much information out of those patients that we can

because just doing a phase one, phase two, phase three separate trial, you're not going to get enough patients for that.

So that's one thing we're always encouraging sponsors is to try to leverage patients. And then, in regards to the statistical analysis, I can't speak for, but I know our statisticians are very flexible. I mean our goal is we know that you can't, it's really difficult to get a good sample size, right, to get statistical significance.

But, and so we do try to work with the data that we have basically. You know, the importance of course is what's the quality of the data, but we do work with like the clinical outcome end points, with the understanding that maybe they won't be statistically significant, but what we do see is still clinically meaningful. I'm sorry, I forgot what else you had.

SHAWN MCCANDLESS: No, I think you addressed some of it. I'm just wondering if you see the innovation in study design coming from FDA, or is it more that there's an openness to consider innovative study design?

ANITA ZAIDI: Well, I mean it definitely, it kind of depends. It comes from us, but we're also open to it too. You know, if sponsors can come to us with a trial design that we think is actually going to be an adequate, well controlled trial, that we'll get good data out of. You know, we're always open to looking at that, so we're always open to ideas because we know that one can help us with another sponsor too, so.

SHAWN MCCANDLESS: And just one quick, two quick

follow-ups. Could you tell me what you mean by seamless trial design is the first question. And the second follow-up is around the statistical analysis. Does that mean that for this division there may not be such a strict requirement for identifying a primary statistical analysis around a primary outcome, and that failure there limits the ability to look at data further?

ANITA ZAIDI: So I guess first, the seamless trial design is when we kind of we'll combine a trial instead of having a separate phase two, phase three, which is the dose finding trial, and then a phase three, which is the pivotal trial looking at the end point that's going to be used for commercialization.

We've asked sponsors to combine that where they'll do the dose finding at the beginning, and then they'll continue to follow those patients, looking at the primary end point that's going to be used for the trial. So it's basically just trying to combine trials, and we're usually open to kind of what the different ideas that different sponsors have.

In regards to end point, we do need to always prespecify the end point. No matter what, you always ask for them to prespecify a primary end point. And I know there's a lot of difficulties because there is no precedence in a lot of diseases. This is very much an unknown territory, which is why we like whatever early, you know, like understanding the natural history, doing kind of that early, kind of the early hypothesis testing is really encouraged to be able to kind of come up with a primary end point.

But we do understand also that you know, there may be failures, which is where we always try to kind of look at everything, right? We look at the totality of the evidence, you know. So, but we do want a prespecified primary end point of where they are expecting to see success, so.

NED CALONGE: Jeff?

JEFF BROSCO: Jeff Brosco from HRSA. It's more of a clarifying question, and maybe some of the Committee members might want to weigh in a well. I can imagine for a lot of people they would say well, there's a newborn screening test, there's FDA approved therapy, why isn't it on the RUSP, and make those connections.

And part of what I heard, and I want to clarify with you is that the FDA doesn't necessarily take into account sort of the timing of things, that is someone has a condition, they're treated for it and it's about safety and efficacy, and benefits outweighing risks, whereas for the Committee it's also partly is treating from newborn screening, additionally beneficial too if you did it in a clinical situation.

And did I get that right? FDA doesn't really include the timing part of it in that sense?

ANITA ZAIDI: No, no, I mean we just look at kind of the data that we have. We don't when we're looking at the approvals we're not going to be looking at whether or not there's newborn screening available. The only time we have considered newborn screening is during the clinical trial design phase, and

if they're wanting to treat, you know, pre-symptomatic patients, and you know, if they have a patient population for that.

JEFF BROSCO: And it also sounded like when you're weighing risks and benefits you're taking into account the context where you know this may be a condition for there's no other treatment. This may be the only option for a doctor and a patient to consider in a shared decision-making way. So it sounds like there's more space for uncertainty in that.

ANITA ZAIDI: Yeah. No, definitely. If there's no treatment available, we do have more flexibility with that because you know, as long as we have some safety and efficacy data, you know, then we'll take that in consideration.

NED CALONGE: Kind of related to that question, when you say well controlled, so I want to make sure that everyone understands this is in the context of when we usually think about treatment, which is after symptoms occur. So this isn't the screening space. But in well controlled, historical controlled, so there's a famous Canadian Medical Journal and JAMA series on when to start using a new drug.

It talked about study design, needed to be randomized control trial, except it provided kind of what I think is still a little bit of a controversial exception. There's the disease that's universally fatal, and you start treating people, and not everyone dies, then that historical control is an adequate control.

ANITA ZAIDI: Yeah. I mean definitely, it's also I

guess an ethical issue too, so but yeah, no it's all about having for historical controls it's really a good understanding of understanding that natural history, and understanding what the historical control is, you know.

If it's a disease that is yes, like we know that it's going to be fatal by the time they're age four, you know, that's a good historical control, because basically kind of the morbidity mortality aspect of it, and the fact that it's a homogenous thing, you know. If it's a heterogeneous disease where some people survive, some don't, then it's a lot harder to consider historical control in that sense.

NED CALONGE: And I think that's where we wrestle a lot because understanding kind of the from a genetic standpoint it would be the phenotypic expression because of the screening to disease proportions and understanding that I think are important.

The other is a comment on the makeup of the Advisory Committee you're planning, and I would just say you might want to think in addition to your small study design, an expert in the methodology around evidence to decisions.

ANITA ZAIDI: Okay.

NED CALONGE: So, there's a rich knowledge base there that spans over nations and internationally grade group for example considers areas where evidence is low, but that evidence, the decision is a little bit different than both novel study designs, and small population study designs, so just something to think about.

ANITA ZAIDI: Thank you, that's helpful.

NED CALONGE: Thanks. Okay. Turning to our organization oh sorry, Jennifer, you're first.

JENNIFER KWON: Sorry, Jennifer Kwon again. I promise to leave time. I just wanted to you made it sound like I just wanted to follow-up on the issue of accelerated approval. You made it sound like when drugs get accelerated approval there are post approval activities that the company should do to try to, you know, make it a full approval.

But my understanding is that's not always the case. Can you help me understand that better?

ANITA ZAIDI: So actually, they are required by law to do a post approval confirmatory trial, so to provide clinical to provide evidence of clinical efficacy, so there's no way around that. If they have accelerated approval they have to it's a postmarketing requirement by law, so.

NED CALONGE: Thanks. I'd like to first turn online to Debra Freedenberg.

DEBRA FREEDENBERG: Hi. Debbie Freedenberg, AAP. And I think you clarified most of my question, but when a drug is approved through the accelerated approval, and has postmarketing requirements, is that significantly different than the phase four monitoring that's required for drugs that come through their traditional pathway?

ANITA ZAIDI: Yeah. So that's--so for the accelerated approval pathway you have to, it's a postmarketing requirement for

efficacy. So it's looking at evidence to make sure that the drug works, and provides efficacy on the clinical outcome. For traditional approval you can do safety PMRs, so that's a postmarketing requirement looking at safety.

So for instance, for like I mentioned with Olipudase it received full approval, or traditional approval, but there was uncertainties about safety in the patient population, so we asked them to do a postmarketing, a PMR looking at specifically the safety, to assess safety in that patient population.

DEBRA FREEDENBERG: Thank you.

NED CALONGE: Thanks Debbie. Robert?

ROBERT OSTRANDER: Robert Ostrander, American Academy of Family Physicians. We--first of all, spectacular, incredibly well-organized and clear, and even the answers are well-organized. I'm so impressed. Anyway, we struggle here all the time with dealing with the end points that are more qualitative and having to do with quality of life and a functional status, and meaningful to the patients in deciding how much to assess just the kind of quantitative disease.

We struggle all the time with – God, my voice usually carries without, I guess we've got to do this online. We struggle with trying to sort out how to weigh and how to measure, and how to consider qualitative patient centered functional and quality of life kind of impacts all the time on this Committee when we're making assessments.

And you know, those same kinds of harms from

indecision, you know, lack of clarity and uncertainty. And I was interested, even some examples of your inclusion of patient input on that impact in the patient's life, the significance to that. And what I'm curious about is how is that gathered?

Is that something that's required of the submitting company to gather? Is it something that you gather? Or is this something that you guide them in gathering?

ANITA ZAIDI: So we usually will ask the company to provide that information, but we also kind of have our own ways to gather that information through we have patient listening sessions through the FDA, and then PFDD, which is the patient focus drug development, in which our other sessions where they provide their input.

NED CALONGE: Chanika?

CHANIKA PHORNPHUTKUL: Chanika Phornphutkul, Committee member. Just to follow up on the accelerated approval. So you mentioned that it's by law that this plan is in place, but if I understand correctly, there is no timeline? And how do we reconcile that?

I think for myself that I prescribed some of these medications that have accelerated approval, and the end point is generally a biomarker that we may or may not be able to obtain outside of the study. For example, the DLL3 accumulation in the kidney, right? So, I'm struggling a little bit of you know, how do I really prove that it is helpful for the patient.

And as a clinician, I also have to justify the

insurance, and then that is often one of the markers. When it's the traditional approval, you know, improve six minute walk, easy. You know, we can show and if there's no improvement, then we can have a discussion. But when it's a biomarker it becomes a little more challenging, and I'd like to get your thoughts on that. Thank you.

ANITA ZAIDI: No. I definitely understand. It's the accelerated approval pathway is very difficult because of the postapproval trial, and so there is a timeline. It depends on what that postapproval confirmatory trial is, but we do have specific requirements of, you know, when they have to have the protocol in, when do they have to have their interim result, and then their final results.

But it's really dependent on the drug, and it depends on what that type of trial that is. And again, like I said, if they fail that trial, or if it wasn't completely statistically significant, then we may allow an extension to that where they can do a new trial. But I understand it's really, really difficult going this pathway, and biomarkers, like you said, like you know, biomarkers aren't significant to patients, you know, they don't know what that means, and so we really try really hard to actually get those post-approval confirmatory trials.

Our division, and I think most divisions, are trying to require that they enroll those trials prior to submission of their application, of their drug application because of the difficulties that we've been running into, so I completely understand.

CHANIKA PHORNPHUTKUL: Just a follow-up question. So when the drug comes into the FDA do you prefer the traditional path, or how do you distinguish between those two requirements aside from being rare and uncommon?

ANITA ZAIDI: It really just it comes down to what the end point is. If there's uncertainty on what that primary end point is, then you know, that's when we confirm accelerated approval pathway because we want to confirm that there is an actual clinical meaningfulness to that drug versus if that primary end point we know is clinically meaningful, then we'll go the traditional pathway, but yeah.

For instance, for the biomarkers it's difficult because we want data to support that, but yes, but it comes down to the primary end point.

NED CALONGE: Michele?

MICHELE CAGGANA: Hi, I'm Michele Caggana, Committee member. I think you said that FDA relies on the company to withdraw a drug from the market, but is there a pathway for FDA to assert that they do that? Is there any mechanism that you have, or a guidance that you're creating?

ANITA ZAIDI: So if the company wants to withdraw the drug, they can withdraw the drug. If we are forcing them to withdraw the drug, there is a pathway, but I'm not 100 % clear on what that pathway, like I can't explain to it, but I know there is a pathway. We've done it before. But I will say it's not common. It's not common to do.

But I think before there was really no pathway, and I think now it's starting to be we're starting to develop an understanding of how to do that so.

NED CALONGE: This is Ned Calonge. Chanika's question made me start thinking about does FDA ever think about the link between FDA approval, especially in the accelerated protocols, and medical necessity, which is the bar for insurance coverage?

ANITA ZAIDI: No. We actually don't look--consider insurance in our decision making.

NED CALONGE: It would be interesting to see the timeline between approval, or whether there's a correlation at all between the approval of a drug from FDA, and coverage because it's medically necessary. Sue Berry?

SUSAN BERRY: Hi, Sue Berry from the Society for Inherited Metabolic Diseases. I actually accumulated several questions, so I hope you'll bear with me. I won't take terribly long. The first question I had for you was definition of appropriate biomarkers, and for our area this has been a source of struggle, finding a meaningful biomarker that is acceptable in the framework of a trial.

Because often such things don't exist, or the biomarkers that are available really don't mean very much. An example, I know it's lovely to reduce phenylalanine and PKU, but is that the only thing that you're trying to do? Is there something more meaningful to the patient and to the long-term outcome for an individual?

Or ammonia is a terrible biomarker, but the only thing we have for urea cycle disorders. This is not a very reliable marker. It's hard to measure, so that's my first question. The second one has to do with the utilization of natural history studies. NIH has paid millions of dollars over the years to assist in rare diseases in promoting as a key element in their rare disease studies.

The use of a natural history as a fundamental element of the rare disease consortia, and so they're at this point are accumulated evidence for many years for some disorders, but none of that data was collected under FDA approved strategies.

And so, those large bodies of data aren't necessarily acceptable as natural history, and I think that's kind of too bad. So if you could comment on what constitutes a natural history. And the final one is rare diseases are rare, and so if more than one company wants to have a drug, those of us who take care of those patients are hit constantly with, bombarded with, can you enroll this, can you enroll this, can you enroll this, can you do these 15,000 things to this patient, and then can enroll in another trial.

And, or you can't be in this trial if you've been in another trial. And so, how do you talk about making the maximum utility for rare populations? So that's a lot, I can repeat any of them if you forget because that's three, thanks.

ANITA ZAIDI: So I guess the first question is on the biomarker. I mean biomarkers are the easiest to measure, which is

why I think a lot of companies and sponsors try to go that route versus looking at clinical outcomes, especially in the rare disease population where it's going to be kind of hard to really assess, you know, whether or not there's efficacy, because there's a lot of what do you call it, because there can be a lot of outliers.

But you know, we kind of--we have to go back to that goes back to kind of the sponsor, that goes back to the academics, to really be able to identify, you know, what is clinically meaningful, and what can be measured as clinically meaningful. And we have to give that back to them to be able to make those decisions.

We can help guide that, but they're the ones that kind of have to look at that. In regards to the natural history studies, natural history studies are great to be able to help. I mean natural history are what's used to help develop the biomarkers, to understand the patient population, to understand the clinical outcomes.

I think if they do want to come in to look at that, then I mean we'd be happy to look at those natural history studies, or those protocols to help kind of guide the design of that, but you know. And I guess the other question is, you know, if there's multiple different natural history studies.

I guess this goes back to, with the sponsors with multiple clinical trials, you know. The one thing we've seen is that we see all the sponsors that come in for one disease, but we

realize that everybody is sort of siloed out, and so we're really trying to encourage a lot of like data collection amongst the sponsors, data collection of their natural history, trying to come together because you know, having different sponsors and academics kind of siloed all over.

It's you know, very small populations, and we'd be able to put that together into one data collection, I think that would provide a lot of like information.

SUSAN BERRY: But do you have to start from the beginning? I mean seriously when there's 20 years of experience in the natural history study, why would you do another natural history study?

ANITA ZAIDI: Well, there is, so I don't know if you know about C-PATH, so if you've heard of them, but they're basically they've been funded by the FDA and it's basically they're looking at trying to collect all of those old natural history data to be able to have it in one collection, in order to be able to try to make something out of that.

So we are trying to encourage basically, just trying to put all this together.

NED CALONGE: And then the final question from Natasha online.

NATASHA BONHOMME: Good morning everyone, Natasha Bonhomme from Genetic Alliance. More so just a comment to add to the discussion here. I just wanted to call out that in the FDA's Omnibus Reauthorization Act of 2022, that there was included for

accelerated approval, provisions that helped FDA to enhance those expedited withdrawal pathways for products that have actually been approved through accelerated approval.

So, if they hadn't met their postmarket requirements, so that is there and has been enhanced as you mentioned. And you know, even for example, really recently FDA worked with a company to withdraw an ALS therapy I believe, that had been approved via accelerated approval, and via the accelerated approval pathway, but didn't show clinical efficacy.

So, I think it's important to know that those pathways are there for withdrawal, and that FDA does do that work collaboratively with companies. So, I just wanted to add that in there that there's actual, you know, federal law around that. Thanks.

NED CALONGE: Thanks. So I hope everyone will join me in acknowledging and thanking Dr. Zaidi for a great presentation and really good discussion, and thanks for coming in and spending so much time with us.

(Applause.)

NED CALONGE: I'll turn things over to Leticia.

LETICIA MANNING: Thank you all for joining us this morning. We're now going to enter into our lunch period. For those of you that are remaining within the building, there is a cafeteria right across the way. If you exit out the doors that you entered there's a little a store, a kiosk, where you can buy some items, some snacks, they have sandwiches in there also.

If you do choose to leave the building, please note you will have to enter back through security, and that may take some time, so plan accordingly. And now we'll break for lunch, and we will return at 1:00 p.m. Thank you.

Lunch

(Lunch).

Duchenne Muscular Dystrophy Evidence-Based Review: Update

NED CALONGE: All right. Let's start our afternoon session, and first up is going to be Dr. Alex Kemper, who is the Lead of the Evidence Review Group, and Division Chief of Primary Care Pediatrics at Nationwide Children's Hospital, and Professor of Pediatrics at the Ohio State University College of Medicine.

Dr. Kemper focuses on the delivery of preventative care services, including newborn screening. Since 2013, Dr. Kemper has also served as Deputy Editor of Pediatrics, and he's going to give us an update on the DMD evidence-based review.

ALEX KEMPER: So thank you, Dr. Calonge, and members of the Advisory Committee. First, before I get into my presentation I want to thank the other members of the Evidence Review Group. I'm not going to read all their names, but I believe the list of

names listed here.

I would also like to acknowledge that Dr. Lisa Prosser has been a member of our team for too long for me to even mention, has taken on a senior leadership position at the university to the north of the Ohio State University, and so I want to publicly thank her for all the work that she's done with us, and we're going to have another person who is going to be leading the decision analytic model, and I'll talk about that in the future.

But really, Lisa has been a linchpin for our work in the past. I do want to acknowledge her. As in our prior work we also have a robust technical expert panel that guides us, and helps us understand the evidence we're looking at, and also plays an important role in identifying evidence that we may not be aware of.

So, again I'm going to thank them for their input into this presentation. I just want to highlight some things about Duchenne Muscular Dystrophy, which most people are aware of, but I think it just helps frame the conversation that we're going to be going into. So as everyone knows, Duchenne Muscular Dystrophy is a severe and progressive neuromuscular disorder.

It's part of the group of inherited conditions characterized by progressive muscle weakness, and it can impact other systems, and for example, can also be associated with intellectual disability. It's an x-linked condition. Some female carriers are symptomatic in terms of the overall incidents, depending upon the population.

You look at it in particular studies somewhere between about 70 and 30 per 100,000 live newborn males, and fewer than about one per million live born females that are affected by DMD. There are other important dystrophies, and one that I would like to highlight is Becker Muscular Dystrophy, which is also caused by a mutation in the same gene, the gene for dystrophin.

Unlike Duchenne Muscular Dystrophy, which has an absence or near complete absence of functioning protein, Becker Muscular Dystrophy has a reduction of functioning in the dystrophin, so it's associated with later onset, and less severe involvement, so it's a later phenotype.

And the incidents of Becker Muscular Dystrophy is, you know, somewhat less than eight per 100,000 live born male births, so less common than Duchenne Muscular Dystrophy. I've spoken about this before in this group, and so I'm not going to go through it in great detail, but just want to highlight the Duchenne Muscular Dystrophy is characterized by weakness that clinically presents beginning somewhere typically around one to three years of age, but the diagnosis oftentimes doesn't happen later, even up to an average of five years.

You've heard about that in the public comment period. Without treatment and often times even with treatment there can be continued muscle weakness, eventually leading to loss of ambulation, comorbidity is associated with loss of ambulation, occur later.

Sometime in the late teens to the 20's, the respiratory

problems become more important factor, which is life threatening. There could be a cardiomyopathy later, and eventually premature death. So, with that by the way of background, just to let you know where we are.

We had the first technical expert panel called back in October, and the second one in March. We've had additional key informative interviews, groups that we specifically looked to for additional information, including the Institute for Clinical and Economic Review about a 2019 report that they did on some of the medications, sometime later.

Another expert, Dr. Kevin Flanigan, who's at my institution at Children's Hospital, about issues of the genotype, phenotype prediction. Dr. Catherine Riley was down the street from the Centers for Disease Control and Prevention around MD STARnet, which collects information on individuals affected by Muscular Dystrophies.

And then Dr. Hadley Smith and Dr. Kurt Christensen, from the Harvard Medical School, about work that they're doing around modeling the potential impact of DMD newborn screening. It's our plan, and we're working towards in the near future Dr. Smith will be playing the role previously played by Dr. Lisa Prosser, and we're very excited about that.

The literature review is still ongoing. The public health system impact assessment, which is the survey of programs regarding readiness and feasibility began in January, and by March about three quarters of the programs had responded. There's

additional follow-up with other states, including two that are planning to implement newborn screening. I'll talk about that in a little bit.

And as you learn a little bit more, the decision analytic modeling is to become--is forthcoming, and really depends upon better understanding of the impact of early identification presymptomatic identification entry, compared with usual clinical identification.

So, I'm going to be talking a lot today about what we know about presymptomatic treatment, but before I get to that I do want to provide a little bit of information about where things are in terms of states, and newborn screening for DMD. So, in terms of the states that are planning to begin newborn screening, there's Ohio, Minnesota, and New York.

Obviously, these slides prior are to April 22, 2024, and what I can let you know is that Ohio has begun their screening. In addition, there's legislation that has been introduced in Arizona and Illinois to implement DMD newborn screening. In terms of how they're going to do it, Ohio plans for first tier CK-MM testing, and then newborns with elevated CK-MM are going to be referred to whoever their primary care clinician is to determine the next steps.

So, second tier testing is a part of it, and it's really going to be guided by what the clinician decides. In terms of New York, and Dr. Caggana if you can correct me if anything has changed since we got this information, but the plan is for CK-MM

with interpretation, the clear tool is going to help interpret it. And then a second tier repeat CK-MM for newborns with elevated CK-MM, unless it's so high that it's above a particular cut off value that seems likely to represent disease, at which point there's a referral to a specialist for diagnostic evaluation, including genetic testing, and the specific approach to genetic testing will be determined by the specialist at that time of referral.

And then Minnesota is planning to have first tier CK-MM testing with second tier genetic testing that's going to be contracted to an outside laboratory. And I appreciate that things change as states move towards adoption, but this information that we have thus far.

APHL did, as I mentioned before, complete the survey of newborn screening programs, and the top challenge is related to implementing DMD screening, including the availability of staff to report and track infants, the need to increase the newborn screening fee to cover the cost of adding CK-MM, and then molecular testing, in terms of figuring out who is going to be responsible, and how that's going to be organized.

But hopefully, as you can tell as I described, there's other states, there's different ways that states can choose to do that. In terms of readiness, nearly half reported that it would take two to three years to implement DMD in newborn screening, after they have the authority to screen, and the programs would need to purchase additional instrumentation to be able to move forward with the screening.

But really what I'd like to do is focus on our work related to presymptomatic identification of DMD versus usual case identification, and you know, that's really our charge for the Advisory Committee is to, or at least one of the many charges I should say, but to illustrate the benefits and the potential harms of identification, through newborn screening versus what might happen through usual care, I'm going to point out gaps.

Obviously, just because we can't find evidence to fill in the gap doesn't mean that that benefit doesn't exist, but I'm going to share with you where the gaps that we've identified are. It's nice that I'm going after the FDA discussion from this morning because as you heard when the FDA gives approval, they're really focused on whether the drug is effective to treat, you know, in our case individuals with Duchenne Muscular Dystrophy, not whether there's an incremental benefit from earlier treatment.

And that's a point that I'm going to be making a lot as we go through this. So, to help you understand how our group thinks, I wanted to talk about a framework that we use when thinking about the benefits to the affected child. These are specific things that we explored as we went through the evidence, so we think about direct health benefits.

So, are there studies that describe improved quality of life, or longer length of life, or are there functional improvements that you expect to see that would be related to those things, so things like motor status, the ability to ambulate, cardiac status, pulmonary status, neuro development.

These are just some of the examples of the kinds of things that we look for to be able to find benefit for the specific affected child again, comparing early identification versus when it might happen through the usual clinical care process.

We actually looked at benefits to the family, so avoiding the diagnostic odyssey, avoiding ineffective therapy. Earlier options for potentially affected pharmacologic and non-pharmacologic treatment, so we talked a lot about drugs, but there are other things that could be provided.

The ability to prepare for the future, issues of making a diagnosis in other family members, and the, I believe, early identification to inform reproductive decision making. We also looked at additional benefits that didn't clear fit in any bucket, but I do want to put them out there.

So, improved health status before eligibility for gene therapy or other novel therapies. So we've heard about how the gene therapy is approved for children who are four and five years old, currently. Maybe early identification, even if they don't get the gene therapy until they're four or five allows them to be healthier at the time that they get the access to gene therapy.

We've looked at earlier access to treatment trials, and then we also looked at evidence around the degree to which newborn screening could help address the issues of health equity. And so, we heard during the public comment period about how minoritized children may not get diagnosed until later, and then miss the

window for gene therapy.

And so we specifically look for information around that as well. We also look for harms, so there's this issue of the prognostic odyssey that's, you know, you have a, you're identified through newborn screening, but you're not, you know, sure what the phenotype is.

We look for evidence around patients and waiting, evidence around limited information to inform decision making or treatment options. Issues that might come up around system barriers, including poor access to care. That may not be a harm in itself, but it's something important to surface, especially if there's a movement towards newborn screening, and increase some of our patients there getting into systems through care.

We looked at adverse effects of earlier treatment. One of the things that we looked into is the issue of if you get a treatment with gene therapy, which is delivered by a viral vector, the AAV vector that you might have ineligibility for future gene therapies because you develop antibodies to the viral vector.

And then of course exposure to ineffective therapy. So, just go back for a second. So, I'd lay this out there just so that you get sort of an understanding of the waterfront of the kinds of things that we were looking for. It doesn't mean that we found something as you'll see for all these categories.

But we are really, really interested in finding whatever we could around these issues for newborn screening. This didn't fit clearly in any other place in the presentation, but I

do think that it's important to highlight, which is there is this industry guidance from the FDA for DMD drug treatment therapy, that really grew out of a really unique partnership between the FDA industry and advocates within the DMD community.

I put a link to the documents, and there's a quote up there about the importance of engaging with the disease community. So this was published in 2018, and there's draft guidance that was published in 2024. Again, this in itself doesn't change what we're doing in terms of the evidence review, but it was just a novel way of showing how the DMD communities partnering to advance things that I wanted to mention it.

All right. So now I'm going to talk about a brief overview of pharmacologic treatments. So, in general, there's no curative treatments currently. Corticosteroids are the standard of care treatment. They reduce inflammation to slow damage. They don't reduce damage that's already there. There is another class of medications the Antisense Oligonucleotides, or the exon skipping therapies. I'm going to apologize in advance. I find myself going back and forth between the two terms, instead of sticking to one. I'm going to do my best to stick to exon skipping therapies, because I think it's easier to remember what it is that they do there, but if I ,slip I apologize.

These are genotype specific exon skipping therapies, so if you they allow you to essentially skip over like a stop codon if there is some other problem, and so that you get more functional protein. And the goal is to increase the dystrophin

expression, you know, perhaps even making Duchenne Muscular Dystrophy more like Becker Muscular Dystrophy by increasing the amount of dystrophin that's expressed.

Gene therapy leads to micro dystrophin expression, so the dystrophin gene and the protein are big, and it's bigger than what you can put into this virus that is used for the gene therapy, and so there's a smaller version of it that puts in what's referred to as microdystrophin, and the idea there is that if effective, you could modify things.

So, an infant with more like a toddler, a four to five year old, would have would be able to be more like an individual Becker Muscular Dystrophy instead of Duchenne Muscular Dystrophy, just by virtue of producing more of this protein. Okay. All right.

So, this is a list of the drugs that are out there, and then indication and how things are dosed. I'm not going to read through each row. Everyone would be happy to hear me say that, but just to point out a few things. One, is that the exon skipping drugs are delivered by IV infusion that's done weekly.

Gene therapy is a one-time single treatment, and then there are different treatment strategies with the corticosteroids. So I'm going to be talking a little bit about that in a second. Many of the medications on this list had accelerated approval, so you know, there was a discussion earlier this morning about Eteplirsen, which was approved in 2016.

There was an FDA, I don't know if it's a request or a

requirement, for a clinical trial with outcomes related to motor function. I'm not sure if that's been done yet. I haven't seen it, but again our focus is on early treatment versus later treatment. So if it's there, and I'm not aware of it, I apologize.

So, what I do want to do though is now dig into key studies related to the potential outcomes of DMD newborn screening, and at the risk of sounding--at the risk of repeating myself, again our focus is on early identification versus later identification.

So, as I think everyone knows, one of the things that we tend to take a hard look at are sibling reports. In rare disease it can be hard to, you know, certainly do perspective studies, and sibling reports can give you insight into earlier treatment versus later treatment.

So, you know, not surprisingly right, siblings typically have the same biological background, and obvious similar environments, and it can fill things up when there's no screening, right, so cases aren't picked up by screening, and there's just not those treatment trials.

And typically when we look at sibling reports there are things that we look for to make sure that we can interpret them. So, the diagnosis or the phenotype of each sibling, just to make sure that, you know, we're not comparing apples to oranges. A description of the therapeutic intervention so we can understand exactly what the older sibling and the younger sibling receive.

One of the things that's really important to our standardized outcome measures when the siblings are the same chronologic ages, right? So you don't want to compare, you know, one person when they're ten to another person when they're three years of age, for example.

And to the degree that it's a measure that's replicable, and understandable is really important. And then whatever information we can find to support the generalizability of the findings. So for example, having sibling reports with multiple families can be helpful.

So, we're not able to find any peer reviewed publications. We did find meeting abstracts, and I'm going to go through them in detail in a second, but none of them presented standardized outcome measures at similar chronologic ages, so it's really just hard to interpret from these sibling studies what the benefits are.

So, there was one abstract that described three brothers with specific deletions who were treated with Eteplirsen, that was one of the exon skipping drugs at a 108 months, 79 months, and 24 months, but it lacked clear information on the outcomes at the same chronologic ages, and was really difficult to draw anything specific from this study.

There was another study that described, and again, these have been presented in abstract form, but not in full publication. Two sets of siblings who were submitted from certified Duchenne care centers from a total of six sibling sets,

so it was a limited number of the siblings that were available.

And the reason that not all six of the sets are listed there. There was, for example, in one case of an error where they weren't actually siblings, so the bottom line is we're just limited to these two sibling pairs. The first sibling set there was an individual who was diagnosed at seven years of age, receive corticosteroids at eight years of age, and lost the ability to ambulate by 14 years of age.

And the younger sibling was diagnosed at five months, corticosteroids were started at five years, and we're told that at seven years he runs with some rest. He has the inability to jump, and does not use mobility aids. But again, this is an example where you're going to have, you know, the same information at the same ages, which again would be helpful for our purpose.

In terms of the second set, there was one who was diagnosed at three years of age, and began on the Eteplirsen also three years of age. Corticosteroids at four years of age, and switched to Viltolarsen at six years of age. And at six years he has age appropriate gait. The other--this individual sibling was diagnosed at four months of age, started Eteplirsen, the exon skipping drug, at 10 months of age, corticosteroids at four years of age, and then switched over again that year to Viltolarsen.

And at four years of age he has age appropriate gait, and does not have--but does have cognitive defects. I apologize about that. But again, this is helpful, but not ideal in terms of not having the same outcomes at the same age. And then the next

one they talked about is a description of 17 sibling pairs.

The younger siblings were diagnosed on average 2.7 years or earlier than their older siblings, and begun on corticosteroids 0.8 years earlier, so it's interesting to me that the diagnosis earlier didn't necessarily lead to the same degree of earlier initiation of corticosteroids.

The abstract says that visual inspection of the North Star Ambulatory Assessment score, we talked about that in the past. It's the standardized metric of motor function, shows that after eight years of age the younger siblings consistently scored higher values, but it didn't provide the actual data for us.

So, next I'm going to switch gears, and we're going to talk about studies that specifically address the issues of early corticosteroid treatment. So the first is a prospective study of twice weekly corticosteroids, so getting corticosteroids just two of the seven days a week, compared with an untreated natural history comparison group.

I'll follow it out for a year. So again, the prospective part was the twice weekly corticosteroids, and compared to an untreated group that didn't receive this care. The primary outcome was the Bayley-III gross motor scale score, which looks at sitting, standing, locomotion and balance. Remember, in this case, higher scores are better.

The average population score is 10 with a standard deviation of three. So, in looking at the baseline, so at the time for the prospective part when patients were followed forward

in time for a year. There were 23 subjects in there whose average age was 1.5 years. And their Bayley-III gross motor scale score is 4.2, with you know, plus or minus 2.5, so some individuals are more impacted at the start.

And they compared that to a natural history group of 12 who were, you know, nicely matched in terms of age. The Bayley-III gross motor skill score on average was a little bit higher than among the 23 followed prospectively.

So what did they find? Well, after 12 months of treatment there was no statistically significant improvement from baseline in the treatment group, so 4.2 to 4.8 over that 12 months of time, again that was the group that received the corticosteroids. But contemporaneously with that natural history comparison group declined by 1.3 points 12 months after baseline.

So the natural history group again went down a little bit. The intervention group, the group that got steroids, you know, has essentially plateaued. They didn't provide a statistical assessment of the difference at the end of 12 months between the treated group, but the different sector 12 months between the treated group and the natural history comparison group was--I'm sorry, let me say this again.

The difference after 12 months between the treated and the natural history comparison group was significantly, significantly different, but it was driven by those in the treatment group who had a low motor score at baseline. So, they reported the P value that was driven by those who had a low motor

score at baseline.

And there's no effective age at baseline on the treatment outcomes, and this is a case where the disease progression appeared to be a more important predictor of the benefits, of the more severely affected individuals than if it weren't.

I do also want to talk about a meeting abstract that gets to this issue of earlier diagnosis and corticosteroid initiation. This was a retrospective look at males with DMD from the Duchenne registry who are born in 2000 or later. The outcome was a subset of the score of the pediatric outcomes data collection instrument, PODCI.

It's based on caregiver or parent report. It has a cumulative score for eight items related to lower lymph functioning, with a score from 8 to 32, and in this case lower scores are better, okay? Lower scores are better. They also looked as a secondary outcome, the age at fulltime wheelchair use for subjects who were over 14, and there was 188 of them.

So, they compared in the snapshot early diagnosis, so diagnosis before one year of age, to the average age of diagnosis, which was four to five years of age, and they compared earlier corticosteroid treatment, so two to three years of age to average corticosteroid treatment five to seven years of age, so these were categories that were selected for the purposes of this study, okay.

So I'm going to repeat this again just to be clear.

They compared two different things. Early diagnosis to average age of diagnosis, and early corticosteroid treatment to average corticosteroid treatment, okay, so two sets of comparisons. So, in terms of the age of steroid initiation, if you were in the early diagnosis group, so you were diagnosed before one year of age, the average age of steroid initiation was 4.2 years.

If you were in the typical diagnosis group the average age of steroid initiation was 5.2 years, so there's it seems to be this one year delta based on early diagnosis. Now, I mentioned before one of the key outcomes in this abstract was average age for wheelchair use. There's no P value provided, but early treatment was associated with wheelchair use by 12.9 years of age.

And typical treatment, which was later, was associated with wheelchair use at 12 years of age. And what this speaks to, and again this is from a poster, we didn't have the full report, is that there's this complicated variability between early diagnosis and early treatment.

So, just because you have early diagnosis doesn't mean you have early treatments, and there are likely factors that confound when you decide to begin corticosteroids, and of course this is a study that went back to 2000, as I mentioned before, and there's been a movement younger for treatment with corticosteroids.

I do want to share this one figure which I took from the poster. This shows the mean score that I talked about, and on the X axis is age at the muscle function survey, and the Y axis is

the score. I'll just remind you all again lower scores associated with lower score is better in terms of the motor ability.

The red stippled line is just the full dataset. The blue line represents those with the early steroid start, and the green line shows those with the average steroid start. So, the scores at 9 and 11 years were lower, if you look at it for early treatment, with mean scores and this is a quote from them, "consistently lower at all ages," but there's no P-value provided.

It's a little tricky to look at this because some individuals had multiple scores, and there is no adjustment for that clustering that would happen over time, and the number of each age wasn't provided. The other thing is, remember that because not all individuals appeared at all time points, the assessment isn't necessarily longitudinal, right, so some may be coming in later versus earlier.

I can't comment on the sample size at each age. We're not able to stratify on what led to the diagnosis. We're not able to stratify based on baseline disease involvement issues of regime, adherence, adverse effects, withdrawal, those kinds of things are considered, and I can't comment on other therapies.

But, you know, this is you know, part of the stream of evidence suggesting that there may be a benefit from early corticosteroid initiation. All right. I'm going to switch gears now and talk about earlier exon skipping treatment. So, this was a recently published study. It's online. I had to print the references there of course.

This study recruited 579 subjects from the manufacturer's patient support program, and they had available the dates of the Eteplirsen initiation, and when it was discontinued, and the date of death, or the last stage that the subject was known to be alive, and they were able to also pull in other information from their clinical trials participation again because of you know, the access to data by the manufacturer.

And what they did was they compared this to natural history studies. They actually took five different natural history studies and combined them all to be able to try to infer the benefits of Eteplirsen. So, among the Eteplirsen treated subjects, the average age that it was started was 11.9 years, with the range from 1 to 35 years of age.

So, and the published report didn't stratify age further. The average duration of the Eteplirsen exposure was 3.7 years. The median survival, you've seen typical survival analysis curves were when you know, people you know, when they weren't sure about people anymore, you know their information was censored.

The median survival overall was 32.8 years compared with the median survival in the natural history group of 27.4 years, and you can see the ranges again. Now, again, it's not-- we're not focused on whether or not the drugs could be effective, but whether or not earlier identification leads to better outcomes. But again, just comparing overall those were treated to those who weren't, there is this difference in survival with the lower hazard of death in the survivor curve analysis.

So, in the study it talks about how effective it is in improving survival, was reported to be better with earlier age at initiation. But the study didn't have the kind of information that we would need to specifically piece this out because they didn't stratify by earlier age of diagnosis versus later age of diagnosis.

They just put it overall into a model, and you know, sort of assumed that things are linear, and there are other potential compounders that weren't addressed, such as what led to the diagnosis, other therapies, the health status diagnosis over time as well. There's one of the things you have to think about too is that you can't, you know, I don't have the specific ages when treatment started, but let's say the subject started at five years of age.

When survival curve analysis you have to be careful not to give the individual credit for getting earlier treatment. They essentially have to survive up to the point when they began with treatment. And that can skew the data, it's called immortal time bias. They tried to look at immortal time bias in the study, but that may have also contributed, but the bottom line is we don't know the numbers of individuals in the younger ages, and how that was tied to outcomes.

So, there's another meeting abstract that I just want to highlight. These were included subjects who were reported by clinicians who began exon skipping therapy before three years of age, and who were treated for at least one year of age, and had

some outcome measure.

And, I've just listed the five cases here. You can see when they were diagnosed, including one subject who was diagnosed prenatally. You can see when they began exon skipping therapy, and again they don't have standardized outcome measures reported. The abstract, and I'll just read this quote, "Gross motor delays were common with only patients three and five, those were the ones who were started two months and five months, meaning typical milestones, including walking at 15 months of age."

Again, we're not able to take this kind of information and infer if there's a benefit of early diagnosis. So, gene therapy, as you all have heard many times, is approved for children four and five years of age. Certainly, early detection could facilitate timely access.

In the public comment period you heard very well, very forcefully about how, you know, without an earlier diagnosis you could potentially miss the window, and there may be disparities related to that. But you know, again, sticking to our requirements for studies we were unable to identify studies about the degree to which early detection has led to improved access or better outcomes for gene therapy.

Now, there was this recent publication that I want to point out about parent perspectives. Again, we're very interested in not only the affected individual, but the whole family. This was a study that recruited parents or guardians of at least two living children with Duchenne Muscular Dystrophy in the United

States from the Duchenne Registry who have completed a web-based survey that was done in partnership with Parent Project Muscular Dystrophy.

And they classified their lived experience with early diagnoses as benefits, harms, either a benefit or a harm, a little bit of both where they didn't experience it. And then they standardized the scores from benefits, which are plus one to a harm minus one. And a zero being, you know, essentially in between them.

And I'm going to just move to show this figure, which shows the perceived benefits and harms. You can see the categories listed in black from everything from access to support services, school preparedness, time to evaluate option site, asked to see clinical trials and so forth.

And then everything, you can see things that were benefits in blue, benefits and harms in yellow, and then the harms in red. The one category where there seems to be more red is around worry, but in general, the parents perceived the benefit, the overall mean across these categories was .39.

I personally feel like you know sort of averaging across all these different dominions. I'm not sure how helpful that is, but again I just want to highlight what these parents perceived. So, I'm not sure about the overall participation rate. There's no form of qualitative analysis, the open-ended questions would have been interesting to sort of drill into things a bit more. And then there was no mixed methods assessment linking

diagnosis treatment, patient family level of outcomes, those kinds of things.

But, I will highlight that you know having done these kinds of presentations a lot, this is the first time that at least we've had parents surveyed like that. So in terms of summary, what I can say at this point is that newborn screening for elevated CK-MM can identify infants with DMD. We talked about that before, but I'm really focusing on treatments here.

As we talked about before, we can also identify other dystrophinopathies, molecular analysis can help predict the phenotype. The experts feel that 90 % of the time, at least with molecular analysis, you can predict whether it's going to be Duchenne Muscular Dystrophy, or Becker Muscular Dystrophy.

States are implementing DMD screening, and ultimately it's going to help fill in some of the evidence gaps that have been identified. There are important evidence gaps around benefits and harms of identification through newborn screening compared with usual case definition.

Limited information from sibling studies, none of which have appeared in the peer reviewed literature, and you know, in previous presentations that's been very helpful for the Advisory Committee. So again, we're still climbing through the systematic evidence review, double checking to make sure that we haven't missed anything, and also looking for new great literature that meets our inclusion criteria.

As I've said to members of the technical expert panels,

certainly if something comes across your desk that fills some of these gaps that helps us better understand the benefits of presymptomatic identification, compared to usual case identification, you know, we would be very much interested in that.

Of course, anybody who hears that call, would be interested in getting that information. The decision analytic model is really on hold while we make sure that we understand what the benefits of presymptomatic care are so we can develop a more meaningful model.

And again, you've heard components of the public health system impact assessment in order to allow me to have time to focus on the treatment stuff, I didn't drill more into the public health system impact assessment. So I'd like to stop there and open things for questions.

NED CALONGE: Thank you Dr. Kemper. Questions from the Committee for Dr. Kemper starting with Shawn McCandless.

Committee Discussion

SHAWN MCCANDLESS: Shawn McCandless, Committee member. Thank you, Dr. Kemper. You know I'm going to have questions. Yeah. I apologize. Shawn McCandless, Committee member. Thank you Dr. Kemper for that nice review. You know I have questions.

At the very beginning you said that you were talking about the incidents, or birth prevalence of the disorder, and I

didn't really follow the data. It looked like it was, I think the numbers were 13 to 18 per 100,000 live born males were affected with Duchenne Muscular Dystrophy, and one per million of females. That makes no sense for an x-link disorder. Is that symptomatic only?

ALEX KEMPER: Symptomatic, symptomatic, yeah, not carriers. I'm talking about affected females.

SHAWN MCCANDLESS: Okay. That wasn't clear. Thank you for clarifying. The next question is you said that the expert panel suggested that the genotype phenotype correlation was predictive greater than 99 % of the time?

ALEX KEMPER: 90 %.

SHAWN MCCANDLESS: 90 %, okay, okay. And how good is the evidence to support that assertion? Or is that the opinion of one or two experts?

ALEX KEMPER: I would say it was a strongly held opinion. Again, you know, the issue is until screening happens on a broader scale. It's difficult to sort that out. We did bring in one expert who often gets called into helping adjudicate the genotype phenotype issues, and based on how he's contacted, and consensus among the ground, it was felt that 90 % of the time you could tease things out.

Now again, I could be wrong, but there is strong agreement on the call about that at least.

SHAWN MCCANDLESS: And is there data available to suggest what the frequency of elevated CKs will be in the newborn

population? I mean what do we expect to see when we do, if we do CK-MM as the first test? How many callouts is that going to be per 100,000 live born infants, because that makes that 90 % predictive value of the genotype very important if it's two callouts per year with a high CK-MM, 90 % is probably fine.

If it's 1,000 callouts per year at 90 %, a 90 % correlation of genotype and phenotype is probably not going to be acceptable for newborn screening.

ALEX KEMPER: So now I have to like channel myself from whatever it was a few months ago, and I hesitate in the public venue to tell you what the numbers are. What I can tell you is, and maybe Dr. Caggana, I know that you know the numbers because I've gotten them from you.

But if you have, you know, if you have you know, a danger zone where, you know, this is clearly elevated and they need to be referred, and then if you have the gray zone where the elevated CK can be from other things, like birth trauma, those kinds of things. It really does dramatically decrease the number of infants that would be referred on for molecular testing.

But I don't want to like to say the number is wrong in front of the person that gave me numbers.

MICHELE CAGGANA: Yeah, and I mean I have the numbers up here from our pilot study, and again our pilot study was done very conservatively because we wanted to cast a wide net to see how CK-MM would predict Duchenne. So using the cutoff values that we have established early on, we referred 1 in about 800 and--not

about, 1 in 876 babies that were screened.

We are--we have a referral level, and then we had a borderline level based on age at collection. Age of the baby at collection. And our general newborn screening protocols, if a baby comes back borderline twice, we make that a referral. One of our babies that actually was diagnosed with Duchenne was in that category.

The other ones were the range that we had was 993 in CK-MM, and that was this baby that was a twice-borderline. And then the highest value we had was 18,547 for CK-MM. When we, as Adam--yeah, as Alex had up on the slide, Dr. Kemper had up on the slide, we are looking towards doing a--getting two specimens, so that we're not referring kids based on these other traumatic events that will elevate CK.

And then using CLIR also helps us reduce even the borderlines that we would request a second specimen for.

SHAWN MCCANDLESS: Using what? The?

MICHELE CAGGANA: The CLIR, the Mayo tool.

ALEX KEMPER: And I do think it's worth bringing a distinction too from Krabbe disease, which you know you obviously you look at where there's this really narrow time window to get somebody into treatment. And so, as long as you don't, you know, have the infant be lost to follow-up repeating the CKs, you know, there's less of that same urgency for treatment.

SHAWN MCCANDLESS: Right. But I think you told us that in the State of Ohio it was a primary screen only. What would Dr.

Caggana, what would you predict? So that's the 1 in 872 would be abnormal on the primary screen?

MICHELE CAGGANA: That, well we set our cutoffs based on our validation study. I am unclear what their cutoff values are, and what they're using to make that call.

SHAWN MCCANDLESS: So they may have a higher they might use a higher cutoff to produce that number.

MICHELLE CAGGANA: And we're planning on having this alert referral level, and then sort of this larger borderline that we can get, kind of remove some of them. You know, we expect it to be a lower referral rate than was in the pilot.

ALEX KEMPER: If I can further frame, Dr. Ream was involved with setting the threshold in those I think.

MARGIE REAM: Margie Ream, Child Neurology Society, also from Ohio. So Ohio is using weight and age base cutoffs, so if you're less than two kilograms you've just got to repeat the either clinically repeat a CK in a NICU or primary care provider, or repeat the whole newborn screen.

Our cutoff for if you're at least 2 kilograms and up to 47 hours old, it's 1,990, and then for each like age kind of bracket of hours it goes down. And so those are all reported as inconclusive until you get to seven days old, and then if you have a CK over about 570, and appear at least seven days old, then that's considered elevated risk, and should be referred, I don’t know if that answers the question.

SHAWN MCCANDLESS: Well, partly, I guess the question

then would be what's the predicted number of callouts that you're going to have per 100,000 newborns?

MARGIE REAM: We don't know. We started two weeks ago, so maybe in August I'll have some actual data. But yet I don't think we really know what to expect.

SHAWN MCCANDLESS: So there was no sort of validation study where they looked, because typically they'll look at 40 or 50,000 samples before they--

MARGIE REAM: Right. Not based on these cutoffs. Duchenne was added by legislative action with a very specific time to require implementation, so the lab I think was celebrating when they were able to get the assay running, didn't have a chance to do a lot of validation studies.

SHAWN MCCANDLESS: Thanks.

NED CALONGE: Ash?

ASHUTOSH LAL: Ash Lal, Committee member. Maybe comment and questions. It's all, the presentation was very illuminating and it's very detailed, and thank you very much for that. The one observation I had was that in the sibling studies, which we are so keen to look at closely. In many sibling pairs the diagnosis of the younger sibling was made after the age of three years, so if you only want to look at how does it point towards an early diagnosis, that number goes on even further in some of the studies.

The second thing is, which maybe some clinicians will be able to answer here, is there's a phenotypic variability in

disease, and looking at the studies that are looking at early treatment, are babies, patients who have a more severe phenotype, are more likely to start treatment earlier. That's another confounding variable. I think you might have pointed out that also.

So that makes interpretation of the value of early treatment worse if not even more complicated to understand in my view.

ALEX KEMPER: Yeah. So just to draw that point out again, for people who might not be able to hear you as well, if more affected, severely affected individuals are more likely to be diagnosed early. It can confound conclusions that you might draw about the benefits of newborn screening because you're just getting, you know, like one particular, more severely affected piece of the population.

ASHUTOSH LAL: Thanks. And the last comment I have is about the state newborn screening programs that are starting. Each of these programs has a different way of going about the primary and the second tiers. The one that I had a question about was during only primary screen and then referring to a primary care physician for doing the genetic testing.

And this isn't part of the review, but I just wonder whether this isn't a condition that has been well studied, and the implications of a positive primary screen, and it's workup not being taken up by the state in a centralized way so it could be standardized, but to give it up to the primary physicians is a

little bit of concern.

ALEX KEMPER: Let me just respond to it. But I think more of a comment, and I'm going to take off my evidence review hat, and speak as a primary care clinician. And it does make me worried if primary care clinicians are going to be responsible for alone, for following up CK. Because there are different molecular tests that can be ordered.

It's not something that they're used to doing on a regular basis, so I'm hoping that if the process continues the way it is that there's careful guidance and good care coordination to ensure that children identified through newborn screening can get the benefit of being found with elevated CK, but I think that gets beyond the evidence review part, but I do think it's important for the Advisory Committee to understand that there are these different approaches that are being used by states right now to screen for things.

And you know, I'm a primary care pediatrician. I love primary care pediatricians, but it does raise some concerns. They're not going to let me go back to Ohio now, I think Margie, but.

MARGIE REAM: So, molecular is not part of the Ohio screen. The letter that we're sending out to primary care providers is, you know, repeat it, repeat the CK or send it into the lab, and if it's still abnormal refer, and we include the list of regional referral centers. So we're definitely not putting an expectation for genetic testing on the primary care providers.

NED CALONGE: Melissa?

MELISSA PARISI: Melissa Parisi, NIH. So I wanted to just make a comment, and perhaps a question rolled into this with regard to the heterogeneity in this condition, and particularly when looking at siblings. Even having, you know, from the sibling reports, with admittedly some limited data, there seem to be some variability in the presentation in the course for two boys who would have the same diagnosis, and presumably the same variant in the DMD gene.

So, my understanding is that most of the exon skipping technologies also do not cross the blood brain barrier, so it seems like you can't even predict whether two boys in the same family might have the same degree of cognitive impairment. One could have cognitive impairment and one could not.

It's also my understanding is that, is that known to be the case, and that if you were to use some of these currently existing strategies, they wouldn't necessarily impact cognitive development. Really they're focusing on motor skills, skeletal muscle predominantly. So that was a question and a comment kind of rolled into one. I didn't like comparing apples to oranges.

ALEX KEMPER: I guess the only thing, I wish I had better information about, you know, exactly what was going on in terms of the cognitive impairment because you know, if a child is not able to interact with the world as well, that can have negative consequences as well.

I just, all I can say, I mean you've seen everything

that we've had from the sibling studies, and there is no full published report, and so you know, what we have.

NED CALONGE: Jennifer?

JENNIFER KWON: Hi. I'm Jennifer Kwon, Committee member. As somebody who treats Duchenne Muscular Dystrophy regularly, and sees patients in her clinic, I would say that to address Ash's question, I don't think that the variability in treatment has to do as much with the severity of presentation as it does with the first sibling's response to treatment.

And I think that the other interesting phenomena that we see in our clinics is that when a boy is diagnosed with Duchenne, they may be diagnosed late, let's say at five years of age, and they often do have younger siblings who are then diagnosed.

And the treatment decisions, and the sort of angst that families go through with their first child, there may be a lot of different reasons why they don't want to initiate that with their next child, or they want to maybe wait for other agents, which seem promising and in the pipeline before marching into what we offer as a standard suit of treatments.

To address the question about cognitive delay. I would say that we do see boys in our clinic who have sort of milder learning difficulty, school difficulties, ADHD, and then we see boys who are more profoundly affected. And I don't know that there's been a clear study about this. I would just say that I would think that the cognitive presentation is not always

so--doesn't seem quite that disparate in my, you know, experience, and just from what I can recollect about studies if that helps address your question.

So no, these treatments are not really meant to address cognitive issues, but yeah, I think that the family's decision making about what treatments to go for, and how to improve the outcomes of their sons is very complicated because these treatment choices are difficult.

And because the outcomes are not immediately obvious, it makes it even more difficult right? So you're trying to interpret, so all you're seeing really are adverse effects because the outcomes are way out there, and so if you don't like how much weight your first son gained, of if they tore the house apart and you're going to blame it on the steroids, then you know, you're going to be very cautious about what you put your next son on, and vice versa.

So I just think it's tough, and I think Duchenne is notable in terms of disorders that have been presented here because I think the sibling studies, or our inability to have meaningful sibling studies is affected by that. There's the stuff in the literature, and then there's the stuff in the real world that we don't see reported.

NED CALONGE: Michele?

MICHELE CAGGANA: I'm Michele Caggana, Committee member. I just, I wanted to make a comment, and then also just ask a question from the presentation. Thanks Jennifer for that

information, that's helpful. But I just wanted to kind of reiterate that when you're an earlier adopter, and you are starting to screen for a condition, you know, you're sort of the pioneer out there.

And newborn screening is a very community-based group. We're a small number of people that do something every child born in the country. And so programs really work hard together to provide guidance to each other, help each other out, and really help each other create a model for how best to perform newborn screening for various conditions.

And I'll say Dr. Joe Rossini in our lab has really helped a lot with harmonizing ALD screening across the country, and as time goes on the screening gets better, people learn from experience. And so at some point the programs that are screening will, with help from APHL and other groups, kind of come up with a best practice for newborn screening.

And so, and I just want to put that onto the record that we really do align with each other as a community. A question I had for Alex, on slide 33, you had a range of scores with a corticosteroid treatment. Do you have the range? You have the mean and the standard deviation, but what was the range for that? One number was 4.2. I don't know if you have that handy, but I just am curious.

ALEX KEMPER: If it's not on the slide I'll have to go back and get it for you later when it's available in the thing. Because I tried to put everything there. I don't know.

MICHELE CAGGANA: Okay. I was just curious. Thank you.

ALEX KEMPER: I try not to go from my memory for anything for public comment.

NED CALONGE: Online we have Christine.

CHRISTINE DORLEY: I think Debbie had her hand up before me, so if she wants to go first, she may be asking the same question as me.

NED CALONGE: I think the protocol, Christine, is members first, sorry.

DEBBIE: That's okay.

CHRISTINE DORLEY: I apologize. Sorry about that, okay. Christine Dorley, Committee member, and I'm going to say I'm a laboratorian by training, and not have any clinical background. But this is a question for Dr. Kemper regarding the AAV gene therapy. You had mentioned that one of the harms regarding this particular type of therapy is that there could be ineligibility for other gene therapies due to development of antibodies.

So I just wanted to know based on I guess experience with other diseases that are treated by gene therapy, what is the likelihood of failure? What is the failure rate that would make kids ineligible for gene therapy if they were treated for DMD? Is there kind of like some information that's out there that gives that indication that it may not work or?

ALEX KEMPER: Yeah. Thank you Dr. Dorley for your

question, and for the opportunity to sort of expand upon the point that I wanted to make. So the current gene therapy is it allows you to produce this small version of the protein, this microdystrophin with the idea of being that it converts you from something more like Duchenne to Becker.

The studies that have been done on gene therapy are really based on proxy measures of protein production, and those kinds of things, not really long-term outcomes. Given that the current gene therapy isn't the whole protein, but just this part of the protein, and given the advances that are being made in gene therapy, my concern, or the concern that I wanted to raise to the group is that if you've been given gene therapy with this viral vector, then my understanding from the experts is it really precludes you from getting a future gene, a different gene therapy that's delivered with the same viral vector because you will have developed the antibodies that would impede the ability for it to work.

So, it's not whether or not this gene therapy is taken up by the muscles, but whether it means that you won't be eligible for future studies of a better gene therapy product. Does that answer the question?

CHRISTINE DORLEY: Yes it does. Thank you.

NED CALONGE: Shawn?

SHAWN MCCANDLESS: Shawn McCandless, Committee member. I feel the need to say this because I'm not going to be here when it comes up the next time. But that point about not being able to

get the same AAV vector is true, but that's an engineering problem that the field will overcome.

So, I don't think that it would be reasonable to make decisions based on the fact that you only ever will be able to be treated with gene therapy once. I just don't think that's going to be the case. There's lots of vectors. There's work going on and immunomodulation to allow repeating the vector, so I don't think the vector is going to be a long-term issue, and I would encourage the Committee not to worry about that for the-- as they think about.

Regarding the other question that Dr. Dorley asked though of how well does gene therapy work. The answer there is we really don't know. When you give gene therapy systematically, there is great variability in the effect that we see in individuals, regardless of what your target tissue is, and what the disease you're treating. And we don't fully understand yet what all the factors that go into the variability are.

So I think we need to be really tempered in our thinking about how good gene therapy is. It's incredibly promising, but there's still an awful lot of work to do, and knowledge to gain about the effectiveness of gene therapies going forward for any condition, not just DMD.

NED CALONGE: Jennifer.

JENNIFER KWON: Thanks Shawn. I guess I would disagree with you Shawn, that I think there are a great many vectors being engineered, but I think that the ones being used for Duchenne

Muscular Dystrophy gene therapy might be close enough that there may be, I would say that there has been some research already going into what I would think of as more extreme measures to clear previous antibodies from children.

And I don't think there's a lot of optimism that a single exposure to gene therapy can be corrected in some way to make sure that future gene therapies might be available to boys. Of course we all hope for that, and we all want vectors to be distinct enough from each other so that we can offer these kinds of diverse gene therapies to our Duchenne population.

But the neuromuscular specialist like myself, work with gene therapy for another condition, and that gene therapy so far has been a one-time treatment that effectively treats the disease, and we see children go from having a disease specific phenotype, to looking fairly typical, so that's a pretty clear change.

With Duchenne, we are being asked very good questions by our patients about the durability of gene therapy, so I hope that we can hear some information about that, and what the chances are that they're going to have to relook at treatment. And these are questions that patients that I think of as being, maybe less medically sophisticated, are asking me.

And, you know, whether they should wait for more promising treatments, rather than take advantage of the window of time that is available to them now with the FDA approved treatment Elevidys. So, I guess I'm not quite as optimistic about gene therapy for Duchenne Muscular Dystrophy being able to be easily

repeated. Let's just put it that way.

The issue that I wanted to also bring up that I think is interesting is this phenomena of newborn screening being used to basically screen for muscle disease. We're not screening for Duchenne Muscular Dystrophy when we have a CK with a one-week cutoff of you know 560 or even 600. We're screening for muscle disease, and that would be interesting to hear about how Ohio manages that.

But it's just that -- I guess, I you know, in response to the comment that the newborn screening community, you know, when we introduce these new tests we try to come together and build protocols to like work with families. Again, it seems like this is a difficult -- this is going to be an interesting set of protocols to develop for families.

We're not just screening for Duchenne. We may be diagnosing something else that is untreatable, or just diagnosing other conditions and how does that sort of impact how the newborn screening lab views their mandate for public health in their community? So I would be interested to hear how the states that are screening manage those expectations.

NED CALONGE: Jeff?

JEFF BROSCO: Jeff Brosco, HRSA. So completely different question, Alex. We hear from families and from others that the kind of physical therapy that you can get with early intervention can sometimes be harmful. Have you found any evidence around that that shows that different kinds of approaches

make a difference, even if it's early or late?

ALEX KEMPER: Yeah. We've certainly heard that from a lot of people. This is another area where we haven't found a particular study to document it. And I spoke to another neuromuscular experts who wonders the degree to which it is really harmful. But what I would say is that this has been and hopefully everyone gets the sense, a hard area to study.

So just because we can't pull out a study demonstrating the harm of early physical therapy, I think it gets to the issue of, you know, not a lot of these kids are being diagnosed early, and then for somebody to put together a study to be able to document the harm would be hard. I would say that anecdotally I've heard it from a lot of people, we heard about it earlier today.

There was one expert who said well, maybe it's not really, but that's sort of what we have.

NED CALONGE: Online we have Debbie.

DEBRA FREEDENBERG: Debbie Freedenberg, AAP organizational rep. Christine, I was actually not going to ask your question, but so I did just want to clarify one thing for the information that's available about AAV vectors, and I am by no means a gene therapy expert.

But on the other newborn screening condition the concern with the AAV antibodies are usually maternal antibodies, and those usually can be breached and cleared, and the child eventually does become eligible for gene therapy, which is

different than a repeat gene therapy attempt.

But what I did want to comment on, and Alex, I know you're aware of it, and Rich Parad had a paper about not in newborn screening, but in neonatology where they did look at the differential diagnosis of the elevated CKs that they saw, and I don't remember their numbers, and I would not presume to want to present that.

But they were a small proportion of those actually were in addition, category addition Becker category. So there are some information out there, and some papers out there about what the elevated CKs, and what waiting and repeating can do for bringing them down towards the normal region.

ALEX KEMPER: Yeah. I know the paper you're talking about, and I don't have it in front of me, so I can't, you know, go through the full differential, but there are a lot of babies who have elevated CKs, just because of you know, issues of birth, trauma, and then rarely there are other dystrophinopathies like, you know, the cardiac and that kind of thing. But I can share that paper with the Committee later.

NED CALONGE: Last comment, Margie?

MARGIE REAM: I just had some data to follow up on your question earlier, Shawn. I think Sharon Linard from the Ohio Newborn Screening Labs, probably listening in and heard the question. So results have only been being reported for about two weeks today. We started screening two weeks ago Monday.

So about 6,000 infants have been born that were at

least two kilograms, 19 of those have results, CK results from within the first seven days of life, so those are, if they're not normal they're inconclusive in Ohio. So of the 6,000 that were at least two kilos, 19 have been reported as inconclusive.

And so, we're waiting to hear back what their repeat CKs are.

NED CALONGE: Great. Well, I want to recognize all the hard work and great presentation of Dr. Kemper, and thanks for answering all our questions. Thank you, sir.

(Applause).

Committee Liaison Update

NED CALONGE: We've had a number of updates as you remember on the evidence around DMD, and as you heard alluded to, I believe, in the public comment period, in February the nominators submitted a letter to the DCO and to myself, DFO. And we've shared this with the other Committee members in the briefing book.

In the letter the nominators requested a postponement of the vote to recommend DMD to the RUSP because they anticipate an additional peer review information on the treatment of DMD should be available in the next couple of months that should and could be incorporated into the evidence review.

So, I'd like to turn to my DFO and say what is our next course of action?

LETICIA MANNING: Thank you, Ned. So we do need to have a vote on a motion regarding DMD at this meeting, but it doesn't need to be a vote to recommend it for addition to the RUSP, so we can entertain other motions, just as postponing the RUSP recommendation, or some other type of motion.

NED CALONGE: I wonder if either of the liaisons have input?

CHANIKA PHORNPHUTKUL: Yeah, so based on the information shared during the evidence review update, and the requests from the nominators, I move that the Committee postpone our vote to recommend the inclusion of DMD on the RUSP until additional information is available to make an evidence-based decision.

NED CALONGE: Can we capture that maybe on the--is there a second?

JENNIFER KWON: Jennifer Kwon, I second.

NED CALONGE: This is a motion, I think that Chanika put forward, the Committee postpone our vote on whether to recommend inclusion of DMD on the RUSP until additional information is available to make an evidence-based decision. Is there further Committee comments or questions?

CHANIKA PHORNPHUTKUL: On the motion, I also added that and the request from the nominators. I don't think it's on there.

NED CALONGE: Oh, on the based on the letter from the

nominators?

CHANIKA PHORNPHUTKUL: Yes.

NED CALONGE: Okay. Sorry. Ash?

ASHUTOSH LAL: Just one information I was seeking, when is -- is there a timeframe in which the vote for inclusion into the RUSP has to happen? And what is that time?

NED CALONGE: No. The statute, as I understand it, just says we have to take a vote with no later than nine months after moving it to the evidence review group. That was why we have to take the vote today.

ASHUTOSH LAL: What's the next timeframe then?

NED CALONGE: There is no timeframe beyond that, so I think, so my suggestion, I mean we could put that in the motion. My only worry is that we can't control the evolution of the information, so I would like to not back us into another vote and leave it.

I guess what I would tell the advocacy, and the nominators is that we want to make sure that enough time elapses, so that if we have additional information that could inform the vote, that that's actually available to us, rather than take a vote, another vote, either postpone or move not to add it to the RUSP. So that would be -- that's why I would think we wouldn't put a timeframe on it to kind of allow us, but my commitment to the nominators is that we would do it as expeditiously as possible. Shawn?

SHAWN MCCANDLESS: Shawn McCandless, Committee member.

I think my comment was going to be the same as Lal. I think there needs to be a timeline associated with this. So, would it be reasonable to say that the vote will be deferred for up to one year, pending new information being made available to the evidence review group?

Because I think to be fair to the evidence review group, if we wait too long they will have to kind of, re--their data will become stale, they'll have to redo, there will be extra work for them, so I think we should pick a timeline that's realistic to be that outer boundary of when it will be voted on.

And then if it's, you know, if the data just aren't there, then we need to vote based on the data that are available, and if the vote is not favorable, then it can move forward again for an expedited review, or something else.

NED CALONGE: Yeah. We can do whatever we would want, I think, except we can't not take a vote, so that's the one thing I know. A year seems reasonable to me because that's the same period of time for an expedited review. And I would have to ask Chanika if she would accept that as a friendly amendment?

CHANIKA PHORNPHUTKUL: I would.

NED CALONGE: And Michele, would you second it as a friendly amendment?

MICHELE CAGGANA: I would.

NED CALONGE: Thank you.

SHAWN MCCANDLESS: Just so not later than one year.

NED CALONGE: It doesn't mean we will wait a year, we

will wait longer than a year, for no longer, oh thank you very much. Nothing is worse than having the world watch you type. Further discussion? All those in favor of the motion--oh no, we need to do a roll call vote. I forgot. I would like to turn it over to Leticia Manning for a roll call vote.

LETICIA MANNING: Thank you. From the Agency for Healthcare Research and Quality Kamila Mistry?

KAMILA MISTRY: Here.

LETICIA MANNING: And so, it's yes or no. Yes?

KAMILA MISTRY: I'm sorry. Yes. I do this every time.

LETICIA MANNING: It’s okay, thank you. Michele Caggana?

MICHELE CAGGANA: Yes, I approve.

LETICIA MANNING: Ned Calonge?

NED CALONGE: Yes.

LETICIA MANNING: From the Centers for Disease Control and Prevention, Carla Cuthbert?

CARLA CUTHBERT: Yes.

LETICIA MANNING: Jannine Cody?

JANINE CODY: Yes.

LETICIA MANNING: Christine Dorley?

CHRISTINE DORLEY: Yes.

LETICIA MANNING: From the Food and Drug Administration Paula Caposino?

PAULA CAPOSINO: Yes.

LETICIA MANNING: Jennifer Kwon?

JENNIFER KWON: Yes.

LETICIA MANNING: Ash Lal?

ASHUTOSH LAL: Yes.

LETICIA MANNING: Shawn McCandless?

SHAWN MCCANDLESS: Yes.

LETICIA MANNING: From the National Institute of Health Melissa Parisi?

MELISSA PARISI: Yes.

LETICIA MANNING: Chanika Phornphutkul?

CHANIKA PHORNPHUTKUL: Yes.

LETICIA MANNING: And from the Health Resources and Services Administration Michael Warren?

DR. WARREN: Yes.

NED CALONGE: Nice to hear your voice Dr. Warren. Let's see, on to something new. I'm hoping there is another slide set coming up. During the last couple meetings--

LETICIA MANNING: Dr. Calonge?

NED CALONGE: Yeah, yeah, yeah.

LETICIA MANNING: Do you mind making just a final statement about the vote?

NED CALONGE: The vote was unanimous.

LETICIA MANNING: Okay.

NED CALONGE: In support of the motion. Does that help? I'm just behind. I'm anxious now. I guess I would pause, first of all to just acknowledge the work of the Technical Advisory Panel, the ERG and the nominators, and thinking through

where we were with the evidence. Not losing the traction on where we want to go, but trying to make sure we have evidence we need to make the best evidence-based decision possible.

So I do thank those who participated in the decision, and thank the Committee for a great discussion.

ACHDNC Decision Matrix Tool: Public Health System Assessment

So, yeah I'll move on now. You might remember that the last couple of meetings we've talked about changes to the decision matrix tool. We created ad hoc groups to look at that. We've come up with a revised version of the tool to talk about the A,B,C and I, and what that means in terms of referring -- recommending a topic to the Secretary for additional to the RUSP.

NED CALONGE: At the same time we looked at updating the public health assessment portion of the decision matrix tool. In the January meeting I provided some proposed updates to the assessment. We heard comments at that time, which took into consideration, and took a revision to the ad hoc topic group to make additional recommendations that I would like to present this afternoon.

So, our decision was to separate out the evidence assessment and assignment of a letter grade and the public health impact, but by statute the matrix has to include a public health impact assessment, and we've had a lot of input from many

individuals on this issue.

So the overview of the assessment process is that the Advisory Committee would initiate the public health impact assessment process when the Committee votes to add the topic to the evidence review group. Pilot states would then be surveyed, and results would be distributed to all other states. And then the survey would represent the diversity of state population size, and overall newborn screening services.

So, thinking about the pilot survey, the items would include questions in the area of the screening test, confirmatory testing, diagnosis and first year of treatment. For each of these areas the questions would cover whether, and what new equipment, staff and medical expertise was required, and estimates of the time and cost involved.

I realize this was a very simple slide, and buried under it is a lot of work, and work that is not easy because these assessments of costs are tough. They're dependent on a lot of issues like you have a relationship with the vendor who could provide a test kit, for example, or are there other additional issues that affect those costs, but I think an estimate is what we hope might be able to come out, and at least is one of the survey items.

So thinking about those topic areas of screening, confirmatory testing, diagnosis, and treatment, and then kind of the areas around staff, expertise, equipment, cost. We would use that information to develop a report that summarizes that

information that other states could look at.

And so this is an example of a pilot test survey report that would break things into things like first tier testing, in terms of equipment, cost, space and installation time, and staff, FTE expertise and time. For higher tier testing when appropriate, when it's not just another repeating the test, or maybe it is, but you just send it out.

So for example, I think a lot of states looking at Krabbe are talking about at least sending out their Psychosine testing before they have the ability to actually bring that testing into their state lab. And so what was that cost per test? If the testing was performed in house, the same questions for first tier testing about equipment and staff.

And then for follow-up and diagnoses it would include the cost per positive test, additional expertise, how much time did it take to develop that system for diagnosis, and then the same level of questions for follow-up and treatment. So that would be-- this would be like having answers to all of those would be provided to the other states.

If possible, cost summaries would include total fixed cost estimate. Fixed costs, for those who don't think about this all the time, that's like the barrier to enter. It's like I had to buy the machine. Once I bought it I don't have to buy it again, so that's a fixed cost. And then the total additional costs per test, which would include first and higher tier testing, diagnosis and treatment tests.

So the other thing is now that I have the technology in place, what does each successive test cost me to apply to my entire population? Now again, it's easy for me as somebody who thinks about fixed and variable costs to put this on the slide, and underlying it would be some really difficult work.

I'm trying to put it up here as like an ideal where all this information might be available, or estimate-able, but recognize that depending on the test and the condition, and the state laboratory, there could be wide variation in the ability to gather and accurately report this information, so this is an example.

So, this report would then go out to the states for a state survey, and the idea is that we would aim for, we would aspire to 100 % response, and then set a bar of maybe 80, 70 or 80 % as the least amount necessary to complete the health--public health impact assessment for the decision matrix. And that in that whatever that proportion did respond, there had to be good representation of states in terms of their population size, and their overall resources.

So, questions would be if the condition is added to the RUSP, what resources or additional support would you need to implement within two years for this test, and those would include things like external support for startup, regionalization agreements, and other issues. The two years, which I know we talked about the last time actually came from looking at states with alignment legislation, and kind of I would say the median and

mean number of years was about two, so that's why we picked the two years.

If the second question would say if you cannot implement within two years, what would be the barriers? So they could be things like competing priorities, like implementing other RUSP tests, or there could be other state laboratory priorities. So for example, Colorado is stepping up to do HPAI testing for raw milk, and milk products in response to the evolving issue with avian influenza.

And there could be funding and staffing challenges as well, so just thinking about what could get in the way to slow this down, to help us better understand. Information that could be added to the decision matrix could be estimated time and cost to implement from the pilot states, what do states report as necessary to implement within two years, and then categorize that required effort as low, moderate or high. So, low would say we can do this probably pretty easily. Moderate is ah, we can see a path to it, but it's achievable, and high effort would mean this is going to be a heavy lift.

We don't have a good definition for those, but as I've talked to state laboratory folks they said we know what this means, so kind of like what category would you say, and what do states report are barriers to implement within two years. We think, along with the letter grade, which is based not only on the evidence of benefit and harms, that this information should also go to the Secretary of Health with our recommendation.

So that would make the decision matrix, if we were trying to fit it on one page, and again this is a draft to kind of give you an idea, to giving the question well, what would this look like? So, it could like something like this. The top part you all know is a letter grade part of the matrix, and then the public health assessment would be for implementation in two years, and could the % of states reporting the effort required as low, as moderate, or as high.

So, that's the proposal that we've come up with now after a couple of cycles of working in the Subcommittee, and I'm going to throw it open for discussion.

Committee Discussion

UNKNOWN: Yes, I'm sorry. Can we put up the--let's open the slide.

NED CALONGE: Oh good, I have Michele, it's reaching for her as a laboratory person, who by the way participated in this, so--Oh, go ahead Ash.

ASHUTOSH LAL: My question briefly is just how will be quantitative about the efforts low, moderate and high?

NED CALONGE: Yeah. Sorry, Jeff you were going to? I think this is a qualitative assessment that I do feel comfortable. Most state labs would say yeah, we can do this, we can do this with additional resources, and it's going to be really hard for us to do this.

And so, I don't know that I feel strongly about putting a strict system of qualifications onto that, but we could. I'm not sure exactly what that would look like. We did want to get it down to just say you know, what could we put on a slide that the Committee should know about how rapidly this might actually be implemented if we added it to the RUSP. Sorry, Jeff?

JEFF BROSCO: Jeff Brosco, HRSA, just to add to this. So part of it Ash, is I think there's sort of big questions for us to decide as a Committee, but then also operationalizing some of these things. And I think if you talk to the experts in the lab, and in the follow-up, they would be able to say I don't know, something like low is this could fit easily into our routine procedures.

We need a little bit more staff, maybe new reagents, you know, it's going to take a little time but it's not extraordinary. Moderate might be we do things kinds of things, but man, we'd have to train a whole bunch of new people. We certainly need new FTDs, we have to do this, this and this. And high might be it's a whole new paradigm. This is going to be urine instead of blood, we may need a whole new platform, right?

There would be something extraordinary that was different, so I think that our experts could come up with something with anchors that gave us some sense of what low, moderate and high looks like.

NED CALONGE: Or at least maybe a narrative like you just did that would be helpful in guiding that decision. Michele?

MICHELE CAGGANA: Michele Caggana, Committee member. I like this, I think the devil is in the details. I'm trying to think how we're going to operationalize these, so a couple of questions that come to mind our we had the earlier talk about the N-of-1. So when you're talking about a pilot state to get kind of that baseline data, what's going to qualify as a pilot because if it's somebody doing universal screening for Duchenne, we have several states.

We're going to be able to find kids with Duchenne, and we'll have some of that information, especially the follow-up, the downstream information. I think long-term follow--up kind of comes into this as well to kind of see, to be able to better define how we're going to do this, and then also as far as the survey of the other states, how are we going to select those states because we have many different models out there for how newborn screening is done.

We have regional states, small states, large states, you know, so I'm just rattling around trying to figure out how we're going to be able to operationalize this, so we get the information to ultimately be able to answer those three questions.

NED CALONGE: All great questions. So if I could start with thank you, and that's why I try to get about the complexity, the devil in the details is really true. And it will honestly I believe be unique to the topic because the topics with great overlap and certainty and understanding about implementation may have all been taken.

And the ones I think coming down the path are going to probably be more complex. I also tried to talk about this would be an example of a report, which could look very different based on what information is available, and the idea is can we do the best we can in providing information.

As far as the state selection, it would be every state not screening is what we would aspire to. So, I tried to say that, the reason I said we might have to accept the lower proportion is just a worry how long it would actually take to reach 100 %, and maybe we don't set a cutoff. We say we don't seem to be learning anything new, but there are different ways to approach that particular issue.

But yeah, I think one of the hopes is that we'll be able to work with APHL who has been doing this already in the evidence-based review group, who also participates and develops a strategy. Alex has actually provided a matrix of an approach that they've used in the past that could be a good start for us.

And you're right, the devils will be in the details, but I think it should be tailored to the topic, yeah.

MICHELE CAGGANA: I mean the readiness tool that's available sort of checks a lot of those boxes. And I think it would really help, actually it will probably help the pilot states, even going through it to see how long it took them, not when it's done necessarily, but how long each of those steps took in order to create that report.

I think one of the other things that's important to

survey is how much clinician support you have in your state for that, for this test, or this screening, the availability of treatment, and are the services available because I think that gets lost sometimes as well.

NED CALONGE: I appreciate that. That point has been brought up several times, and trying to figure out how to put that--I tried to at least anticipate it, it's in the kind of survey topic areas without saying you know, how are you going to find that out. Jannine?

JANNINE CODY: Jannine Cody, Committee member. So I'm trying to understand, get my brain around how this is really going to work, and how we integrate both of these components. So do we come up with the letter grade for the magnitude of benefit, and then address the public health impact, and/or one, if we vote against the magnitude of net benefit, then not bother with public health?

I mean how do they relate to each other? How do they weigh one versus the other, and does one come first or second?

NED CALONGE: Yeah, these are good questions, and I think very early in the slide set there was when we would start the process. So, one of the things I've been, issues I've been nervous about is would we delay a vote pending the completion of the public health assessment?

So my desire would be say no, we would not delay the vote, so the idea is can we start the assessment at a time where the changes of it being completed will line up with the completion

of the evidence-based review and the vote, and that's the reason why I picked that time.

So that's the answer to the other, the first issue. The second issue is that the public health impact assessment should not affect the letter grade. So, our decision is based on the letter grade, but understanding both from the nominators and the advocacy groups, understanding of the difficulty, and the Secretary's understanding of how implementation is going to unfold I think is a useful piece of information to have publicly available.

It would not--by separating the two out you shouldn't ever vote to add a condition just because it was easy to add if it didn't meet the other criteria. On the other hand, I would not, unless the Committee as a whole feel differently, I would not change the recommendation to add or not add on the basis of public health impact assessment.

The only area where I think that would happen is that if 49 states said there's no way we can do this, and I have not heard that come up as a possibility yet.

JANNINE CODY: So what we might do then in fact, is send two recommendations to the Secretary, one for each category, and they may not even be coinciding with the same meeting. One might get voted on first, the benefit, and then what?

NED CALONGE: Well, my aspiration is that they be done at the same time.

JANNINE CODY: Well, I know.

NED CALONGE: Which is what happens now.

JANNINE CODY: Yeah. But you just said they wouldn't have to be, so that made me think about that.

NED CALONGE: No, what I wanted to say is you wouldn't have to, you would not forward a recommendation to the Secretary because the public health assessment said it was too hard.

JANNINE CODY: Oh.

NED CALONGE: Or it would just, it's information for both the community, the states, advocates, and the Secretary to consider. That would be my aspiration because I get really nervous about using nonevidence based data in an evidence-based decision. Now this is evidence-based, but it's talking about the impact on public health.

It's talking about implementation. It's not talking about evidence benefit versus harm. So that's kind of where I was hoping to go. Carla?

CARLA CUTHBERT: You may have mentioned this. Carla Cuthbert, CDC. You may have mentioned this, but just looking at this image here, do I understand that we're still going to vote for a letter grade, and then vote again? Because the way it's set up is action as long as it has the letter grades A, C, and I believe E, there's no vote associated with it.

So, I'm just wondering do we vote on the letter grade, or is it just I don't understand--I don't see how we can automatically agree unless we go around the table and agree. Does that make sense?

NED CALONGE: Yeah, so operationally the way it would work is an A you don't vote beyond the letter grade. C and I you don't vote beyond the letter grade, and a B you vote on the letter grade, and then vote to add.

CARLA CUTHBERT: And then who decides on the letter grade?

NED CALONGE: That's us.

CARLA CUTHBERT: And so?

NED CALONGE: Yeah. There's a first vote on the letter grade.

CARLA CUTHBERT: Got it, that's what I wanted to understand.

NED CALONGE: Yeah.

CARLA CUTHBERT: There is a vote on the letter grade as long as you decided on the letter grade, then the action is as its stated there then, right? Okay.

NED CALONGE: Right. The only difference is that the B is where there might be additional information where we say well, there's at least moderate net benefit. And so, we could bring in additional considerations to say whether we're going to move it forward, or we're not going to move it forward.

And that's what we've been doing, okay, for that. Melissa?

MELISSA PARISI: Hi. Melissa Parisi, NIH. So, I apologize because maybe I missed an earlier conversation, which is entirely possible, but I guess I didn't remember us agreeing on

the letter grades, so am I like way out of touch? I guess I'm a little concerned.

NED CALONGE: We got that.

MELISSA PARISI: We did? Okay. Looking at kind of, today at least, it does raise a few concerns for me, only in the sense that C seems to be gathering a lot of different scenarios, including negative net benefit, which really means harm, does it not? And so, I just wondered whether we were comfortable seeing it displayed like this, and whether there's any value in sort of saying maybe we need a D grade for harms because that's really pretty separate from something where there's either a moderate certainty of maybe a small benefit that would benefit from additional research or inquiry that could actually boost it into the A or B range, just my thoughts.

NED CALONGE: Well, one of the things is I was trying to simplify it. And the other thing is that if you did have a small net benefit that was voted on by the group it can always come back.

MELISSA PARISI: So a C does not mean that it couldn't come back for another review?

NED CALONGE: Well, actually to be honest, none of these would say you couldn't come back for another, including the A and B. We just haven't got to the methods of how to rereview something already on the RUSP. Let me start with Scott online? Oh, I'm sorry, yeah your card has shifted away so I couldn't see the type.

PAULA CAPOSINO: So, during the review the Committee is going to have evidence that this is possible. It's not like you're going to come up with an A or B grade where 100 % of states say they can't do it?

NED CALONGE: Right, since there has to be a pilot state that found at least one case, that won't be true. One of the reasons the pilot in finding one case is important is a proof of concept that says it can be done. So at least you know that it can't be done is not an answer. It's just whether or not the other 49 states, is it going to easy, high, moderate or low effort.

PAULA CAPOSINO: I'm still trying to figure out how this comes together. So there is some understanding that once you get through the evidence base there is some likely possibility that a good % of the states are going to be able to do it, are going to be at least moderate.

Or what happens if that doesn't pan out and you've already made a vote to recommend?

NED CALONGE: Well, so that is a good issue for everyone to discuss. My interpretation would be that the decision to add should be based on evidence of benefit versus harm, and then the rest is implementation. And so, there could be a topic where the effort is high for every other state.

I'm not certain I would say that we wouldn't then send it on to the Secretary to add. We just would do it with the understanding that there are going to need to be additional

resources, or additional time in order for this recommendation to actually show up on additional states' screening panel.

Now, if the group feels differently that they are universally low, or some cutoff levels of sorry, high effort for implementation should impact our vote on the evidence, or what we do with our vote on the evidence, I'm certainly open to that. Michele?

MICHELE CAGGANA: I think during the discussion of the evidence review that the public health impact does come up, right? Because we hear from the technical expert panel. We hear experience out there, and so I think while it's not formally part of it, it's still part of it, right?

I think potentially having federal, we've heard many, many times about how long it took states to implement skid screening, and it took long because states did not have molecular laboratories. Some had to build new rooms. They had to put additions on.

And you can understand when you're doing something in your home how long it takes. You can imagine how long it takes a laboratory to get the funds to be able to do that. To do the testing in the right way because it's important that we do it correctly. And so, I think perhaps having that sort of there's going to be a good net benefit. We're going to add this to the RUSP, but yet it's going to take a while, and take some of that pressure off, so that states really can implement a screening, and do it correctly in a timeframe that is reasonable for them.

That's just my thoughts on that.

JANNINE CODY: Jannine Cody, Committee member. Just make sure I'm interpreting this correctly. Magnitude of benefit is to the identified patient, correct? And public health is the burden on the public health system? So, can we add those words on the matrix that net benefit to the patient, and not have people thinking benefit to society as a whole because then that implies people get into the cost, you know, because it's ultra rare, and it's going to be, I don't know, $50.00 a test or something.

Does that make sense? And we're talking about for the A, B, and C grade, we're only talking about health benefit to an individual. Is that correct or not? Because now we've moved the public health benefit, or assessment down to the other section. Does that make any sense? Jeff isn't following this. Sorry I confused everybody.

JEFF BROSCO: No, no, this is really hard. Jeff Brosco, so part of what we're trying to do is separate out should this be something that we think should be screened for, for every baby, and the benefits are for the individual, also family, also societal. It is good for everyone that sort of this general discussion of the magnitude of benefit.

The public health impact is more about what resources are required for implementation? And we're trying to, we haven't, again this is trying to capture what we've been doing anyway. We haven't historically said, you know, we're going to set a limit of 50,000 per life saved, and we're not going to go above.

We haven't, this is not what this is trying to capture. And I think that's what Ned's been saying, is that we're just trying to separate that out.

JANNINE CODY: Yeah, okay.

JEFF BROSCO: And so it's how much resources are needed to actually do it.

JANINE CODY: Okay.

NED CALONGE: Historically, this section was added. I could say this because I was there, was added because of cyanotic congenital heart disease, which was approved at a meeting of the Committee before anyone was ready to do it. It was so uniquely different in that it's a point of service test. And how many state laboratories at the time had any relationship with their hospitals, other than the mail, right? And the information that came with the cards.

And so when it hit the Secretary's desk, the Secretary said okay. And just got blasted by saying how could you approve this? We have no way to do this. There's no way we're prepared, there's no way it's feasible, all of that hit at once. And the Committee, and a group of very nice smart people, plus me, which I would put outside of that group, were supposed to come together and say how could we have readiness and feasibility included in the decision-making process?

So, that's when we came up with the A's, and then the B1, B2, B3, that I know everyone in the room absolutely loved--no. It was, and we wrestled with it and actually couldn't quite follow

it because these B's, the A's were taken. Maybe there will be new A's, but maybe not.

The B's was where the work of the Committee now is, and so didn't we need some way of saying we understand what A is, we understand, sorry Melissa, for the most part what the, let's not do it right now are. We know--but the B's are where there's a little bit more richness, understanding about benefits and harms, and an area where we really need a diverse Committee with lots of different experiences, insights, and way of looking at newborn screening, in order to have a decision that we feel is in the best interest of newborn screening and public health.

So that's where that came in, and that's where we're trying to pull it out, and not lose it.

JANNINE CODY: So that has not changed?

NED CALONGE: That's not yeah. Except now you can vote for a B where before B's were not supposed to be voted on, just so you know, okay. Carla?

CARLA CUTHBERT: Carla Cuthbert, CDC. I don't remember if this is included in your letter to the Secretary, or our response back or anything like that. But because we're going to be having this categorization for the public health impact assessment included, and because as Michele said, if we include that this is going to be very difficult, that it can take some of the pressure off of the states to get everything done in two years because there are other competing priorities.

Can we make sure that we include a statement in there

to that effect, so that there would be documentation on letters going back and forth that indicate that we recognize that this, that there's a lot of benefit? Not benefit for doing this, but we also recognize that this might be difficult, and would require additional resources, so it may give time if there are feds that are able to help with that funding support to be able to lean in.

That doesn't happen overnight. Everyone knows that, but if it could give us a bit of time to be able to get this going. And again, as Dr. Caggana said, to do it in a right way, as opposed to very quick, where it may not be the most efficient.

NED CALONGE: Yeah, I appreciated that, because that is actually what we thought about doing, and so that's what it says. This information would be included in the letter of recommendation for addition to the RUSP to the Secretary, so we're thinking exactly the same way. Shawn?

SHAWN MCCANDLESS: Yeah, I'm sorry to bump in line ahead of Scott and Natasha, because I'm sure after their comments there will be drop the mic comments, so mine will not be. I have three points I want to make. The first is a question. What is the role of the National Academy of Science, Engineering and Medicine's workgroup on this topic?

Would there be value in waiting to hear what they come up with, or is that totally separate, and we should just move forward?

NED CALONGE: What a great question. I think the issue is that I want to have something in place for the new conditions

that come in starting at the end of this month, and I don't want to hold any of those up. So I would like the pause to be over, and I would like to at least be operating under this matrix approach, while we wait for the NASEM report because there may be--I don't know how many conditions that there could be.

I know there's going to be at least one, and probably three that will come out prior to the NASEM report coming out.

SHAWN MCCANDLESS: Thank you. That makes perfect sense. The second is just a comment that the idea of having a sort of a short narrative with anchors for the various public health assessment is very valuable. I think it would be valuable to have that for the certainty and magnitude of net benefit as well.

And that we're recognizing from the look on Jeff's face that that may be challenging. I think there would be value in that. And I think the value in that is that the Committee turns over, but what would be good over time is if there was some sense that the Committee, even though the people are different, the concepts and the way that people think about things are relatively similar, that there's precedent that's followed when it's appropriate.

That there's rational reasons when precedent is not followed. But just to be really--just to create a sense of continuity over the years for the work of the Committee. The third comment that I wanted to make is that I think this is in response to something you said, Dr. Cody, that I really do think

that we need to be thoughtful about what the purpose of population based compulsory newborn screening is, and I think that we need to be really careful to not think about it as being done only for people that have the conditions.

Because this is a thing we do to the entire population. There is no choice. It is currently a compulsory program, although you're probably aware that there was a Senate bill introduced in the State of California, Senate Bill 1250, that would have treated newborn screening the same as direct to consumer testing, requiring full, informed, written consent for newborn screening, which would in fact make it no longer a mandatory or compulsory population based program, but an optional program.

And I think that everyone would agree that that's not an ideal situation for, but I won't belabor the point, although I would love to. But I think that it's really important that this Committee continue to be very careful and thoughtful about thinking of newborn screening as a public health program that affects the entire population of newborn infants and their parents.

And that the benefit of that accrues to a very small proportion of the population, but it's a very big benefit, and very important to those people. But the program is not for them only. It is for them as part of the population, and we need to really always keep that in the forefront of our thinking in my opinion.

NED CALONGE: So, I have a response to exactly one question, which was there is great literature on the levels of certainty by many different evidence to decision groups, and they're all similar. They're all--and they can include quantitative, qualitative, mechanistic, analogic. I haven't seen real world until today, but you can use all those different evidence streams and come up with a certainty level.

The magnitude is much more difficult, and so I think that's where opportunity costs and overall costs, which we don't currently consider come into the concept of what is the magnitude of net benefit.

SHAWN MCCANDLESS: Thank you. I appreciate that. I do think though that it's really important to kind of circle back to what is the underlying societal basis for this compulsory newborn screening. And that has traditionally been the benefit to the individuals identified with the condition are so large that there can be no reasonable explanation why a parent or a family, or anyone else would choose to not know that information, and would choose to not act on it.

So for PKU, phenylketonuria, if a family said we don't believe that diet is important, and we're not going to do that, there would be legal action taken. Child Protective Services would be called. That's the bar that we set, and that our society tacitly agrees to for this essentially unconsented compulsory newborn screening program.

And so, what I think we just need to be really, really

careful about that, and so the magnitude of the net benefit is really important in that issue, and so I do think that anchors would be valuable, because current, you know, it's the low hanging fruit we've already done.

Most of the conditions--now, there maybe will be new therapies that really convert a condition that didn't have effective treatment into something where there's a slam dunk, no question about it this is beneficial, and those will continue to be easy decisions.

But for most of the decisions that we're going to be faced with, both the certainty and the magnitude is going to be different. The harms are going to be different, and so I do think that having some guidance and anchors for those decisions will be helpful going forward.

NED CALONGE: Thanks. Let me turn to the internet and Scott Shone?

SCOTT SHONE: Thank you. Scott Shone, org rep for ASTHO. So, you know, I feel this Committee over the last few meetings has acknowledged that the readiness and feasibility assessment, and the public health impact assessment, was not really ever incorporated into the decision-making process, nor was it really intended to, was really what I heard over the last few meetings.

We talked, and almost joked about the fact that the timeline for implementation has always been two to three years, and in fact, in Alex's presentation this morning, or this

afternoon on Duchenne, it was again two to three years, and I wrote it down on my notepad prior to even uttering the words of putting the slides on the screen.

And so, and as someone who has presented to this group several times on implementation, and the system, and I'm not talking laboratory. I'm talking public health system, is that the barriers haven't changed. Individual screening, you know, the test methods and follow-up may change from condition to condition, may.

But the overall challenges that our newborn screening systems have to add conditions are no different than when NewSTEPs looked at this years ago, and the readiness tool that Dr. Caggana mentioned, was built on that. I mean it is years and years old. It's been refined as we've learned more and used it. So I'm struggling to understand why we keep asking programs, what are your barriers to implementation?

Because you know, I don't run an individual program anymore, but I would say you all haven't been listening to us. And so, I don't know the utility of saying that, and I would argue that putting a timeline into the questions of two years based on RUSP alignment, and then suggesting that putting the outcomes of those questions into a letter to the Secretary to take pressure off, isn't going to happen because the legislation itself is the pressure.

Those of us who have RUSP alignment laws, whether they're two years or three years, have that requirement. And so,

articulating in a letter to the Secretary that the system in any given state, or multiple states are going to have trouble implementing this in two years, even though they're required by law, I'm struggling to see how that benefits.

And instead, what I think would be beneficial for this Committee to do, would be instead of just recommending conditions, recommending to the Secretary that they continue to focus on funding the amazing programs coming out of HRSA, like PROPEL, the wonderful programs coming out of CDC, and also the work done by NIH to help identify how to break down those barriers that the system has been saying have existed for years because we have success stories.

The programs who are receiving this funding are doing great work with it, and we need to highlight those, and instead stop asking over and over again what are your challenges? We've articulated them, and we're starting to address them, and that's where I think this Committee can do the best benefit, is continuing to push for those things that are winning, and those things that are breaking down the barriers because we all want to go fast, and we all want to do the right thing.

I encourage you to focus on whatever is coming back up again around this high, moderate and low, certainty of benefit because I think that's a big piece of what this Committee needs to do, but I would beg you to reach out to the Secretary, and tell them to continue to fund those agencies, because the money that's coming out to the program is going to do better work at bringing

down these barriers.

NED CALONGE: All right. I really appreciate that, Scott, and I hope to think you're preaching to the choir, that we all kind of agree that that's the important ongoing recommendation. I would ask, just since you've got the square on the screen, we have to do this because it's in the statute. We have to do something about public health assessment.

What do you think would be useful to the Committee in its considerations, and to the Secretary? Given that we are required by law to do something.

SCOTT SHONE: Well, isn't that the same law that--let me go in a different direction. That was a--I caught myself. So, you know, instead I think that our recognition of the tools that have been developed to address I think the impact that is at the heart of what the law wants. I mean the law doesn't say you have to do a survey. I mean I don't think it does. Am I wrong?

NED CALONGE: It says assess public health impact. Scott? Scott, I wanted to honestly Scott I wanted to take it off, and I have my friends at HRSA saying, well we know what you would like to do, and then they said and then there's a law. So I'm trying to find something in the law that might be helpful, other than I suppose we could say public health assessment, 12 states have already added this to their list, or something.

We could do something really simple that says appears to be feasible because, you know, I'm trying to remember what the count was on the MD, but there's a number of states that have

already added it, so. I'm not trying to be facetious or challenging. I'm honestly asking a question that's asked of me.

And so what you've seen was me trying to move from me and others, and HRSA and our kind of Advisory Group, moving from where we are to something that we could still have that might be useful, and that's what I'm really interested in is since we have to do it, is there something that would be useful? Maybe I'll let you think about that. That's more fair than calling it out. Yeah, go ahead Jeff.

JEFF BROSCO: So, Jeff Brosco, HRSA. Scott, I wanted to remind you of the work that we did together in Florida some years ago. And just to tell you how useful it was, so for those who don't know, when we--I forget it was SMA. This was when I was Deputy Secretary there, and we had to put in place SMA. I think it was SMA.

And we asked Scott as a consultant to say well, what would it take for our lab, for a follow-up program for our clinicians? And as an objective outsider with some expertise, he provided this great report.

So we, as a state, at the Department of Health, could then turn to the legislature and say this is what it would require to do this, and these are the sorts of things we need to have in place.

And it allowed us to have, it wasn't just us, the Department of Health saying it, it was this nice objective outside person saying it. So we were thinking of one of the ways, Scott,

to make this more useful is we think that there are probably conditions that have relatively a small amount of resources that would require--some might be extraordinary, probably most can be in the middle, but something from this Committee that said to the world, here's what we think about this particular condition, and how hard it would be to implement in two years, would then allow the states to be able to say for us it works out this way, but you know, there is this national information that we can tap into.

So that was the thinking behind this approach. Flipping it from how long would it take you because in theory with infinite resources you can do it really fast, right? And with no resources you can never do it, so this is flipping it around to say if you have to do it in two years what would it take, and that allows the state labs, state fellow programs and clinicians to kind of be able to better present what their position is.

NED CALONGE: And I mean I love your question about the survey because you know I have an N-of-1 for state labs doing newborn screen, right. So my state, and my health department. And they're already looking at everything that we're nominating, and already think about what it would take.

They probably would call Michele, or another state, or someone in their region and say what did it take? So maybe we don't have to do this survey at all, maybe we just ask people this is this new test, this is the algorithm, this is the equipment it requires, this is the clinical expertise to deal with at least first year, if not long-term follow-up.

And then say give us your best assessment of the effort to do it in two years. That's way more simple than the checklist for readiness. The utility of the information needs to be worth the effort to collect it, and that's where I would like to get to. So we'll think about that, some of us, as well. Natasha I see your hand, I'm sorry Carla first.

CARLA CUTHBERT: This is Carla Cuthbert, CDC. Scott, I always appreciate your passion, and appreciate your comments, but I do want to comment about the repetition of the public health impact assessment in these reports. I know that well, I suspect that within our own community this information has been repeated, and it's known.

Putting this in documents like this allows that information to be a talking point as it passes through our reporting system, so that it reminds our leadership that are not always only thinking about newborn screening because there are other--you know very well, they're thinking about other public health issues as well that are--that may be more emergent in their eyes.

But it gives us a talking point to remind them that the states are struggling, so that if there are opportunities for funding pathways that don't currently exist, we can use that as a way to be able to engage in a discussion to help facilitate. So I will absolutely support this being put in red in any memo. I know red is not allowed, but you know what I mean.

But to be put in there over and over again, so as our

leadership are signing off of these documents that they see that it is an issue, so that it continues to come to mind.

NED CALONGE: Let me--I'm a little uncertain, but I think Natasha is next, and then Susan. Natasha?

NATASHA BONHOMME: Great, thank you. Natasha Bonhomme, Genetic Alliance. I have a couple of things to respond to, it's been quite the discussion today. First, to the public health impact and assessment for implementation. I think one thing that this discussion is really showcasing, maybe some of our advocate partners, is how challenging the legislative language is.

And that may be something to, if there's an opportunity, for them to revisit in those efforts, so that we're not getting so caught up in kind of these almost logistics of what has to happen before what because of the legislative language, but really get to the heart of what are we trying to accomplish.

I found this conversation really difficult to track, which I think maybe many of us have, and wanting to so easily say if public health impact is about impact, and not about the decision, why don't we just separate it out as has been brought up? Why don't we actually have a fuller conversation about impact, which is more than readiness.

It's you know, what happens. And if that maybe is the goal, or is a desire of this Committee to have that type of a conversation longer term, again that may be helpful for those who work on the Newborn Screening Saves Lives Act reauthorization language, to take that into consideration.

One other thing that I wanted to bring up, which we haven't talked too much about, is that reporting from the pilot programs, and I'm assuming in that pilot just means any state that is doing a screening before a condition is on the RUSP. Is that correct?

NED CALONGE: Yeah. I think you've got it.

NATASHA BONHOMME: Okay. Sorry. It's hard to see you all, so if you were nodding your heads I couldn't tell. And so, that's helpful to know, and helpful to those who are doing the nominations around how important it is to go to the states, even though so often we say you go to RUSP first, and then you go to states, but there is no RUSP without states.

And so I just want this Committee to acknowledge the actual logistics and realities of what--to have all of this data, and to be able to report out all the things that we're talking about, what the actual process is. And then, lastly, you know this theme came up between Dr. Cody and Dr. McCandless, and I brought up the question last time we met in person of what does this Committee think newborn screening is supposed to be, or is about?

And I think it's really hard that we have that theme come up again within the context of the decision matrix when it really seems that that needs to be a conversation in and of itself, so thank you.

NED CALONGE: Thanks Natasha. Susan?

SUSAN TANKSLEY: Susan Tanksley, Association of Public

Health Laboratories. I want to thank Scott and Natasha for their comments, and work off of part of their comments to start off. And that being the use of the data from the public health system impact assessment in the past, and it essentially being almost a checkmark, yes we did it. Thank you.

And utilizing that information to actually highlight the issues, to talk about them more than just it's going to take two to three years, 10 minute part of the evidence review when it's presented to the Committee, and these are the barriers, but we don't speak of them again, and therefore you don't fix them.

And Scott mentioned the grants, and how like the new HRSA PROPEL grants that many states are taking advantage of, and that's fantastic, and that's fixing small parts of the system. When we talk about implementing new conditions it is a completely different level of funding to get over those hurdles.

And so, it would be great I think in another part of public health right now, we just very recently had rules come down on PFAS testing from the EPA, and the level of funding that is available to implement PFAS well in general across water systems, hopefully for the labs that will need to be testing that water, but huge amounts of money.

Whereas, we are greatly appreciative of the funding that we've been given, by both HRSA and CDC to address parts of our system. I work in the State of Texas, and to implement a condition takes a huge amount of money, just the start-up costs, and luckily we do have some funds set aside for those start-up

costs right now, but in the future it may not be enough.

And depending upon the rate that conditions are added to the recommended uniform screening panel. So that's one comment that I have. Also, emphasize the piece on the RUSP alignment legislation that is there, and for those states where there is a timeline locked in, that is a deadline, so if it does become a mandate to add that screening doesn't matter in most states how hard it is, how big the barrier is.

And I don't know what the consequences are. We are fortunate in Texas that the legislation that was recently passed basically says we have to write a report and talk about those barriers, and so we are in the process of doing that right now.

But it does--anytime a condition is added to the RUSP it becomes a timeframe, a deadline for states to add it. It is felt as states are going to do whatever they can do to do the right thing, and they will most likely never tell you they can't do it, but it will take a lot of time.

But it's still not viewed greatly by parents who have children with those conditions. It's, you know, anyone who's missed in those states, it's heartbreaking. It would have been fantastic if we could have been screening for these conditions for years, but we haven't been, you know, due to X, Y and Z, but that doesn't fix that child who wasn't identified.

And it is seen. Programs feel that, so despite our efforts, we aren't able to add conditions in a timely manner sometimes, but that is a component of this. A couple other

things, just on the information that's gathered from pilot states as what has been proposed to gather from pilot states, it's essential.

Does it have to be done as part of this process? I don't know if it has to be done as part of this process, but it does need to be gathered. I mean that's something that APHL could assists with gathering along with the costs to help determine what that fiscal barrier may be, those are things that need to be gathered.

Does it need to be done by the Advisory Committee as part of the evidence review? Maybe not, but it is very useful for any other state program who hasn't implemented yet. Thank you.

NED CALONGE: I want to ask a question, but I don't want to put you on the spot. Yeah, you can say no. Do you think the Advisory Committee could choose not to forward a voted on recommendation to the Secretary until we were confident about states with alignment legislation could implement it within their timeframe?

SUSAN TANKSLEY: That's a little bit like holding--

NED CALONGE: You could say I don't want to answer that.

SUSAN TANKSLEY: It's a little bit like holding a result that you know, you test it in the lab, and you know that it's positive, but you know your group can't follow-up on it until, you know, Monday. So sometimes we, you know, there are hard decisions. I think the better solution is to fix the

legislation in those states to allow for a reasonable timeframe.

NED CALONGE: That was nicely answered, thanks. So Debbie?

DEBRA FREEDENBERG: Yeah, so thank you Susan, for all of your comments. Which having come from the same state face some of the same issues. But what I was going to say is that although it's not the purpose, when the public health assessment was done it gave the state a better look at where we were, and what was available.

So for instance, if we sent out a question to clinicians, and we got divergent answers back, it kind of let us know that there was going to need to be a lot of work done before it actually got implemented, so it kind of served almost as an early warning system to let us know where our pain points were, and where we need to do a lot more work on to get to ready to do implementation.

And so, I know that's not the purpose of it, but it did serve as that for certainly for the follow-up components of the state newborn screening program.

NED CALONGE: Thanks Debbie. Sue?

SUSAN BERRY: Sue Berry for SIMD. I know that we can't fix all things with the matrix, but something that has never been included in this that has I would say a broad impact is the ability of any given state to provide services to children who are diagnosed by newborn screening.

If you had Krabbe, are you going to be able to make

sure they get transplanted in a timely fashion? Is Medicaid going to pay for it? And while I know we can't have all of these things encompassed into this, that's the significant barrier at the level of the state.

In our own state, again just speaking for myself, our Department of Health team works to try and understand what resources are available, but sometimes they simply aren't there. We're lucky we have a decent portfolio of people who can provide those services, but what about other places where they simply don't exist at all?

And then we ask them to add a disorder. I don't even know how to begin to address this in a decision matrix, but it is a significant impact on the whole newborn screening system. Thanks.

NED CALONGE: Appreciate it. Well, we managed to talk about the one issue for almost the whole time, so that's really good. I think we highlighted other issues in the matrix, it's broad ranging. I think in the interest of time we know that some of the people who signed up for public comment won't be joining us tomorrow, so we're going to save a little time there.

I would like to recommend that we move the update on the nomination and prioritizations process to tomorrow. And we just have to be vigilant about getting done on time, and there's a couple things I would like to do with the end of our time together today.

Awards and Acknowledgements

NED CALONGE: So, I want to add to Alex's comments in acknowledging the work of Lisa Prosser. Her additions to the evidence review group, her ability to model outcomes and information based on slivers of evidence is truly impressive, and I think the impact of Lisa's work on our decision making over the many years she provided that service is almost immeasurable.

So, if you have the opportunity yourselves personally, and with your whatever emails you have, to let Lisa know how much you appreciated what she brought to this Committee. I think that is well deserved, and we will miss her. Alex, you'll be impossible to replace, but I know you'll figure it out.

So, I wanted to start there to acknowledge Lisa's work. And I wanted to end today with recognizing that Shawn McCandless's last meeting is today, this meeting. And so, that we didn't shortchange it at the end of tomorrow, I wanted to make sure we all had the opportunity to recognize Shawn's commitment, and his addition to the working group over time.

I know there are phrases that Shawn says that I don't see a lot of eye-rolling from the audience, Shawn, but I can almost hear it. And you say the things you say over and over again because of your desire for this to be a successful public health program.

It's an unusual program because it is at the interface between direct care services and public health. If it were a

consented process it would fall out of public health into the area of clinical medicine. And as it is a population-based screening program, it falls in the area of public health.

And I think the last hour and a half, or two hours, of discussion have really been us wrestling with individuals with experience in both areas about that interface, and where is the sweet spot and where it should be. So, I do want the Committee to think about how we keep that public health perspective in mind.

I mean I'll try to do it from the Chair position, not so much to channel Shawn and his decisions, but to channel that admonition and that reminder to the group that we're talking about a public health program that is used for every infant born in the United States. Not for every condition yet that's been added, but that's the intent.

And so our charge and our responsibility is actually really very high. And I know everyone here is here because of their commitment to the benefits that that could provide our population on the population standpoint. So Shawn, sorry. I want to make sure you know that we couldn't be more pleased with your commitment and your time.

We will hear your voice echoing in this room as we move forward, and personally I get the opportunity to work with Shawn, because I am the administrator for a rare disease advisory council that Shawn is the Chair of in Colorado, and so I get to keep working with you, but I want everyone else to recognize what you've meant to us. Thanks Shawn.

SHAWN MCCANDLESS: I've said enough today, so I'll just say thank you, and thank you to the team at HRSA for the opportunity to be part of this. It's an amazing group, an amazing group of people, of advocates, of supporters, and I feel like I have learned so much.

And I hope that I haven't--I hope that what I have had to add has been useful and received in the light of someone who cares very deeply about both the individuals that we're serving as well as the public health program, so I just want to thank all of you for the opportunity, and it is time well spent, and thank you.

NED CALONGE: I also would like to point out that for those of you who are keeping track, it is not Jennifer and Chanika's last visit. We have asked, requested and been allowed for extensions on their terms. It's very important to try to maintain continuity and not lose turnover the Committee so fast that the institutional knowledge and experiences all goes out at the same time.

So, when they both heard it, neither one said no, I don't want to do it, which is good, because I don't know what we would do if you said no, but I do want to tell you that Jennifer and Chanika will be with us for a little bit longer, and I appreciate that, and your willingness to continue.

And if there's nothing else from the Committee, I would recommend that we adjourn for today to start again promptly at 10 o'clock tomorrow. Thank you all.

Adjourn

(Whereupon the Advisory Committee on Heritable Disorders in Newborns and Children adjourned at 3:47 p.m.)