THE ADVISORY COMMITTEE ON HERITABLE DISORDERS

IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS

5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Tuesday, January 30, 2024

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P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks, and Committee Business

DR. CALONGE: Good morning. I hope everyone had a restful evening. Again, I just want to express my gratitude to the presenters yesterday, members of the public that provided comments and the discussion, presentations, and dialogue from yesterday will greatly aid us today and in moving forward.

We got a lot of good comments during the session, but I want to recognize that some people hadn't had the opportunity to make comments. Some people might want actually to look at the materials and think about them a little bit more before they make comments and so we're publishing a request for information in the Federal Registry notice. I'll be on the Committee's website, so anyone can submit comments to HRSA, and we will review everything received and will continue the discussion at the May meeting.

I also want to reiterate that as we looked at revising the nomination package and the process, our intent is not to add additional burdens. We really are looking for a way to reduce the burden on nominators and at the same time stay true to making our decisions based on the available evidence.

So, those are just some introductory comments to get us started. We have a few topics on the agenda today. We're going to start with public comments. We'll then have a presentation from the Evidence Review Group on the Krabbe Disease expedited evidence-based review. Then we'll have a Committee report from the Committee Liaisons on Krabbe Disease. We'll have discussion and then we have scheduled a vote on whether to recommend Krabbe Disease to the Recommended Uniformed Screening Panel.

Assuming we have time, towards the end of the day we're going to have updates from NewSTEPs, from APHL, and any other new business. With that, let me turn things over to Leticia for some administrative issues.

CDR. MANNING: Good morning and welcome to all our visitors here today. I'm going to first start with roll call and then I'll give a couple of announcements. I'm going to start with the Committee Members. From the Agency for Healthcare Research and Quality, Kamila Mistry.

DR. MISTRY: Here.

CDR. MANNING: Michele Caggana.

DR. CAGGANA: Here.

CDR. MANNING: Ned Calonge.

DR. CALONGE: Here.
CDR. MANNING: Carla Cuthbert, from the Centers for Disease Control and Prevention.
DR. CUTHBERT: I'm here.
CDR. MANNING: Jannine Cody.
DR. CODY: I'm here.
CDR. MANNING: Christine Dorley.
DR. DORLEY: Here.
CDR. MANNING: From the Food and Drug Administration, Paula Caposino.
DR. CAPOSINO: I'm here.
CDR. MANNING: From the Health Resources and Services Administration, Michael Warren.
DR. WARREN: Here.
CDR. MANNING: Jennifer Kwon.
DR. KWON: Here.
CDR. MANNING: Ash Lal.
DR. LAL: Here.
CDR. MANNING: Shawn McCandless.
DR. MCCANDLESS: Here.
CDR. MANNING: From the National Institute of Health, Melissa Parisi.
DR. PARISI: I'm here and Mollie Minear will be covering for me during the few times when I won't be available this morning.

CDR. MANNING: Noted. Thank you. And Chanika Phornphutkul.

DR. PHORNPHUTKUL: I'm here.

CDR. MANNING: And for our organizational representatives, from the American Academy of Family and Physicians, Robert Ostrander.

DR. OSTRANDER: Here.

CDR. MANNING: From the American Academy of Pediatrics, Debra Freedenberg.

DR. FREEDENBERG: Here.

CDR. MANNING: From the American College of Medical Genetics, Cindy Powell.

DR. POWELL: Here.

CDR. MANNING: From the American College of Obstetricians and Gynecologists, Steven Ralston. His hand is raised. I think he's here. From the Association of Public Health Laboratories, Susan Tanksley.

DR. TANKSLEY: Here.

CDR. MANNING: From the Association of State and Territorial Health Officials, Scott Shone.

DR. SHONE: Here.

CDR. MANNING: From the Association of Women's Health, Obstetric and Neonatal Nurses, Shakira Henderson.

(No response)

CDR. MANNING: From the Child Neurology Society, Margie Ream.

DR. REAM: Here.

CDR. MANNING: From the Department of Defense, Jacob Hogue.

DR. HOGUE: Here.

CDR. MANNING: From the Genetic Alliance, Natasha Bonhomme.

MS. BONHOMME: Here.

CDR. MANNING: From the March of Dimes, Siobhan Dolan.

DR. DOLAN: Here.

CDR. MANNING: From the National Society of Genetic Counselors, Cate Walsh Vockley.

MS. WALSH VOCKLEY: Here.

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

DR. BERRY: Here.

CDR. MANNING: And from the Association of Maternal and Child Health.

(No response)

CDR. MANNING: That completes roll call. Thank you. I just have a few announcements for folks. Just a conflict of interest reminder, this is a note to

Committee Members that you must recuse yourself from participation in all particular matters likely to affect the financial interest 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 Health and Human Services authorizing you to participate.

As in the case today, when a vote is scheduled or an activity is proposed and you have a question about a potential conflict of interest, please notify me immediately. You can also email me or just come up and find me.

According to FACA, all Committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register and/or are announced at the opening of a meeting. Today we will have one public comment period. Only with advanced approval of the Chair or the Designated Federal Officer, may public participants question Committee Members or other presenters. Public participants may submit written statements, and we did receive written statements and those were shared with Committee Members.

For visitors in this building, you must

remain on the fifth floor. There is a cafe with some bites across the way here. There's also a smaller store where you can self-pay to buy drinks. They have snacks and things to your left there. There are two bathrooms over by the cafe and then two bathrooms just behind us on each side. And if, for whatever reason, we have to evacuate the building, we will evacuate the same way that you all entered the building, out of that door there to the left.

For those of you that are joining us online, please note, since we'll be beginning with public comment, you will be promoted to a panelist and able to speak, but it may be a slight delay, about five to ten seconds. And those are all the announcements that I have, and I'll turn it back over to Ned.

DR. CALONGE: Thank you, Leticia. I want to thank Committee Members and our organizational reps for reviewing the February 2023 meeting summary and providing us -- sorry, November. I appreciate you reviewing February too, but this time I appreciate you doing November, providing us comments, the changes were made, and we sent you a new version for you to consider today. With that, are there any other corrections to the November meeting summary?

(No response)

DR. CALONGE: Hearing none, could I have a motion to approve the November 2023 meeting summary?
DR. MISTRY: Motion to approve.
DR. CALONGE: Who's online?
DR. MISTRY: Kamila Mistry.
DR. CALONGE: Thanks, Kamila. So, Kamila moved, and Michele seconded it.
DR. CAGGANA: Yes, thank you.
DR. CALONGE: Any further discussion?
(No response)
DR. CALONGE: Seeing none, Committee Members will do a roll call vote.
CDR. MANNING: Kamila Mistry?
DR. MISTRY: Approve.
CDR. MANNING: Michele Caggana?
DR. CAGGANA: Approve.
CDR. MANNING: Ned Calonge?
DR. CALONGE: Approve.
CDR. MANNING: Carla Cuthbert?
DR. CUTHBERT: Approve.
CDR. MANNING: Jannine Cody?
DR. CODY: Approve.
CDR. MANNING: Christine Dorley?
DR. DORLEY: Approve.
CDR. MANNING: Paula Caposino?

DR. CAPOSINO: Approve.
CDR. MANNING: Michael Warren?
DR. WARREN: Approve.
MS. MAINNING: Jennifer Kwon?
DR. KWON: Approve.
CDR. MANNING: Ash Lal?
DR. LAL: Approve.
CDR. MANNING: Shawn McCandless?
DR. MCCANDLESS: Approve.
CDR. MANNING: Melissa Parisi?
DR. PARISI: Approve.
CDR. MANNING: And Chanika Phornphutkul?
DR. PHORNPHUTKUL: Approve.
CDR. MANNING: Thank you.
DR. CALONGE: The meetings notes, or summary is approved. I appreciate your vote.

Public Comments

DR. CALONGE: We're going to move into the oral public comment period. By my count, we have eight oral public comments. The majority, but not all, will be focused on Krabbe Disease. I have an order and I will call folks up to the microphone in that order. And then I'll remind the two folks providing comments online, it takes just five to ten seconds before we hear

you.

First, I have Matthew Ellinwood.

DR. ELLINWOOD: My name is Dr. Matthew Ellinwood and I'm the Chief Scientific Officer at the National MPS Society. I'd like to thank HRSA and ACHDNC for the chance to speak with you today.

The National MPS Society is a 50-year-old patient advocacy organization that advocates for the mucolipidosis and mucopolysaccharidosis disorders. We have the distinction of having the greatest and most successful experience with this Committee and RUSP nominations.

When I came before you two years ago to speak in support of the nomination of MPSII, I pledged that the Society and its members and staff would do everything we could to support successful implementation of MPSII newborn screening. I'd like to come before you today to provide you with an update of our activities over the last year.

In the areas of scholarship, the Society's been active in the research of Dr. Michael Gelb, by assisting in the re-consenting of dried blood spots to improve newborn screening, second tier testing for the MPS disorders. With Michael, we've been able to publish endogenous biomarkers that reduce the false positive

rate to virtually zero for MPSs I, II, IIIA through IIID, IVA, VI, and VII.

Additional areas of scholarship from the Society included an invited publication, commentary, and seminars of micro genetics from the Society's perspective of and guidance of an optional RUSP nomination submission. Finally, the Society has been helpful and cosponsored and convened and continues to manage an active Delphi consensus effort on the clinical management of MPSII cases identified through newborn screening.

The Society has been active in areas of outreach to newborn screening programs through co-sponsorship with the University of Minnesota and APHL on a three-day symposium on newborn screening in the MPS disorders this last April. This was followed up by a luncheon held by the Society for APHL attendees at the APHL Newborn Screening Symposium in Sacramento this past October. These were incredibly well received events and we've got an excellent commentary on them.

We brought newborn screening into our Society in the person of Amy Gaviglio, who now sits on our Scientific Advisory Board. We've expanded our Extramural Funding Program to include newborn screening efforts. And I'm pleased to say that we have an active

program funding RTI International to expand MPS screening beyond MPS1 and II.

Beginning in 2018, and with the vision and support of our board, and in response to MPSI nomination, the Society began having a social work outreach program called Pathways. This is a program that involves outreach to families during their first year of diagnosis. This has been incredibly successful and is now being expanded to include two full-time social workers. One of whom is a trained genetic counselor. They spend 100% of their time traveling and visiting with families to provide support to them where they are, including home visits.

We administer to families who are English and non-English speaking, and these include languages such as Spanish, Portuguese, Mandarin, Farsi, and Urdu. After their first year in Pathways, families are encouraged to continue family support services through our family support. I'd like to emphasize that membership in the Society is free, and these services are free. Membership, I guess, is free for all of you as well, so I encourage you to think about joining.

In addition to these outreach programs, we've also identified that we're not serving the entire patient population, so we've started outreach programs

in underserved areas through our Crossing Paths Program and have hosted events in Texas, Georgia, New Jersey, Colardo, and California over the last two years.

In addition to these social outreaches and scholarship, the Society's been active to advanced advocacy at the state level, including discussions with diagnostic labs and newborn screening programs. Board members, staff have bene presenting at state newborn screening programs in Wisconsin, Maryland, Pennsylvania, Alabama, Texas, Oregon, Arizona, and Iowa and we have participated in outreach to clinical programs through Pediatric Grand Rounds and presentations to follow-up groups in places like Children's Hospital Colardo, Children's Hospital of Orange County, Harbor UCLA Medical Center, and the University of Iowa Stead Family Children's Hospital.

AS we look forward to full implementation of newborn screening for MPSI and II, I'm pleased to report that we now have two additional states who are screening for MPSII, as well as a host of others to follow. Based on the Society's calculation and incorporating RUSP alignment, we predict that by the end of 2025 over 55% of the birth population will be screened for MSPII in the United States.

We feel certain this is an underestimation.

I know there are representatives on the Committee now from Tennessee and New York who are actively working to implement so their numbers don't necessarily count to our estimates based on RUSP nomination. That number for MPSII we expect to reach 95% of the birth population by the end of 2025.

As I conclude, I would like to remind the Committee and observe that advocacy is here now to assist, and in fact, we have been here from the beginning. The very foundation of medical genetics as a subdiscipline rests on the combined work of clinicians like Eva R. Folling and parents like Britt Egalon.

The beginning of newborn screening by Bob Guthrie is intimately related to his perspectives as a father and an uncle. We helped to build and strengthen newborn screening systems in this country and our mutual mission will only profit from greater advocacy engagement. With that closing, I thank you for your time.

DR. CALONGE: Thank you, Matthew. Next, I have Anna Grantham.

MS. GRANTHAM: Good morning. I am Anna Grantham, the Newborn Screening Director at the Hunters Hope Foundation. For 25 years, we've wept with families reliving the same nightmare caused by a symptomatic

diagnosis of Krabbe Disease. Their baby is born seeming to be perfectly healthy. Just a few months later, the baby is relentlessly screaming in pain. Those who have encountered a baby as they become symptomatic with Krabbe Disease are forever haunted by the baby's piercing, high pitch scream. It's unlike any sound a typical baby would make and it's indicative of the agony these innocent babies endure.

After weeks or months of suffering and misdiagnoses, parents learn their baby will continue to suffer as they rapidly lose milestones until they are unable to swallow, cough, speak, laugh, smile, and have lost almost all basic and voluntary function. Parents are told they will need to use a suction machine at all times to manage their baby's saliva, that their baby will need a feeding tube, and that it's too late for their child to receive any disease-altering treatment. They're told to take their baby home, make them comfortable, and to prepare for their funeral.

If you think the benefits of infantile Krabbe newborn screening are insufficient, then you do not understand the horror of Krabbe Disease. We're not just talking about an early death. We're talking about an early death preceded by agonizing suffering. Krabbe disrupts every system and function within the body and

100% of these children die, usually by their second year of life. No child should have to suffer like this when there's a screen and treatment available.

Newborn screening for Krabbe profoundly improves length and quality of life. Children diagnosed and treated early are spared from the suffering untreated babies experience and they are so full of life. They go to school, they play with their siblings and friends, they're independent, they smile, laugh, communicate, and they live.

The current nominated protocol was developed following discussion with Dr. Calonge and others last spring and includes psychosine to identify babies with infantile Krabbe Disease without falsely identifying babies who are not at risk. These babies can be cost effectively screened at birth with other RUSP conditions and diagnosed in time to have a chance for a better and much longer life. They deserve to have this chance.

When there is a newborn screening process that avoids false positive screening outcomes, why wouldn't you give affected children a chance to live? In 2009, Krabbe wasn't added by a vote of eight to seven. Last year, it was a vote of seven to seven. We are so close to giving every U.S. child with Krabbe Disease a chance at life. Please, help us save these

precious children's lives. Vote to add Krabbe to the RUSP today. Thank you.

DR. CALONGE: Thank you, Anna. Next, online we have Carlita Blackwell.

MS. BLACKWELL: Good morning.

DR. CALONGE: Good morning.

MS. BLACKWELL: My name is Carlita Blackwell and I live in Missouri with my husband, Ryan, and our vibrate seven-and-a-half-year-old boy, Ezra. I'm sitting here before you once again as the mother of a child whose precious life was saved by newborn screening. There's not a day that goes by that we aren't aware of the vastly different lie that Ezra would have if he had not been transplanted after receiving the diagnosis of Krabbe Disease.

To be honest, I strongly feel that I shouldn't be sitting here before you again. I wish that a year or more ago you saw the indisputable, lifegiving opportunity that the screening for Krabbe Disease gives children and their families, but tragically you did not. And since your vote last year, we've lost numerous children in our community to this devastating disease because they were not given the opportunity to be screen at birth like my son.

After receiving Ezra's diagnosis through

newborn screening, we were devastated, but to be handed this diagnosis with all hope taken away of being able to receive a treatment because it's too late is quite simply cruel. I can't fathom what parents who live in a state that does not screen and receive this devastating diagnosis experience when they learn it's too late and that if only their child had been born in another state, they could've received a treatment that would've allowed them to live a full and happy life.

A full and happy life, how does one define that anyway? I can confidently say that anyone who meets Ezra does not see Krabbe Disease. They see a bright, social, and comedic little boy. We're met with looks of disbelief when they learn of his disease and realize that had he not been born in a different state he would not be here today spreading his infectious joy.

I want to take the opportunity to not only tell you what we see as Ezra's parents, but what any person who's fortunate enough to meet him sees, a vibrate first grader who has recently moved from spending 60% of his time in general education to now spending over 80% of his time in general education with his grade-level peers. Ezra loves school and has continued to excel.

He's a seven-year-old boy who loves riding

his bike, eating ice cream, and helping make dinner. A boy with a lot of opinions, he's a pro at telling you exactly how he's feeling whether a squeal of happiness or giving us a hard no when he's done with something. He has countless meaningful friendships at school and in our community. If you're met him, you know he's never met a stranger, but kids have a special magnetic draw to him.

To see these friendships develop over the years has been a true gift. Ezra's just a typical boy who loves to play tag at recess, attend summer camps, swim in the ocean, and tell silly jokes because laughter is truly his best medicine. I'm not sure what more I can say today to convey to you the critical and urgent importance of adding Krabbe to the RUSP. A fun-loving, joyful child leading a full life should be enough. And there are so many others doing so, just like Ezra.

It's no debate that newborn screening for Krabbe vastly improves the lives of children with this devastating disease. I plea that you not only hear, but truly listen to the stories of children living with this disease after a transplant. In the end, I hope that you recognize that all children, as well as their families, are deserving of the same opportunity as Ezra, not only to save their life, but to live the life they love.

Thank you for your time.

DR. CALONGE: Thank you, Carlita. Next, we have Amy May, who's also online.

MS. MAY: My name is Amy May. I want to give you a family perspective about Krabbe Disease. It's a cruel disease that leads to horrific death if left untreated. Dylan was the happiest of our three sons until he was six months of age. At that time, he started regressing in skills and we went on a diagnostic odyssey. We were blindsided by the diagnosis of Krabbe. We felt robbed of our heathy baby. We felt deceived by the clean bill of health he was given with his newborn screening results.

Krabbe could've been on the screening panel in Tennessee, but it wasn't. We lost Dylan's chance to live because he wasn't screened at birth. I'd like to describe to you what it was like to have a child with Krabbe Disease. Dylan survived until he was almost five years old. We spent four years of our lives dedicated to his care, but there was no hope for his survival.

Please picture your child or your grandchild with these symptoms. He was a gorgeous, happy baby until shortly after his six-month checkup and his first symptoms were that he could no longer suck his thumb. He started crying a lot and he did not sit up on time.

He was diagnosed with Krabbe Disease at eight months of age. The disease progression happened slowly and painfully over the next four years.

Dylan lost the ability to move his arms and legs of his own accord. He lost his abilities to eat solid foods. We spent five hours per day feeding him thickened milk and pureed foods because he loved it. He never spoke, he went blind. Those beautiful blue eyes could not connect him to us or to the world. He had seizures, he cried a lot, and we held him for a large portion of the day to try to ease his pain and let him know that he was loved.

Dylan died one cold January morning in 2009. We had to put our son form our arms into the arms of an employee at a funeral home, then we had to walk away. We had to lower a child-size casket into the ground. No one should have to do these things with a child. Dylan could've lived if he'd been treated for Krabbe shortly after birth like Carlita's son was.

Our other two sons and our adopted daughter experienced this loss also. We've all dealt with complicated mental health issues as a result of this grief and complex drama. If you can save a child through treatment after newborn screening, you can also save the whole family.

Now, picture this, my husband and I are both carriers of the disease. Our older two sons have been tested and they're also carriers; therefore, Krabbe Disease could affect one of our grandchildren. Can you imagine going through this twice when you have the power to prevent that? Screening for Krabbe Disease at birth will save the lives of innocent children. I implore you to add Krabbe Disease onto the RUSP. Thank you for listening to a family perspective.

DR. CALONGE: Thank you, Amy. Next, we have Kelly Danoy.

MS. DANOY: Good morning, Members. My name is Kelly Danoy Bonacorsa. I'm joined today by my husband, Mike Bonacorsa and our daughter, Sophia. Sophia and I were here with you about a year ago in November of 2022. It was seven months after she was diagnosed with early infantile Krabbe Disease, a diagnosis that came too late for early treatment and intervention.

Tragically, now my child and my family are trapped in a painful numbers game where Sophia suffers needless because she was born in the wrong state. As an active-duty family, we are required to move frequently and these moves often come with costs, whether it be emotional or financial; however, I never thought that

our military move to Virginia would come at a real-life cost for optimal intervention and improved health outcomes for our daughter.

I feel so unlucky that Sophia was born in Virginia where she was unable to get newborn screening for Krabbe Disease since the Commonwealth does not screen for Krabbe, largely because the disease is not on the Recommended Uniform Screening Panel.

If Sophia had been born in my husband's home state of New York, she would've been screened for Krabbe and able to benefit from early treatment and intervention. Our state's newborn screening practices impacted a timely diagnosis, worsening Sophia's symptoms. She did not gain the expected developmental skills, she lost skills previously achieved, she suffered needlessly for months with irritability, difficulty feeding, and gastrointestinal reflux.

She developed additional conditions, including loss of motor skills, inability to feed, difficulty seeing, stiffness and spasms in the muscles, as well as seizures. She experienced extended pain and suffering from countless medical errors in clinics and long hospital stays. The damage to Sophia's brain caused by the undiagnosed Krabbe Disease, made it impossible for her to be offered a treatment or therapy

to treat the disease.

On account of this, Sophia is now a medically complex child with severe limitations and physical disabilities, all of which are permanent. She depends on around the clock skilled care, special equipment, and assistance with activities of daily living because she cannot walk, sit, talk, or eat.

Newborn screening for Krabbe Disease sets the condition for affected children and their families. It gives children and families the opportunity to receive early treatment and intervention to help stop the progression of the disease. While Krabbe Disease is rare, the ability to screen early is lifechanging for a child and you will see evidence of it right here in this room when you look at Sophia and you look at Owen, who's here today.

Newborn screening for Krabbe Disease is the kind of lifechanging opportunity that needs to be available for all children and families. This Committee's decision last year to not recommend Krabbe Disease to the panel of conditions was a decision in favor of a delayed diagnosis and children that suffer. It's time to implement recommendations in favor of newborn screening for Krabbe Disease. I urge the Committee to support newborn screening for Krabbe.

Any further delay will only guarantee that more children and their families suffer needlessly and miss the opportunity to receive optimal benefit from early treatment and intervention. More children in the U.S. should not have to suffer and die to force change. Thank you for your attention today. I truly value the opportunity to be a voice for my daughter and my family, and for other children and families impacted by Krabbe Disease and newborn screening.

DR. CALONGE: Thank you, Kelly. Next, Christin Webb.

MS. WEBB: Hello. I'm Christin Webb. I'm a mother of two beautiful children, both affected by Krabbe Disease, but with very different outcomes. Our daughter, Mabry Kate, who's obviously not here with us, was born in 2014 when Krabbe was not yet screened for in our state of Tennessee. Because of this, my husband and I spent an agonizing four months of her short ten months and three weeks of life, in and out of doctors' offices and hospitals desperately searching for a diagnosis, much like you heard some of the other families describe that was a lot like her life.

But we were desperately searching for her diagnosis when a simple screening could've told us what we needed to know from the start. It wasn't just

agonizing for us, but we cannot even begin to describe the amount of pain that Mabry Kate was experiencing during this diagnostic odyssey. Voting against Krabbe to be added to the RUSP, not only robs children of their lives, as it did Mabry Kate, but it also robs parents like us of the right to obtaining crucial information about the health of their newborn baby, as well as the at autonomy to make the best decision for their family.

It's crucial that we put this life-or-death knowledge in the hands of the parents. My husband I would give anything to have had the opportunity to decide what was best for our child. Had we had this information to begin with, Mabry Kate's life would've looked drastically different. In fact, it would've looked a lot like her brother, Owen.

Owen also has Krabbe Disease. The difference is it took his sister's suffering and death to give him a chance for early diagnosis and lifesaving treatment. He will be nine years old in March, nine. His sister died before her first birthday. The difference is so drastic. The treatment he received has radically improved his life. With Mabry Kate, each day we were scared of what Krabbe would steal from her next, but with Owen we get to wonder what successes and milestones he will reach.

We are here today, Owen, especially, to hopefully help you see beyond labels and statistics on a piece of paper. He's a vibrant, second grade little boy who has participated in sports, such as T-ball, soccer, and he loves golf and is a thrill seeker willing to ride any roller coaster. He's tall enough to ride. He's hilarious and loves to tell jokes and he's the local celebrity at his school. Every student wants a high five, a fist bump, or a hug every time they pass by him in the hallway.

Yes, he uses a walker. Yes, he uses a wheelchair. Yes, some things come hard for him, but these things are not what defines his life. It's the pure joy that radiates from within his beautiful heart, mind, and soul, his infectious laugh, his determination and fight he willingly puts forth each day, and the love that he has to give through his extra tight hugs, and so much more. That's what defines him. All of this has been worth it, and every child born with Krabbe deserves the same chance that Owen has had. Thank you.

DR. CALONGE: Thank you, Christin. Next, we have Joanne Kurtzberg.

DR. KURTZBERG: Hi. My name is Joanne Kurtzberg and I'm a pediatric transplant physician at the Duke University School of Medicine. For the past

three decades, I've studied the treatment of patients with leukodystrophies, lysosomal storage diseases and inherited metabolic diseases with hematopoietic, also known as blood stem cell transplantation. The goal of this therapy is to replace the patient's blood and immune system with donor cells producing normal enzyme, which is missing in the patient. In addition, enzyme-producing microglial cells are replaced in the brain.

We know that this therapy corrects enzyme levels in the blood and has variable penetration in the central nervous system. After transplant, as long as full engraftment is achieved, normal blood enzyme levels are observed for life. In Krabbe Disease where both the central and peripheral nervous systems are affected and transplants rescues the central nervous system, but it's less effective in the peripheral nervous system.

In addition, in infantile disease, transplantation is most effective if performed in the first three to six weeks of life. This both justifies and challenges newborn screening for Krabbe Disease. As you know, newborn screening for Krabbe Disease has evolved over the past two decades thanks to the outstanding and courageous work of Dr. Joe Orsini and his team in the New York State Newborn Screening Lab,

Dr. Mike Gelb of the University of Washington, and Dr. Dietrich Matern at the Mayo Clinic, the algorithm for newborn screening for Krabbe Disease has been developed and optimized.

Today the application before the Advisory Council for Inheritable Disorders in Newborns and Children to add Krabbe Disease to the RUSP reflects over two decades of work which has allowed us to (1) define the best testing algorithm for use in newborn screening for Krabbe Disease, and (2) define the core disease to target.

This is the third time Krabbe Disease has come before this Council. The first nomination in 2009 was not approved because of problems with low specificity of the testing algorithm, a high incidence of false positive results, and disappointing outcomes of transplant in the initial patients identified with infantile Krabbe Disease in New York state.

By 2021, when Krabbe Disease was renominated for the core condition of early and late infantile disease, the testing algorithm using a GALC screening assay followed by reflex or second tier testing of psychosine at screen positive samples had been implemented in some states and was shown to have high sensitivity and specificity for diagnoses of infantile

Krabbe Disease, but lower specificity for later onset of Krabbe Disease.

In addition, the benefits of transplants in baby with infantile Krabbe Disease, that is the disease with an onset of clinical symptoms in the first 12 months of life were published and shown to be significantly improved over prior reports, although it wasn't clear that this was appreciated by all of the reviewers. However, identification of babies with a risk for later onset Krabbe Disease was not as specific and resulted in notification of risks to some families where in reality a risk was not present. Concerns related to these issues lead to a tie vote, which is a negative outcome.

So, why are we back again? First, we know that the diagnosis of Krabbe Disease through newborn screening is the only way to rescue affected babies from the pain, suffering, and early death associated with infantile Krabbe Disease. It also prevents parents from undergoing months of suffering with their babies while experiencing long diagnostic odysseys only to learn of the diagnosis at a time when it's too late for treatment.

We know that transplant is beneficial for these babies and strongly believe that parents are

entitled to learn about their baby's diagnosis and options for treatment in the newborn period.

So, what is different about this nomination? How did we improve over the prior ones? First, we narrowed the core disease target to infantile Krabbe Disease where the results of newborn screening are clear. That is, the GALC is low and psychosine is greater or equal to 10 nM. Second, we included in this nomination the clear recommendation that the testing algorithm should consist of a GALC screen followed by reflex testing of psychosine in all screen positive cases.

With this approach, the rare baby with infantile Krabbe Disease can be diagnosed in the first week of life and referred for consideration for a transplant today and maybe gene therapy or other therapies in the future.

I want to spend a minute dispelling myths about transplant for infantile Krabbe Disease. First, I know transplant is not the final answer and that it's not perfect, but it dramatically improves the survival, function, and quality of life outcomes of babies with infantile Krabbe Disease. It's the first of what I believe will be a series of steps leading to continuous improvement of the effective therapies for this disease.

I know, as a hematologist/oncologist, that if we had stopped treating children with acute lymphoblastic leukemia 30 years ago after the first drugs produced remissions only lasting three months, we would not be curing 80% of children with ALL today. Progress in the treatment of challenging diseases is incremental, but it has to start in order to succeed.

Second, I know that no babies are transplanted without evidence of an active, clinical disease which is present on nerve physiologic and the imaging studies of babies with infantile Krabbe Disease in the first few weeks of life. Third, I know that the preparative regime, high dose chemotherapy, does not cause the peripheral neuropathy associated with Krabbe Disease. I know this because I've transplanted many other young infants for congenital and metalogic or hematologic diseases using the same chemotherapy and these children do not have peripheral neuropathy post-transplant.

Lastly, I know that rapid referral for evaluation and treatment of newborns with infantile Krabbe Disease is possible if the proposed testing algorithm and a perspective roadmap for rapid referral and treatment is in place.

In summary, newborn screening for Krabbe

Disease saves lives. It also significantly improves the quality of life for these babies and their families. In the past seven years, 51 babies were born in states who were not screening for Krabbe disease, and these 51 babies had no chance. We listen to the feedback from the Committee and addressed your concerns. It's time for you to vote in favor of adding infantile Krabbe Disease to the RUSP to improve the lives of affected babies and their families. Please vote to approve infantile Krabbe Disease for addition to the RUSP today. Thank you.

DR. CALONGE: Thank you, Joanne. I want to thank all of our public commenters today. I especially want to thank the parents who've come here or talked with us online. This is important work that the Committee does. I think recognizing the ramifications of decision-making in terms of real people and real families and real experiences is an important part of the process for the Advisory Committee on Heritable Disorders in Newborn and Children, so I thank you.

We're going to take a brief break, about 10 minutes. We'll start promptly at five 'til the hour, and thanks again.

DR. CALONGE: All right, we're going to get started again. Thank you. There was an additional

person who signed up, doing everything right for public comment that somehow got dropped of the list, and for that I apologize and to make up for our error, I wonder if we could start with a public comment from Timothy Miller, who is online.

DR. MILLER: Hello and thank you. I'm hoping to try to get our voice out there as well, but I'd like to thank the Advisory Committee for providing both myself and Forged Biologics the time to voice our support for the adoption of Krabbe Disease to the Recommended Uniform Screening Panel. Now, my name is Tim Miller. I have a Ph.D. focused on gene therapy and I'm the CEO of Forged Biologics, the only biotech company advancing a gene therapy for patients with Krabbe Disease.

I've been developing gene therapies since the late 1990s and have worked in both academia and industry for over 25 years. As a side note, I'm including gene therapies for the MPS disorders and fully support their addition to the Recommended Newborn Screening Panel as well.

Today I wanted to just add my voice the symphony of voices urging you to recognize the impact your vote holds for our community and the potential future of patients with Krabbe Disease. Timely

identification through newborn screening is vital for the success of not only intervention with transplant, but also for the potential of newly developing gene therapies as a potential future treatment option. It's not just a recommendation. It's a necessity.

There's plenty of published evidence demonstrating that HSCT demonstrates efficacy in Krabbe patients and their lives after they've been diagnosed as newborns and certainly outweighs many of the risks compared to not receiving any treatment at all, as clearly evidenced by Owen before you today and the potential for that help the 51 babies mentioned by Dr. Kurtzberg.

If the infantile Krabbe population is left without access to newborn screening, this will undoubtedly slow the progression of any new treatments and as irreversible damage will have already occurred by the time of a symptomatic diagnosis. Early identification equals early intervention and like most therapies, particularly those gene and cell therapies, the earlier that we can treat the earlier we can beat this devastating disease.

As outlined by the Committee's bylaws, the overarching goal of newborn screening is to improve the health-related quality of life of newborns, and I would

encourage you in your role as Committee Members and even parents to evaluate the benefits to those being screened or with the potential to be screened.

Yesterday we released news that five infantile Krabbe patients that have been treated with our novel gene therapy, FDX101, were following a transplant. It's important to note that all of those children were identified through newborn screening. These children are walking, running, climbing, speaking, a milestone that children with Krabbe Disease are typically robbed of and enhancing the benefits of transplant.

We believe that this continues to show the benefit of screening every baby for this disease. Our job is to help to provide hope for these families affected by this horrifying disease. And again, I would just like to urge the Committee to act decisively this time in support of addition to the RUSP and embrace the transformative potential it holds for countless future families. Thank you for your time and for recognizing the gravity of this matter. I appreciate it.

DR. CALONGE: Thank you, Tim. At this time, I've become aware that there's a question one of the panel members would like to ask of Dr. Kurtzberg if she's willing to come back up to the microphone.

Thanks, Joanne. Scott.

DR. MCCANDLESS: Thank you, Dr. Kurtzberg. I wondered if you could comment on the availability in your clinical experience as everyone agrees you're the expert in this area. In your clinical experience, are there potential challenges in availability for donors for HSCT for patients from a non-white background. And just, if you could, recognize that this is an off-the-cuff question and that you don't have access to all of your data, just your thoughts on that.

DR. KURTZBERG: Sure. So, full disclosure, I'm a cord blood banker and transplanter and I run a public FDA licensed cord blood bank, which has really become the source for rapid donor procurement for people who are non-Caucasian and need a quick transplant. It also causes less Graft-versus-host disease and fortunately doesn't have to match as closely as adult donors.

And in the setting of Krabbe or other leukodystrophies, monocytes from cord blood and macrophages from cord blood actually have better engraftment in the brain than from adult donors, so there are many advantages to cord blood. You can do a search to the NMDP in like 10 minutes and identify a roster of potential cord blood donors and because you

can go as low as what we call a four of six or eight of 10 match, there are always donors regardless of race or ethnicity.

Then working up those donors takes five days and so a donor can actually be shipped -- because it's an off-the-shelf cryo-preserved product, it can be shipped to the transplant center within a week from start of the search to the end of the process. Even in Krabbe, where we recommend you screen for GALC level in the cord blood unit, which is possible, so you don't pick a carrier donor, it's that short an amount of time which is much shorter than the child actually getting to a transplant center.

But to your main question, 95+% of individuals, including babies with Krabbe, who are of non-Caucasian ethnicity or ancestry, can find a cord blood donor.

DR. MCCANDLESS: Thank you. I appreciate that.

DR. CALONGE: Thank you, Joanne. Before we start our series of presentations on Krabbe, I just wanted to provide a couple of reminders to Committee Members and people in the room about the vote today. For the purpose of the vote today, the Committee will be using our current decision matrix tool rather than what

we've talked about, thinking about changes and modifications going forward.

Our approach to evaluating the evidence uses a decision matrix that assesses net benefit of screening, net benefit of screening all newborns. The certainty of the evidence regarding the net benefit, the feasibility of implementing a comprehensive program of screening for the condition, and the readiness of the public health programs to implement such a program of expanded screening, including an assessment of the costs to the newborn screening programs to expand screening for a condition under review. All Committee Members have been given the current decision matrix, as well as guidance to the use of the tool.

Newborn Screening for Krabbe Disease: An Expedited Evidence-Based Review

With that reminder, we're now going to hear from Dr. Kemper and Dr. Lisa Prosser on the Krabbe evidence review. Dr. Kemper is the lead of the Evidence Review Group at Nationwide Children's Hospital and professor pediatrics at the Ohio State University College of Medicine. Dr. Prosser is the Marilyn Fisher Blanche Research professor of Pediatrics and Director of the Susan B. Meister Child Health Evaluation and

Research Center. Dr. Prosser also holds an adjunct faculty appointment at the Harvard School of Public Health.

Her research focuses on measuring the value of childhood health interventions, using methods of decisions, sciences, and economics. She's currently a member of the Evidence-Based Review Group for the Advisory Committee and is a member of the Advisory Committee on Immunization Practices Zoster Working Group. With that, I'm going to turn things over to Dr. Kemper.

DR. KEMPBER: Thank you very much, Dr. Calonge. Dr. Prosser is going to be presenting remotely towards the end of the presentation and I'm going to go ahead and get things started now. I do want to begin by acknowledging that there is no question that infantile Krabbe Disease is a really terrible disorder.

The presentation that I'm going to give today is going to be relatively brief in that we've presented at the last meeting extensively on issues of Krabbe Disease. This is our first expedited evidence review where we're really going to focus on the change in the nomination and then present the population modeling that Dr. Prosser does. There is going to be no public health system impact assessment that's going to

be presented today.

First of all, I want to acknowledge and thank members of the Evidence Review Group, but I do really want to make sure that I express our gratitude to the Technical Expert Panel members, many of whom are sitting over there in the front row. We certainly couldn't do the work that we do without their input and the work that they do to help us understand the complex issues that we're assessing.

So, let's talk first a little bit about the nomination. So, with this revised nominated condition, the target condition to be detected is infantile Krabbe Disease. As you all know, and as we talked about this morning, it's associated with significant and progressive neurologic impairment by 12 months after birth with death in early childhood without targeted treatment. In this case, we're going to be talking about HSCT or the transplantation.

The goal with this new nominated condition is to again focus on infantile Krabbe Disease and not later onset Krabbe Disease, which for the purpose of this evaluation is really everything that has onset after 12 months after birth. Screening is nominated as a two-tiered process. The first tier is looking for low galactocerebrosidase or GALC enzyme activity, and for

those that are found to have low GALC enzyme activity the second-tier test is psychosine and 10 or more is considered to be positive.

One question that I've been asked a couple of times and I'll just put in here now is that the psychosine test is complicated enough that it simply can't be done as the first-tier test and that's why there are these two tiers, but again, both of these can be done off the same dry blood spot.

So, right now there's variation in how newborn screening for Krabbe Disease occurs across the states to use it, so for example, some states use molecular testing. Most states, but not all, use psychosine as a second-tier tests, but right now the states that are using psychosine as a second-tier test have a threshold of one or two, between one and two to consider it to be positive, not the 10 that we're going to be talking about this morning.

So, I do want to highlight, first of all, the sources of new evidence that have emerged since our most recent presentation. So I'll be talking about information that we've learned from the state newborn screening programs that include dry blood spot. Psychosine is the second-tier test. These were surveys and conversations that we had with those newborn

screening programs, and we'll be talking about the accuracy, considering psychosine thresholds of 10 or more. We'll also be talking about the number of infants with infantile Krabbe Disease that would be identified that way.

I'm going to be talking about the published surveys of families regarding attitudes about Krabbe Disease newborn screening, a published study of health disparities related to Krabbe Disease identification and then I'm going to be spending a significant amount of time talking about an abstract that's going to be presented at an international meeting, actually the international meeting is next week, so you're getting the first public look at this information about outcomes for infantile Krabbe Disease who've received transplantation around one month of life.

So, first, let's begin by talking about newborn screening clinical validity. It's important to recognize that many of the cases of infantile Krabbe Disease actually have psychosine levels that are far above the threshold of 10 and there's likely to be a very low risk of infantile Krabbe Disease with newborn dry blood spots psychosines below 10.

There are some reports of psychosine less than 10 in residual dry blood spots, but the thought is

the reason that these levels were below 10 is because of lack of stability of the psychosine. There's also one case, and we talked about this case in-depth last time of a child that had an initial dry blood spot psychosine concentration of around one, who was later diagnosed with infantile Krabbe Disease. When you read the case report and talk to the people who were involved in this patient's care, there are some thought that the atypical course raises concern about whether the subject met the clinical criteria for infantile Krabbe Disease or there was something else going on. But in any case, there was this one case that's out there.

There is no case of infantile Krabbe Disease with psychosine below 10 that's been identified by the newborn screening programs, and again, I'm going to be showing you those data in a couple minutes. There's also a low risk of identifying later onset Krabbe Disease with a newborn dry blood spot with psychosine of 10 or more.

So, there was one article that described 11 cases of late onset Krabbe Disease and of those ones had a dry blood spot psychosine above 10. It was 12 at 460 days, so certainly outside of the newborn period, but the others had psychosine concentrations between about two and close to, but below 10. Again, importantly,

there's no case of later onset Krabbe Disease with psychosine 10 or more that's been identified by the newborn screening programs.

So, before I drill into the information that we've gotten from the newborn screening programs, again, I mentioned before that there was some variation in screening and that extends to first-tier screening as well and the use of molecular testing. There are two state newborn screening programs that do not include psychosine as a second-tier test, Ohio, and New Jersey. And there are nine state newborn screening programs that do include psychosine as second-tier screening test, and as I mentioned before, their threshold is between one and two.

Now, they've identified 11 cases of infantile Krabbe Disease all with psychosine of 10 or more. I'm going to be showing you this and you know what's funny as I present this the number 11 appears a bunch of times referring to different cases, different groups of 11, and I'm going to try to do the best I can to make sure when we talk about 11 that we understand where these 11 cases came from.

And I apologize for how small this is, but I really do want to have it all on one screen. What you can see is a list of the individual newborn screening

programs as well as the total, which it's totally impossible for me to read because my words show as I look at it.

We asked these newborn screening programs to share with us their screening data from the time they began using psychosine as a second-tier test to as far as close to the present as possible and you can see because of that there is variations in the days that are available and the number of infants that have been screened, but overall, there have been about 3.5 million infants that have been screened for which we have information.

The next column over is the number infants who had a positive first-tier screen that would then go on to needing to have psychosine as the second-tier test, which ranges from – the low that was in New York of 6.6 per 100,000 screened up to in Missouri of about 172 per 100,000 screened. So again, I want you to pay attention to the denominator that the number with a positive first-tier screen is a rare event.

Now, the next column that I've just added in shows the number of infants who had a positive second-tier test, that being psychosine, with a setting to a threshold of 10 or more. Again, remember these newborn screening programs use a lower number, so I asked them

to tell me how many babies would have been positive with a threshold of 10 or more and you can see that for a few of the newborn screening programs there was actually none and the numbers ranged from one to three in total and it's on the order of like 1 or 2% of the infants who had a positive first-tier screening test.

Now, how many of those with a threshold of 10 or more were diagnosed with Krabbe Disease and what's the overall rate based on the population screens. That's what this column answers and you can see that, overall, it's about 3.1 per million infants screened. I'd like to point out in Missouri there were three cases that had a positive second-tier of psychosine of 10 or more, but only one case diagnosed infantile Krabbe Disease. There was a particular issue with the laboratory. That's been resolved. I'm going to be talking about that further, but in all other cases it was 1:1. All infants who had a threshold of 10 or more were diagnosed with infantile Krabbe Disease.

I'm going to be talking about the outcomes of these cases that were identified. I do want to point out that the Illinois newborn screening program was not able to provide that information directly to us, but I was able to reach out to a treatment center in the state and was able to find out about all but one of the cases

that were diagnosed with infantile Krabbe Disease, so just store that for later when we talk about them.

Now, one of the concerns from the previous presentation and consideration about adding Krabbe Disease newborn screening was about the issue of identification of later onset Krabbe Disease. So, what this column shows is if you were to set the psychosine threshold at 10 or more how many cases of later onset Krabbe Disease would you not have picked up. So, this is just showing that setting the threshold to 10 eliminates the identification of these later onset cases and it shows you that the number ranges from about 3.5 per million to about 36.8 per million infants screened. So, again, setting a threshold to 10 does seem to pick up all the cases of infantile Krabbe Disease and cuts out detection of later onset Krabbe Disease.

I do want to highlight, though, that later onset Krabbe Disease doesn't mean Krabbe Disease that presents after a decade or more of life. This could be infants who would go onto to develop significant symptoms after a year of ago, so again, we're really targeting infantile Krabbe Disease that is significant signs and symptoms and progression in the first year of life.

Now that I've overwhelmed you with that

complicated table, I do want to just pull out what I think are the important lessons. Infantile Krabbe Disease case detection with second-tier psychosine set at a threshold of 10, based on the information that the states provided, would lead to identification of about 3.1 million cases per million infants screened.

I mentioned before the issue of false positives. What happened there was that there were two simultaneously submitted samples that had low GALC enzyme activity that were contaminated with a psychosine standard, so there was a high index of suspicion at the time that they were false positives. Out of an abundance of caution, those two infants were hospitalized and psychosine was repeated at another laboratory as fast as they could do it and that was normal, and it led to a change in the laboratory process to keep that contamination from happening again. I think this is such an outlier that I think it would be unlikely to happen again and in the modeling and further analysis we discounted those false positives.

In terms of false negative second-tier screens, none of the newborn screening programs reported a case that would've been missed with the psychosine concentration of 10 or more. Now, there is one state that identified twins with psychosine concentrations of

around five, who received transplants around 100 days after birth, but they did not classify those as having infantile Krabbe Disease and the thought is that they likely would not have gone to develop significant signs and symptoms until after the first year of life. This does highlight some variability in terms of how transplant centers operate, but there was consensus from reading the publications about these infants, as well as discussing this with the Technical Expert Panel that they really would not be classified as having infantile Krabbe Disease.

There was no cases of later onset Krabbe Disease that would've been identified setting the threshold at 10 and moving the threshold for second-tier psychosine testing to 10 for diagnostic referral would eliminate the detection of about 9.3 cases of later onset Krabbe Disease per million infants screened.

Now, I want to transition and talk about the impact of detection of newborn screening compared with usual case detection. First, I want to talk about these 11 subjects, so these are the 11 that came from the newborn screening programs. As I mentioned, we don't have any information about one of the cases. So, for one out of the 11, we don't have follow-up information available. Of the remaining 10, three declined

subsequent transplant and we just don't have any information about what the thinking was in terms of why they declined it, but it's important to recognize that some families do decide not to proceed with transplant for their child.

Of the remaining seven, six out of the seven who receive the transplant, and they received transplants between 24 and 48 days, are alive to at least two years. And in terms of their age, the median is two and a half years with a range from two to five years. Of these children, one child did receive a second transplant, one also received gene therapy and one is planning to go for gene therapy. And again, this is the level of granularity of the detail.

I should have mentioned before that I'm purposefully not talking about the particular states that these infants came from because it's such a rare disease, I feel like it's important for us to do everything we can do to protect their privacy. There was one out of seven of the children who proceeded with transplant who died around seven months of age due to graft-versus-host disease.

Now, Dr. Kurtzberg led a team that's going to be presenting at the WORLD Symposium of lysosomal disorders, I think that's what the name of the meeting

is, next week and she was kind enough to share her poster with our team ahead of time and answer about 5,000 emails, so Dr. Kurtzberg, thank you for that.

That is an abstract that describes six cases of infantile Krabbe Disease who received a transplant between three to six weeks of age, so five of the six cases were reported in an article that we discussed previously, and they were recruited between 2016 and 2019. There was one additional case that was added. These cases were consecutively identified based on referral for transplant.

Of these cases that we're going to be talking about, two out of the 11 cases that I talked about before that were identified by the states are included within this study that I'm going to be talking about. The outcomes include the final and adaptive behavior skills, third edition. For those of you who don't know, the Vineland is a well-accepted, high-quality assessment of development that's based on a parent report of how the child is doing. It is broken down into four adaptive domains of communication, daily living, socialization, and motor skills, as well as an overall composite.

They also assess the pediatric quality of life inventory. The quality-of-life data really matches

up with the Vineland's and to allow us to really focus on the key issues. That's what I'm going to be talking about this morning. So, who are these six cases I'm presenting here? The middle column is the age at transplant, the column on the far right is the age at which this neurodevelopmental assessment was done. It's sorted by age from youngest to oldest, so 2.2 years through 7.1 years and then you can see their initial psychosine level. I'd like to point out that these psychosine levels are far above 10.

So, these are the Vineland scores for the individuals again from two to seven. This is the composite and I added in these stippled lines showing, according to whoever it is that makes the Vineland's, how they classify different categories. But the composite, I think, doesn't really tell the whole story.

I think it's important to look at the domains. So again, you can communication, daily living, socialization, and motor skills. So, it's really the motor skills that are far below the other scores and you can see that these subjects are generally doing better in terms of communication, daily living, and socialization. The poster also includes a Kaplan-Meier survival curve, and it includes seven cases, so these six cases, plus the other one that couldn't be included

for the Vineland's.

I want to take a little bit of time just to orient everyone around the Kaplan-Meier survival curve. So, the orange line shows 51 individuals with infantile Krabbe Disease born in states without newborn screening, so these are infants who developed signs and symptoms and past the period at which transplantation would be an option and you can see the steep decline in the first two years of life and then tail out a little bit longer. That survival curve really matches up with our previous presentation in terms of the expectation of early mortality.

The blue line across the top shows the survival of the infants who were included in the study, so these are infants who received transplants around one month of age. The nuance that I want to point out here is that that represents survival from infants who received transplant and survive the transplant, so it's not necessarily what you would expect from newborn screening, right? So, with newborn screening there are going to be some families that are going to choose not to have transplants and that would be affected by risk of mortality that would follow along the orange line that's there. And then, there's the risk of mortality related to transplant that we typically talk about being

around 10% or so.

In either case, though, you can see that transplantation for infantile Krabbe Disease during the time period that we have certainly decreases the risk of mortality compared to what typically happens in states without newborn screening.

So, there was a study on family perspective. I did not highlight this at the last meeting, although we knew of the study. This was a survey of 170 respondents who were affected by Krabbe Disease, whether it be a parent or other caregiver that was done through an Internet-based study and other direct outreach. And essentially, everybody felt that Krabbe Disease newborn screening should be implemented in any state.

This doesn't include the perspectives of those not directly impacted by Krabbe Disease, so the general public, and it's hard to figure out exactly what the response rate was and who's responding and who's not responding, as is typical for Internet-based studies that are shared across social media.

There was also another study that dealt with issues of health disparities. It suggests that Krabbe Disease newborn screening reduces disparities by race and ethnicity in detection and treatment. From a pure evidence standpoint, though, we rated this as low

quality based on methodologic limitations. First of all, it didn't focus on infantile Krabbe Disease. The study, in terms of the timing of symptoms and treatment, excluded the major Krabbe Disease treatment centers. There's a risk of misclassification of race and ethnicity and it's not really possible to determine the timing of symptom onset and diagnosis looking at hospital administrative claims because normally it's not the kind of thing that occurs in there. There was no record review, so I do want to make sure that the Committee knows that this report is out there and we describe the findings more in depth in the report that's been previously given to you, but it was just we don't want to drill into the particular findings just because we're concerned about quality. Again, it does not mean that newborn screening doesn't reduce health disparities. In general, that's a great function of newborn screening, but for this particular study we didn't think it was reliable enough.

So, with that, now I'm going to transition to my friend and colleague, Dr. Lisa Prosser, who's going to be talking about projecting the population health outcomes. This is where we model what would be expected if all of the newborns were screened for infantile Krabbe Disease each year.

DR. PROSSER: Thanks, Dr. Kemper. As in past condition reviews, we're using a decision analysis to model the population health outcomes for newborn screening for Krabbe Disease compared with critical presentation. And just a couple of slides on background so the science underlying the modeling is using decision analysis, which is the systematic approach to decision-making under conditions of uncertainty. And our goal here is to project ranges and so when I go through the slides of modeling outcomes, again, I would encourage you to focus on the range as opposed to our best-case estimates.

Decision analysis allows the decisionmaker to identify which alternative is expected to yield on the greater health benefit, but importantly, it can also identify the key perimeters and assumptions that are driving the results. So, for this analysis, similar to the previous analysis of newborn screening for Krabbe Disease that was presented last summer, the objective is to project population level health outcomes for an annual U.S. newborn cohort of 3.65 million, health outcomes, both for newborn screening and for clinical presentation on the newborn screening side, of the focuses on screening outcomes, numbers of positive screens, identified cases of infantile Krabbe Disease,

receipt of transplant and transplant outcomes, and mortality at 2.5 years of life.

For clinical presentation, I will be projecting identified cases of Krabbe Disease, both infantile and later onset, again, projecting the receipt of transplant and transplant outcomes within the first year of life and mortality at 2.5 years.

Now, this slide shows a simplified schematic of the simulation model, so I'll just walk quickly through the top branch here. This is the same structure of the model that was used for the previous analysis of Krabbe Disease with the exception that this has now been adjusted to reflect the revised nomination protocol, so you'll seed the grayed out boxes in the middle of the screen and so with the revised protocol submitted in this nomination with the criterion of psychosine 10 or greater that once a baby has screened positive and is referred for diagnostic evaluation there's a probability that being confirmed as infantile Krabbe Disease and referred for transplant evaluation or will be classified as not infantile Krabbe Disease. There could be follow-up pending or declined follow-up.

We'll be modeling essentially the cases that Dr. Kemper has just presented from the most updated newborn screening program data with the 11 cases in the

model. Again, just walking through the top of the model, if a baby is confirmed and recommended for transplant, they could either receive transplant or not, and typically that would be a family decision. If they receive a transplant, we're modeling 100 days survival from transplant-related complications or not and then whether or not the baby survives up to the 2.5 years of life.

On the clinical presentation slide, the simulation model projects a number of individuals, again within a 3.65 million annual newborn cohort with Krabbe Disease or without Krabbe Disease. If they're identified with Krabbe Disease, what the proportion has infantile Krabbe Disease of onset within the first year of life compared to later onset and again, similarly, whether or not those babies would be likely to receive transplant or not, and again, the same set of outcomes following transplant.

So, I'm not going to go through the next two slides in detail because most of the perimeters into the model have not been revised since the last analysis from last summer, but I will walk through where we have changed assumptions. So, highlighted in blue at the top, we've revised the probability of screening positive and referral for diagnostic evaluation to match the data

that Dr. Kemper just presented, roughly 11 and about 3.1 million since that's the number of babies that have been screened so far, collectively, across all of those screening programs, and then the proportion here that were referred for diagnostic evaluation at the top of the screen. The rest of the perimeter inputs remain unchanged from the last analysis and were based on published data and expert opinion as well as primary data from state newborn screening programs.

On the clinical presentation side there has been a revision on this side of the model to update the projected number of infantile Krabbe Disease cases expected to be observed for clinical identification to identical to the incidents of infantile Krabbe Disease derived from the newborn screening program data.

And I just want to make a couple of comments on this. That in the previous model clinical identification estimates were based on historical published data, differences in timing of identification, definition of the phenotypes of Krabbe Disease and study populations and some likely contributors to the differences between these historical published estimates and the lower observed incidents from newborn screening programs.

But given that more than three million

infants have been screened, collectively, across the newborn screening programs that are in place right now, the observed incidents are likely a more accurate estimate going forward. But as with many conditions there is often and will continue to be uncertainty around these numbers, given the rare nature of these conditions. Again, these have not changed since the previous modeling analysis and are based on published data.

So, this slide shows the projected outcomes using the revised nomination screening algorithm. So, for a newborn screening cohort of 3.65 million newborns, we would expect to see a most likely number of cases of 11.3 with a range of 5.6 to 20.2 is expected based on the current experience that all of those would be identified as infantile Krabbe Disease and referred for consideration for transplant.

In the base case, zero projected for not infantile and for false negative, but again, keep in mind that there's a range around those, given the small numbers of these conditions.

This slide shows projected base case and ranges for outcomes under clinical presentation. Here the projected number of cases -- and again, this is considering an annual incidence, but this is really the

lifetime incidence for an annual newborn cohort, so we expect to project 24.2 cases of Krabbe Disease of which could be identified at any time over the lifetime. Of those, 11.3 are expected to be infantile Krabbe Disease cases with a range of four to 23 and 12.9 post-infantile, in the absence of newborn screening, would present following the first year of life.

This slide just combines those two slides to present the outcomes from newborn screening at the top with 11.3 cases compared to clinical presentation at the bottom and highlighting that those are projected to be similar.

So, I'm going to take just a moment to walk through this slide in detail since this provides the projected outcomes at 2.5 years of age for newborn screening, using the revised nomination algorithm compared with clinical presentation. So, in the middle column labeled "Newborn Screening," 9.9 babies, so a portion of those that were identified with infantile Krabbe and recommended for transplant consideration actually would be expected to receive transplant, again, with a range of 3.5 to 19.9. Of those, one would be expected to die within 100 days of the transplant, 8.9 would be expected to survive.

And just skipping to the bottom, so those

that would have died from Krabbe Disease, so that is of those that did not receive transplant, the 1.4 that did not receive transplant, so resulting at total across those two categories who are projected to have died either by complications of transplant or as a result of Krabbe Disease by 30 months of 2.1.

Compared to clinical presentation, again, starting with a cohort of 11.3 cases of infantile Krabbe Disease, only 1.1 of those would be projected to receive transplant by one year of age. Of those, 0.1 are expected to die from complications, one would be expected to survive, again, with ranges around those projections, and 10.2 would be expected to not receive transplant by one year age of the original 11.3 cohort. Of those that did not receive transplant, 7.8 are expected to have died from the condition by age 30 months, and so the total across those two groups is 7.9.

So, in terms of difference, that's shown in the last column, 8.8 additional cases would be expected to receive transplants within the first year of life, and again, a range of 3.3 to 16.6. And then skipping to the very bottom with almost six deaths averted by the age of 30 months, again, with a range of 0.5 to 10.5.

So, that is the summary of the modeling outcomes, so I'll turn it back over to Dr. Kemper.

DR. KEMPER: Great. Thank you very much. Thank you, Dr. Prosser, for that great presentation and I just want to highlight too that you see these wide ranges and that reflects small numbers and uncertainty, but it's really important to focus on the ranges, as Dr. Prosser mentioned.

So, these are some of the important references to everything that's in the report that the Committee is given. With that, I'd like to end and open things up for questions from the Advisory Committee.

Committee Discussion

DR. CALONGE: Thank you, Dr. Kemper. Thank you, Dr. Prosser. Thank you for pointing out the wide confidence intervals. Let me open it up first, please, to questions from Committee Members. And if you're online, please remember to use the raised hand function. Michele.

DR. CAGGANA: Thanks for that overview, Lisa and Alex. I just had a quick question about the two false negative cases. They were not picked up via newborn screening, but became evident via clinical presentation?

DR. KEMPER: Are you talking about the two false positives?

DR. CAGGANA: The twins.

DR. KEMPBER: The twins? So, they were picked up by screening and had psychosine levels of five and so they were below the threshold to 10. So, if the threshold is moved to 10, then obviously those twins wouldn't be picked up by screening. The question that we really focused in on is whether or not those children had infantile Krabbe Disease because if they had infantile Krabbe Disease then that would be false negatives with a threshold of 10, but the consensus was that these were really later onset cases that got transplanted earlier. And again, this gets into the nuance of the terminology around Krabbe Disease as well, but I think the key thing to recognize is that those two infants were transplanted very early on before the development of signs and symptoms associated with Krabbe Disease and that some wouldn't really classify them as infantile Krabbe Disease. And there was a discussion around whether or not some people would've even transplanted them at that age or would've waited until longer.

DR. CAGGANA: Okay, technically, they weren't false negatives from the newborn screening.

DR. KEMPER: They were cases that wouldn't be picked up by 10, but unlikely to be infantile Krabbe Disease.

DR. CAGGANA: Correct. Okay, thank you very much for the clarification.

DR. CALONGE: Ash, online.

DR. LAL: Thank you again for the presentation and the outcomes. So, I think there are two ways of presenting the data and so one is the table you were shown in reduction mortality based on the newborn screening program, and including every infant that tested positive, whether they were ones for follow-ups and refused treatment and there was a mortality that was transplant related.

When you look at the Kaplan-Meier survival curve, so the overall benefit, just from the raw numbers from total cases and defining newborn screening is somewhere in the mid-sixties, leaving aside the ranges. I think maybe we could just talk about the means at the moment. The survival curve -- and again, you have to be just cautious that these are small numbers and early results, suggest that mortality from Krabbe is exponentially eliminated by transplant.

The question really is how do you reconcile the two numbers because the reason for refusal may have to do with specific circumstances under which this condition is diagnosed and the need for the very rapid decision-making and that a few weeks needed in which to

do a lot of workup, plus bring the family along to make an informed diagnosis in terms of transplant.

So, this is mostly a comment. I think that when we're looking at the benefits from positive identification of infantile Krabbe Disease newborn screening, I think that number, which is currently in the mid-sixties in terms of the survival, may be something subject to change with a wider availability and greater experience and as the processes are further refined of taking the infants from newborn screening diagnosis to the transplant. Thank you.

DR. KEMPER: Thank you. And just to reflect back on what you said, I mean, clearly there's a big difference in risk of mortality and just the top curve it doesn't represent every baby that received newborn screening because it didn't include those who, for whatever reason, refused transplant or the small percentage who die as a result of transplant.

What I can't comment on simply because we don't have the information, we don't know, is the decision-making for those who choose not to have transplant. We can't comment on that one way or another.

DR. CALONGE: Shawn.

DR. MCCANDLESS: Shawn McCandless, Committee

Member. This maybe is a question for both of you, but probably more for Dr. Prosser. In the modeling, it appeared that the proportion of families choosing to have transplant was different that the revealed data that we saw. Am I misunderstanding that where it looked like around 30% of families opted not to have transplant; was that the number that was used for modeling or was it different?

DR. KEMPER: Lisa, if it's okay, let me preface your comments by saying, we have a lot of historical information about the rates that families refuse transplant at and then we had this limited number from these 11 cases and so one of the things that we wanted to make sure that we included was the right number in the range and the baseline most value is probably less useful than looking at the range. And so, the sensitive analysis was expanded to include what we learned from the states in these 11 cases, but Dr. Prosser, I probably shouldn't have jumped in yet, so I hope that I said that right.

DR. PROSSER: That's exactly right. So, just the note that the range includes what has been most recently observed from those three cases who declined transplant and so the base case that we've used in the model was derived from published data, so a larger

denominator of cases, as well, but important to note that includes the range so that those three cases, if you look at the ranges, are included there.

DR. CALONGE: Let me turn to our organizational representatives to see if there are questions or comments. I'm going to start with Sue.

DR. BERRY: Thank you for the opportunity to comment, so I'm speaking on behalf of the Society for Inherited Metabolic Disorders. So, SIMD, as you may recall, is our professional organization for research and care for person infected with inherited metabolic condition of which Krabbe is a representative. We are comprised of professionals of all types, including physicians, scientific researchers, dieticians, advanced practice providers, genetic counselors, and our Board of Directors is made up of people representing all of those interests.

So, as this was revisited, we reviewed this issue was a group with great seriousness and we took a formal poll of the Board of Directors about their considered opinion regarding this plan and our result was unanimous with no member of the Board favoring this addition. This noted this with sadness because we truly, as providers and professionals, under the importance and gravity of this condition and its impact

on affected babies and their families.

So, in our discussion, several points were raised. First, the group was concerned about the degree of evidence that supported the impact of therapy, particularly for infantile disease as that's the target of the planned addition. There was some skepticism about the recommended intervention and its effectiveness, which is one with significant morbidity and mortality.

The feasibility of doing the transplant in the recommended timeframe that has been suggested is pretty unrealistic, so I recently had the opportunity to explore this because my own state elected to add this test to our screening panel, so our transplant team, a highly skilled group that is eager to undertake transplant, was uncertain that they could complete the necessary preparation in a fashion that would permit initiation of therapy in 30 days. I really can say with assurance that if anyone can do this, our team will make every effort to do so, but won't be without major challenges.

We heard a little bit about cord blood as an opinion, but the likelihood of finding perfect matches or even suitable matches is variable and can be difficult. This is particularly true for person of

ethnic backgrounds whose pool of donors is more limited. And given the time constraint, this could present an impediment to the recommended intervention and is an issue of justice in health care assessment.

And more importantly, from my point of view, the justice of access for care is also limited, anticipating that all the comers would be able to have a transplant, particularly in the timeframe needed presents significant financial uncertainties to families under the system. It's common for children not to be enrolled in Medicaid, for example, until well after this therapy would have to be initiated. And while retroactive payment is often accomplished, there's no real assurance that this would happen for children depending on this means of support. This is particular true of the transplant can't be performed in the state providing Medicaid coverage.

So, initiation of a time-sensitive therapy that can't be initiated until financial arrangements are available presents a potential for significant inequities in care. So, we asked the Board what would change their decision. We offered four possible factors in the poll that might impact their decision, and these were an FDA-approved treatment, additional evidence about the transplant from more transplant centers,

additional funding for follow-up services, and additional access for patients to treatment centers. And of these, the most frequently chosen response was additional evidence regarding utility of transplant.

In the end, we're professionals. We care deeply about the families we serve, and if you make this change to the panel, we will do our very, very best to serve these children, but based on the criteria chosen for addition this particular condition doesn't fulfill the criteria for the RUSP. And so, for that reason, our Society recommends against its addition. Thank you for the opportunity to speak.

DR. CALONGE: Thank you, Sue. Now Scott Shone.

DR. SHONE: Thanks. Scott Shone, ASTHO. So, I have a technical question and a modeling question. So, you mentioned on one of your slides and in the report that there was mention of sensitivity, psychosine stability. So, what's known about the stability, just thinking about that most laboratories would likely send this to one of the options that you highlighted to the commercial option and a need to make sure that the marker is picked up accurately. What's known of the stability and would there need to be environmental controls because I acknowledge the reference was to like

a six- or 12-month stored spot, but are we talking weeks, are we talking months in terms of stability? That's my first one.

DR. KEMPER: I'm going to give you sort of a non-laboratory, my understanding of how the universe works. So, a lot of those early studies were done on dry blood spots that were stored and who knows what environment and that's really what raised concern about the stability. Psychosine, when it needs to be measured, is going to be sent off immediately to one of the handful of referring centers. And I asked their questions and there was no concern about the stability of the psychosine within the days period that it would be done.

The bigger concern was that going back to these dried blood spots that I always think about that warehouse at the end of Raiders of the Lost Ark, who's stored back there somewhere under what environment, who knows, but there was no concern from the experts, the people that we spoke to about the stability. Again, I don't know of any particular studies that I can point you about that.

DR. SHONE: Okay, I appreciate that, and it sounds like under routine circumstances it would be stable. My question, I think, is on the modeling side

for Dr. Prosser was with the refocus of the expedited review on infantile Krabbe in the model there is a reference to the non-infantile forms and if I'm reading it correctly, and that's my question is it looks like by using the proposed algorithm of low GALC followed by psychosine higher than 10 there is the likelihood that a greater number of children would not be identified. I think it's 12.9, Dr. Prosser, if I'm reading your slides correctly, would not be identified through newborn screening. I understand that that's the whole point of this. I just want to make sure that I'm reading.

DR. KEMPER: I'm going to jump in, Lisa, and maybe let you respond, but in the modeling it's completely true that when set the threshold at 10, you're not identifying those later onset cases. That's the function 10, as you talked about, but if you're following children over time, even though they're not picked up by newborn screening, some infants are going to develop -- as they age, are going to develop the later onset forms and so the modeling had to take into account those children that would be identified through newborn screening, which would have the infantile form, as well as those infants just over time, as time progressed would present with the later onset forms. And now I'm nervous again, Lisa. I hope I said that

right.

DR. PROSSER: That's exactly right. I think that the question that Dr. Shone is also asking is if we compared to the previous version of the model, if those are likely to be the cases that would fall into that recommended for either high or low risk follow-up following screening under a different screening algorithm.

DR. SHONE: I appreciate that because when this group decided on SMA and focused on due to the deletion of exon 7, there was at least time that acceptance said that about 5% of children with SMA wouldn't be identified and so just understanding that it sounds to me that you're saying with this algorithm the model would say 100% of early infantile would be identified, none of the other forms would be identified, and then subject to the routine medical system.

DR. PROSSER: Correct.

DR. CALONGE: Robert.

DR. OSTRANDER: Robert Ostrander, American Academy of Family Physicians. Part of your presentation, and you appropriately said it's hard to sort out the reasons that someone identified might or might proceed with hematopoietic stem cell transplantation for this because it is a very, very

difficult decision because the risks are absolutely real, as everyone's been pointing out and with such small numbers the magnitude of those who would or would not choose to proceed I think is impossible to estimate and so the relative effect of that on the survival numbers is probably hard to sort out.

I would suggest that in addition to the hard survival numbers, which I think is very important for evidence review, that, as at least one of the family members pointed out, that the opportunity for parental autonomy and decision-making, one way or the other, is, in my mind, a net benefit of diagnosing things that are potentially treatable stage when -- I mean, shared decision-making is what has to happen and happens all the time in medicine with treatments that have high risks and high benefits and the actual decision often comes to rely on the value system of the family and not necessarily out of hard number, one way or the other. But if the diagnosis is made late, the opportunity is lost, so I think that's one aspect in favor of adding it to the RUSP.

DR. CALONGE: Shawn.

DR. MCCANDLESS: Thank you. It seems that the updated nomination hinges very strongly on the requirement for a dried blood spot psychosine

measurement greater than or equal to 10 as a second-tier test prior to reporting the result to the family and so that raises several questions in my mind that I hope you may be able to address.

The first is that you commented earlier that it's apparent that state labs will use one of several commercial laboratories to do the second-tier testing; is there evidence to support that? The second question is if there are different labs used, what is the evidence around the variability in measurements of psychosine? Is a 10 in one lab a 10 in every lab or is there likely to be variability between individual labs in terms of the measurement? And the third question then, is there evidence about what states will actually do and state newborn screening programs will actually do around a recommendation that they only report out values that are extremely abnormal and not report values that are clearly abnormal, but not meeting the threshold for reporting for newborn screening?

DR. KEMPER: So, those are three questions and hopefully I'll remember all three. So, one question was about the number of labs that are out there, so again, I'm not a laboratory person, but from talking to experts who are, that measuring psychosine is not a trivial thing and it doesn't come up a lot, as you could

see from the numbers that I showed. So, this is probably something that will remain within -- I'm projecting this, of course, within a limited number of laboratories. So, it's done at the Mayo, it's done through whatever PerkinElmer's lab is called. It's done at my institution, Nationwide Children's Hospital. I think there was somewhere else, and I can't remember where off the top of my head.

So, there's a limited number of labs. It's a complex test. I'm hoping Dr. Prosser can weigh on that once I finish with this part. We did find one study where they compared across the labs the amount of variability and there was varied concordance across the labs, so again, that was reassuring.

The third question you asked is one that's difficult for me to project, so what would states actually do? So, we did talk about that as a group. One of the people who works at one of the references labs said that if you told me the state just wants us to report less than 10 or more than 10, whatever it is, we would be happy to do that, and I think that's supported also by the recent paper that Dr. Matern shared around.

But ultimately, as we've seen from other conditions, states do whatever it is that states want to do, right? Some states report back carrier information

from some children and there are differences in methods and thresholds and stuff like that, so it goes beyond what I can tell you from evidence review what states would actually do. Now, I'm nervous. Did I hit all three questions?

DR. MCCANDLESS: Yes, you did address all three questions. I do think that we came to different conclusions around the publication regarding variability between individual labs. As I recall in that publication, the concordance occurred after normalization to a gold standard was shared, but that the raw testing there was a great amount of variability between labs and that really raises the question of whether there will need to be and who will provide the oversight regarding where second-tier testing is performed and is there any way for this Committee to impact that.

DR. KAMPER: I want to agree with what you just said. It is my understanding that part of the process described in that paper was to bring people to that standard, but that was the final outcome. In terms of what the Committee can do to ensure uniformity in measure that, of course, I'll defer to Dr. Calonge and others.

DR. CALONGE: I'm sorry, Shawn. I will

provide you with an anecdotal piece of evidence, that Colardo would have to refer it out, so I know one state. The other thing I'd point out is tandem mass spec has a number of signals that have never been turned on and aren't reported routinely I'm pretty certain by almost labs in the U.S., so I would say there's evident to having the discipline of not reporting out abnormal signals in newborn screening, but I can't say how that would happen in this specific condition. Carla.

DR. CUTHBERT: That was a very good question and thank you for asking that. Our role at CDC, as you know, is to provide proficiency testing and support for laboratories and so on. What do we hope to do, regardless of the outcome of the vote, is to make sure that we have a psychosine test in house at CDC so that any of the programs across the country that want to do psychosine within their own state programs they will have an opportunity to do that. We have, through our partnership with APHL, we do have a mass spec-based hands-on training that happens and we're aiming to expand to two times a year.

That is when we bring in state programs to learn, as principals, new methods and that sort of thing and we anticipate that we will include methodologies for psychosine for any of the programs who are willing to be

able to do as well. So, there will be an opportunity for them to learn to do it in-house if they would like and we'll provide any support over time as they need.

Harmonization is something that is also very interesting and that we find to be very valuable. We do have a lot of laboratory-developed tests across the country, so one number in one state is sometimes different than another number in another state and we do recognize that across the board for many of these non-kit-based testing platforms. There are a number of states that have taken the initiative from different funding sources to look at harmonization studies, using CDC reference materials to be able to understand how do they actually perform when you harmonize the data, and I do anticipate that that will happen as well with psychosine because that is going to be very important because of the attachment of the numerical value as part of the screening strategy.

So, we will play a very active role with the states that have an interest. We'll work with various APHL committees and subcommittees as well to ensure that there is good conversation around how this gets done, how effective it would be. Any of the needs that are being identified over the course of time will have the experience of the states that are currently doing it so

that we can have some examples as to what challenges they run into and so, to be able to help fulfill that role. And hope that that's helpful and that addresses some of the technical challenges that are not unique to psychosine, but we've been finding are very important as part of an overall best practices for newborn screening so that you don't feel alone with your own number that is internally consistent, but may not have meaning across the states. So, that's our role and we're looking forward to being able to support states in that way.

DR. CALONGE: Michele.

DR. CAGGANA: Thanks for that, Carla. Just from a newborn screening perspective, we always work together, as you mentioned, with APHL and CDC in order to provide the best testing and outcomes possible for babies and I'd say out of almost all of the conditions that have been discussed around the core, Krabbe probably has the largest number of advocacy experts, transplanters, newborn screening programs that have worked to refine the algorithm for this.

And with respect to psychosine testing, right now there are several labs that you can do a send out. If the laboratory that we use receives the sample by 1:00 p.m., we have the results that day, so the

turnaround time is very quick, even if it's a Saturday, which happened recently. They all use the same methodology. They use the same set of calibrators, and they also do external PT right now before a CDC-type PT is available and so there is a lot of crosstalk between the labs that do the second-tier testing to make sure that they are all getting the same answer. Thanks.

DR. CALONGE: Debra.

DR. FREEDENBERG: So, my question is actually a little follow on to Shawn's concerns and a little bit of a clinical question in that we know in many of these conditions when we say late infantile those children are not entirely without problems and they may be more subtle, but they also have difficulties and so my questions was about psychosine levels that are clearly abnormal for what you would expect from a normal population but don't reach that 10.

So, the question is if the late infantile kids may be having some symptoms, and I'm not really sure about that. I was hoping somebody could comment on that, whether that would be something that should be considered as well.

DR. KEMPER: Let me address this just from the evidence standpoint and then others may want to weigh in. So, it's true, based on what we've seen, that

the infants who have infantile Krabbe Disease have really levels in excess of 10. It's not like just on the other side of 10. It's also true that later onset Krabbe Disease, as I'm calling it, is really anything after 12 months of age. So, it doesn't mean those infants are going to go onto have a this is really benign core, so it's just that they're going to present with signs and symptoms after one year.

Based on the previous evidence review, there was concern about the balance of benefit and harm for identifying those children who were going to go on to have later onset Krabbe Disease, which is what lead to this nomination with the threshold of 10 to really focus in on the infantile Krabbe Disease population. So, I agree with you and I don't want to minimize potential outcomes for infants with later onset Krabbe Disease and I think -- and again, I don't want to cross beyond the evidence, so I'm going to turn things back to the Advisory Committee, right, but of course individual states can do what individual states want to do with levels below 10, and certainly we've seen that for other conditions.

But the nomination in front of us that we were charged to look at was really the benefits and harms of identifying infantile Krabbe Disease identified

as signs and symptoms within the first year of life and this psychosine level of 10 or more. I hope that answers it.

DR. CALONGE: Thanks, Alex. Susan.

DR. TANKSLEY: Thank you. Susan Tanksley, Association of Public Health Laboratories, and I just wanted to speak as a member of a state lab. I'm with the Texas Newborn Screening Program and so any tests that we bring online has to go through verification if it's FDA-approved validation, if it is a lab-developed test, so if we decided to bring on psychosine, we would rely upon CDC and PT materials to ensure that we appropriately set our cutoffs and our cutoffs would based upon that versus like a hard number. So, depending on what our program decides, do we only want to pick up the early infantile or do we want to be a little more conservative? We would make those decisions as far as what our goal of the newborn screening program is, and I couldn't safely speak for all newborn screening programs that CLIA validation process is really important and each program makes a decision.

We're required by our statute to screen for anything that is on the Recommended Uniform Screening Panel, as funding allows. And so, if early infantile is added to the RUSP, then we would definitely at least

screen for those.

DR. CALONGE: Thanks. Margie.

DR. REAM: Margie Ream, Child Neurology Society, org rep. I've looked at Krabbe Disease newborn screening from many different angles. I also direct the Leukodystrophy Clinic in Nationwide Children's Hospital in Columbus, Ohio. I'm on the Ohio Newborn Screening Advisory Committee and worked with Alex on the Evidence Review Group.

Yesterday, Shawn McCandless asked me about Ohio's experience because we have been screening for Krabbe Disease for several years, but as was pointed out yesterday, Ohio does not use psychosine in the official newborn screening paradigm. Shawn asked that maybe the Committee would like to hear a little bit more about Ohio's experience with that. WE have identified four infants with infantile Krabbe Disease in Ohio all with psychosine well above 10, forties, mid-thirties and above.

Of those four, all opted for transplant. One actually resided out of state, was born in Ohio, went back to their home state for transplant and succumb to transplant-related complication. The other three were transplanted at Nationwide and all within five weeks of life. Our most recent one that we transplanted

I think was November was day 28, so regarding feasibility, it is a multi-step process that requires a big team. And obviously, Nationwide is not representative of many hospitals that all of the other countries have access to, but we were able to go from never having done it to being able to do it within 28 days. And so, there is feasibility, but I definitely acknowledge that not everybody has access to a hospital like that in their backdoor.

Of the three that were transplanted in Ohio, one was lost to follow-up. The other two are alive and doing okay. One is still quite young, so we don't really have outcomes from them yet. But those four infants were not included in the 11 that the states that were using psychosine reported to the Evidence Review Group because we did need to focus on psychosine as part of the newborn screening lab paradigm. And so, I don't know what the other states not using psychosine have found, if they've identified any cases, but that's what Ohio's experience has been so far.

DR. CALONGE: Thank you, Margie. Scott.

DR. SHONE: So, just real quick, I wanted to mention both Susan and Carla had mentioned laboratory developed tests and I just think for this Committee for the future, given what's going on with FDA and CMS that

that probably needs to be on the radar for the future because it's going to dramatically impact where we go. But my comment is -- Scott Shone, org rep from ASTHO, so it's from a public health system perspective, and it goes back to Shawn's question about what will states do.

And everybody, so far, in front of me has said states will do what states will do and I think that we also need to recognize that decision of whether or not we honor just a 10 or above is largely outside the laboratory or even the follow-up teams. That is a public health decision with counsel and health officials who are going to weigh the impact of doing or not doing and every state is going to be a little different and I feel that that ability to guide or control is outside the purview of this Committee.

It's understandably a potential risk, as some of you may feel, but I don't know that it is necessarily pertinent to that, but I do feel that it does play into an individual state in the Committee's assessment of the benefits versus harms of wherever you make a recommendation in terms of that decision. And I think because the psychosine test is quantitative and there is going to be, as Susan was alluding to, whether or not people decide to look at like a borderline range that lab you send out to doesn't actually articulate,

but you decide to work on or you validate yourself. That is going to be up to the state, but it is fundamentally different, and I'll go back to the SMA discussion, which is when you're just looking at the absence of exon 7, whether it's there or not, is very different from this gray line of a second-tier test of psychosine.

So, I think the data is good, but I would suggest to the Committee that public health and the public health officials of each state are going to have to sit down with newborn screening and look at whatever the recommendation is, if it does go forward or not, to make a decision on where that line is and will have to deal with the outcomes that are associated with that, but that there are obviously risks and benefits that you need to weigh in terms of where that line is, so appreciate the moment.

DR. CALONGE: Thanks, Scott. That brings up to the end of this discussion. First, I want to recognize and thank Dr. Prosser, Dr. Kemper, and the entire ERG Team for a great evidence review and great presentations. Thank you.

(Applause)

DR. CALONGE: We're now going to break for lunch. We're going to start promptly again at 15 after

1:00 on our time. Remember there is a cafeteria across the way, a store that you can get from as well. And if you go outside, you have to be rescreened to get back in, so see you in 45 minutes.

Committee Report: Newborn Screening for Krabbe Disease

DR. CALONGE: Next, we're going to move on to the Committee review of Krabbe. As most of you know, for each condition that we consider for full evidence review, we select two Committee Members to serve as liaisons to the ERG for that topic. They're tasked with presenting a summary of the evidence review, formulating a recommendation for the condition rating and assisting the Chair in leading the Committee discussion.

So, I'm going to turn things over to Dr. Shawn McCandless and Dr. Jennifer Kwon, and then recognize that, as they talk, we work with the decision matrix that we might be able to put up on the screen after their presentation, so I think we'll go ahead and do it that way.

DR. KWON: Thank you, Ned. So, Shawn and I have served again as the liaison to the Committee, and we sat in on the TEP meetings with the Evidence Review Committee to look at the revised application for infantile Krabbe Disease, the expedited review. The

disorder of interest is infantile Krabbe Disease. The newborn screening test would be two-tiered, dry blood spot screening, the first tier is low galactocerebrosidase enzyme activity, and the second tier is psychosine greater than 10.

This psychosine cutoff is more specific for infantile Krabbe Disease and it reduces the number of late onset cases with uncertain outcomes who need to be followed. Overall, the new two-tier screening improves the net benefit of screening. As you know, Krabbe Disease is an autosomal recessive disorder to due to the deficiency of galactocerebroside enzyme activity, which leads to early injury to myelin and brain cells.

Nerve degeneration is the hallmark of the disorder, earlier age of onset is associated with earlier mortality. As you have heard very eloquently, in infantile Krabbe Disease infants may appear normal at birth, then within weeks to months develop difficulty feeding, accompanied by irritability, poor head control, and poor responsiveness. Clinical exams show increased muscle tone, abnormal reflexes, and death occurs in early childhood.

The treatment for Krabbe Disease is hematopoietic stem cell transplant, which can improve survival and developmental outcomes in those with

infantile Krabbe Disease, who are treated pre-symptomatically. That is before the development of significant symptoms and signs. HSCT procedures are associated with known morbidity and mortality and since this is the only treatment offered currently to infantile Krabbe Disease patients, families who are appropriately counseled have refused treatment, as you've already seen. In reviewing the data from state programs currently using incorporated psychosine in their KD screening, no infantile case was identified with the dry blood spot psychosine of less than 10 nanometers.

There was one reported case from authors in New York who presented a child with symptoms of infantile Krabbe Disease who died at two years of life who had multiple psychosine levels less than two. As you've already heard, there was some discussion of whether or not the child perfectly met criteria for infantile Krabbe Disease. I only bring it up as something that was discussed during the evidence review.

Thanks to the new algorithm, the specificity is greatly improved, using the psychosine cutoff of greater than 10. All cases of Infantile KD identified by states currently using psychosine have had psychosine levels of greater than 10. Confirmatory testing for

infantile Krabbe Disease should also include other tests, such as GALC genotyping, MRI and nerve electrophysiology.

This is the final slide, the table that Alex presented, showing the distribution of the cases identified in states that incorporate psychosine screening into their newborn screening protocol and using that with a cutoff of 10 they were able to identify 11 cases. The outcomes of those 11 cases identified by screening show that one of them there's no follow-up information available; three, declined treatment. Of the seven who received treatment between 24 and 42 days of life, they are alive for at least two years. One received an additional transplant and also gene therapy and one died around seven months due to graft-versus-host disease.

So, the potential harms that exist for infantile Krabbe Disease under this current protocol include treatment-related harms of morbidity and mortality associated with stem cell transplantation. There have been concerns raised and also discussed about equity around the availability of appropriate donors and access to appropriate sites.

The higher psychosine cutoff of greater than 10 nM, to date, appears to eliminate many of the harms

that we were concerned about associated with the diagnosis of indeterminate diagnosis, shall I say, of Krabbe Disease. Those children with biologic GALC variants and psychosine levels between two and 10. These children are no longer patients in waiting and are no longer at risk for potentially unnecessary stem cell transplantation. The childhood onset disease will also not be detected under this protocol.

It is possible that Infantile KD cases may be missed using this cutoff. For example, in that article from Corre et al maybe the did describe a patient with Infantile KD. That's possible, but it has not been found yet.

Again, just reviewing the projected outcomes using results from Dr. Prosser, yearly we would expect around 5.6 to 20 cases of Infantile KD identified. As noted before, this markedly improves the specificity of Infantile KD diagnosis. The range is zero to five for not identifying Infantile KD and -- I'm sorry. For identifying an infant who doesn't have Infantile KD and then the false negative also has a range that includes zero, so zero to five.

So, part of Shawn and my job was to wrestle with the level of benefits versus harms in the current protocol for KD newborn screening and under the revised

screening algorithm that incorporates the higher level of psychosine, we agree that there is evident benefit and survival for those undergoing and surviving early stem cell transplantation. The treatment data are limited and there remain honest differences of opinion regarding the value of treatment in infantile onset cases as evidenced by family decisions. The summary of harms with this approach really is related to the treatment mortality.

So, here's the decision matrix that we reviewed, and in reviewing it, there were a certain number of points that came up. And I think I will let Shawn take over from here.

DR. MCCANDLESS: Thank you. Again, to summarize the evidence, as we see it, for the recommendation to the Committee for families that choose therapy there is a measurable improvement in the child's lifespan and in the neurodevelopmental course. Some families do not find this improvement compelling enough to opt for the therapy that is offered and there's very limited evidence that’s available from the newborn screening data presented today is that that's in the order of 30 to perhaps as many as 40%, although one of those patients was lost to follow entirely and I'm not sure that it's fair to conclude that that was a

considered decision.

It appears to me that there continues to be a risk that if psychosine value is less than 10 are reported as high risk by some state programs, the balance of benefits and harms may be impacted. And the slide says negatively impacted, but I think as we've heard today and as we've heard during the previous evidence review, I think there could be honest differences of opinion about the value of identifying late onset cases and the potential harms related to the same situation and so each Committee Member has to weigh their thinking about that individually, I think.

It does appear that newborn screening programs are ready to enact screening for Krabbe and would be able to implement in a reasonable amount of time. We want to acknowledge what we heard earlier today form a variety of different individuals that the process of diagnosing and treating infantile Krabbe Disease within four to six weeks will be challenging, but as Dr. Kurtzberg pointed out, not impossible with potential for errors and delays as there is with any medical procedure, especially things that need to be done quickly. And unless state programs tightly coordinate with their newborn screening callout diagnostic testing and referral, so every state that

does this is going to really need to have a tight system in place when they initiate the project.

When we put this all together, for the two of us, the conclusion that we come to is that the overall net benefit regarding outcomes of newborn screening for a mandatory population based newborn screening program for infantile Krabbe based on low GALC activity and psychosine equal to or greater than 10 in the dry blood spot that there is moderate certainty that screening would have a significant benefit. Therefore, our recommendation is that infantile Krabbe Disease, defined by low GALC activity and psychosine equal to or greater than 10 is not recommended for inclusion as a core condition on the RUSP.

That said, I think I speak for both of us when I say that we want to first acknowledge and thank the families who've shared their lived experiences with us today on this Committee and there's no doubt that Krabbe is a devastating and heartbreaking condition. The Committee is not immune to that emotional power. The charge of the Committee, however, is to make evidence-based recommendations about the public health impact of adding conditions to the Recommended Uniform Screening Panel for mandatory population-based newborn screening.

The Committee is charged with assessing the net benefit of the entirety of the population screened, not just individuals affected. This recommendation takes into account that earlier decisions by the Committee were not necessarily based on a single concern, rather that they were based on the preponderance of the evidence available at the time.

The latest nomination effectively addresses one of the concerns that was raised the last time by revising the case definition. The result, though, and that definition is outside the purview of this Committee to enact or enforce and there remain concerns about benefit and harms from the potential for states to identify individuals with psychosines that are below the recommended cutoff of 10.

We also want to honor and take into account the real-world choices of families who've been informed of the risks and benefits of therapy when they choose not to pursue treatment. We can't assign motive or make judgments based on that, beyond the undeniable fact that when informed of this devastating diagnosis and the options available, not every family finds the option of treatment to be of value and to be valuable to them and wish to honor that, but we also don't want to add meaning to it where there is not evidence to support

that meaning.

Finally, I just want to say that we realize that this decision will be one that each Committee Member makes independently and thoughtfully based on your own understanding and weighing of the evidence regarding benefits and harms. There will be differences of opinion and we respect each of your thoughtfulness and autonomy in voting the way that you feel is right based on how you interpret the data.

So, thank you and we're very interested to hear the discussion.

Committee Discussion

DR. CALONGE: Thanks, Shawn and Jennifer. Would you be happy to take your seats and take questions and comments from there? At this point, I'd like to throw the floor open to start with discussion among Committee Members. Christine.

DR. DORLEY: So, I'm just wondering if it's the purpose of this Committee to recommend how screening be performed and how an algorithm should be put into place to detect kids with --

UNIDENTIFIED SPEAKER: We're having trouble hearing online.

DR. DORLEY: So, I'll repeat myself. This is Christine Dorley, Committee Member. I was just

wondering if it's our responsibility as a Committee to make a decision on how screening should happen or how a screening algorithm should be developed. And I know that the nominators, in putting up this disease for consideration, had to come up with a very clearcut case definition, which means low GALC enzyme and psychosine greater than 10.

And with that being said, I'm feeling like maybe we're blurring the lines between the case definition and then what laboratories should do. And then I, too, was wondering do we have any opinion on the individuals who were actually diagnosed with late onset Krabbe Disease how they felt about knowing that eventually they may develop a disease later on in life and whether they prefer to know about this decision because in speaking from a laboratory perspective and somebody already doing screening for Krabbe Disease, implementing the psychosine is definitely very necessary to decrease your false positive reporting.

But where you set that cutoff, as far as meeting the case definition as defined by this nomination versus just considering reporting anything that's above, say, a two, makes a big difference in the life of those patients. So, I'm just wondering if we make this decision and we say that screening should be

low GALC enzyme and psychosine 10, how do those individuals who would later on be diagnosed with late onset Krabbe Disease who could've gotten treatment much, much earlier would feel about us in this particular algorithm.

DR. CALONGE: I think I can answer that. The broader definition of screening for Krabbe that would include additional potential late infantile -- sorry, I still have trouble with that phrase, but late infantile was concerned and was not passed, so this is a different definition that narrowed it down to Infantile only. As such, the evidence that we had presented today versus the last time we talked about Krabbe was really narrowed down to that definition.

And so, what we're asking you to do today, as a Committee, is consider screening with that case definition of low GALC and high psychosine or psychosine above 10 and made that into the case definition that we would then recommend to the -- if we voted for it, recommend to the Secretary to add to the RUSP. So, I don't know if that helps, but our intent wasn't to again at this meeting re-adjudicate the issue about low GALC in the setting of a psychosine less than 10, and your point is well taken. Michele.

DR. CAGGANA: Michele Caggana, Committee

Member. I just want to review the harms a bit because the harms that were being put forward for Krabbe are treatment-related mortality. This question of whether late onset would be identified or missed and the false positive rate and the fact that we would require tightly coordinated networks and family refusals and what the rationale for those were.

And so, stem cell transplants there's a risk no matter what the condition is when someone is transplanted, and we screen for ALD with a similar type of treatment and so that's a well known and this data that we presented show about what the rate is across many different conditions.

And Dr. Tanksley and Dr. Dorley said, the idea of whether or not you can identify the late onsets really will be subject to what the state feels is appropriate for their own, based on either advice from the Commission or the Advisory Committee or whatever. And I will say, as I alluded to before, amongst all the conditions on this screening panel, I would say that Krabbe Disease is really the most tightly coordinated. We follow these kids all the way through and so a timeline that we just observed not too long ago was specimen arrived on day of life three, psychosine elevation came on day of life seven, plus two DNA

variance. The baby was seen in the clinic by day nine, admitted on Day 13, and is undergoing conditioning and will be transplanted within the timeframes that were proposed that were necessary for the best outcomes for these families.

And lastly, the concern over families' refusing therapy we see this for other conditions. We see families lost to follow-up and we see families refuse for any number of reasons and so I'm just struggling with the fact that these harms would be substantial enough to go one way or the other with a recommendation because in reality we deal with these related to newborn screening for many different diseases, same kind of harms, if you will. Thanks.

DR. CALONGE: Jennifer and then Shawn.

DR. KWON: I would say that I agree. There are other conditions on the RUSP in which you have families refusing to follow-up and refusing to follow through with treatment. Unlike a lot of the clinicians who sit on this Committee, I really think of newborn screening as a compulsory and unconsented laboratory intervention.

And I think that because of its nature the treatments that we propose for these infants should be so effective that parental refusal would be rare. I

think that the machinery of public health in compulsory testing has a high bar and that is not a bar that has been reflected in prior conditions on the RUSP and so I appreciate Michele bring up the fact that invoking it now doesn't seem fair when you consider other conditions approved. However, for me, for my personal view of this program, I think that it is not a program that public health systems -- I think that it's a program that laces burdens on public health and medical systems across the country because of the fact that we cannot reliably say to families that the efficacy involves than more survival and the developmental outcomes that come with that survival. And I understand that for some families that's huge, but unfortunately, in my mind, newborn screening as a public health activity is not to give families an autonomous option and information about their child that may change. But I think currently when I think of newborn screening, I don't think of it like that.

DR. CAGGANA: May I respond.

DR. CALONGE: Yes.

DR. CAGGANA: I understand where you're coming from, but I would argue that there are conditions we screen for that create very medically complexed children already and there's not been any discussion on

removing some of those conditions from the panels and so I think you need to think about it in the context of how programs operate and some of the therapies are not 100% effective and they are complicate and I just feel as if with experience and with the expertise that's across the country for this condition that these children will be taken care of.

DR. CALONGE: Shawn.

DR. MCCANDLESS: Shawn McCandless, Committee Member. I just want to clarify. Perhaps we misspoke when we presented the data. I don't think that either of us see families refusing treatment as a harm, just to be clear. We see that as one way of understanding how parents in this situation value the benefit of therapy. So, this whole discussion is extremely nuanced and challenging in this setting and I get that. And I feel like it's just a very difficult discussion to have in this forum to be able to be vulnerable and honest and I want to acknowledge that, and I want to make clear that I'm also challenged by that.

There is something special, in my opinion, about compulsory population-based newborn screening that we need to be very careful to protect. And you raised the point, Michele, that there are other conditions were families may choose to not pursue therapy, but that's

actually a very small number and those are ones that have been added later and it's part of the slippery slope of where -- slippery slope sounds bad. It's part of the discussion of what newborn screening can and should be. And I come back to the fact that population-based, mandatory newborn screening started with conditions like PKU, it expanded to conditions like MCAD, we would not in our clinic tolerate -- we would make a social services referral for a family with a baby PKU that opted to not choose treatment. We would never do that for Krabbe or for MPS1, or for XALD.

And so, you raise a really good point that there are qualitative and quantitative differences in these conditions that we need to be thoughtful about, but I also don't feel that that means that every decision just means the next one needs to be more aggressive or that we need to continue to push the envelope.

I think it's a really nuanced decision, and as I said, I totally understand that different people will have different perspectives on this and they're all valuable and each of us has to vote the way that our heart and mind tells us is the right thing to do. Sorry, that was long, but I apologize for that.

DR. CALONGE: I'll come to the people online

in just a minute, but Dr. Warren.

DR. WARREN: First, I want to thank our Committee colleagues for their review of the review and their report out, and appreciate the acknowledgement that reasonable people can disagree and that this is a nuanced conversation. I also want to comment on sort of a point where we find ourselves in newborn screening and the evolution and you've heard some conversations about that and I appreciate that there's work going on with the National Academies, for example, to be able to give us some sense of what does that new frontier look like and for some of these things we're already at the border of that new frontier. But it will be helpful to understand what are those rules, because it may be that those criteria that got us here are not the same ones that get us there.

I think, for me, where we are now is we've got a nominated condition with these revisions where we can identify children who may be affected. There is a therapy that saves lives. We've got the opportunity to give parents a choice. And as you all noted, not all parents may choose that and that is very different than a family who would choose to refuse treatment for PKU, but it gives them a choice that they wouldn't otherwise have.

I also just want to say -- I'm sorry. This is more of a comment than a question. There were numerous reflections today about system opportunities and I don't want to diminish the system issues. And I think everyone of us sitting around this table, and frankly, everyone sitting in this audience and watching is part of the system, whether we work in state or federal governments, whether we work for advocacy organizations, whether we provide clinical care, all of us has a voice, a different voice, but a voice in that decision-making process.

And we've heard examples today of where folks have figured this out and have done this and does that mean that if this Committee votes to approve and that it's going to be seamless every time, probably not, but we at least create the space where we can all continue to push, so thank you for your review and your work here.

DR. CALONGE: Let me go to Jannine online.

DR. CODY: Jannine Cody, Committee Member. First, thank you Jennifer and Shawn for such a thoughtful review, but I feel like there are two things that received sort of outweighed consideration. And I apologize, Shawn cut out a little bit online, so I didn't hear all of what he had to say. But considering

or worrying about what states will do is really beyond what we can control and try to guess at and consider. And also, I guess I agree with Michele, as point out, to treat or not treat is not compulsory. To not screen at this point is compulsory for not treating, so we rob families of the opportunity even make that choice on their own if it's not screened.

So, the fact that some families choose to not, after careful consideration with their clinician, does not seem to be a strong factor to me in whether to approve or disapprove. I guess I agree with Michele on that, so thank you.

DR. CALONGE: Thanks. Ash.

DR. LAL: Thank you. I'm just going to keep my comment focused on the one thing I wanted to mention and that's the net benefit certainty. And I was thinking through this I was wondering why I may come to a different conclusion, and I realized that I was thinking of net benefit from treatment versus net benefit from screening. That's what's in the decision matrix.

But if one separates out and thinks about the treatment itself, what we've been shown today is that those who have received stem cell transplant there is -- and I'm repeating myself. There's an elimination

of the disease-related mortality and there is stability of response to the extent that follow-up allows us to pursue them.

The transfer of morbidity of around 10 percent is what one would expect for unrelated donor transplants and in many conditions where the disease itself carries a high mortality, there are families and their patients who might accept a higher related to mortality and then 10%. What we're comparing it with is immediate survival of less than one year, if I remember the graphs correctly and putty much zero survival beyond five to six years of age.

So, the relative benefit of the risks of one or the other you really can't calculate it because you're comparing close to 100% with 0%. So, where does the decision about the benefit lie. I think it might be with the quality of life that is shown after a successful treatment and that's where it becomes rather subjective. I, from looking at the data today, and hearing form the experts and the families, do feel that the quality of life that is assured after a transplant would, in my mind, justify going ahead with the treatment and therefore as far as the treatment itself is concerned, I think there's a high certainty of a benefit.

And I agree that when you extrapolate that to the population level that one may have to take some other things under consideration, but the treatment itself I would rate it as a high benefit. Thank you.

DR. CALONGE: Thank you. Shawn, is this in response?

DR. MCCANDLESS: I just want to respond briefly to Dr. Lal's comment. Shawn McCandless, Committee Member. I want to be clear that the statement that we made about moderate certainty of significant benefit is related to the overall net benefit of public health mandatory newborn screening program for Krabbe Disease with low GALC activity and psychosine greater than 10. It includes both potential harms and potential benefits.

No one would argue with you that the mortality benefit is clear, even from the very limited data that we saw today. I don't want to leave anyone with the conclusion that we doubt in any way the mortality data. That is very clear. The neurodevelopmental outcomes were definitely improved compared to the baseline. There's no doubt about that.

The statement about the certainty of the net benefit is related to the overall population-based newborn screening program, not just the benefit of

treatment for those people who survive the bone marrow transplant and I just want to be clear about that.

DR. PHORNPHUTKUL: Chanika Phornphutkul, Committee Member. This is more of a comment as I am listening and thinking through this. There's a small number of cases and I'm thinking about the cases that decline treatment. I think we all have to keep in mind it will depend on who the family met, the historical natural history may tip the scale one way or the other.

Because the number is so small, I think we just need to think about this and be very sensitive that the decision it could turn into 50% if one more patient declined treatment, so that's just something that I try to incorporate in terms of trying to make this I think would be this decision. Thank you.

DR. CALONGE: Melissa.

DR. PARISI: Melissa Parisi from NIH and I just wanted to thank everybody for a really thoughtful discussion. I think this is a challenging decision to make. I have three points that I wanted to make. One of which is that, as you mentioned, Shawn, I mean I think everybody weighs the benefits perhaps a little bit differently than others. I think we all wish that the outcomes were better for these kids with infantile Krabbe Disease after stem cell transplantation, but they

are alive and for many families that, in and of itself, is a significant benefit.

I took care of a baby with Krabbe Disease over 20 years ago now before transplantation was even an option and it was devastating for this family to watch their child just regress and finally succumb around one year of age and I so wished that those parents had had an option of transplantation or at least something that might have given them some hope.

And I also feel that just because some families may decline hematopoietic stem cell transplantation does not necessarily mean that that would justify taking away the option for other families that would like to have that as a possibility, recognizing that it is not a trivial procedure and not a benign procedure and that there is a certain mortality associated with it.

My second point is really related to the concerns about the availability of hematopoietic stem cell transplantation, and I know this was raised by the very thoughtful comments that Sue Berry made from SIMD. I guess thinking about the prevalence of this condition now that we think that we have better estimates and the number of infants impacted and the experience that has now been garnered in the 11 different states that are

doing screening that have some fairly broad distribution across the country, not complete, of course, that with the support of the advocacy groups and with the transplant centers that do have a great deal of experience my hope is that the approximately 11 babies per year born with this condition, if screening is accepted, would be able to access those resources and get efficient transplantation from a qualified center in a timely manner.

And then, thirdly, I have to put on my NIH research hat and suggest that recognizing that the current cutoff of low GALC and a psychosine greater than 10 helps to make this condition better defined and allows for reduced false positives, but it does break my heart a little bit that there's the potential to lose the very valuable data from those babies that would have a psychosine level between approximately two and 10 who are risk for a late onset Krabbe Disease form that would be incredibly valuable to know more about to be able to follow longitudinally and potentially have very reasonable and possibly positive outcomes from transplantation.

So, I know that that's not what we're debating today and that's not what we're going to vote on, but I guess my call as a researcher is that would be

valuable to know more about those babies if this condition is accepted to the RUSP. Thank you.

DR. CALONGE: Thank you. Cindy.

DR. POWELL: Thank you. Cindy Powell, organizational rep from ACMG. I did not survey the ACMG members nor our Board of Directors about this. I'm speaking as someone who's tried to keep an open mind about all of the evidence that's been obtained. I was still a Committee Member and presented on behalf of the N&P Workgroup in May of 2022 where we recommended that Krabbe be put forward for a full evidence-based review and I've thought a lot about the benefits and risks of Krabbe newborn screening.

In listening to all the data presented, and I wish that there were more follow-up data available, but I know Dr. Kemper and the group did their best in getting what data was available, but it really seems to boil down to one of the main criticism is the timeliness of treatment and the challenges of this, and I just don't think that's enough to say that it's not worth including on the RUSP.

I mean there's been publications for the clinicians in Virginia that this is going to present so many challenges, but frankly, we've always had challenges whenever there's been a new condition added

and we have been able to overcome those. Yes, I'm in a state where we have the Transplant Center with the most experience here in North Caroliina, but the experts there are willing to share their knowledge with other states, other sites, and to be able to expedite treatment so that babies can get transplants within four to six weeks I think is doable for the most part. And yes, there will be challenges, but I think they can be overcome.

So, I think the other things Dr. Caggana definitely touched on several of the points I wanted to make, so I won't repent those now, but basically there are a number of other conditions already on the RUSP that have a lot of the same concerns that have been brought up about Krabbe Disease. Thank you.

DR. CALONGE: Thank you, Cindy. Natasha.

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. First, I have a question, I guess, to the Committee, maybe it's to you. We heard from Dr. Kwon and Dr. McCandless their views on what newborn screening is and the purpose of it. Does this Committee have a shared definition or view or idea of the purpose of newborn screening that it works from? I just think that that might help when people are thinking about what are we voting on.

Some people say newborn screening is meant to reduce morbidity and mortality, maybe that isn't the full definition here, so that's just a question; is there a shared working definition of that that this Committee is working from? I don't know if you want to answer that before I get my next topic.

DR. CALONGE: I think there's what we have written down and then I think it's evolving, so I would say it's not a discussion we had.

MS. BONHOMME: Okay. And then to the comments around therapy and understanding the perspectives when speaking to the fact that some families refused and appreciating the comments that trying not to weigh too much into that, but it seems like we're weighing into that because we're discussing it so much. And just a reminder that we talk about we want informed decision-making for families. That means they get to make a decision, informed both on the knowledge that we have, but also the knowledge they have about their own lives and how they want that to go. So, I think that's a really important piece to this.

And PKU has bene brought up because it's always brought up when we talk about newborn screening and I think it's already happened, but on the Hill right now there is someone giving a speech, someone in

Congress, about the fact that we need better access to medical foods, so even for PKU it is not guaranteed, even if you choose for that treatment and want to pursue it that you consistently have it. We have families who have PKU who still struggle to get the formula.

So, I think it's important to know that these issues are part of the newborn screening system and, yes, we're all working towards it, but just to have that be really clear that these issues are not new and, in fact, they are a part newborn screening and why there are so many other programs to support families, support states, this isn't a one and done. That it's evolving.

DR. CALONGE: Jennifer, did you have another comment?

DR. KWON: Yes. I can't find the actual 2006 article that came out in the ACMG when this Committee was brought together, but I think that we all struggle to remember that newborn screening currently is for the best interest of the child and so when there are treatments that are highly effective and are lightly to make a significant difference in the life of that child, then I do think that the community medical family, et cetera, come together to try to make sure that those resources and treatments are available.

And so, when treatments are effective, it is

very rare that we have issues with parental refusal, and part of the reason we may be focusing perhaps to much on the families who refuse treatment for Krabbe Disease is because clearly the treatment is different from let's say the A list of disorders that are on the newborn screening panel.

But I think that the charge of the Committee comes from that document, right? It comes from saying that it's the interest of the child first. If we need to look at population-based net benefits and harms, I think we do have somewhat different places that we draw the line and set our threshold and you've already heard that, but I think we start from that basic beginning and then have our different experiences that come into it.

DR. CALONGE: For one moment, Shawn. As somebody who worked in state public health for nine years and I'm now in my tenth year, I think, for me, there is a big struggle at the interface between public health and all too rare diseases. The ability to have a population health impact in very rare disease doesn't fit within the public health framework.

I'm not saying it's not valuable or we shouldn't do it, but you recognize there is an automatic conflict between thinking about the burden of health for a state on the whole and the resources you bring to bear

on moving the health of the entire state forward and where does that get impacted when the number of people impacted gets smaller and smaller.

Tom Friedman, I think, a lot of people would argue was a pretty good director of CDC and basically if it didn't impact lots and lots of people, he said we're not going to pay attention to it. And I'm not saying that's right or wrong, but it's attention around public health and the public health system when that system is used to address individual disease.

Now, the reason why we do newborn screening in public health is that's the way to get the entire population. So, we have a population-based screening strategy that overall helps lots and lots and lots of kids and in any one condition helps very few, and Krabbe is an area where it's very few. So, that to me, for my own decision-making, will always be an issue, a strategy about I have to think in a tax limitation state of opportunity costs of where other places funds could go, even though we charge the hospitals more, in Colardo it's under the same rubric of you can only expand spending so much. That's not anyone else's problem, but that's my problem and so I'm always thinking about opportunity costs and if we do this what are we not going to do? And I realize that's not a problem a lot

of people think of, but it's one that we live with in public health in many places and I live with really every day in Colorado. So, I'm just telling you about the tension.

The other thing I want to point out is that I get the issue that there were six deaths that didn't occur because of transplantation. I have to tell you from a population standpoint, that is a dramatically thin dataset. That is a very small amount of data on which to base a population-based decision and you remember there were confidence intervals around there where it went down to less than a complete life, which is not a possibility, but it's a statistical measurement.

And so, even my certainty around the significant benefit is challenged a bit by the small numbers and the math, and so I just wanted to comment. I mean he said it's a significant benefit and I said, yes, based on a very small evidence-base. Shawn. I'm sorry. Paula.

DR. CAPOSINO: Thanks. Paula Caposino from the FDA. I have a question. If a state implements this for infantile Krabbe, does that make the diagnostic odyssey for the late onset Krabbe babies more difficult or is that still something that's going to be picked up

irrespective of the screening program?

DR. KWON: I think I can answer that. If a state lab calls out Krabbe results according to this algorithm, then those who have late onset Krabbe Disease will never know that they have late onset Krabbe Disease. And so, if they develop symptoms, then someone will need to be aware that late onset Krabbe is not being screened for and they should think of that as a diagnosis.

An analogy might be to SMA screening, which screens for homozygous deletion of the SMN1 gene, which accounts for probably just over 95%, maybe more of cases of SMA, but there is a percentage of cases that we don't diagnose by newborn screening we have to be aware of every time we see a hypertonic baby and not just assume that everyone was screened and so we don't have to think about SMA. I hope that answers your question.

DR. CALONGE: Shawn, I think you had something to add?

DR. KWON: it doesn't look like he did.

DR. MCCANDLESS: I do want to add to what Dr. Kwon said, which is that that's a concern that's been raised for a variety of conditions as they're added to newborn screening because of the concern that pediatricians will assume that the disease has been

ruled out completely and not because they don't fully understand the implications of a screening test.

The fact that there are these long diagnostic odysseys already shows that as a group of physicians we're not always that great at thinking of the entire differential diagnosis, so I think that's a hypothetical concern, but I would be very, very hesitant to consider that a potential harm of the proposal that's on the table today because I just am not aware of evidence to document that, at least compelling evidence. So, it's a reasonable thought, but I would encourage the Committee not to think of that as a potential harm related to the decision we have to make today because there just aren't data to support it one way or the other. So, it's a fair thought, but not maybe one that I would recommend we take into consideration today.

And may I continue with a couple of other thoughts responding to earlier comments? Several comments have been made that by screening we're giving families choices, but I think it's also important to keep in mind that by screening we are taking away choice from other families. And Dr. Goldenberg alluded to this yesterday in data he represented, and I have person experience with this, of families that are diagnosed with this particular condition in Ohio who felt very

angry and upset that their choice of enjoying their normal baby for the first several months of their life was taken away from them by the newborn screening program.

So again, I don't disagree with any of the points that have been made or the arguments that have been made today. I think this is a very challenging discussion, but I just think that we have to be really thoughtful about all of the potential, unintended and intended consequences of the decisions that we make and remember that regardless of what we decide someone is not going to have a choice.

The other thing I just have to come back to is that there are very few public health mandates in the United States that you don't get to choose, that are compulsory and newborn screening is one of them. And the basis for that, starting in the sixties, as I understand it, was the reasonable person argument. That a reasonable person would not be able to make an argument for not treating that condition and I think that is, in large part, what underlies public support for mandatory newborn screening and that the more we get away from that maybe that's the right thing to do, but I think we just need to be thoughtful that one unintended consequence of making this kind of decision will be loss

of support for public support for mandatory newborn screening. And I believe that the mandatory nature of newborn screening is one of the most compelling arguments that nominators bring to this Committee for why it needs to be in newborn screening, so that no baby is missed.

If we lose our public mandate for mandatory screening, then we will lose that benefit for everyone. Again, maybe that's beyond the scope of this discussion and this decision-making, but I feel like -- this is clearly not black and white. If the question before us today were should every parent be given information and have the choice to have screening done, there's no doubt in my mind the answer would be unanimous yes. That we would like every family to be able to choose for themselves whether to have this for a variety of reasons that's not popular and not felt to be acceptable.

Carrier screening is not felt to be a viable option. This would be a great example of where carrier screening would be valuable. I think it's really complicated. I think the decision is difficult. I just want to be really clear that when Dr. Kwon and I make a recommendation it's not because we disagree with anything that people are saying. We have different concerns, different values, and also, I'm not trying to

convince anybody that I'm right because I'm not sure I am, but I have my way of thinking about things, and I wanted to share that with people.

DR. CALONGE: Michele.

DR. CAGGANA: Thanks for that and for all the great discussion today. I just want to remind people that we always talk about PKU as the star of newborn screening, and in reality, when we began compulsory screening for PKU the AAP came out against screening and time changes and opinion shifts and now it's held up there as a success story that everyone gets taught about, whether you're in genetics class or medical school.

The other thing related to the net benefit and the number of children impacted there's many conditions on the current panel that exceedingly rare. We don't find in New York for one, two, three years. For example, GAMT Deficiency. We began screening on October 1, 2018. We've picked up one child. I think the same in Utah who began screening before us or picked up a baby before us.

Other conditions like homocystinuria have been on the panel since the eighties, at least in New York, and we find one every year or two. And so, I don't know that it's fair to talk about numbers. It's a

rare disease, a lot of effort has gone into trying to develop the best possible algorithm to get these children into care as soon as possible and I think on some level it's actually a benefit that there's so few infants because that allows us to focus our efforts on those few families and be able to assist. As we mentioned, the treatment centers are very involved in helping out to make sure these kids get seen and into care and formal diagnosis and everything necessary for a transplant as soon as possible. And so, I do think a lot of the pieces are in place. Thank you.

DR. CALONGE: Thanks, Michele. I appreciate that. Natasha.

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. I appreciate the conversation. It definitely seems like outside of this vote there are a number of conversations that this Committee may want to take up in terms of the themes that have been discussed within this vote. I did want to build upon what Michele just said in terms of rare diseases and, yes, there are small numbers, but there are 30 million Americans who have rare diseases. So, let's think about which numbers we want to include in the dialogue and when we're talking about which numbers and the impact of that.

And I have to say that I don't know if

concerning is the right word, but it's interesting to be talking about such small numbers because we're talking about rare diseases. So, if we're not talking about that, then what are we talking about, right? What is the purpose of this Committee and where is its focus? So, I just think that these themes that have come up are not just Krabbe related, and they're not just related to this vote. They're related to, I would they, the work of this Committee and the work that is connected to newborn screening overall, so again, it's not just about Krabbe.

DR. CALONGE: Thanks, Natasha. Robert. Bob Ostrander.

DR. OSTRANDER: Robert Ostrander.

(Audio difficulty.)

DR. CALONGE: Bob? Bob, we can't understand you.

DR. OSTRANDER: I'm sorry. I'm stuck here in the airport. Never mind.

DR. CALONGE: I would, at this point, like to entertain a motion. The Advisory Committee on Heritable Disorders of Newborns and Children recommends adding infantile Krabbe Disease as defined by low GALC enzyme activity and psychosine greater than 10 nm for inclusion as a core condition on the RUSP. Is someone

interested in making that motion?

DR. MCCANDLESS: Shawn McCandless, Committee Member. I make the motion.

DR. CALONGE: Thanks, Shawn. Is there a second?

DR. KWON: I second.

DR. CALONGE: Thanks, Jennifer.

DR. MCCANDLESS: If the vote goes the wrong way, we want to be on record has having at least moved and seconded .

(Laughter)

DR. CALONGE: Is there any further discussion?

(No response)

Vote On Whether or Not To Recommend Krabbe Disease For Inclusion On The Recommended Uniform Screening Panel

DR. CALONGE: Seeing no further discussion, I really do appreciate the vulnerability people showed, the thoughtfulness people put into their statements, and I want to underlie the understanding and hope that people respect people for the values and experiences they bring to the table, their willingness to discuss them in open forum, and to have them visible to people who disagree and then to do that in a respectful way. I'd like to hold that and keep it in mind going forward,

regardless of the outcome of the vote, or the individual voting decisions that people around the table and online make. With that, I wonder if I could turn to Leticia for a roll call vote.

CDR. MANNING: Thank you. From the agency for Healthcare Research and Quality, Kamila Mistry.

DR. MISTRY: Here.

CDR. MANNING: I'm sorry.

DR. CALONGE: Would you please answer, yes, you approve the motion or no. Thank you.

DR. MISTRY: Yes.

DR. CALONGE: Thank you.

CDR. MANNING: Michele Caggana?

DR. CAGGANA: Yes.

CDR. MANNING: Carla Cuthbert?

DR. CUTHBERT: Yes.

CDR. MANNING: Jannine Cody.

DR. CODY: Yes.

CDR. MANNING: Christine Dorley?

DR. DORLEY: Yes.

CDR. MANNING: From the Food and Drug Administration, Paula Caposino?

DR. CAPOSINO: Yes.

CDR. MANNING: From the Health Resources and Services Administration, Micheal Warren?

DR. WARREN: Yes.
CDR. MANNING: Jennifer Kwon?
DR. KWON: No.
CDR. MANNING: Ash Lal?
DR. LAL: Yes.
CDR. MANNING: Shawn McCandless?
DR. MCCANDLESS: No.
CDR. MANNING: From the National Institute of Health, Melissa Parisi?
DR. PARISI: Yes.
CDR. MANNING: Chanika Phornphutkul?
DR. PHORNPHUTKUL: Yes.
CDR. MANNING: And Ned Calonge?
DR. CALONGE: No. The result of the vote? The result of the vote is 10 to three, so the Committee has voted in favor of recommending Krabbe Disease to the RUSP. I will prepare a letter for the Secretary with the recommendation from the Advisory Committee. Please remember that the Secretary makes the final decision on whether or not to accept the Committee's recommendation. This decision will be posted on the Committee's website.
I'd like to thank everyone involved in the nomination, the evidence-based review, and decision-making process, including members of the

Committee, the ERG, the Technical Expert Panel, and of course, my fellow Committee Members, our organizational representatives, and the fine staff of HRSA that put together such a great meeting.

Finally, I again want to thank the members of the public, advocates, and family members alike for your willingness to come here to help the Committee make its decision and to move newborn screening forward.

At this time, I understand we're not going to go with APHL presentation today, which is good. I would ask if there is any additional new business to bring in front of the Committee today?

(No response)

New Business

DR. CALONGE: Seeing none, I would thank everybody I just thanked a second time, especially the folks who helped get us here and get us back home, help set up the meeting, that wonderful staff that Michael, Jeff, and the rest of the teams put together to help these meetings move smoothly, almost smoothly completely. And I want to thank our AV folks as well because it really was about as good as it's ever gone since I've been here, so thank you so much. We will be meeting again in May. And if I could remember those days, that would be miraculous. There it is the 9th and

10th. It is a miracle, so thanks again and safe travels for all of you getting back home. Thanks.

(Whereupon, the meeting was adjourned at 2:28 p.m.)