The Advisory Committee on

Heritable Disorders in Newborns and Children

Virtual Meeting

9:30 a.m. until 3:00 p.m.

Thursday, February 9, 2023

Attended via Zoom Webinar

- I N D E X -

COMMITTEE MEMBERS

Kyle Brothers, MD, PhD
Endowed Chair of Pediatric Clinical and
Translational Research
Associate Professor of Pediatrics
University of Louisville School of Medicine

Ned Calonge, MD, MPH (Chairperson)
Associate Dean for Public Health Practice
Colorado School of Public Health

Michele Caggana, ScD
Deputy Director, Division of Genetics
New York Department of Health

Jannine D. Cody, PhD
Professor, Department of Pediatrics
Director, Chromosome 18 Clinical Research Center
Founder and President
The Chromosome 18 Registry & Research Society

COMMITTEE MEMBERS

(continued)

Jane M. DeLuca, PhD, RN
Associate Professor
Clemson University School of Nursing
Metabolic Nurse Practitioner
The Greenwood Genetic Center

Jennifer M. Kwon, MD, MPH, FAAN
Director, Pediatric Neuromuscular Program
American Family Children's Hospital
Professor of Child Neurology
University of Wisconsin School of Medicine

Ashutosh Lal, MD
Professor of Clinical Pediatrics
University of California San Francisco
UCSF) School of Medicine
UCSF Benioff Children's Hospital

COMMITTEE MEMBERS

(continued)

Shawn E. McCandless, MD
Professor, Department of Pediatrics
Head, Section of Genetics and Metabolism
University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

Chanika Phornphutkul, MD, FACMG
Professor of Pediatrics and Pathology and
Laboratory Medicine and Genetics
Director, Division of Human Genetics
Department of Pediatrics
Brown University
Hasbro Children's Hospital / Rhode Island Hospital

EX – OFFICIO MEMBERS

Agency for Health care Research & Quality

Kamila B. Mistry, PhD, MPH

Senior Advisor

Child Health and Quality Improvement

Centers for Disease Control & Prevention

Carla Cuthbert, PhD

Chief, Newborn Screening and Molecular Biology Branch

Division of Laboratory Sciences

National Center for Environmental Health

Food & Drug Administration

Kellie B. Kelm, PhD

Director, Division of Chemistry and Toxicology Devices,

Office of In Vitro Diagnostics and Radiological Health

EX - OFFICIO MEMBERS

(continued)

Health Resources & Services Administration

Michael Warren, MD, MPH, FAAP

Associate Administrator

Maternal and Child Health Bureau

National Institutes of Health

Diana W. Bianchi, MD

Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development

ACTING DESIGNATED FEDERAL OFFICIAL

LCDR Leticia Manning, MPH

Health Resources and Services Administration

Genetic Services Branch

Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES

American Academy of Family Physicians
Robert Ostrander, MD
Valley View Family Practice

American Academy of Pediatrics
Debra Freedenberg, MD, PhD
Medical Director, Newborn Screening and Genetics, Community Health Improvement Texas Department of State Health Services

American College of Medical Genetics & Genomics
Robert Best, PhD, FACMG
Interim Chief Executive Officer

American College of Obstetricians & Gynecologists
Steven J. Ralston, MD, MPH
Chair, OB/GYN Pennsylvania Hospital

ORGANIZATIONAL REPRESENTATIVES (continued)

Association of Maternal & Child Health Programs
Karin Downs, RN, MPH
Maternal and Child Health Director (retired)
Massachusetts Department of Public Health

Association of Public Health Laboratories
Susan M. Tanksley, PhD
Manager, Laboratory Operations Unit
Texas Department of State Health Services

Association of State & Territorial Health Officials
Scott M. Shone, Ph.D., HCLD(ABB)
Director
North Carolina State Laboratory of Public Health

Association of Women's Health, Obstetric and Neonatal Nurses
Shakira Henderson, PhD, DNP, MS, MPH, RNCNIC, IBCLC
Health Board Director
Vice President, Research Officer
University of North Carolina Health

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Child Neurology Society

Margie Ream, MD, PhD

Associate Professor

Director, Leukodystrophy Care Clinic

Director, Child Neurology Residency Program

Nationwide Children's Hospital, Division of Neurology

Department of Defense

Jacob Hogue, MD

Lieutenant Colonel, Medical Corps, US Army

Chief, Genetics, Madigan Army Medical Center

Genetic Alliance

Natasha F. Bonhomme

Vice President of Strategic Development

ORGANIZATIONAL REPRESENTATIVES (continued)

March of Dimes

Siobhan Dolan, MD, MPH, MBA
Professor and Vice-Chair, Genetics and Geonomics
Department of Obstetrics, Gynecology, and
Reproductive Science
Icahn School of Medicine at Mount Sinai

National Society of Genetic Counselors

Cate Walsh Vockley, MS, LCGC
Senior Genetic Counselor
Division of Medical Genetics
UPMC Children’s Hospital of Pittsburgh

Society for Inherited Metabolic Disorders

Gerard T. Berry, M.D.
Harvey Levy Chair in Metabolism
Director, Metabolism Program,
Division of Genetics and Genomics
Boston Children's Hospital
Director, Harvard Medical School Biomedical Genetics
Training Program
Professor of Pediatrics, Harvard Medical School

DAY 1

WELCOME

NED CALONGE: Good morning, everyone. Welcome to the first meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2023. I'm Ned Calonge; I'm chair of the Committee. And I'm excited to get started. We have a very busy agenda, good presentations and good information that we've put together working with HRSA staff and our other colleagues to move forward.

I'd like to start the meeting by welcoming our newest Committee member, Dr. Michele Caggana. Michele has been employed with the Wadsworth Center of the New State Department of Health since 1996. She's currently the Deputy Director of the Division of Genetics, Chief of the Laboratory of Human Genetics, and the Director of the New York State Newborn Screening Program.

Michele also serves as the Chair of the Association of Public Health Laboratories Newborn Screening Committee, and a member of the

National Advisory Child Health and Human Development Council.

We are excited about Dr. Caggana joining the Committee, as she will bring tremendous expertise in piloting and implementing new conditions, screening molecular genetics, and state-level newborn screening systems.

Let's welcome Dr. Caggana.

And, Michele, if you'd like to say just a couple of words, that would be great.

MICHELE CAGGANA: Good morning, everyone, and thank you. I'll thank Dr. Calonge for that nice introduction.

I'm very excited to be a member of this very important Committee. And as people who have been following us for a long time know, I've participated in different capacities over the years. I have presented to the Committee and shared, as just mentioned, pilot data and results from our newborn screening, and also I'm a member of the Laboratory Workgroup, and I've been a technical expert/participant for several of the

conditions that have been discussed.

So, I'm very pleased to work with the chair and the members of this Committee. And I think my task is to ensure that the experiences of the Newborn Screening Committee are included in this discussion. So, thank you very much.

NED CALONGE: Thanks, Michele. And again, we all welcome you.

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NED CALONGE: It's also our opportunity to welcome Dr. Robert Best as the new organizational representative from the American College of Medical Genetics and Genomics. Dr. Best is the Interim Chief Executive Officer of the ACMG and Genomics -- sorry, there's two Gs now.

He's a medical geneticist and a Distinguished Professor Emeritus at the University of South Carolina School of Medicine, Greenville. He is a founding fellow for the ACMG and past board member for the ACMG Foundation.

Please help me welcome Dr. Best. I

don't know, Dr. Best, if you'd like to make a couple of comments?

ROBERT BEST: Well, so first thank you very much. It's a great pleasure and an honor to join you all. The college really values the work of this Committee, and we're delighted to participate in it. This is my first time. So, I'm here mostly to learn. And I'm delighted to be supporting this group. So, thanks so much for the welcome.

NED CALONGE: Thanks, Robert. And I hope you can remember to bring the thanks of the Committee to Marc Williams for his serving as the interim organizational representative for the past couple of meetings.

ROBERT BEST: I will do that. He regrets -- we both have some schedule conflicts today and tomorrow. So, I was the more open of the schedules. But he sends his greetings and is also delighted to be a part of this group.

NED CALONGE: Hey, I'd like to now turn things over to Leticia, who's going to do

roll call and go over some other logistics and informational items.

Leticia.

ROLL CALL

LETICIA MANNING: Thank you.

Good morning, everyone.

NED CALONGE: Good morning.

LETICIA MANNING: I'm going to go through roll call.

For the Agency for Health Care Research and Quality, Kamila Mistry.

KAMILA MISTRY: It's Kamila.

LETICIA MANNING: Kamila, sorry.

KAMILA MISTRY: But I'm here. Thank you.

LETICIA MANNING: Kyle Brothers.

MALE VOICE: Kyle has let us know that he will be late, probably maybe a half-an-hour late or so. So, he will be joining us.

LETICIA MANNING: Thank you.

Michele Caggana.

MICHELE CAGGANA: Present.

LETICIA MANNING: Dr. Calonge.

NED CALONGE: I'm here.

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

CARLA CUTHBERT: Good morning, everyone. I'm here.

LETICIA MANNING: Jannine Cody.

JANNINE CODY: Good morning. I'm here.

LETICIA MANNING: Jane DeLuca.

JANE DeLUCA: Present.

LETICIA MANNING: From the Food and Drug Administration, Kellie Kelm.

KELLIE KELM: Present.

LETICIA MANNING: From the Health Resources and Services Administration, Dr. Michael Warren.

MICHAEL WARREN: Present.

LETICIA MANNING: Jennifer Kwon.

JENNIFER KWON: Present.

LETICIA MANNING: Ash Lal.

ASHUTOSH LAL: Present.

LETICIA MANNING: Shawn McCandless.

SHAWN McCANDLESS: Here.

LETICIA MANNING: From the National Institutes of Health, Melissa Parisi.

MELISSA PARISI: Here.

LETICIA MANNING: Chanika Phornphutkul. My apologies for pronunciation.

CHANIKA PHORNPHUTKUL: I'm here.

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

ROBERT OSTRANDER: I'm here.

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

DEBRA FREEDENBERG: I am here.

LETICIA MANNING: From the American College of Medical Genetics and Genomics, Robert Best.

ROBERT BEST: I'm here.

LETICIA MANNING: From the American College of Obstetricians and Gynecologists, I'm

not sure if we have a representative.

(No audible response)

LETICIA MANNING: From the Association of Maternal and Child Health Programs, Karin Downs.

KARIN DOWNS: I'm here.

LETICIA MANNING: From the Association of Public Health Laboratories, Susan Tanksley.

SUSAN TANKSLEY: Hi. I'm here.

LETICIA MANNING: Thank you.

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

SCOTT SHONE: Here.

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

Sorry.

From the Child Neurology Society, Margie Ream.

MARGIE REAM: I'm here.

LETICIA MANNING: From the Department

of Defense, Jacob Hogue.

(No audible response)

LETICIA MANNING: From the Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Bonhomme, yep.

LETICIA MANNING: Bonhomme, sorry.

NATASHA BONHOMME: I'm here.

LETICIA MANNING: The March of Dimes, Siobhan Dolan.

SIOBHAN DOLAN: Good morning. I'm here.

LETICIA MANNING: For the National Society of Genetic Counselors, Cate Walsh Vockley.

CATE WALSH VOCKLEY: Vockley, Cate. I'm here. Thank you.

LETICIA MANNING: Sorry.

And from the Society for Inherited Metabolic Disorders, Gerard Berry.

(No audible response)

LETICIA MANNING: Okay. Thank you.

And that is roll call.

OPENING REMARKS

LETICIA MANNING: So, now I'm just going to go over a few things regarding ethics and conflicts of interest. I just want to remind the Committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner unless you are also an employee of the organization or unless you have received a waiver from the Department of 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 email me at lmanning@hrsa.gov.

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.

For the main meeting in the Federal Register notice, we said that there would be a public comment period. Only with advance approval of the chair or the designated federal official may public participants question Committee members or other presenters.

Public participants may submit written statements. Also, public participants should be advised that Committee members are given copies of all written statements submitted by the public.

As a reminder, it is stated in the FRN, or the Federal Register notice, as well as the registration website that all written public comments are part of the official meeting record and are shared with Committee members. Any further public participation will be solely at the discretion of the chair and the designated federal officer.

If there are questions, once again you can email me at lmanning@hrsa.gov.

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(Slide)

LETICIA MANNING: Thank you.

And now I just want to go over a few webinar instructions. Many of you are already logged in, and I see names, so that's good. When you log into Zoom, you'll be prompted to enter your name as you would like it to appear in the Zoom display name to ensure the meeting host can easily identify you in the audience. Please use your first and last name along with any relevant organization name.

If this screen does not appear to you, and your name is not clearly conveyed in the display name, please email Emma Kelly at ekelly@lrginc.com. And please note that when you are prompted or promoted to be a panelist, the system will briefly log you out of the meeting, and then you will automatically be joined within 10 seconds.

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LETICIA MANNING: This is an instruction on how to enable closed captions. You can do that for yourself if you need to.

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LETICIA MANNING: This is the schedule for the ACHDNC meetings for 2023. May 4th through 5th will be in-person and virtual. August 10th through 11th will be virtual only. It is a new date. November 2nd through the 3rd is in-person and virtual, and it is also a new date. So, please mark your calendars accordingly.

And now I turn it back over to you, Dr. Calonge.

NED CALONGE: Thanks, Leticia.

Before we turn to Committee business, I want to make mention of two important funding opportunities from the Maternal and Child Health Bureau to strengthen newborn screening systems. The two programs are NBS Propel and NBS Excel.

The purpose of the State Newborn Screening Priority Program for NBS Propel is to

strengthen the NBS system to provide screening, counseling, and health care services to newborns with or at risk for inheritable disorders.

There are two focus areas, one which is activities related to improving collection of specimens, testing of specimens, and reporting results; and implementing screening for newly added RUSP conditions.

The other focus area is in regard to activities related to improving short-term follow-up to long-term follow-up and helping families understand how to navigate the process from confirmation of the diagnosis to treatment.

The National Center for Newborn Screening System Excellence, or NBS Excel, will fund an organization to support state NBS programs. The program will also fund stakeholders as well as programs by providing leadership, technical assistance, and quality improvement expertise.

I hope you'll look for more information on the grants.gov site and search

there for newborn screening. And you can see the due date for the applications on the website.

I also want to make the Committee aware that there is a nationwide antibiotic solution supply shortage, which can affect children with sickle-cell disease. We use the liquid form prescribed for babies and young children with sickle-cell disease who are unable to swallow pills as a standard of care.

But there are alternatives that have been posted on the Sickle-Cell Disease Association website that I would refer clinicians and families to while that shortage is in place.

I'll turn now if I could to Committee business.

COMMITTEE BUSINESS

NED CALONGE: I'll first announce that Secretary Becerra on January 4th approved the addition of GAMT deficiency to the Routine Uniform Screening Panel. The Secretary considered the utility of current screening technologies, the treatment for GAMT deficiency, and the impact on

public health systems, and with that recommended to expand the RUSP to include GAMT deficiency.

I remind folks that the addition of GAMT deficiency to the RUSP is a recommendation. It does not constitute a requirement for states to implement screening.

In addition, the Secretary requested a report of state implementation of GAMT deficiency screening to look also at potential barriers to treatment and especially look at long-term follow-up and health outcomes in five years. So, I hope our state lab will start looking at the implementation of GAMT and hopefully, if need be, take advantage of the two new grant programs to help implement the new screening.

Finally, when I just close these introductory comments, I'm noting that we are making two decisions during this meeting. We'll be voting whether to recommend to the Secretary to add Krabbe disease to the Routine Uniform Screening Panel. We'll also be voting whether to send Duchenne muscular dystrophy onto the Evidence

Review Group for an evidence-based review.

I want to pause and just remind the panel and the rest of the attendees that the integrity of the decisions we make at this meeting are really based on the integrity to which we adhere to the process that we put forward.

The evidence-based review and evidence to decision framework we use at the Advisory Committee has been in place with some modifications since the Committee first started it four years ago and has stayed relatively the same, if you will, under different secretaries and different presidential administrations.

The systematic evidence review that looks at peer-reviewed published reports, decision modeling analysis that helps us make decisions within the context of a public health program, and the public health assessment that gives us information on how implementation might be possible, feasible, and appropriate moving forward -- all things that we use in our decision making.

The process is a scientific process,

and while there are a lot of ways to make decisions, choosing an evidence-based approach brings to bear a science and a process and a methodology that's well-established for screening and other settings, including infants, children, adults, adolescents, and pregnant people, all of which is looked at by the United States Preventive Services Task Force. But for newborn screening it's this Committee.

And I just want to remind people that it's the science that drives the integrity of the process. It's the science that underlies our decisions. And our judgments are based on our expertise and how we view and weigh the different elements that will bring forward and evidence-based review that will look forward and how we weigh the available information for the nomination process that we will do in discussing muscular dystrophy.

I also want to just pause and let members of the public and families and other advocates know -- and I feel like I speak for the

entire Committee -- how much we value your presence, how much we appreciate and need you sharing your very personal stories, and how much we acknowledge, recognize, and respect your personal investments into the process that we've put forward.

And we hear your stories. We weigh those as we look through the scientific evidence. And we make our decisions in view of the impact on you. So, regardless of the outcome of the votes, I want to make sure I express my gratitude for your being here and your involvement in the process.

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(Slide)

NED CALONGE: We have the November 2022 meeting summary, which has been put into the packet. I want to thank Committee members and organizational reps for reviewing that, and at this point ask if there are any corrections to the summary before we accept it.

(No audible response)

NED CALONGE: Hearing none, I would entertain a motion to accept the November minutes.

SHAWN McCANDLESS: This is Shawn McCandless.

I move to accept the November minutes.

NED CALONGE: Thanks, Shawn.

And is there a second?

JENNIFER KWON: This is Jennifer Kwon.

I move to second.

NED CALONGE: Thanks, Jennifer.

Leticia, would you please do a roll call vote?

LETICIA MANNING: Yes.

Kyle Brothers.

(Pause)

LETICIA MANNING: I'm sorry. I know he's running late.

Michele Caggana.

MICHELE CAGGANA: Abstain.

LETICIA MANNING: Dr. Calonge.

NED CALONGE: Yes.
LETICIA MANNING: Jannine Cody.
JANNINE CODY: Yes.
LETICIA MANNING: Carla Cuthbert.
CARLA CUTHBERT: Yes.
LETICIA MANNING: Jane DeLuca.
JANE DeLUCA: Accept.
LETICIA MANNING: Kellie Kelm.
KELLIE KELM: Yes.
LETICIA MANNING: Jennifer Kwon.
JENNIFER KWON: Yes.
LETICIA MANNING: Ash Lal.
ASHUTOSH LAL: Yes.
LETICIA MANNING: Shawn McCandless.
SHAWN McCANDLESS: Yes.
LETICIA MANNING: Kamila Mistry.
KAMILA MISTRY: Kamila. Yes.
LETICIA MANNING: Kamila. I'm so sorry.
Melissa Parisi.
MELISSA PARISI: Yes.
LETICIA MANNING: Chanika

Phornphutkul.

CHANIKA PHORNPHUTKUL: Yes.

LETICIA MANNING: Michael Warren.

MICHAEL WARREN: Yes.

LETICIA MANNING: That is the full Committee.

NED CALONGE: So, looking at the vote, that passes. I appreciate that. And we will move on.

NED CALONGE: Just to remind you of what we're doing today and tomorrow, we'll do public comment and then presentations from the Evidence Review Group on the systematic evidence review on newborn screening for Krabbe disease. Then there will be a presentation on the Committee report on newborn screening for Krabbe and a vote on whether to recommend adding Krabbe to the Routine Uniform Screening Panel.

Tomorrow -- next slide.

(Slide)

NED CALONGE: -- we'll have report out from the Prioritization and Capacity Workgroup

in their update. We're going to have another opportunity for public comment. Then we'll have workgroup updates from follow-up and treatment, laboratory standards and procedures, and education and training.

After that we will have a nomination summary for Duchenne muscular dystrophy and a vote on whether to move DMD to the ERG for a full evidence review. Then finally, we'll have grantee presentations on the HRSA State Interoperability Program.

At this time I'd like to move to public comments.

PUBLIC COMMENT

NED CALONGE: I want to assure those in the public comment period that I recognize we're a bit behind schedule, but we will allow the entire schedule, 45 minutes.

We received nine requests from individuals to provide oral public comments to the Committee today. And they will provide their

comments in the following order: Michael Wilson with his parent, Tammy Wilson; Stacy Pike-Langenfeld; Wendy Tierney; Lana Grujicic; Karlita Blackwell; Jim Kelly; Joanne Kurtzberg; Maria Escolar; and Dietrich Matern.

At this time I would like to turn public comments over to Michael Wilson.

(Inaudible conversation)

MICHAEL WILSON: Good morning. Thank you for inviting me to see me. I'm going to read a pretty good report on why it's important to do newborn screening for Krabbe.

Hello. My name is Michael Wilson, and I am 12 years old with a rare disease called Krabbe disease. I am the youngest of six children. My brother Marshall was also born with the same disease as me. He was born 15 months before me, symptomatic at 12-13 months, diagnosed at 18 months.

When I was born, my mom and dad had me tested for the same disease as my brother, and it turned out that I had Krabbe disease too. Even

though I was too young to remember, here is what I know. I know I had a stem-cell, cord-blood transplant for Krabbe disease when I was four months old at Doernbecher Children's Hospital here in Oregon. I also know without the treatment I would not be alive today.

I know my brother was not treated for the disease. He was in and out of the hospital in his short lifetime, and at the age of six he passed away. Marshall was not able to be treated because the disease was already spreading throughout his body when he was diagnosed.

Because of my brother's diagnosis, there was time for me to get a lifesaving treatment. If Oregon was screening for Krabbe, my brother would have had the similar outcome as me. Oregon newborn screening could have saved my brother.

I came into this hospital as a normal baby, then finding out I had Krabbe disease. I was in the hospital for a very long time. My mom and dad share stories with me about when I was a

baby in the hospital and coming home and recovering from transplant.

I remember I had a whole team of doctors. My parents took turns staying with me at the hospital. My earliest memory of my brother, Marshall, is laying in his bed in the living room not able to move or talk. I remember the hospice music teacher coming to our house, and Marshall and I got to hear and play music.

I now run three businesses of my own. I run a lawn-mowing business, sno-cone, and lemonade stand. I hope to soon offer car-washing. I just finished playing soccer for the season. I also have played basketball in the past. I just started lessons to play the electric guitar. I also have an interest in learning to play tennis.

In my lifetime I have been able to travel and help different organizations fundraise and bring awareness to rare diseases and newborn screening. Last year I was a patient designer for the Nike Freestyle Program. I was recently asked by our local children's hospital to be their 2023

Ambassador for the Children's Miracle Network.

I know I am reading my story in front of a Committee that makes decisions on whether or not to do newborn screening on children across the country. The reason why all babies across the country should be screened for Krabbe disease is because if they don't catch it in the early stage of disease, they will not make it. They will live with the disease and die in a short time.

If they are tested and treated, then it means they have a better chance of living their entire life. I am proof that if treated they can live their best life just like me. My brother was not given that chance or that treatment even though it was available.

Thank you.

NED CALONGE: Thank you, Michael.

Next, Stacy Pike-Langenfeld.

STACY PIKE-LANGENFELD: Hi, everyone. Thank you so much for this time for talk. And, well, thank you, Michael, for sharing your story. I want to extend a special thank-you to all of the

Committee members today.

I am Stacy Pike-Langenfeld, President at Krabbe Connect. And I am also the mother of a child who had Krabbe disease. Her name was Makayla. She died on May 4th, 2001, at the age of two.

Probably today you will hear many amazing stories about Krabbe disease, so I have chosen to use my time to address the readiness of this disorder on the RUSP. Krabbe disease meets the pediatric onset criteria. The science shows 90 percent of our cases each year are the early infantile Krabbe disease cohort.

In these cases, immediate action is required. The only -- and I need to stress the only -- way these children can live a quality of life is by undergoing a hematopoietic stem cell transplant conducted in the first 30 to 45 days of life.

Other challenges with transplant everyone knows in this room. There's always a risk with any medication or treatment. But the

challenge of the transplant to help treat Krabbe disease will never compare to the challenges of the non-treated early infantile Krabbe disease cohort.

Yes, time is of the essence. But we've witnessed the great work that the 10 states currently screening for Krabbe disease, each of whom have helped families successfully seek transplants, and these children are living well today.

Krabbe disease also meets the level of severity criteria. Science shows and written medical descriptions state that Krabbe disease is a severe metabolic disease. It causes premature death if the baby does not receive treatment in the first 30 to 45 days of life.

Babies identified too late for treatment are completely immobilized by tragic miscommunication to all 10 of their body systems: their skeletal, muscular, nervous, endocrine, cardiovascular, emphatic, respiratory, digestive, urinary, and reproductive systems.

Transplant children may have gross and fine motor delays, but they do not experience a war on all 10 body systems. In fact, transplant children, as you see with Michael, are happy, interactive with their family members, and even attend school.

Number three, Krabbe disease meets the treatment intervention criteria. Science shows transplant has been utilized for Krabbe disease since the early 1990s. The number one thing we've learned from transplants is early intervention is key.

If you seriously believe transplant is not a worthwhile treatment for Krabbe disease, I urge you to change the treatment intervention criteria for newborn screening to only diseases with curative therapies will be considered.

And lastly and most importantly, Krabbe disease meets the effective testing criteria. We can without a doubt effectively diagnose early infantile Krabbe disease. I have been tightly tied to the research on Krabbe

disease since 2007. This was the criteria severely lacking in the 2009 RUSP submission.

The research and clinical experts have implemented the right testing mechanisms to properly identify this disease. Do we wish we had all the specifics on genotype versus phenotype to help navigate the cases? Absolutely. However, this is not listed as a criterion for newborn screening readiness.

In fact, the genotype/phenotype correlation in cystic fibrosis and the role of modified genes is still evolving, and we've been screening for cystic fibrosis for 14 years.

So, I understand it's not easy to be in your seats. Many of you know and feel the stress of newborn screening expansion. Some of you sit on your states' newborn screening advisory committees and hear about the labor and funding shortages.

Today I have one simple ask. Please keep your focus on the readiness of Krabbe disease. Because from where I sit, we're ready

for all states to screen.

Thank you.

NED CALONGE: Thank you, Stacy.

Next we have Wendy Tierney.

WENDY TIERNEY: Good morning. Thank you for this opportunity to share our story and the importance of Krabbe newborn screening with you.

My husband Chad and I have been blessed with two beautiful daughters. Our oldest daughter, Grace, was diagnosed with Krabbe disease when she was five months old, after she became symptomatic and therefore unable to receive the treatment for the disease.

Because of Grace's genetic history, we pursued pre-implementation genetic diagnosis for our next child. Even though this minimized the risk of another child having Krabbe, we had our youngest daughter, Madison, tested when she was born for our peace of mind.

Tragically, a potentially grave mistake was made by the clinic and Madison tested

positive for Krabbe. So, at five days old, Madison arrived at Duke University Hospital to begin her transplant process. Since Madison was tested for Krabbe at birth, she has an amazing and full life, unlike her sister, Grace.

To help you understand the impact of early detection and treatment for Krabbe disease, here is a timeline of their lives.

Grace was born on September 14th, 2000, and Madison was born on May 31st, 2004. Around two months old, they both smiled for the first time. At three months old, they both began to grab at toys. At four months, Madison began passing toys from hand to hand. Grace began having difficulty eating.

At five months, Madison was sitting in her Bumbo seat playing with toys. Grace was diagnosed with Krabbe disease and couldn't hold her head up. At six months, Madison was learning to roll over. Grace was getting a feeding tube and smiled for the last time.

Around nine or ten months, Madison

was sitting on her own, playing peek-a-boo and patty-cake. Grace had lost all milestones and had no voluntary movements. At 11 months, Madison was saying Mama and Da-da, waving bye-bye, blowing kisses, eating Cheerios for the first time. Grace was requiring oxygen and suctioning around the clock.

Around one year old, Madison was crawling, doing the motions for Itsy-Bitsy Spider and stacking blocks. Grace was beginning to have seizures. At two years of age, Madison was walking, taking swimming lessons, climbing a ladder to slide, and counting to 10. Grace was lying in a vegetative state.

At three, Madison began taking gymnastics, attending preschool, reciting the Pledge of Allegiance, and reading books while Grace was requiring 24/7 medical care. At four years old, Madison began her second year of preschool, swimming on a local swim team, and riding a tricycle. Grace was no longer with us.

At five, Madison was in kindergarten,

was still swimming, or was still active in swimming and gymnastics, but Grace was no longer with us. Madison successfully completed first grade and began dance lessons. Grace was no longer with us.

Madison has continued to grow and develop like all of her friends. She's excelled academically and participated in school dances, field trips, and clubs. In high school, she received student of the month several times and was inducted into the National Honor Society, enjoying times honorary. She was enrolled in honors classes and dual-credit college courses.

Madison got her driver's license at 17 and her first job at a retail clothing store. Madison graduated with honors in 2022 and is now in college majoring in criminal justice and minoring in forensics. She finished her first semester and was on the dean's list. Needless to say, we are beyond proud of her.

We also have so much to look forward to with Madison as she continues through her life.

If Madison could accomplish all this because she was given the opportunity for a test when she was born, what could Grace have accomplished if she received the same test? What amazing things could I be sharing about her today?

As happy as we are to celebrate all the accomplishments and achievements of Madison, we are just as saddened by not having Grace with us here to share whatever her life would have brought had she also been tested at birth.

So, today I'm asking that you please add Krabbe to the Recommended Uniform Screening Panel so that U.S. babies no longer suffer the tragic outcome of Grace, but have that opportunity to live and excel the way Madison has in her life.

Thank you.

NED CALONGE: Thank you, Wendy, so much for sharing.

Next, Lana Grujicic.

(Pause)

NED CALONGE: Lana, I see your name, and it appears as if you're muted.

Thank you. Yes.

LANA GRUJICIC: Good morning. Oh, gosh, I'm going to try to keep it together. I'm sorry.

(Pause)

LANA GRUJICIC: My name is Lana Grujucic, and this is my son Nikola.

(Pause)

LANA GRUJICIC: And Nikola was diagnosed with Krabbe disease when he was six months old. He is going to be turning five in March.

Nikola's symptoms started when he was six months old, but they were not very severe. But they've already progressed past the point of any type of stem cell transplant.

To be honest with you, when I was asked to speak today, my first thought was no, I can't do this. The timing couldn't have been worse. My husband and I just spent a whole week taking care of Nikola.

While he cried from nerve pain and

breathing difficulties, not sleeping for a week, and having to give our young child rescue breaths to keep him alive, the last thing we want to do is tell a bunch of strangers our story at the risk of them brushing us off.

But here I am because it is important. And I would do anything to keep another child from suffering from this cruel disease.

At first Nikola seemed like a normal baby boy. He met all his milestones, and he was really happy. But when he was diagnosed, the doctor told us there were no treatment options, that Nikola had two years to live, so go home and take lots of pictures. He also said that our children -- we were not to plan to have any children because there was a high risk that any other child would have the same disease.

That morning we walked into that office with the hope that our child was dealing with something like cholic. But we walked out with a death sentence. We were in shock. And we

were not willing to accept that fate for our son. We found an expert who helped us manage Nikola's pain with the right medication, told us what to expect going forward, gave us information about all of the equipment we would need to help Nikola have the best quality of life possible.

Today Nikola gets 13 medications daily. He takes no food by mouth. He has not smiled or laughed in four years. He's losing his sight. He does not move. He requires breathing treatment, chest therapy machines, and round-the-clock oxygen. And he needs collective suctioning to manage his secretions, as I'm sure he's going to get right now.

Because Nikola cannot move on his own, he depends on a wheelchair, a stander, activity chair and a bath chair. It's normally a two-person job. On average, children like Nikola have over half-a-million dollars in medical costs each year. That's just for one child for one year.

Before learning about Krabbe, I

thought the worst diagnosis you could get was cancer. And boy, was I wrong. Even someone with a cancer diagnosis has a chance of surviving with chemo and radiation.

As doctors, would you deny your patients chemotherapy? Not every cancer patient has the best possible outcomes. But they're still given a chance to fight and live. We want that same chance for our babies.

Krabbe without early diagnosis has no chance of survival. Newborn screening gives our kids a chance at treatment and a chance to live, like Marshall. Yes, Krabbe is rare, but it should not be ignored. Our kids should not be disregarded like they do not matter.

I really hope you consider all the facts and the testimonies and make the right decision for our nation's children. A vote against Krabbe means more children would suffer and die. And you have the power today to make the chance at life.

Thank you for your time.

NED CALONGE: Thank you, Lana.

Next I'd like to welcome Karlita Blackwell.

KARLITA BLACKWELL: Good morning. Thank you for allowing all of us to speak, and thank you, Lana. That was very powerful.

My name is Karlita Blackwell. And in October of 2016, my husband and I became parents to a perfect baby boy named Ezra. After just two weeks at home navigating the task of becoming new parents, we received our son's newborn screening results confirming the diagnosis of Krabbe leukodystrophy.

To say this left us incomprehensively devastated is an understatement. In an instant our hopes and dreams for our son's life felt like they were stripped by a diagnosis we had never even heard of. However, with infinite gratitude, I am here today to say that that is not at all what happened.

Because Krabbe was on the newborn screening panel in Missouri, Ezra was able to have

a lifesaving treatment in the form of a stem cell transplant at Duke University. Today Ezra is six years old. And everything we hoped and prayed for his life prior to his diagnosis has come to fruition in one capacity or another, the same hopes that all parents have for their children.

To get an education. Ezra has been thriving in kindergarten, and just this month he was awarded Super Student of the Week and Employee of the Month for his excellent communication skills, respectfulness, and interpersonal skills.

To have meaningful relationships. The first thing people typically notice about Ezra is his smile. He thrives in social situations. And the way that he connects with his peers has been the most magical thing for us to watch.

To gain independence. We are so grateful to live in a time where there is a way to modify almost anything if there isn't already a piece of equipment for it. Ezra loves riding his bike. He loves to help us cook. He is constantly learning. He's kind to those around him. And he

voices his wants, needs, and emotions.

To feel loved, happy, and safe. The ripples Ezra has created go beyond our friends and family. The number of times that he's been described as "sunshine" is more than I can count. Ezra lives a full and joyful life. Our family will never take for granted the fact that without newborn screening, Ezra's life would look very differently.

We are reminded each time when another unscreened child in our Krabbe community passes away far too soon and their parents are left coping with the fact that this could have been prevented through newborn screening for Krabbe.

Thank you for your time.

NED CALONGE: Thanks, Karlita.

Next I'd like to welcome Jim Kelly.

JILL KELLY: Good morning. Well, I wish I was Jim Kelly. But I don't throw a football. So, he'll have to deal with his wife instead.

NED CALONGE: I'm sorry, Jill.

JILL KELLY: That's okay. That's okay.

Good morning, and thank you for allowing me to share this morning. And I also just want to thank everyone that has shared so far. These are amazing people, amazing stories. And I am blessed to know each one of these people who shared. So,.

My name is Jill Kelly, not Jim Kelly. And I'm the co-founder of the Hunter's Hope Foundation and the wife of Hall of Fame quarterback Jim Kelly and the mother of Erin, Cameron, and Hunter.

When I found out that our second child would be a son, I was filled with joy. We already had a healthy two-year-old daughter, and now we would have the son that Jim always wanted. He comes from a family of six boys, so he wanted a boy. This son would follow in his daddy's footsteps. The son who would do with his dad what fathers and sons do, and of course that would

include football.

Hunter was born on Jim's birthday, Valentine's Day, February 14th, 1997. As a newborn, Hunter had a perfect Apgar test and passed all the newborn screening tests in New York State at the time. When we took him home from the hospital, we assumed we were bringing home a beautiful, healthy baby boy.

But early on in Hunter's life it was clear that something was wrong. We had a nephew born 10 days before Hunter who was reaching all the milestones, smiling, holding his head up, and thriving. Hunter wasn't. Hunter was very irritable, crying most of the hours that he was awake. We thought it was cholic because his sister Erin had cholic. It wasn't cholic.

Eventually, it took me over an hour to feed Hunter an ounce of formula. So, we tried changing the formulas because we thought it was maybe the problem. Maybe it was the formula. It wasn't the formula. Hunter was unable to eat because he couldn't swallow.

As Hunter's symptoms continue to get worse, we continued to seek help from doctors. Unfortunately, our search for help and answers only led to more pain, tears, and frustration. Hunter was misdiagnosed numerous times.

And it wasn't until some bloodwork was done by a neurologist that led to an answer. An answer we never expected, an answer that is a parent's worst nightmare and greatest fear. An answer that was a diagnosis that devastated our family and changed our lives forever.

On a beautiful sunny day in June, when Hunter was four months old, we were told that he had Krabbe disease. We were told there was no treatment and there was no cure, and that we should prepare for him to die before his second birthday.

Miraculously, Hunter lived to be eight-and-a-half years old. And although every day was a battle that included seizures, suctioning, broken bones, excruciating nerve pain, pneumonia numerous times, many trips to the ER and

ICU hospital stays, medications too many to count, interventions like physical and occupational therapy and respiratory therapy, 24-hour oxygen, and much more.

Despite all of this, Hunter wanted to live. And we did everything possible that we could do so that he could live. Hunter was and still is the most amazing person I have ever met. The impact his life has had on mine is beyond measure. And the loss and grief is oftentimes unbearable.

Hunter changed my life. And hopefully his story and all the stories that you've already heard will change yours and the lives of every child born in our country from this day forward.

Today I urge you to remember children like Hunter who deserve a chance to live. Since 2009 when this Committee voted against having Krabbe, adding Krabbe to the RUSP, 136 children that we know of were born in the United States and like Hunter diagnosed too late to receive

treatment. One-hundred and thirty-six children died. One-hundred and thirty-six families were devastated like ours.

Those children should be here. Those children should have been screened at birth for Krabbe so they could get a chance to live.

I've had the privilege of getting to know several children who were identified through their states' newborn screening who received a transplant for Krabbe. These children, like Michael, are independent, playing, speaking, laughing, attending school, thriving in so many ways. They're living.

For children with Krabbe who aren't screened at birth, the outcome is always fatal. Without Krabbe's inclusion on the RUSP and on every state's newborn screening panel, children will continue to go undiagnosed, and they will die just like Hunter.

The question we are faced with today is, Do children with Krabbe disease deserve a chance to live? And the answer is yes. They

deserve to live. Hunter deserved to live.

Thank you all so much for your time, and God bless all of you.

NED CALONGE: Thank you, Jill.

Next we would like to hear from Joanne Kurtsberg.

JOANNE KURTSBERG: Hello, everyone. And thank you for the opportunity for me to testify in favor of adding Krabbe disease to the RUSP.

My name is Joanne Kurtsberg, and I'm the pediatric transplant physician who pioneered the use of hematopoietic stem cell transplantation using unrelated cord blood donors for treatment of pediatric patients with Krabbe disease.

Over the past 24 years at Duke Health, my team and I have transplanted nearly 400 infants and children with leukodystrophies including 60 with Krabbe disease. In the mid-1990s when we first started transplanting patients with Krabbe disease, most of the babies whom we treated were three to ten months of age with

multiple clinical manifestations of the disease.

In those days, the parents of these babies had suffered through months of diagnostic odysseys which began with reassurance. And after it became clear that their baby just didn't have cholic or reflux, multiple referrals, until MRI was obtained showing white-matter disease and testing for leukodystrophies revealed Krabbe disease.

By the time we evaluated them, these babies were spastic, severely developmentally delayed, and failing to thrive because of inability to take sufficient nutrition by mouth. Some also had lost vision and developed seizures. And to me the saddest symptom was that the mothers of these babies couldn't comfort them due to the extreme irritability caused by the disease.

During the first years using transplantation, we treated these symptomatic babies hoping that the procedure, which provides enzyme replacement through engraftment of donor cells in the blood, bone marrow, and brain, would

reverse some of the existing brain damage and help these babies recover lost developmental milestones.

Sadly, we learned that this was not the case and that the transplant did not help babies who already had progressive clinical symptoms. However, we also transplanted 11 babies, including Madison, who Wendy Tierney told you about, in the first three to six weeks of life who were diagnosed in utero or at birth because of the family history of Krabbe disease.

These pre-symptomatic babies, who could be compared to the fate of their untreated siblings, dramatically benefited from transplant, which prolonged their lives by decades and improved their neurologic function and quality of life.

Since these early days, we've restricted transplant for use in babies with the infantile disease who could be treated in the first month or so of life, or for older children with later onset disease and minimal

symptomatology.

While transplant is not a cure, it is highly effective. And it's a treatment that transforms the lives of babies and children with infantile Krabbe disease and the lives of their families, as you've heard today.

Most parents who carry mutation for Krabbe disease have no idea that this is the case and only learn that they're carriers when the diagnosis is made in their sick baby. Newborn screening is the only way to identify these babies at a time when treatment can make a difference.

While this is true for transplant today, it will also be true for gene therapy and other innovative therapies that are in the early clinical trials and are expected to be available in the next several years.

I've heard that there's concern that state screening for Krabbe disease will struggle to be able to diagnose it and refer babies for treatment within the first few weeks of life. But this is not the case.

There are also questions about whether babies need to be referred out of state for optimal treatment. There are over 100 pediatric transplant programs in tertiary care medical centers throughout the United States. These programs have the expertise needed to transplant infants with a variety of life-threatening conditions.

We've shown in the last nine babies diagnosed through newborn screening over the past seven years that referrals can be accomplished quickly and that outcomes are equivalent whether the baby is transplanted in an in-state transplant center or in a referral center like Duke.

Whether the babies in these last seven years were transplanted in-state in four, including twin siblings who were referred to Duke, all nine babies are surviving durable and grafted, off all transplant medications, free of graft I versus host disease and gaining developmental milestones.

In contrast, every few weeks I hear

from a family of a symptomatic baby desperate for treatment when it's already too late to help that baby.

Yes, it will be necessary for states performing newborn screening for Krabbe disease to rapidly refer a baby with infantile Krabbe disease. But this is entirely possible with advanced planning and referral to a collaborating pediatric transplant program whether in or out of state.

I've also heard that some have questioned whether the newborns transplanted with Krabbe really have Krabbe disease. I can assure you that all of the babies transplanted as newborns had evidence of Krabbe disease in neurophysiologic and neural imaging studies.

Newborns with infantile Krabbe disease referred for transplant may look clinically normal, but they already have the evidence of disease on these diagnostic studies, and that disease will progress without treatment.

For these reasons, and as a physician

and a person who has directly witnessed the human suffering caused by Krabbe disease and the benefits of cord blood transplant in pre-symptomatic babies, I strongly encourage the Advisory Committee on Heritable Disorders in Newborns and Children to vote in favor of recommending that Krabbe disease be added to the Recommended Uniform Screening Panel.

Thank you.

NED CALONGE: Thank you, Joanne.

Next, Maria Escolar.

(Pause)

NED CALONGE: Maria, I see your name and it looks like you are muted.

MARIA ESCOLAR: We would like to thank the Advisory Committee on Heritable Disorders in Newborns and Children for providing Forge Biologics, and me in particular, the time to voice our support of the adoption of Krabbe disease to the Recommended Uniform Screening Panel.

My name is Maria Escolar. I'm a

neuro-developmental pediatrician, and I have dedicated my last 20 years of work to treating patients with Krabbe. The last two years I have been Chief Medical Officer of Forge Biologics, a biotech company advancing gene therapy for Krabbe disease.

As a clinician, I provided care for more than 190 babies from 49 states and other countries with infantile and late-infantile Krabbe disease, which is about half of all the patients diagnosed in this time period. Most babies were unfortunately diagnosed after symptoms.

I also took care of those who were diagnosed before symptoms because of newborn screening or previously affected siblings, such as those we have heard today, and those were treated with transplantation, which is now the standard of care.

This experience led to the largest prospectively designed published study of the progression of this disease and also the long-term transplant outcomes in infantile and late-

infantile Krabbe onset. I know of which you heard today, and I collaborated in many of these studies with Dr. Kurtzberg.

I would like to highlight that not only the asymptomatic infantile onset patients are benefiting remarkably after transplant, but also the asymptomatic late-infantile onset patients results are even better, with completely normal developmental outcomes.

At Forge, we have recently presented data from the first two infantile Krabbe patients treated with our gene therapy, FBX-101. They were identified through newborn screening. The gene therapy is administered intravenously after hematopoietic stem cell transplant, and it was safe and well tolerated.

Increasing significantly the division in single galactocerebrosidase. It decreased psychosine. It resulted in normal brain growth, no demyelination, and improved motor development above the range of that achieved with only transplant.

Gene therapy for infantile Krabbe has the potential to normalize outcomes when babies are treated early, following transplant. If the infantile Krabbe population is left without accessing newborn screening, this will undoubtedly slow the progression of not just our product, but any other new treatment. Since no matter what new therapies used, by the time the patient develops identifiable symptoms, there is irreversible damage to the brain. And this is because the brain myelinates so quickly in the first months of life.

The clinical trial evaluating FBX-101 is currently active and enrolling patients in the U.S. The potential impact of this program has been recognized through designation as a priority medicine by the European Medicine Agency and fast-tracked designation by the U.S. Food and Drug Administration, along with recognition as an orphan drug by both agencies.

These designations are awarded only to those programs that have demonstrated evidence

that a treatment has the potential to result in clinically meaningful outcomes in patients with a seriously debilitating or life-threatening condition when there are no other treatment options.

Similar to FBX-101, so genes now, is a gene therapy that was in clinical trials while spinal muscular atrophy was up for adoption to the RUSP back in 2018. Like Krabbe disease, SMA is a severe disease with less than 20 percent survival beyond two years. Where there is a drug, Spinraza, that's most progression of the disease and where early treatment is necessary to achieve good outcomes.

With SMA patients needing more readily able to be diagnosed by newborn screening, it was within a really short time that Zolgensma was approved by the FDA and found to be a transformative medicine. It is based on all this evidence already proven that transplant can prolong life and good outcomes of Krabbe disease when treated early.

Also, the promising evidence of efficacy that FBX-101 offers. The similarities to SMA, the significant impact newborn screening has on the ability to continue to develop new therapy for Krabbe disease that I urge the Committee to adopt Krabbe disease to the RUSP.

Thank you for your time.

NED CALONGE: Thank you, Maria.

And next we have Dietrich Matern.

DIETRICH MATERN: Thank you, Dr. Calonge, for giving me the opportunity to return to the Committee as a private person and speak in strong support of the nomination of Krabbe disease to the Recommended Uniform Screening Panel.

As you know, New York State began screening for Krabbe disease already in 2016 with a procedure that was highly sensitive, but not very specific. As I said previously, especially for a devastating disease like Krabbe disease, I firmly believe that the false positive rate must be kept as low as possible so as not to scare unnecessarily young families for even only a few

days or weeks.

We learned a lot from the New York experience. For one, screening for Krabbe disease cannot rely on the measurement of GALC activity alone.

And second, molecular genetic analysis of the GALC seen as a second kit test improves specificity but not sufficiently. That is because of the more than 1,000 GALC variants that have been reported to date, only a third we know whether they cause disease or not.

Therefore, most babies with reduced GALC activity, though, have a GALC genotype that includes at least one variant for which their effect is not fully predictable.

Luckily, however, Dr. Orsini from the New York screening lab was first to show that psychosine can measured in dried blood spots and is elevated in babies affected with Krabbe disease. Psychosine is a toxic byproduct generated when galactocerebrosidase activity is deficient.

Given this knowledge, at the Mayo Clinic we made psychosine analysis an integral part of our screening approach for Krabbe disease. When the Kentucky newborn feeding program asked us whether we could help them fulfill a new legislative requirement to provide screening for Krabbe disease, we employed the strategy.

Next Wednesday, we will conclude the seventh year of Krabbe screening of babies born in Kentucky, 700 miles away. Also included in our newborn screen of Kentucky babies are currently Pompe disease, MPS I, and ALD.

Among the almost 380,000 Kentucky babies screened, we identified two babies with low GALC activity and elevated psychosine. Both babies were then diagnosed with infant type Krabbe disease and received bone marrow transplants. So, far, we have zero false positive cases -- zero.

The first Kentucky baby with Krabbe disease was transplanted on the 24th day of life. The second baby was born three days before an extended holiday weekend, but results were still

reported on the fourth day of life, and the transplant occurred on the 30th day of life.

Not only do I want to emphasize timeliness of the screening process that includes shipping samples from the birthplace through the Kentucky Department of Health and then on to Mayo Clinic, but also of the speedy path to transplant, especially because both babies were transplanted out of state, one at the University of North Carolina and the other at Pittsburgh Children's Hospital. Both patients are alive and doing well at six and one year old.

Clearly, we can already say the transplant was lifesaving for both patients, given what we know about the natural history of infant type Krabbe disease. Please also know that neither patient had a genotype of certain significance, meaning there was one known pathogenic variant in combination with a variant of uncertain significance in the first case, and with only a likely pathogenic variant in the other.

Accordingly, I am certain that these babies would not have received the diagnoses and transplants as quickly as they did if psychosine had not been part of the screening process.

A good amount of misunderstanding, if not misrepresentation, is associated with discussions of newborn screening for Krabbe disease. The cause appears to be an assumption that nothing has changed in the last 17 years of screening for Krabbe disease.

While it is true that the screening approach as recommended in the nomination you will be voting on today is not yet fully employed in all 10 states screening for Krabbe disease, it is also true that significant progress has been made. Except for Ohio and New Jersey, the other eight states now include psychosine in their screening approach.

Additional states, like Minnesota and South Carolina, which are currently reviewing the addition of Krabbe disease to their screening panels, are very likely going to follow the

screening strategy as nominated.

Thirty percent of U.S. newborns are already doing screening for Krabbe disease. Since Krabbe was renominated in July of 2021, our laboratory alone diagnosed 12 patients with Krabbe disease who were born between March 2019 and April 2022 in states not yet screening for Krabbe.

They were already six months old at diagnosis, and all of them had progressed too far to be considered for transplant. Therefore, suffering through the pain and agony of the relentless brutal disease process until they passed away or they will pass away.

But it doesn't have to be this way. And in 2023, it shouldn't be that way any longer. As Dr. Kemper will tell you, the evidence shows that

(a) the nominated screening procedure for Krabbe disease is sufficient and effective, and states already screening for Pompe disease or MPS I can easily get Krabbe disease through their panels;

(b) relevant follow up in monitoring guidelines have been published in peer-reviewed articles, and as ACMG ACT sheets and follow-up algorithms; and

(c) experts in the field working with patient advocacy groups stand ready to facility timely and appropriate triaging of screened-positive newborns at any time necessary.

In conclusion, I beseech you to vote for the addition of Krabbe disease to the RUSP as described in the nomination package. Newborn screening for Krabbe disease is currently the only and equitable means to minimize the suffering caused by this devastating and truly horrific disease.

Thank you again for giving me the opportunity to speak to you, and I'm happy to answer any questions you may have.

NED CALONGE: Thank you, Dietrich.

I want to again pause and thank everyone who has come to the meeting today to provide public comments. I especially want to

acknowledge and thank those parents who shared very personal and emotional stories about their children. This is an important part of federal advisory committees and an important part of the deliberations and considerations by the Committee.

And I know I'm speaking for every Committee member when I let you know of our appreciation for your time today.

It is time then to turn to evidence review for Krabbe just to provide some background.

NEWBORN SCREENING FOR KRABBE DISEASE:

A SYSTEMATIC REVIEW OF THE EVIDENCE (PART 1)

NED CALONGE: In July of 2021, the Committee received a nomination for Krabbe disease to be included on the RUSP. In the May 2022 meeting, the Committee voted to move Krabbe disease forward to the Evidence Review Group for a full evidence review.

At the August 2022 meeting, the Committee received the phase 1 update on the evidence review, and in November 2022 the Committee received the phase 2 update. Today the

Committee will receive the systematic review of evidence for Krabbe disease from Dr. Alex Kemper, Lead for the Evidence-Based Review Group.

After lunch, Dr. Kemper will be joined by an ERG member, Dr. Lisa Prosser, to continue the presentation on the evidence that includes review of a public health assessment survey.

By way of introduction, Dr. Kemper is the Division Chief of Primary Care of Pediatrics at the Nationwide Children's Hospital, and Professor of Pediatrics at the Ohio State University College of Medicine. Dr. Kemper's research focuses on the delivery of preventive care services, including newborn screening. Since 2013, Dr. Kemper has also served as the Deputy Editor of Pediatrics.

At this point, Dr. Kemper, I would like to turn the meeting over to you.

ALEX KEMPER: Thank you very much, Dr. Calonge. And before I begin with the evidence review, I too would like to thank those who came

forward during the public comment period. I think what they did was very helpful to have that context as we talk about the evidence. And there is no question that Krabbe disease is truly devastating and a terrible condition.

Next slide, please.

(Slide)

ALEX KEMPER: So, I do want to acknowledge the partners that I have on the Evidence Review Group, including those who are with me here at Nationwide Children's; those with the Association for Public Health Laboratories to help us assess what's going within newborn screening programs; K.K. Lam, my larger partner at Duke University; Lisa Prosser and her team at the University of Michigan -- we will be talking later; Scott Grosse with the CDC, as well as Anne Comeau and Susan Tanksley, who provided their laboratory expertise to this work; and then finally, you will hear this afternoon from Dr. Jennifer Kwon and Dr. Shawn McCandless as they present the summary of this material and begin the

process of deliberation.

Next slide, please.

(Slide)

ALEX KEMPER: I'm also very grateful for the technical expert panel members that are listed here who provide a feedback during the course of their review and having an opportunity to review an earlier draft, which again helped us to improve the clarity of our message. Again, we couldn't do this work without that input survey very well.

Next slide, please.

(Slide)

ALEX KEMPER: So, over the next little bit I'm going to summarize information about the natural history of Krabbe disease. I'm going to talk about screening. I'm going to be talking about issues of outcomes, comparing earlier identification to LIM, individuals with Krabbe marked disease might become diagnosed through the usual clinical care.

We're going to talk about what we

know from the newborn screening programs in terms of their ability to adopt and influence Krabbe disease newborn screening. And we'll be talking about what might happen if all 3.65 million infants born in this country each year was screened for Krabbe disease.

This presentation is really going to try to draw out the key, important points from the full review. But the full review, which is in the briefing book that you have, really includes additional information, including the methods that allowed us to develop this review.

Next slide, please.

(Slide)

ALEX KEMPER: So, as you've already heard this morning, Krabbe disease is an autosomal recessive lysosomal disorder.

Next slide, please.

(Slide)

ALEX KEMPER: The causative issue is low functional levels of galactosylceramidase, which I'm going to be referring to as GALC over

the course of this presentation. GALC degrades galacto lipids including psychosine. And individuals with Krabbe disease have depth of myelin-producing oligodendrocytes and Tron cells.

And there's also accumulation of these globoid cells, which accumulate around the areas of active demyelination and is one of the pathologic hallmarks of Krabbe disease.

Next slide, please.

(Slide)

ALEX KEMPER: The clinical findings associated with Krabbe disease are due to the white matter damaged in the central nervous system, as well as peripheral nerve demyelination.

Next slide.

(Slide)

ALEX KEMPER: Now I want to provide additional information about the natural history. So, Krabbe disease really presents across the spectrum of ages and can be associated with a broad range of onset --

Please advance.

(Slide)

ALEX KEMPER: And one more time.

(Slide)

ALEX KEMPER: So, untreated, most individuals with Krabbe disease will develop signs and symptoms by 36 months of age. And the earlier that signs and symptoms develop, the worse the prognosis is. The earlier developments in signs and symptoms is associated with more severe illness and more rapid progression of the disease.

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ALEX KEMPER: The typical presenting signs, and you heard a little bit about this earlier this morning, are feeding problems and then irritability, which becomes more and more prominent.

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ALEX KEMPER: And then without treatment, Krabbe disease is associated with death in early childhood.

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ALEX KEMPER: This is a summary of a systematic review of case reports and case series from 1982 through 2017. And I just want to walk through the different ages of presentation and the expected outcome in the absence of treatment with stem cell therapy.

So, first you'll see early infantile, which in these reports is up to six months of age. The age of onset is when symptoms became apparent, which is four months with this range. Here three to five months, these infants are associated with median survival of one-and-a-half years.

This report describes late infantile phenotype between seven and thirty-six months. Those individuals came to diagnostic attention around 14 months of age with a range of 10 to 24 months and had a median survival of nine-and-a-half years.

There's also a juvenile and adolescent, or adult, onset form that you can see

is associated with further increasing age of onset and a much greater likelihood of survival.

Our focus for this morning is going to be on what's listed here as the early infantile and late infantile phenotypes. That is, children affected with Krabbe disease with significant involvement by 36 months of life.

Over time the terminology has changed a little bit in terms of what's considered early infantile and what's considered late infantile. I'm going to try to be specific around ages when I talk about it. But you can really think of early infantile for the purposes we talk as those between zero and six months, and the late infantile as those after six months.

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ALEX KEMPER: So, the case definition -- that is, what we're looking for with newborn screening as nominated, is Krabbe disease with expected onset with signs and symptoms by 36 months of age. It's associated with low GALC

enzyme activity and elevated psychosine concentration. We'll be talking more about psychosine in greater detail.

But there's also one specific deletion that is 30 kilobase, or 30-Kb deletion that is uniformly associated with significant Krabbe disease. Or there can be other pathogenic variances. Dr. Matern talked about the gene findings can be supportive, but not necessarily diagnostic.

And then the diagnosis also depends on findings from neurophysiologic studies and/or neurologic imaging tests I all sort of put together. I'm going to drill into these issues in greater detail in a little bit.

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ALEX KEMPER: The *GALC* gene is located on chromosome 14. It's about 60 kilobases, or 60-Kb, long with 17 exons. As I just mentioned, the most common variant is associated with significant pathology is the 30-

kilobase deletion that has an allele frequency of about one in twenty-seven hundred. And depending upon the study that you look at, it's associated with between about 25 percent and about 65 percent of cases of Krabbe disease.

I've listed here figure for databases the genome aggregation database, which has one in fourteen-hundred *GALC* gene variants reported. And you can see that 62 of them have been characterized as pathogenic or largely pathogenic, and another 179, which are benign, were likely benign.

I've also listed here ClinVar. You can think of ClinVar as your curated database that variants can be submitted to. That has fewer GALC variants reported, 964 of which 207 are described as likely pathogenic or pathogenic, and 340 that are considered benign or likely benign.

But the key message just for this particular slide that I think is worth remembering is that it's the 30-kilobase deletion that accounts for many of the cases of Krabbe disease

and is associated with newly significant disease and that there are many, many variants of the *GALC* gene, not all of which have been fully categorized.

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ALEX KEMPER: How common is Krabbe disease? Well, I'm listing here some studies of the birth prevalence of Krabbe disease based on clinically identified cases. So, there's one recent study from Finland that estimates about 1.1 cases of Krabbe disease per 100,000. Another report from Sweden which reports a higher birth prevalence, 2.6 per 100,000.

In contrast to that, I've also listed two studies that report a much lower prevalence, one from the United Kingdom, which estimates the number of cases at 0.5 per 100,000; and a report of pediatric hospitalizations, they reported 0.3 per 100,000.

I think it's safe to say that the study of hospitalizations, the one that's listed

0.3 per 100,000 likely really underestimates the number of cases, because it depends on case identification and proper coding. And the denominator leading to those hospitalizations is less clear as well.

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ALEX KEMPER: There's also another report that recently estimated the prevalence to be as high as 8.3 per 100,000 live births. That was based on working with potential pathogenic variants, including those that are associated with adult-onset disease, not really the focus of this report today.

I think as a number to carry with you as we talk about it, it's probably really on the order of about 1.1 per 100,000 live births.

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ALEX KEMPER: With that, I'm going to transition and talk about issues with screening and diagnosis.

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ALEX KEMPER: So, Krabbe disease newborn screening is fundamentally based on identifying low GALC enzyme activity on dried blood spots. So, all programs that screen for Krabbe disease use low GALC enzyme activity as their first tier.

That could be done using tandem aspect, which is the case for most of the programs, or through a fluorometry process, which only one state is using. MS/MS, or tandem aspect, can also be multiplexed with other lysosomal storage disorders. When you're multiplexing, it can increase the incubation time, but there is that efficiency, obviously, of multiplexing.

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ALEX KEMPER: There's also, and Dr. Matern spoke about this, second-tier testing. So, for blood spots that have a positive screen based on low GALC enzyme activity, psychosine, measuring

the psychosine concentration, which can be done on the same dried blood spot, can greatly increase the specificity, help remove things like phytochemical pseudodeficiency.

The psychosine concentration itself, measuring that requires precise equipment and experience. So, psychosine concentration now is generally sent to a referral laboratory.

I'm going to be talking a little bit about cases that have been identified and their outcomes. One of the things that it's important to remember is that psychosine concentration measurement has only been available after 2015. So, we don't have psychosine for a lot of the cases that we're going to be talking about.

GALC molecular analysis can also be helpful, especially if their 30 kilobase deletion is identified, or if the other variants have been identified.

Now, it's not going to be surprising to anyone that newborn screening programs have adopted various strategies of testing, especially

for second-tier testing. And the process that has evolved with newborn screening programs have gotten experience with doing that.

I'm going to try to group the different states to help with understanding how the current map is. But just know that that is part of natural evolution. There have been these changes. And I also want to highlight that the nomination package itself specifies scrutiny with first tier GALC enzyme activity and second-tier psychosine testing.

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ALEX KEMPER: So, in terms of going from screening to diagnosis, I just want to be clear again that one of the challenges with Krabbe disease is it has variable ages of onset. And in the ideal diagnostic process, after newborn screening would not only identify which infants have Krabbe disease, but also help with predicting the age of onset to guide monitoring and treatment.

For many cases, that can be done. For example, there's already seen an involvement or involvement that can be identified or in testing or the baby has the 30-Kb deletion of alleles.

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ALEX KEMPER: So, there have been expert panel recommendations for follow-up after positive newborn screening that's based initially on the dried blood spots psychosine level.

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ALEX KEMPER: So, first it classifies with individuals with dried blood spot psychosine levels. Two or greater is being at normal.

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ALEX KEMPER: And 10 or above is strongly predictive of early infantile Krabbe disease. And those are the children for whom follow-up is really time-critical.

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ALEX KEMPER: Now, this expert panel recommends three different pathways that I'm going to go over. The first is for the babies who have likely early infantile Krabbe disease based on their psychosine level. And those are infants who are recommended for immediate referral for diagnostic evaluation and treatment.

And because of the time pressure for treatment, that diagnostic evaluation really can happen as treatment plans are developed so that there's no slow-down.

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ALEX KEMPER: The second pathway is what's referred to as at-risk for late-onset disease. So, to use our infants again between the two and ten psychosine level who require follow-up in two to four weeks by a specialist or a primary care provider and consultation with a specialist for further testing. And of course genotype can

further help clarify what to do and can be used to stratify infants, too.

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ALEX KEMPER: A high-risk category, which requires more intensive follow-up.

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ALEX KEMPER: Or a low-risk category. So, individuals who are not identified with pathogenic variants who still require close follow-up, but not as intensive as those in the high-risk group.

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ALEX KEMPER: Then for those infants who are not expecting to have Krabbe disease, then there's no specific follow-up that's needed.

So, these are the three pathways that you can classify a child based on first the GALC enzyme activity, and then with the psychosine concentration.

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ALEX KEMPER: The diagnostic evaluation includes measuring the GALC enzyme activity. That is a clinical sample, not the dried blood spot, newborn screening sample. And the same thing with the psychosine concentration, as well as molecular testing with the *GALC* gene if that was not previously done.

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ALEX KEMPER: Those children also need a complete exam, so neurophysiologic studies, neurologic imaging that includes -- these things all include MRIs, nerve conduction studies, electroencephalogram, or EEG, auditory and visual evoked potentials, and looking at the CSF, the cerebrospinal fluid protein concentration.

All these tests can help establish whether there is disease involvement and help chart the course for --

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ALEX KEMPER: So, again, the timing of the specific studies and when imaging needs to be done can be based on the risk classification, as I talked about earlier.

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ALEX KEMPER: And there are staging systems that have been developed that help synthesize the findings based on the laboratory results and these other neurophysiological and neurological imaging tests that I've just described.

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So, I now want to transition and talk about newborn screening in the United States. So, there are 19 newborn screening programs that currently include Krabbe disease newborn screening. You've already heard that represents about 30 percent of the births in the country.

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ALEX KEMPER: If you look at when screening began, and regardless of like how the screening algorithms have changed and those kinds of things, if you just look across all the newborns that have been screened since screening was first reported --

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ALEX KEMPER: -- there have been about 7.4 million infants screened.

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ALEX KEMPER: And there have been 28 infants with expected onset prior to 12 months of age, or the equivalent of about 0.38 per 100,000 infants screened.

And I'm going to take a little pause here and talk about -- because of variation in how we were able to obtain information from the state newborn screening programs, you're going to hear me talk a lot about expected onset prior to 12 months of age compared to expected onset after 12

months of age, which is the convenient way to be able to combine somewhat disparate data.

And, you know, of those with expected onset prior to 12 months of age, it's likely that half or so or more are going to have the early infantile phenotype, that is, between zero and six months. So, I just want to be clear about why we're using that classification of 12 months.

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ALEX KEMPER: These are published reports of newborn screening, and I'm just going to go through each of them. There's two reports of newborn screening in New York that covered the period from 2006 to 2015. Again, this was pre-psychosine.

So, there's a molecular analysis second- tier test that they used; 2.2 million infants were screened in New York during this period of time. And you can see that there were five identified with early infantile Krabbe disease and fifty-five at risk for later onset.

Missouri is the state that uses the fluorometric process and a second-tier molecular analysis in its report. They covered a period from 2012 to 2015, and there were two infants with disease-causing variants. Two at the time of this published report were asymptomatic.

Illinois published in the peer-reviewed article their experience from 2017 to 2020. And this is where you can see psychosine concentration coming in as the second-tier test. They screened about half-a-million infants with the identification of two with infantile onset and six with suspected late onset.

And then Kentucky, Dr. Matern talked about how the Mayo Clinic conducts the Krabbe disease, usually screening for Kentucky and the Mayo Clinic. Also includes other lysosomal storage disorders. The published report covers the period of February 2016 to February 2017 with psychosine second-tier testing in that report.

There were a little over 50,000 infants who were screened, with one infantile

onset case that was identified. And the references for this information is listed here.

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ALEX KEMPER: This is a slide that lists the 10 programs that are currently offering Krabbe disease newborn screening and the year at which newborn screening began. How they're currently testing for GALC enzyme activity, whether or not they're using second-tier psychosine testing. If so, who is doing the analysis?

You can see that some states are sending their samples to the Mayo Clinic, and others are using PerkinElmer. PerkinElmer is using a slightly lower threshold for their psychosine testing.

And I just also want to draw your attention to the fact that there are two states, New Jersey and Ohio, that currently do not use second-tier psychosine testing. And you'll see the impact of not using psychosine testing as the

second-tier test in a second.

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ALEX KEMPER: So, this is a slide of newborn screening outcomes, newborn screening for Krabbe disease. I want to thank our partners at APHL for working with these state newborn screening programs to get these data for us.

We group states generally based on the protocol during this period of time. So, you can see Ohio and New Jersey, which refer based on GALC enzyme activity alone. We have grouped together Missouri and Tennessee based on their use of looking at the 30 kilobase deletion. And then we group the remainder of the states based on whether they would refer based on psychosine concentration alone in the end, or the 30 kilobase deletion.

The real difference between these states, however, is really Ohio and New Jersey compared to the others. And so, I just want to draw your attention to a few things. First is the

number of referrals per 100,000 screened are higher in the states that do not use psychosine second-tier testing -- 54 per 100,000 in Ohio and 28.9 per 100,000 in New Jersey.

There is some variation in terms of rates of referral in the other states. And I can't comment on why that variation exists.

Next I want to point out the Krabbe disease with expected onset. And here's a -- I just noticed an error in this slide. It should be less than 12 months, not greater than 12 months per 100,000 screened. And so you can see that there's some states that haven't identified a case with expected onset.

In the first 12 months we have some follow-up for those that were identified in these states, including, for example, if you look at Kentucky. They during this period of time identified 0.6 cases per 100,000. And those two infants received stem cell transplanted 24 and 30 days of life.

The next column you can see those who

were at risk for onset after 12 months per 100,000 screened. And then the final column is those infants who have either pending classification, they're still working their way through the system, families that have declined follow-up, or who were lost. And what I'd like to point out is that most of the cases of pending, declined, or lost were from Ohio, which does use the first tier GALC enzyme activity.

Again, because of the way the data are collected, pulling this kind of table together can be difficult, especially because, you know, we know that the children are working through the diagnostic system. And the information that the laboratory has about cases that have been identified and the information that the follow-up coordinators might have, you know, there's sometimes a delay and sometimes the assistants don't talk.

So, there is a risk of ominous classification. So, for example, in New York they have -- we learned that there were two cases that

were classified as having Krabbe disease with expected onset in the first year of life. But it turned out those infants didn't need to have stem cell transplant based on their psychosine levels and the lack of symptoms.

And those two infants, as you'll hear about in a little bit, did receive a transplant after 12 months of life. And I'll highlight that when we talk about outcomes.

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ALEX KEMPER: So, what I want to highlight, though, from what we just talked about is that since 2016 with about 3.6 million infants who have been screened.

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ALEX KEMPER: If you look at referrals for newborn screening programs that use GALC enzyme activity alone, that's about 47 per 100,000 infants screened. And if you combined all the other states that use psychosine and/or

molecular analysis, that is associated with a referral rate that's much lower, at 7.7 per 100,000 infants screened.

In terms of diagnoses, the Krabbe disease with expected onset in the first 12 months, there were 13 cases, or about 0.3 or 0.4 per 100,000. In terms of expected onset after 12 months, there were 15 infants in that category, or about 1.5, 1.46 per 100,000. And then there are a number of pending classifications, lost their follow-up. And most of these come from a single program that just screens using GALC enzyme activity.

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ALEX KEMPER: And there was one identified case of expected Krabbe disease in the first 12 months of life where the family refused stem cell transplantation.

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ALEX KEMPER: And I already talked

before about the risk of this classification in the previous table.

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ALEX KEMPER: So, as we are required, we do look at the direct cost of -- not the direct, I shouldn't say direct -- at the cost of newborn screening from the laboratory perspective.

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ALEX KEMPER: So, the estimated cost from the program perspective, above and beyond the fixed cost of the existing newborn screening, has been estimated to be between two and seven dollars. I want to thank Dr. Scott Grosse at the CDC for helping us with this estimate.

Again it's a fairly broad range. It can be hard to tease out the specific value associated with Krabbe disease, in particular because it's oftentimes multiplexed with screening for other lysosomal disorders. Most of the costs reflect equipment costs from agents and laboratory

technician and laboratory scientists assigned for the first-tier screening. Again, there's a relatively small number of infants who will need to go on to get psychosine concentration testing.

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ALEX KEMPER: What do we know about the impact of early treatment?

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ALEX KEMPER: So, hematopoietic stem cell transplantation, HSCT or sometimes you'll just hear me refer to it as stem cell transplantation, was first described in the late 1990s.

There is a case series from 2005 that really established the recommendation for treatment by around six weeks of life for those with early infantile Krabbe disease that's been included with 11 subjects who were diagnosed prenatally or shortly after birth, again this is before we were screening, with early infantile

Krabbe disease who received a transplant around 19 days of life when they were asymptomatic.

And those 11 subjects were compared to the 14 subjects who were diagnosed from four to nine months of age and who received transplantation around 142 to 352 days of life. So, in terms of the outcomes, there were no deaths in the asymptomatic group with follow-up to about three years. And compare that to 16 and 14 infants in the symptomatic group who survived for a median follow-up of about 41 models.

In terms of motor development, 10 of the asymptomatic group had follow-up. There is one with severe delays, four with mild to severe delays, two with truncal weakness. And in the symptomatic group, during the period that those subjects were still alive, they were described to have the "developmental level equivalent to that of a one-month-old."

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ALEX KEMPER: The clinical practice

guidelines was developed by the Hunter's Hope Leukodystrophy Care Network and was published in 2019. And quoting from that protocol practice guideline, "HSCT does not offer benefit to infants with EIKD" -- early infantile Krabbe disease -- “after symptoms have developed." And that really, again, emphasizes the goal of stem cell transplantation by four to six weeks after birth for infants with early infantile Krabbe disease.

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ALEX KEMPER: As Dr. Escolar talked about, there are experimental therapies in progress. So, there's an intrathecal delivery of a stem cell line designed from umbilical cord blood that can be used in addition to transplantation, which is still under study.

There are two gene therapy products. These are both delivered by an adeno-associated virus. They're in phase 1 and 2 trials after FDA fast-tracked clearance for investigation on these drugs and for human trials.

Given that this is not an FDA-approved product and given our evidence reviews, I'm not going to be talking about gene therapy further and again want to highlight for the Committee that it's HSCT stem cell transplantation which is the current recommended therapy that's targeted for Krabbe disease.

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ALEX KEMPER: So, we're going to talk about treatment studies and cases of early identification versus later identification. And I think it's worth taking a step back just enough for us all to -- you know, potential that the method of diagnosis could impact the outcome. So, if you were identified by family history or diagnosed by key testing in utero, that can help expedite treatment.

So, we've heard from experts that could even impact the decision to deliver the child a little bit earlier to help protect the developing nervous system by transplanting at a

slightly lower gestational age when they've been exposed to the -- when the infant's been exposed less to the harmful effect of Krabbe disease.

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ALEX KEMPER: The other thing that's important to understand is that our understanding of Krabbe disease and treatments and, you know, the best way to go about doing things has evolved over time. And so, you know, I think it's important to have sort of a historical context as we look at the treatment studies as well.

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ALEX KEMPER: And there's a lot of information that I think will be of interest to the Committee that we are not going to be able to answer. So, for example, the specific pathway to diagnosis and the method of categorizing phenotype. Sometimes genotype isn't provided. Psychosine concentration, clearly, you don't have for the cases that were treated before psychosine

concentration became available.

And then there's a gap in the literature related to having standardized outcome measures as specific ages. So, it would be nice to have the same developmental outcome measure as standardized ages for all the infants and we could easily compare across and summarize things. That's generally not done, and it makes summarizing outcomes more difficult.

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ALEX KEMPER: So, in the full report we talk about all the studies of treatment outcomes that we could find. Not all those studies provided granular enough data where we could, with confidence, pull out individual cases so we could talk about the different cases. Sometimes aggregate information was provided.

So, what I'm going to go through is the subset of subjects where we could clearly get aggregate information, and I'm going to begin by talking about the cases that were ascribed as

being identified based on family history.

The classification that you see in the first column is based on the classification that is provided in the report. The next column is about the GALC genotype information and the psychosine concentration.

And NR is not reported, and you can see it again for most of these cases it's not reported. That very last case, which is described as a late infantile case, was a compound heterozygote, compound heterozygous for the 30 kilobase deletion. So, we don't have psychosine concentration, so many of those infants.

I've ordered this table based on the age at stem cell transplantation. So, you can see the youngest at 3.3 weeks, and the oldest at 4.5 months.

And the next column is the age at last follow-up, so you can see that most of these infants were followed to five years or older. At the time of the report, there was one report, the second from the bottom, where we have information

out to only 11 months.

And again, I talked before about the challenge of the lack of standardized neurologic outcome reporting. So, instead, I have it qualitatively described.

So, the first case is an infantile case who -- that child received transplantation at a little over three weeks is now five years of age and described as going to kindergarten with an aide, able to walk, talk in five-word phrases, feed herself, has some ankle clonus, upgoing plantar responses, and the tendency to toe-walk.

The next case transplanted around the same age, in contrast, is described as having spastic quadriparesis, needing a g-tube, having some speech and "dependent for all cares." Again, these are quotes.

So, I'm not going to read the outcome at each stage, but just highlight that there is heterogeneity in these cases.

You know, one thing that I didn't talk about before about how we put this together

is that it's clear that some cases are reported multiple times and given case reports. And we did group things together as best we can. Looking at clues in terms of, you know, when the transplant was done and genotype, that kind of thing. But there is a risk that a case could appear more than once in this table.

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ALEX KEMPER: I'm now going to highlight the cases that were identified through newborn screening. And this table is similar to the last one except for in the left-hand column, I have the state newborn screening program that led to identification.

There is one report that didn't say exactly which state the subjects came from, but said that wherever it was, it was not New York, which is why you see "not New York" listed in that column. So, the only outcomes that we have in the study are from New York, Kentucky, and not New York.

I just want to highlight some important things. And one is some of these studies are relatively older, especially some of the reports of outcomes from New York, which were from a publication in 2016. I would also like to point out heterogeneity in terms of follow-up at outcomes. This table, like the previous one, is organized by the age at which transplant occurred.

So, if you look at the early infantile cases who were transplanted before 18 months, which is typically everybody, but the last two you can just see that the heterogeneity now comes, including some infants who did die after transplantation.

There was one family who refused stem cell transplant, and that subject died by 18 months.

The last two rows were recently reported in an abstract. Those were the two cases that I mentioned before from New York. They were transplanted at 18 months of age, and at five years are reported as "normal." So, maybe I'll

just leave this. It's in the briefing book, but I'll just leave this here for one second just so that you can scan the range of status that's described.

(Pause)

ALEX KEMPER: Okay, let's go on to the next slide.

(Slide)

ALEX KEMPER: This slide continues what we had before but were for infants who were classified as being high-risk, and being followed but not transplanted. So, it doesn't have any further information except for I do want to highlight that case from New York in the middle of -- which was identified as high-risk, but later retrospectively assigned as onset in late infancy.

This case report describes an infant who was considered to have likely pathogenic bearings, but an initial psychosine concentration of 1.2. That infant was followed closely and did eventually develop signs and symptoms of Krabbe disease after the window of treatment had closed.

And that infant died by 26 months of age.

This is the one case that we've seen where there was a non-elevated increase, where psychosine is not elevated and the infant turned out to have significant Krabbe disease.

The authors of this case report point out other characteristics of the case that just didn't fit with what's standardly expected with Krabbe disease and suggested there might have been some secondary condition. So, again, it's hard to generalize from that, but I do want to point out that one particular case.

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ALEX KEMPER: So, there are a number of reports that are not clear about how the case was identified, whether it was through family history or screening or some other way. And this slide is just, you know, like the others. And you can see the age at which transplant was done, ranging from 2.6 weeks of life all the way out to six months of life. And you can see that there is

some heterogeneity in outcomes.

And so instead of reading that column of the Age of Follow-up and Status, I'll just leave it there for a few seconds for people to look at again. Again, this is in the briefing book, again part of the full report.

(Pause)

ALEX KEMPER: Okay. Next slide.

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ALEX KEMPER: So, let me summarize these slides. So, first, stem cell transplant is the recommended treatment for individuals with Krabbe disease with expected onset of signs and symptoms by 36 months of life.

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ALEX KEMPER: For those with expected early infantile Krabbe disease -- that is, expected to have involvement by six months of life -- HSCT transplants is recommended with the goal of treatment four to six weeks after birth.

Timely transplant can reduce the risk

of child mortality, so we reduce the risk of death. But the other outcomes are more variable, and there's insufficient evidence to allow us to predict these outcomes. So, again, Krabbe disease is rare, and because of the data that are reported in individual studies, it's just not possible to kind of buildup that model.

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ALEX KEMPER: For individuals of Krabbe disease with expected onset of signs and symptoms between six and thirty-six months, the available evidence suggests that treatment before the development of signs and symptoms reduces the risk of mortality. And although the evidence base is limited, there does seem to be an association with improved cognitive, language, and fine motor development.

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ALEX KEMPER: And I didn't go through the data in this presentation. But it's important

to recognize that the greatest risk of mortality following transplant is within the 100 days after transplant. There can be harm from the chemicals, from the treatment regimen that's needed before the transplanter's risk of graft-versus-host disease, and there's also a risk of infection during stem cell transplant.

So, it's really in the 100 days after treatment that there's the highest risk. And the limited data that we have suggest the risk is about 11 percent. But that comes from centers with expertise in transplant for Krabbe disease. And we're not able to comment on other potential long-term negative outcomes associated with transplant outside of that 100-day window.

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ALEX KEMPER: So, I now want to take a step back and talk first about potential benefits of screening.

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ALEX KEMPER: So, Krabbe disease newborn screening can eliminate the diagnostic odyssey. You heard about that during the public comment period. There are no studies that address the diagnostic odyssey specifically for Krabbe disease.

Based on the natural history studies, though, infants with early infantile Krabbe disease develop feeding problems and extreme irritability. The natural history studies suggest that when there's no family of Krabbe disease, the diagnosis of infantile Krabbe disease is delayed beyond the recommended period of four to six weeks when transplant would be an option.

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ALEX KEMPER: Detection of early infantile Krabbe disease for newborn screening allows families to decide whether to have their infant receive a transplant within that recommended period of four to six weeks. And what we found from looking at the evidence, there is at

least, you know, one case identified where a family chose not to have their infant receive a transplant.

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ALEX KEMPER: And that stem cell transplant by four to six weeks of age for early infantile Krabbe disease is associated with decreased risk of childhood mortality. You're going to hear more about this when Dr. Prosser presents the modeling.

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ALEX KEMPER: And that HSCT by four to six weeks of age for early infantile Krabbe disease is associated with improved functional outcomes, although these outcomes, as I mentioned before, can be variable and difficult to predict. A limitation of the evidence base is that the studies lack specific outcome measures at specific ages related to standardized health outcome measures and of quality of life.

Similarly, the articles do not specifically address the impact of Krabbe disease with or without transplant on the family.

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ALEX KEMPER: And there's a limited evidence base that suggests that transplant for late infantile Krabbe disease early in the disease course is associated with decreased mortality and improved functional outcomes, with some variability as I discussed earlier.

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ALEX KEMPER: So, as with all screening programs --

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ALEX KEMPER: -- there's potential harms associated. And I want to talk about those as well.

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ALEX KEMPER: So, a false negative screen would be a harm because it could lead to false reassurance and potentially delay diagnosis until after signs or symptoms appear. We did find one report that talked about how premature infants might have a higher likelihood of false negative first-tier GALC screening, first-tier enzyme activity screening.

It's hard to know if this is just a theoretical risk. We certainly couldn't find any cases of missed screening for premature infants. And then I already talked about that one infant who had low initial psychosine concentration. Again, it's hard to generalize from that. The authors suggest this infant might have had a secondary condition.

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ALEX KEMPER: Treatment with stem cell transplant when it's not required would be a harm. But using the current diagnostic approaches -- that is, low GALC enzyme activity and elevated

psychosine level, looking at the *GALC* gene variants and doing the complete neurologic evaluation like I talked about -- the risk of transplant being performed for Krabbe disease when it's not indicated is assumed to be low.

Again, we don't have the direct evidence of that, but it's likely to be the case.

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ALEX KEMPER: And then Krabbe disease newborn screening could lead to transplant in centers with less experience than the small number of treatment centers that currently provide most of the outcome data that were included in this report, potentially leading to worse outcomes. You know, most of the cases have been treated at Duke University or Children's Hospital of Pittsburg.

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ALEX KEMPER: And then infants at risk from late-onset Krabbe disease can require

long-term clinical follow-up. And little is known about the impact of that follow-up on families. We didn't identify any reports that specifically addressed that.

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ALEX KEMPER: So, now I'm going to transition and talk about the public health system impact assessment. There's a much more in-depth analysis that's in the briefing book. For the purposes of this presentation, I'm going to just talk about really the key points.

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ALEX KEMPER: So, as we've mentioned, there are 10 programs that have implemented Krabbe disease newborn screening.

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ALEX KEMPER: Virginia, the Commonwealth of Virginia, recently chose not to implement Krabbe disease newborn screening.

That's described in an article by Dr. Vergano. It was recently published.

Their reason for not adding it is that it's currently not on the Recommended Uniform Screening Panel. There are concerns about risk prediction when an infant had a positive screen. And they identified challenges in assuring that a stem cell transplant would be available by 30 days after birth.

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ALEX KEMPER: There was a filed letter by a number of experts who emphasized that transplant can be given up to six weeks for those with early infantile Krabbe disease.

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ALEX KEMPER: So, in terms of evaluating the ability to add Krabbe disease newborn screening, APHL sent a survey out to all 53 newborn screening programs. I'm going to focus on the 44 that did not include Krabbe disease

newborn screening. Thirty-four of those forty-four responded to the survey that APHL sent.

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ALEX KEMPER: At the very highest level, expected time to implementation after a recommendation might be made by the Secretary of Health and Human Services to add it to the Recommended Uniform Screening Panel is as follows: in less than two years, 36 percent; two to three years, 43 percent; three to four years, 12 percent; and more than four years was 3 percent.

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ALEX KEMPER: The survey did ask about barriers and facilitators to adopting Krabbe disease newborn screening. Some of the facilitators were advocacy activities, the ability to multiplex screening if you're using tandem aspect, and then the expected clinical outcomes were considered to be a positive facilitator.

They also listed a number of barriers

including the availability of treatment; other program activities that they needed to focus on; the need to increase the newborn screening program; the newborn screening fee; the availability of GALC enzyme activity testing; the availability of specialists for diagnosis fee; expected clinical outcomes; administrative challenges; availability of second-tier psychosine testing; and the availability of staff for short-term follow-up.

But by far the most common barriers were related to concerns about availability of timely HSCT and also other program activities including adopting other recently recommended newborn screening tests.

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ALEX KEMPER: A question has come up about treatment center availability. And our methods including evidence review and the surveys that are sent out to the state programs cannot directly identify treatment center availability

for HSCT.

What I'd like to point out is that in the Leukodystrophy Care Network there are currently 12 centers. There is the Hunter's Hope Krabbe Newborn Screening Advisory Council, which was developed as a resource for influencing things.

And we were told by Hunter's Hope, Krabbe Connect, and other advocacy organizations and other experts in the field that there is willingness to share expertise. But again, we can't comment on the degree to which, you know, having stood up a program and having great experience influences outcomes and the ability for this technology transfer to occur.

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ALEX KEMPER: So, Dr. Calonge, would you like this to continue with Dr. Prosser's modeling? Or take a break? We're still before noon, and I think Dr. Prosser can do that quickly.

NED CALONGE: Well, it was your last

frame. Do that quickly.

ALEX KEMPER: Sure.

NED CALONGE: Made me wonder. But I wonder if we could, Alex, just take a five-minute bio break. Everyone sat for a long time. And just a little break, and then we'll try to reconvene in about 10 minutes before the hour.

Please try to be prompt.

ALEX KEMPER: Thanks.

NED CALONGE: And, Alex, thanks for an outstanding presentation.

We'll see you all in about five minutes.

Though I do want it noted that Kyle Brothers joined us in time for the evidence presentation. I want the minutes to reflect that.

And welcome, Kyle.

KYLE BROTHERS: Thank you. Sorry to be late.

(Whereupon, a short break was taken.)

NEWBORN SCREENING FOR KRABBE DISEASE:

A SYSTEMATIC REVIEW OF THE EVIDENCE (PART 2)

NED CALONGE: Welcome back. We're right at 10 minutes to the hour, so in the interest of moving forward and maintaining our momentum, I'd like to bring us back to the table.

At this point, Dr. Kemper will be joined by Dr. Lisa Prosser to continue the presentation on the systematic review of the evidence of Krabbe disease.

Dr. Prosser is the Marilyn Fisher Blanch Research Professor of Pediatrics and the 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 decision sciences and economics. Current research topics for Dr. Prosser include newborn screening programs, vaccination program, and methods for valuing family spill-over effects of illness.

And Alex and especially Lisa, I would like to turn things over to you at this point.

ALEX KEMPER: Thank you very much. And I just wanted to make sure that -- Lisa was promoted.

NED CALONGE: Congratulations, Lisa.

LISA PROSSER: I am fully promoted here.

ALEX KEMPER: Permitted to speak. She's already high in my book.

LISA PROSSER: Great. Wonderful.

Well, thanks so much. Thank you, Dr. Calonge, and thank you, Dr. Kemper. Thank you to the Committee and to all of our expert panel, as well as everyone who contributed to developing the modeling.

If you could, please, next slide.

(Slide)

LISA PROSSER: Great. Thank you.

As in previous condition reviews, we've incorporated decision analysis, which is an approach to decision-making under conditions of

uncertainty. And what this allows us to do is to project ranges of short-term outcomes, comparing newborn screening to clinical identification of the condition being considered.

It allows decision-making to identify which alternative is expected to yield the most health benefit. At the same time, it also identifies key parameters and assumptions, and allows us to identify where there are key gaps in the evidence base.

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LISA PROSSER: So, using modeling, the objective for this part of the evaluation is to project population-level health outcomes comparing newborn screening to clinical presentation. So, using an annual US newborn cohort of 3.65 million events, we'll be projecting outcomes on the newborn screening side; short-term screening outcomes, so numbers of positive screens; confirmed cases of Krabbe disease; confirmed infants at risk for Krabbe; and other

screening outcomes.

We'll also project the number of newborns who receive transplants, transplant outcomes, and mortality at 2.5 years of life. And we'll compare this to clinical identification with the numbers of identified cases of Krabbe disease for infantile and later-onset, and again comparing mortality at 2.5 years of life.

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LISA PROSSER: This slide is just a preview of one of the table's outcomes that will be projected using this simulation model, and then just a preview of the outcomes that we'll be focusing on in the left-hand column.

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LISA PROSSER: In the next few slides, I'm going to review some assumptions that underlie the construction of the simulation model here that are derived directly from the evidence review that Dr. Kemper just completed. And also

augmented by additional discussions with our clinical expert panel that met with us several times and the condition review.

So, the classification used in the modeling will divide the cohort into two age groups, those that are identified at less than 12 months of onset -- and Dr. Kemper reviewed this earlier -- compared with those at 12 months or later for onset.

We are assuming that for newborn screened identified newborns recommended for immediate treatment that transplant occurs before the development of overt symptoms.

Another assumption underlying the modeling is that differences in outcomes for transplants occurring at less than or equal to 30 days of life or greater than 30 days of life are not included in the model.

This is a threshold that's used in many of the published papers. But there's extensive discussion that, for example, if a newborn received transplant at 32 or 38 or 48 days

of life, the primary determinant on the outcomes for that infant would be more likely due to other factors than to the exact date of the transplant itself.

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LISA PROSSER: Thank you.

And just a few other assumptions here before we start reviewing the models. So, another assumption is that newborns identified with markers suggesting Krabbe disease onset by 12 months are recommended for transplant. This slide says most of these will be symptomatic, but again this could be signs and symptoms and markers, but not again overt symptoms of Krabbe disease.

Another assumption in the model is that the probability of mortality due to transplant-related complications within 100 days of transplant is the same for infants identified through newborn screening or clinical presentation.

And another assumption related to

transplant is that transplant-related morbidity beyond 100 days post-transplant is typically not life-threatening, and this is not included in the modeling.

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LISA PROSSER: And just sort of the implications of the evidence on treatment when reviewed, specifically for integration into the modeling analysis that again assume that newborn screen identified newborns, recommended for transplant, likely represent the most severe phenotype.

And when we compare to clinically identified newborns who receive transplant, these represent a wider range of severity of illness at the time of transplant than in published studies. And just to note that's a typo that then should not be here. This is just considering the universe of published studies that this is a wider range of illness for those infants.

And because of this, the subjects in

these two groups of studies are not comparable. And therefore, these results have not been integrated directly into modeling of long-term outcomes.

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LISA PROSSER: So, next we're going to review the structure of the newborn screening simulation model.

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LISA PROSSER: So, I want to go through this slide in detail. But just to orient to the structure of the model that on the left-hand side we're starting with identical cohorts of hypothetical newborns who are not at higher risk for Krabbe disease.

And so then comparing with the outcomes for those two identical cohorts of newborns, 3.65 million, would be across a group that received newborn screening compared to infants who presented through clinical

identification.

So, moving across the top of the decision tree, for those infants that received newborn screening, we have some proportion. And each of these arrows in the schematic represents a probability that we will see on the next few slides what the data are that are going to these probabilities.

So, there's a probability that a newborn can screen positive and be referred for diagnostic evaluation. Following that evaluation, an infant can be referred for transplant evaluation, can then receive transplant, or may not receive transplant either due to the progression of disease at the time or potentially declined by the family.

Following transplant, you can survive or die based on complications. What's grayed out in the very last segment of this model are longer-term outcomes based on the quality of life of following a transplant. And that's where there was insufficient evidence to quantify what those

outcomes would be at 2.5 years of life. So, those are represented here as gray-out and not presented in our quantitative outcomes.

And then just to focus on kind of the middle column, which will be our primary screening outcomes, will be quantifying the number of infants that are again at risk for late onset Krabbe disease, either high risk or low risk, follow-up pathways, and those that are not recommended for a regular follow-up.

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LISA PROSSER: We'll then be comparing to infants who present with Krabbe disease through clinical identification. And again, if you follow the structure of the model -- so again this is the full cohort of 3.65 million infants, so some will present with Krabbe disease. Most will not.

But those that present with Krabbe disease, some proportion will present before one year of life. And this is the comparison cohort

that we'll use for the newborn screening again of that cohort that is recommended for transplant.

Again, a proportion of these infants will receive transplant. Under clinical presentation, the primary defense here is that many of these infants are likely to not be recommended for transplant given the progression of their disease at the time of clinical presentation. Then again, we'll be presenting mortality at 2.5 years of life.

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LISA PROSSER: This slide shows a summary of some of the data that Dr. Kemper presented earlier. These newborn screening data for all of the outcomes that we've included in the model -- the screening outcomes.

Important to note that across the second row for "Referred," that there are wide differences across states. And this is due to the different algorithms that are being used to identify which infants are referred at that first

stage of screening.

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LISA PROSSER: So, important to note that for the modeling what has been done is to adjust the state-reported data to reflect a referral protocol that is based on a low GALC enzyme level and high psychosine levels.

So, essentially, assuming that all of the newborn screening programs nationally would be using that protocol that would be incorporating the GALC levels as well as psychosine as part of the initial screening determining which infants move on to referral for diagnostic evaluation.

This slide just goes into some detail on how those adjustments were made state by state.

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LISA PROSSER: So, this slide shows the adjusted data again. So, this represents what would be happening at the state level for states that -- state newborn screening programs that we

have data for if all of the states were following a screening protocol that referred based on the GALC enzyme levels, as well as the psychosine.

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LISA PROSSER: So, translating this, this is just translating this into our probability inputs into the model. And so, to focus on the right-hand panel, which are the adjusted projections. So, for the combined number of newborns that have been screened to date across all of the screening programs, there would be -- this shows the adjusted numbers.

So, there would be 51 that would be referred for diagnostic evaluation. And then looking at the very final column, the conditional probability, given a referral, would be 20 percent for infantile Krabbe disease; 73 percent of those would be identified as at risk for late-onset Krabbe disease; and 6 percent of those would not be recommended for any regular follow-up following diagnostic evaluation.

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LISA PROSSER: And then this slide is just translating this into the specific parameters that were incorporated into the model. And so, what has been added to this slide is the range. Again, there is uncertainty around all these inputs. We have small numbers with newborn screening.

The ranges for most of the parameters that will be presented on the following pages have been derived using an assumption of binomial distribution. And so, some of these, as you will notice on there, aren't very wide, which again represents the small numbers that we typically have for newborn screening.

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LISA PROSSER: The next few slides I won't go through in detail. But just to know that the source of these data either come from the newborn screening programs that have been underway

in the states, from the public literature, or from the clinical expert panel that we worked closely with during the evidence review.

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LISA PROSSER: This slide shows the parameter inputs for the clinical presentation. A sub-model, I'm shown the proportion of infants that are likely to be diagnosed at less than 12 months of life, and those that are likely to be diagnosed beyond 12 months of life, and of the ones that are diagnosed at less than 12 months of life, what proportion are likely to receive transplant.

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LISA PROSSER: On the newborn screening side, this just shows the final branches of this tree, the probabilities of transplant outcomes, and survival at 30 months both with and without transplant. They've published, yes.

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(Slide)

LISA PROSSER: So, this slide shows the results of the model on projected screening outcomes, again for an annual cohort of 3.65 million newborns, assuming that all states are using the protocol based on the low GALC enzyme levels, as well as psychosine levels.

So, the projected number would be roughly 75 annually with a wide range, as you can see on the right-hand side. Of those, about 15 would be projected to be identified as having infantile Krabbe disease.

Fifty-five would be identified as at-risk for late-onset Krabbe. And of those, about 40 percent are identified as needing to follow the high-risk follow-up pathway, and 33 of those for the low-risk follow-up pathway. And just under five would not be recommended for regular follow-up.

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LISA PROSSER: On the clinical

presentation sub-model, on the projected cases for infantile onset, less than 12 months of age, it's roughly 19 per year with those identified as post-infantile onset, about 21 per year.

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LISA PROSSER: Now, this slide is just taking some of the information from the previous two slides, specifically focusing on the number of infants. So, infants and early years of life that are identified with Krabbe disease.

So, the most important part of this slide is on the right-hand panel at the bottom right, comparing the projected incidence for newborn screening compared to clinical presentation of 1.02 per 100,000 compared to 1.1 per 100,000 under clinical presentation. Again, there's a range around these, but kind of roughly similar projected incidents under newborn screening compared to clinical presentation.

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(Slide)

LISA PROSSER: So, this slide shows the projected outcomes following screening in terms of the numbers of infants expected to receive transplants. So, I'll just walk through this slide in a little bit of detail.

So, across the first row, of the newborn screening presents 13.4 infants would receive transplant compared to 1.9 under clinical presentation. Again, this is for that cohort of newborns who are identified with Krabbe disease and expected to present before 12 months of life.

Of those infants under newborn screening, 1.4 would be expected to die from complications of transplant compared with 22 under clinical presentation because there are fewer undergoing transplant. And those who survive transplant, there would be 12 under newborn screening compared to 1.7 under clinical presentation.

And for those who did not receive transplant, 1.9 under newborn screening compared to 16.9 under clinical presentation, again

assuming that those infants under clinical presentation are presenting at a later stage of disease and would most likely not be eligible for a treatment except for a small proportion.

So, then skipping to the bottom row. So, the outcomes at 2.5 years of life are those that combined or projected to have died even from transplant by way of complications or by Krabbe disease by age 30 months is 2.9 under newborn screening compared to 13.2 under clinical presentation, representing 10.3 deaths averted under the newborn screening compared with clinical presentation. And again, there's a range there of likely 7 to 14.

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LISA PROSSER: So, this slide is again just presenting these data in a slightly different summary format. So, on the left-hand side with universal newborn screening for Krabbe disease, 15 infants projected to be referred for evaluation for transplant; 13.4 would receive

transplant; 1.4 would die from complications of transplant within 100 days of life; all others would be expected to be alive at 2.5 years.

An additional 22 would be identified at high risk for Krabbe disease and would require close clinical follow-up.

Compared to clinical identification, without universal newborn screening, 18.8 events would present before age one year. Of those, 1.9 would be eligible for and receive transplant, and 13 infants would be expected to die from Krabbe disease for this cohort by age 2.5 years.

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LISA PROSSER: So, from the modeling projections, the outcomes show differences in survival at 2.5 years of life for identification under newborn screening compared with clinical presentation. An additional 10 babies would be alive at 2.5 years with newborn screening compared to clinical presentation.

The evidence on treatment outcomes

relating to quality of life were insufficient to model improvements in quality of life across cohorts at that 2.5 year time point.

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LISA PROSSER: So, now I will turn things back over to Dr. Kemper for any questions.

ALEX KEMPER: So, thank you, Dr. Prosser, for going over the model.

There were a couple of things I just wanted to correct in the record. These are kind of low level. I don't think they're going to affect any decisions. But just for making sure that everything is right.

One is in the study that was done at Mayo Clinic with the samples that were sent to Kentucky, that first case that was identified having the initial psychosine 61, so far in excess of the threshold of 10 that we talked about before. And I'm certain this would be in the slide somewhere. But I just want to put that in there.

Another thing is I got asked to clarify the issues about incubation time. So, I do talk about incubation time with the fluorometry test that's used in Missouri -- what is it? And that's not multiplexed with anything because I didn't bring it up. But that requires an overnight incubation period.

There's incubation that's required for the first tier GALC enzyme activity test with tandem mass, but that's separate from the fact that they're multiplexed. But I just wanted to bring up the issue that there is this incubation period that is required, just because it impacted the flow within the newborn screening program. So, I just wanted to clarify that in case anyone's confused.

NED CALONGE: Thanks, Alex. Thanks, Lisa.

I'd like to open it up to Committee members and see if there are any questions for Alex and Lisa.

(Pause)

NED CALONGE: Shawn.

SHAWN McCANDLESS: Thank you. Shawn McCandless, Committee member.

Alex, thank you for that presentation. And the data are complex, and that was a tremendous amount of work. So, thank you to you and your Committee for providing such a clear presentation of the evidence.

I have a question about the recommendations for follow-up of those patients that are not thought to need immediate HSCT. And so, there's two categories, low risk and high risk. And they're different. There are different follow-up strategies.

Can you just enlighten us about why and how those two strategies came about and whether there's any data supporting the difference between the low-risk and the high-risk strategy?

And the second follow-up question would be: do we know, using those strategies, do we have a sense of what proportion of those individuals will end up eventually being

transplanted?

Thanks.

ALEX KEMPER: So, in terms of how that algorithm was developed, it was really an expert consensus process recognizing that if there is known or the potential for pathogenic bearings to be involved that those kids should be more closely followed. I would say, you know, it's a rare disease. So, it's hard to come up with ways to test the algorithms.

I did ask at one point, "What do you do if it's unclear if the variants are pathogenic or not?" And you know, the best I can tell you is that it's a small community and people talk. And it's just a matter of clinical consensus. So, I think that's really the best that I can do in terms of that process.

How many of those infants will eventually go on to transplant is something that I can't tell you from the evidence.

SHAWN McCANDLESS: Thanks.

I think Dr. Ream may have been an

author on that paper.

Is it okay if I ask her if she has any better answer than that?

(Crosstalk and laughter)

MARGIE REAM: Yes. So, the decision point of the low-risk versus high-risk follow-up pathways is primarily based on genotype. So, if the genotype is associated with younger onset earlier in childhood, that's a high-risk pathway. And so that follow-up is more frequently, more intense because we do expect, you know, earlier onset of disease.

And earlier onset therefore means, you know, more rapid progression. Where if a genotype is associated with adolescent or older onset, then that would be in the low-risk pathway.

SHAWN McCANDLESS: And how about if the variants are not clearly associated with a specific genotype?

MARGIE REAM: That is a much more difficult situation, and that is a situation in which what Dr. Kemper said, that many of the

experts would discuss and look at the psychosine level and the GALC activity level and kind of come up with a most reasonable approach.

SHAWN McCANDLESS: Thank you.

NED CALONGE: Ash.

ASHUTOSH LAL: Thank you.

It was a really enlightening presentation.

My one question is if you come across the difference in the outcomes post-transplant between infants identified through family history, which already planned for newborn screening, and if there is a difference, then one might lie behind it. Oh, are you muted?

ALEX KEMPER: So, again, being a rare disease, the way the reports are, we can't, you know, specifically model outcomes from detection through family history versus newborn screening. I would say that when I spoke to experts, they said that if there's an expectation that an infant is going to be born with Krabbe disease, that there might be the decision to deliver a little

bit early and to expedite, further expedite the treatment.

So, I can tell you in the studies that we've looked at, they don't -- that that level of granularity is not reported in terms of, you know, whether a decision was made to deliver early what the gestational age was and those kinds of things. Those are also families that are more prepared to go on to transplant if needed. So, there's less of this, you know, shock to the family.

But again, the evidence base is insufficient to really tease those things apart. And from what we can tell from the evidence, most of the cases that are identified are not identified by family history. They're new findings to the family.

Does that answer your question?

NED CALONGE: You're muted, Ash.

ASHUTOSH LAL: Yes. Yes. Thank you.

NED CALONGE: Jennifer.

JENNIFER KWON: Hi. I was going to

try to keep to the evidence talk that Alex gave, but Shawn opened the door. And so, I'm going to continue.

I am curious, and this is again probably more for Margie and people who are involved with long-term follow-up in this population.

What if any are plans for experts like you to come together and sort of revisit these follow-up guidelines to see how effective they are? These guidelines were developed partly in response to the number of families who are lost to follow-up because of the high false positive rate, or the high call-out rate, shall we say, that earlier programs experience.

So, I'm wondering how you're going to measure the success of these new guidelines?

MARGIE REAM: Should I go ahead with that question?

NED CALONGE: Yeah, yeah.

MARGIE REAM: Okay, great.

I think that's a very, very important

point to heritable history and context for that. The initial follow-up guidelines out of New York State resulted in very intense follow-up for the individuals considered at risk for disease onset outside of the elevated -- outside of the initial, you know, early infantile type of disease.

And those intense follow-up recommendations that required a recommended, repeated lumbar punctures and nerve conduction studies, and things like that were in some cases felt to be a little daunting for families. And so, then families perhaps didn't follow up with the recommendations.

So, the newer paper which Rob Stone was the first author on and involved many of us that are in this meeting today was an attempt to address those concerns, bringing, you know, very close follow-up to the children that were at most risk and relaxing the follow-up for the children who were at less risk.

I think that, you know, we haven't been at it long enough to really see the outcomes

of those two pathways. But we're actively discussing. In fact, a meeting last week and an email this week actively discussing a way to follow those -- you know, to collect outcomes data on the follow-up pathway to see how often children are following the recommended testing schedule.

And then also hopefully evaluate if the recommendations were appropriate. Are we using the right decision plants for putting kids in one pathway or the other?

I feel like there was another part to your question, Jennifer. I think I lost it.

JENNIFER KWON: Yeah, I probably did, too.

But I was just curious based on what you said. So, how many states are participating with you in this long-term follow-up?

MARGIE REAM: We're just at the beginning of conversations about that. So, if you can ask again in a few months I might have a more specific answer for you.

JENNIFER KWON: Thank you so much.

MARGIE REAM: And I think it's a really important -- a very important point because, based on information that was discussed earlier, 90 percent -- historically we believe that 90 percent of patients with Krabbe disease had early infantile.

But in the modeling that Lisa Prosser's team did, you know, there were more patients following -- more newborns following it to the need for follow-up, long-term follow-up than the patients being referred immediately for transplant.

JENNIFER KWON: Thank you.

NED CALONGE: Chanika.

CHANIKA PHORNPHUTKUL: Thank you so much, Alex, for this wonderful presentation, and Dr. Prosser as well.

I was struck by one of the slides that looked at the transplant of -- and I recognize that it was in older literature, that there's kind of a variable outcome of the children, you know, that at older ages in

wheelchair and all that.

So, the question for the group, for you, is, "How do we take into account the evolving technology and outcome of transplant itself?" Because could it be that, you know, the children who are transplanted at later years, which we don't have a long-term outcome, will do better?

And is there other -- you know, using transplant as a -- not using Krabbe, but using transplant to kind of counteract that effect of time and evolution of transplant? I'm not sure that I'm making myself clear.

ALEX KEMPER: You're making yourself 100 percent clear. It's not a question I'm going to be able to answer satisfactorily just because, until we have the data, I can't say anything.

What I can say is certainly there has been, you know, since the late 1990s significant advancement in knowledge about transplants and improvements. But still with that, there does seem to be variability of outcomes. So, I think the question you asked is probably one for later

in the day to debate.

And I think tied to that as well is, you know, are there centers of excellence -- we've already talked about two of them that clearly have a lot of experience with transplants for Krabbe disease, and what does that mean for how other centers will be brought along, or should there continue to be these centers of excellence?

NED CALONGE: Thank you.

Now I'd like to open up questions to the organizational representatives.

And I see Debra Freedenberg has her hand up.

DEBRA FREEDENBERG: Yes. So, I guess my question really is about access to resources in care. And I don't know whether I specifically suspect it wasn't specifically addressed. But in doing the overall review, were you aware of any difficulties that were identified in screen-positive kids that were felt to need a transplant obtaining that transplant?

Because we know that some states

don't have those resources, and we know that some insurances are more difficult to deal with than others. So, I was wondering if you had any information on that.

ALEX KEMPER: I don't. And I don't know if that's because those cases just don't appear in the literature or the degree to which that hasn't been borne out to be a problem.

I can tell you that Virginia opted not to add it on because of concern about getting those transplants done within 30 days. But we didn't find a single case of an infant who was recommended to get a transplant that wasn't able to get one.

There are some, as described in the report of the not New York screenings, you know, whatever those states are, where they were certainly pushing up around the six-week mark. But I can't describe a particular case of someone who, where the family was recommended to get a transplant and they went to get a transplant, but were not able to get one. It may exist; it's just

not described.

DEBRA FREEDENBERG: Thank you.

ROBERT OSTRANDER: Thank you. Yeah, Robert Ostrander, AAFP.

I just want to follow up. I thought about Deb's question, and that is that I think we have to be careful how much we use some of the information about things like access in making this firm-end decision, because that is a data point that is going to change based on our actions.

You know, as soon as these things get implemented or put in a widespread way, we have to think about whether there are going to be barriers to access. But we shouldn't use our baseline access, whether there's not a universal process, to assume that that's going to be the same access once we implement.

You know, this is one of these, you know, Heisenberg uncertainty kind of things where our action is going to change the data.

ALEX KEMPER: I agree with you. One

of the things that I'd like to add in that I meant to mention before is that we know that states that are not using the psychosine second-tier testing are having a much harder problem because they're identifying so many babies, of tracking them. And there's a greater risk in those states of children being lost.

NED CALONGE: I would also point out that we've historically, looking back at SCID, the Committee did not make a recommendation to add until the Committee felt certain that there would be treatment available to children identified through screening. So, I understand that things are changing. There is an issue, though, about being uncertain, about access to treatment when you start screening.

So, just talking historically about past Committee actions, I just point that out.

Scott.

SCOTT SHONE: Thanks, Dr. Calonge. Scott Shone, organizational rep from ASTHO.

So, Alex, I guess two quick things.

You know, Dr. Ream commented that the model reflects the likelihood of finding these other types of Krabbe than what is predicted. And I would submit that that's pretty much been the case in newborn screening for every disorder we've added going back, as Dr. Calonge just said, for SCID.

I mean, how many idiopathic T cell lymphopenias do we deal with? How many -- you know, Pompe and MPS I. I mean, it just goes on and on. And I think we all recognize -- and I see a lot of nodding heads, so thank you -- that that's pretty much been what we've set ourselves up for with all this.

So, I just want to confirm my understanding is that probably the biggest data gap that we have in your evidence review is that, what else are we going to find that some have suggested can fall in the harm bucket or some fall in the benefit-to-be-determined bucket? That's one. Do you agree that there's a big data gap on all of that and what that means for those babies

and families?

And then two, it seems to me that one of the biggest questions is that significant diversity in response to HSCT, that we've had amazing public comments throughout this process from families that have had wonderful outcomes with -- let me back up and rephrase because I don't want to say that because life is a wonderful outcome. Let me pitch myself and my comments.

That have had outcomes with less severe sequelae, almost some children having apparently none, and others, as you articulated in your evidence review, wheelchair bound or having more profound developmental or intellectual disabilities.

So, it seems to me that that is another potential data challenge. So, one is, what are we going to find that we don't know and the benefits and harms of that? And then also, this diversity of outcomes of the same therapy perhaps at the same timeline. Is that fair?

ALEX KEMPER: Yeah. Yeah. So, I

think that as we summarize, you know, the evidence does suggested the decrease in mortality, but the morbidity is more variable.

And I think it probably -- I mean, you know, I'm sure it depends on a million different features related to the variants. Who knows what else it's involved with? Even just the tradeoff. All these things can affect it. So, I can't comment on that further.

And it is true that screening will identify children who will need to continue to have follow-up. And I can't comment on comorbidity outcomes either that would harm somehow the family. So, yeah, I agree with you.

NED CALONGE: Thanks.

Michele Caggana.

MICHELE CAGGANA: I just want to take a couple of minutes to make a couple of comments and kind of remind people where we came from.

So, I agree with Scott. I mean, when we do newborn screening, we always find things we don't anticipate. We've also seen that states,

including New York, began screening for Krabbe all the way back to 2006. It's been quite a while. And so, we have identified different kinds of issues and different hardships along the way. And we've done our best to report those and make those available for Alex's review.

When we began in 2006, there was no precedent. We were in uncharted waters, and we were filling a mandate. So, we had risk categories that were set at low, moderate, and high risk. And as Margie said, there was a very thorough follow-up protocol that was agreed upon, and that was back in 2006, as I said.

These consensus guidelines that we had access to that were published by Dr. Stone and some of my colleagues from New York and across other parts of the country, people who treat Krabbe, are kind of the best because it's the third iteration of their plan for consensus guidance now.

And I will say that for a lot of newborn screening conditions, we haven't really

had even that to start with when we began screening.

To the question of the longer-term follow-up, we do -- it was mentioned in Alex's presentation, we have a set of twins who were followed. They were closely monitored, and they were transplanted. And they are doing quite well. So, that does work.

And as far as access is concerned, when we began screening for Krabbe in New York, as I said there was really no precedent. We didn't know how many babies we would find and who would be referred. And so, we spent considerable time comparing, I would say, a good year-and-a-half or so. But we talked to insurers, and we also talked to our Medicare people within the health department.

And we were able to sort of set off the expectation that if they needed to get a stem cell transplant, that they may have to travel, but it had to be quick. And we were successful in making that happen.

And so, I think some of these things are difficult and take time. But they certainly can be worked through. And I will say with the addition of psychosine, we use molecular to gauge. But the use of CLIR and psychosine helps us to really narrow down the number of expected infants that we refer and therefore will need all of this follow-up downstream.

So, thank you.

NED CALONGE: Thank you, Michele.

Bob Best.

ROBERT BEST: Yes. So, regarding the long-term issue, I don't think any of us like about-ism. But it's important for us to remember that long-term follow-up is an issue for all of the conditions.

I think it's fortunate that in GAMT endorsement, the Secretary asked for an update in five years. And I expect that that will be the case in the future. So, I think status quo is not just an acceptable outcome, anyway.

NED CALONGE: Thank you.

I want to first thank Margie for being willing to be part of this question-answering team. I appreciate you stepping into that role.

I again thank Alex and Lisa, and the entire ERG team. I want to thank the expert advisory committee, which I know provided great information to help guide the ERG through the evidence review.

I think people understand this is and was an extraordinarily complex evidence review based on what I would firstly characterize as an evolving evidence base. We have to, as a Committee, make decisions based on evidence that we have. And I appreciate the presentation, because I think Alex and team, you've given us information we can use to move forward in decision-making.

So, what we're going to do is take a break for lunch. After lunch, at 1:30 Eastern Time, Shawn McCandless and Jennifer Kwon from the Committee will do the presentation on the

Committee report, after which we'll have discussion and vote.

Let me just check with my colleagues at HRSA to make sure there aren't any other announcements I need to make.

(Pause)

LETICIA MANNING: No. I don't think there's any additional announcements.

NED CALONGE: So, we have a little bit more than 45 minutes. We will start promptly at 1:30 Eastern Time. And I hope you all take the advantage to get up, move a little bit, have a little something to eat. And we'll see you back soon. Thanks.

LUNCH

(Whereupon, a lunch recess was taken, to reconvene at 1:30 p.m. Eastern Standard Time.)

NED CALONGE: So, just to get us started and remind folks, when we have a full evidence review, I select two Committee members and ask them to serve as liaisons to the review group. And they're tasked with presenting a

summary of the evidence review and formulating a recommendation for the condition rating. They will also help me in leading the Committee discussion.

Just a reminder that the Committee assesses the magnitude of net benefits and the certainty of the evidence around net benefits. We also look, as Alex talked about, at state public health programs, readiness, and feasibility.

And with those elements, we use an evidence-to-decision feedback that we call the matrix and adhere to the principles of evidence-based and make sure that we pay most attention to outcomes that accrue to the person being screened.

And we'll show the major decision moving forward. The A ratings are high certainty that adoption will lead to significant benefit. And then the Bs are moderate certainty of significant net benefit or high certainty -- I'm sorry. Moderate certainty of significant benefit. And below that are all of the lower ratings.

And then we use the matrix to help

our discussion and to inform our final vote.

I'm just going to remind organizational representatives that unless I direct otherwise, deliberation for the presentation is for Committee members.

So, with that, I'd like to turn things over to Shawn McCandless and Jennifer Kwon.

COMMITTEE REPORT: NEWBORN SCREENING FOR KRABBE DISEASE

JENNIFER KWON: Okay, great.

So, Shawn and I decided to go alphabetically on this by both first name and last name.

So, liaisons to the Evidence Review Group, Shawn and I will summarize and distill what we thought were the important points from the previous talks and the final report, or at least the version of the final report in the briefing book, that we hope will help our fellow Committee members reach a decision about adding Krabbe disease to the Recommended Uniform Screening Panel.

Next slide.

(Slide)

JENNIFER KWON: As Ned said at the start of the meeting and he just repeated just now, our decision about Krabbe disease newborn screening needs to address the following: understanding the level of certainty of net benefits of newborn screening for identification of infants affected by Krabbe disease. We also are looking at the states' readiness to implement newborn screening for Krabbe disease.

And then finally, the feasibility of Krabbe disease newborn screening with feasibility encompassing those other features that bring together high throughput screening procedures that are completed by the public health laboratories, then having a clear approach to diagnostic confirmation.

And then having an acceptable treatment plan with an established approach to long-term follow-up to those who don't need early treatment, but who are still at risk for disease.

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JENNIFER KWON: So, this is the decision matrix itself. And the three components I just described are represented in graphical view. The criteria, let's say grades A1 through A4 on down, are based on the net benefit and the certainty of that benefit, as well as on the readiness of laboratories. But as you can see, feasibility is still an important component.

And we'll come back to the matrix later, but let's first have a quick re-review of Krabbe disease and the rationale for Krabbe disease newborn screening.

(Slide)

JENNIFER KWON: Thanks.

So, as you know, Krabbe disease is an autosomal recessive disorder due to deficiency of GALC enzyme activity which leads to early injury to myelin and brain cells. Neurodegeneration is the hallmark of the disease with earlier age of onset associated with earlier mortality.

And the literature showing that onset at zero to six months is associated with a with median age of death by two years. And onset from six months to three years is associated with death during childhood. We've also heard of the significant disability of children with untreated Krabbe disease and of the burdens of their families there.

Next slide, please.

(Slide)

JENNIFER KWON: Thank you.

The path of physiology of Krabbe disease is linked to psychosine. Psychosine accumulates when GALC enzyme is deficient, causing injury to myeline-producing cells and irreversible damage to brain cells, or neurons.

Furthermore, recent work has shown that psychosine levels correlate with disease severity, being higher in those with infantile onset disease. Those with infantile Krabbe disease may appear normal at birth and within weeks develop the challenging symptoms that we

heard about, including poor feeding, loss of head control, loss of normal responsiveness, stiffness, and abnormal reflexes.

MRIs can show abnormal white matter findings and brain morphology, and peripheral nerve electrophysiology is abnormal.

So, how do we detect this devastating disease before the onset of symptoms?

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(Slide)

JENNIFER KWON: States which have been screening for Krabbe disease use low GALC enzyme activity from dried blood spots as their first tier. But as you've heard, screening by GACL activity alone leads to unacceptably high call-out rates. So, if your target is infantile Krabbe disease, then the false positive rate is unacceptably high.

Most states reduce referral rates and false positive screening results using psychosine from dried blood spots and/or GALC molecular testing from dried blood spots. That is, Dieter

Matern pointed out in his public statement GALC molecular testing is understood to be -- is challenging because of the number of variants whose pathogenicity is poorly understood.

This is why he and the nominators of this condition have recommended that Krabbe disease newborn screening include psychosine as a second-tier test to reduce the number of referrals and the false positive rate.

Confirmatory testing to more definitively diagnose Krabbe disease then includes GALC enzyme activity, psychosine levels, and GALC molecular testing. Decisions about treatment may also require additional testing and consultations.

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(Slide)

JENNIFER KWON: The treatment for Krabbe disease is hematopoietic stem cell transplantation. And this is only recommended for those without significant symptoms of disease. And I should say it's only recommended in the setting of early infantile Krabbe disease if you

don't show significant symptoms of disease.

We have heard about individuals with later onset Krabbe disease who actually may have some early symptoms, who are still successfully transplanted and seem to have fairly good outcomes.

Based on what we've heard about stem cell transplantation in infantile Krabbe disease, it may be a surprise that the evidence base about the efficacy of stem cell transplantation is so challenging to interpret. What we have been asked to evaluate as a Committee is the evidence of efficacy of stem cell transplantation, especially in those identified by newborn screening.

As Shawn has said, we want to compare apples to apples. There are data on the efficacy of transplantation in cases that have been identified through family history, and while we want to keep those cases in mind, we want to focus on the evidence for infants identified by newborn screening.

Equally concerning were the

particular stem cell transplantation for very young infants. Centers that are very experienced with Krabbe disease transplantation still report about a 10 percent morbidity and mortality rate.

Therefore, as a community of newborn screeners and medical professionals, we do understand and support those families who refuse treatment even though their infants are eligible. Because we understand that that risk is part of the reason, and the variability of the outcome may be another part of the reason.

So, with treatment, the most severe cases -- that is, the early onset cases -- are likely to live longer. But the evidence shows variable neurologic disability.

As I have said before and as others have noted, we are learning that later onset cases may have greater benefit from stem cell transplantation in terms of prolonged life and improved quality of life. But still the data are lacking to say this with confidence.

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(Slide)

JENNIFER KWON: So, as Committee members, we need to decide on the net benefit and the certainty with which this benefit can be assessed. The peer-reviewed evidence base contained several case reports and case series, but the data are still challenging to interpret with confidence.

Therefore, much of the assessment of the value of newborn screening understandably relies on expert opinions. Overall, there is evidence to show that newborn screening and early treatment benefit those with early onset of disease by improving survival.

And we have appreciated the views of advocacy groups and families, and appreciated them sharing their experiences and their strong feelings about the value of treatment.

It is possible too that later onset cases, while less common, may have more significant benefit from stem cell transplantation. But as we have said, the data

are limited.

Next slide, please.

(Slide)

JENNIFER KWON: So, here are the modelling results shown by Lisa Prosser, which show that projected annual numbers with U.S.-wide KD newborn screening.

I just wanted to highlight the number of infants likely to be referred to early treatment. That would be approximately 15 a year across the U.S. and the number who would need ongoing follow-up. That would be about 55, with 22 of them needing what we would call closer follow-up.

Now, before I pass the mic on to Shawn, I guess I wanted to add one thing, which is that even though, as others have said -- Michele Caggana, Scott Shone, and Dr. Best -- that follow-up of indeterminate diagnoses is part of the business of newborn screening, I will say that as a neurologist, as a child neurologist who follows children who have been diagnosed with XALD or

Krabbe disease by newborn screening, I think that those who need this type of ongoing follow-up and surveillance also represent a harm.

Yes, they exist, and yes, we need to care for them, and yes, we need to counsel them. But these families are affected by newborn screening in ways that are not positive. And so, they should be considered more as a net harm then a net benefit, in my opinion.

Anyway, Shawn, I'll give it over to you. Thank you.

SHAWN McCANDLESS: Thank you, Jennifer.

I want to echo what others have said, and you can go ahead and advance the slide, please.

(Slide)

SHAWN McCANDLESS: That we greatly appreciate all of the comments that we've heard from families, from experts, from our colleagues in the ranks of the organizations representatives.

As we think about the benefit to

affected infants and children, we thought it would be valuable to summarize. You can see on the left the slide that Lisa Prosser presented earlier that approximately 15 patients per year will be referred for evaluation for hematopoietic stem cell transplant. And of those, about 13 will receive the transplant.

A very small number of those, but a significant number, will die from complications of the treatment within the first 100 days. All others would be alive at 2.5 years.

This assessment was not able to take quality of life into account. But there is no reason to minimize the opinions of the parents that we have heard from that, regardless of residual disability, their quality of life is better as a result of the treatment.

So, I think that we believe that it's a reasonable assumption to assume that the quality of life is better for these children, but we don't have any way to measure the magnitude of that.

And then an additional 22 would be

identified as high risk for Krabbe disease and require the very close clinical follow-up. And an additional group would be requiring the lower-risk follow-up, which still is recommended currently, twice yearly follow-up visits, neurologic exams, discussion of the potential to develop symptoms, as well as MRI scans that would require general anesthesia every few years.

So, when one looks at these data, steps back to look at the data, for infants with expected onset of symptoms before six months, the current data suggest about 80 percent would benefit from therapy. And that benefit is in a longer lifespan and regardless of residual disability.

It is also not clear in the long-term whether children that undergo therapy are stable forever, or if they will have deterioration later in childhood or later in adolescent or adult life.

Twenty percent of those children that would be expected to have onset of symptoms before six months would not benefit from the treatment,

and in fact half of them would actually have a significant harm of the early diagnosis, in that they would die as a result of the transplant.

And 10 percent of families have indicated -- 10 percent of families, or half of those who would not benefit, have indicated that they would not opt for the transplant. I'm not sure that it's fair to say that they would not benefit from screening, but they would not have benefited from the treatment option.

An additional three to four times as many patients would not be diagnosed with early onset Krabbe disease and would enter follow-up protocols, either a high-risk or low-risk protocol. The risk of eventually developing symptoms and undergoing transplant is not clear from the data for those patients, nor is there evidence regarding the impact of that on quality of life for the families.

Some of those children, perhaps many, will likely benefit from newborn screening because they will eventually be having an earlier

diagnosis of Krabbe disease and be amenable to whatever treatments are available at the time for that condition.

But as I said, we don't have any data about the effects of the repeated clinical visits and the concerns about a very dire diagnosis for those families with indeterminate status.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: So, we believe that reasonable assertions, based on this very challenging data regarding early onset cases at a very high level, are that we can expect increased lifespan, more achievement of developmental milestones in those patients identified by newborn screening than those identified clinically, although some will have substantial disability.

And that there is treatment-associated mortality. So, there will be a small proportion of patients who would die as a result of the therapy.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: The potential harms are difficult to assess because of the lack of data. And the lack of data should not be assumed to mean that they don't exist, but just means that they haven't been evaluated carefully. And there are many reasons for that that we don't need to go into here. I think most of them are obvious.

But that does not mean -- the fact that the data don't exist doesn't mean that there are not harms. And those of us who have worked in states and provided follow-up after newborn screening for Krabbe disease are well aware of the toll that this makes on families that either have an indeterminate diagnosis and need to do follow-up, or even those that have a false positive result and are eventually reassured that their child does not have the disorder.

The potential harms of NBS include the harm that we've already discussed, premature death as the result of the therapy, hematopoietic

stem cell transplant. We think that there is significant risk from false positive results and especially if there is not some sort of reflex testing for psychosine.

And I would just ask that, regardless of how you vote for this nomination that, if this goes forward, it must, must include reflex testing for psychosine before results are called to the family to minimize the impact of the false positive and the pseudo-deficiency allele.

The compressed timeframe for this complex diagnostic process that follows an abnormal screen and planning an initiation of therapy in our opinion increases the risk that errors will be made and increases the risk that a child who does not actually need to be transplanted will be transplanted.

Or, alternatively, that a child that really might benefit from a transplant will not receive a transplant because of uncertainty about the follow-up data. We think that this is likely to improve with time and as processes improve.

But it will never go completely away because it's a very tight timeline for initiating therapy.

There is one report of a false negative result, or at least it's presumed to be false negative, although as you heard from Dr. Kemper, there is some question of whether there was another unidentified diagnosis in that infant. And that the cause of death may not have been Krabbe disease; it is not at all clear.

But at least as reported, it was suggested that the child did have Krabbe disease and the psychosine was not a reliable indicator of disease or disease progression in that case. I think it's important that we not over-emphasize that, but we do need to recognize that that happened and that that is a potential risk.

Probably the largest potential harm, in our opinion, is the potential for psychological and financial burdens for families after false positive indeterminate diagnostic testing. With indeterminate diagnostic testing being more burdensome and the more prominent outcome,

particularly because of and for those that require ongoing follow-up.

There's costs associated with that, including time lost from work. There is almost certainly lower quality of life for the family as a result of anxiety and stress associated with that. And the fact that there are a number of patients who are lost to follow-up during that process indicates that there is at least some parental dissatisfaction with the process.

Again, we need to be careful not to read too much into that because we don't have more direct data. But it at least raises a serious concern that there is parental dissatisfaction with the process.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: So, if you have been to one of these meetings in the last few years, you've seen this slide before.

And this is just to remind ourselves that the decision matrix criterion, or this

decision, is the net benefit. It's the balance of benefit minus harm in the population screened, not just in patients that are affected, not just in patients that have false positive results, but in the entire population screened.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: Regardless of what state you live in, it is appropriate to recognize that the benefit and the harm accrue to different individuals in the population and that it is reasonable to ask whether different groups will be affected differently by benefits or harms related to this screening program.

Is there any reason to think that there would be inequities in the population of individuals who encounter the harms of the screening program versus the population that encounter the benefits of the program? And is there a reasonable justification for that inequity if it exists?

And I'm not saying that it does

because I don't know. We don't have those data. But I think that this is a question that this Committee should always take into consideration. It is: Is what we're providing equitable? And is it just?

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: So, is there a significant net benefit, benefit-less-harm, for compulsory, population-based Krabbe disease newborn screening? The benefits can be summarized as moderate to significant benefit to most, but not all, confirmed infantile onset cases.

And I say "not all" because some families elect to not undergo the treatment. And if they receive benefit, it's of a different measure than how we would measure the benefit in children undergoing the hematopoietic stem cell transplant.

And we see a potential benefit for uncertain diagnosis in later onset cases. And it is possible, although we do not have data to show

this, but it is possible that that group would actually have the greatest benefit from newborn screening.

To summarize -- the harms, there's treatment-related mortality. There's a small potential for misclassification of disease onset, leading to inappropriate treatment. And I reflect on a statement that was made earlier. The question is not, "Are all the cases that were reported in the literature having had stem cell transplants, do they all have Krabbe disease? " There's no question about that.

The question is, "In all of those cases where there's not objective data presented, how can we assess whether they actually have a later onset form of the disease or not?" And it's not that anyone doubts the sincerity or the evidence that was in front of the people who published those results.

But when we're looking for evidence-based review, it is helpful and important that we look objectively at those patients that clearly

and objectively would have early onset disease. And what were their outcomes? And the total numbers that meet those criteria are much smaller. So, we have a smaller evidence base on which to make the decision.

Another potential harm is that there is a relatively high number of individuals that cannot be clearly classified early on. And if one looks at the high-risk group, that's about the same or slightly more than patients that can be clearly identified as having early onset.

If you include the low-risk patients that still have families living with the fear and expectation that their child may have a terrible disease, that's as much as four times as high as the size or as large as the size of the group that have clearcut early onset diagnosis.

There are, we believe, potential harms from these uncertain diagnosis and later onset cases, as well as potential benefits. And the other concern is whether in all cases the diagnosis before symptom onset is possible with

current follow-up protocol.

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(Slide)

SHAWN McCANDLESS: So, to put this in the framework of the matrix, as you've already heard, we're looking for -- the matrix limits us to making a determination of certainty and the magnitude of significance of the net benefit.

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(Slide)

SHAWN McCANDLESS: As we think about this, newborn screening for Krabbe disease does have an evidence of some positive net benefit. But the potential harms, as we discussed, are quite significant as well. And that tends to dilute the benefit, the positive benefit. I guess "positive benefit" is saying the same thing twice.

The magnitude of the potential harms appears to be relatively large compared to the magnitude of the potential benefit, which does tend to temper the net benefit assessment.

Regarding readiness to enact

screening for Krabbe, it appears to us from the data that were presented that developmental readiness is there. Most states should be looking to implement this in two to three years with a few outliers due to funding or local response times due to backlogs of other new conditions to be added or other issues.

It has been said that states will obviously use psychosine as a second-tier or reflex text. But we don't see evidence that confirms that for sure, and we know that there are currently two states that have opted not to do that. So, it is unclear if all states would incorporate psychosine testing.

It's also unclear, at least to me, whether this Committee is in a position to force that or include that in the recommendation. But I certainly think if we do recommend Krabbe disease, it must be included in the recommendation.

We think there is limited evidence to address feasibility of screening, and screening, testing, and treatment follow-through. There

certainly have been concerns raised that screening should not be a problem. It does appear that most states would be able to implement screening.

The complexity of the diagnostic process that follows the positive screen, or the high-risk screen, is less clear. It is very complex, and it will be different in every state, the follow-up measures. Others have made the comment that that is of lower concern, because until there is pressure to do it, many states will not build the structures that they need. And that's very true.

The other concern that we have is the process of diagnosing and treating infantile Krabbe within four to six weeks will be challenging. And there are potentials for errors and delays unless the programs tightly coordinate call-out diagnostic testing and referral. And even then, we think that the tight timeline has the potential to create errors.

Hopefully, we have a medical system that is able to have multiple checkpoints to avoid

errors for something as significant as a hematopoietic stem cell transplant. But as we know, in every medical system, regardless of how sophisticated the error prevention approaches are, there will be things that fall through the cracks and errors are likely to occur. And that's true regardless of whether screening occurs or not.

So, feasibility of screening has multiple components, and we think that the screening itself is highly feasible. We do have concerns about readiness for follow-up in some states.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: So, just to state clearly, in terms of readiness we think there is developmental readiness. Feasibility is probably moderate to questionably low in some states for follow-up.

But the big issue is the significant benefit. And it is our assessment that the overall benefit less the harms is modest in this,

based on the data that are available to us today. And the certainty of that is again moderate. We think that the data are, while there's lots of data, they're just very difficult to interpret.

This is not to imply that we doubt the veracity of any of the reports or the integrity of any of the reports that are out there. It's just that, as one of the speakers earlier today alluded to, this field is changing and improving rapidly. It's hard to compare old data to new data because of the changes that are occurring.

But overall, it is our assessment that the net benefit, the benefit less the harms, is modest in this situation.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: The next slide, please. Oh, I'm sorry.

So, we do rate this as a category -- we would say that the best fit under decision matrix is category C1. We think that the ability

for screening programs to enact screening is ready and that there's moderate to low evidence of feasibility -- moderate evidence of feasibility for screening, and low to moderate for readiness for treatment.

May I have the next slide, please?

(Slide)

SHAWN McCANDLESS: So, our recommendation is that at this time Krabbe disease does not meet the threshold for addition to the Recommended Uniform Screening Panel as a core condition.

May I have the next slide, please? That may be the end. Yeah.

So, that is our assessment of the data. I would like to make a few acknowledgements, that we appreciate all of the comments that were made earlier today, and we truly appreciate the families who have so clearly and strongly expressed their desire for screening to happen.

Our charge is to make a

recommendation regarding population-based compulsory newborn screening based on evidence of net benefit and feasibility of testing.

The fact that this recommendation will be disappointing to parents and to advocates, or this nomination is not intended to minimize and should certainly not be characterized as minimizing the impact of the condition on affected children and families, nor does it imply that treatment is not beneficial.

You've heard the rationale for the recommendation. These are -- everyone on this Committee is moved by the stories of the families that we've heard. There is just no other way to say that. We're moved by it. But we need to act based on the totality of the evidence presented to us.

The last thing I want to say is that this should not be interpreted as brushing off the concerns of the families or not attending to the concerns of families, nor should it be interpreted as in any way disregarding the value of your

children living longer with or without disabilities. We hear you, and we value their lives. I hope we value their lives as much as you do.

But our charge is to the entire population of the country, the 3.65 million newborns a year, and we have to take into account all of the evidence and all of the concerns and consider all of those infants when we make a decision.

So, finally, and I don't want to belabor the point, but as you can see, this is a balance like the picture of the rock, the balancing rocks I showed. And unfortunately, we don't have objective measurements for how to weight each of these components. So, each person on the Committee will have to make that decision for themselves. How do you weigh the various pieces of evidence that we've heard?

Dr. Kwon and I have given you a recommendation based on how we perceive and weigh the evidence. But each of you will need to use

your own values and way of thinking about the data to come to some conclusion about where that balance lies for you.

So, thank you for giving us the opportunity to be involved with this. I would like to say a big thank-you to the evidence review group. Their work was incredible on this. The data -- we looked at all these papers. We reviewed the data. We listened in on the meetings.

It was an incredible amount of work, and it was a heroic effort to summarize it and distill the evidence into the presentation that you heard today.

Thank you.

NED CALONGE: Thank you, Shawn. Thank you, Jennifer.

COMMITTEE DISCUSSION AND VOTE

NED CALONGE: Now at this point I would like to open the floor for questions, discussion, comments from Committee members. I will ask you to use the raise hand feature in

Zoom. And when you speak, please unmute yourself and state your first and last name.

And with that, I would like to recognize Jannine Cody.

JANNINE CODY: Yeah. First I apologize. I briefly lost the connection twice.

So, I have a comment and a question -- I guess two questions.

I don't understand about putting the risk of treatment into the harms. Because treatment is a choice; it's not a mandate. So, that's not really part of the mandated aspect of this because the parents will be faced with a discussion about the risks and benefits, and then make their own choice. So, that part I didn't really understand.

And also, because I'm new to this and this is what I may have missed. In the report, and it said the cost was two to seven dollars. And I have no reference for that. I don't know if other new things that are added are 50 cents or if they're 50 dollars. So, I don't know where that

amount -- I don't know how to judge that amount.

Thank you.

SHAWN McCANDLESS: I'll take first pass, Jennifer, unless you want to.

JENNIFER KWON: Go ahead, go ahead.

SHAWN McCANDLESS: First off, Ms. Cody, thank you. I think your first comment is well taken that the risk of the transplant is a risk of treatment, not necessarily a risk of newborn screening. I think that the intention of including it in that way was thinking about it in terms of the overall outcomes of the screening program.

And I think it is hard to avoid the conclusion that those patients would not have had -- if they were not diagnosed, it would have had a premature death, but it would not has been as early as it was because of the transplant. But your point is very well taken, and I appreciate it.

The second around the cost. It's often difficult because there are up-front costs

in many newborn screening labs. If you have to buy a new mass spectrometer, then there's an up-front cost that's quite significant.

But I think that the two to seven dollars is generally assumed to be the cost related to the additional reagents, technician time, the actual cost once the equipment is in place of doing the testing. And it's quite variable and hard to -- I think those numbers are sort of hard to pin down.

Typically for newborn screening, from what I've seen in the past and from literature that's been published, it's quite variable. It depends anywhere from less than a dollar per sample tested to ten or fifteen dollars per sample tested. And it really just depends on the assessment.

But typically -- and again this is my opinion and my observation of what's been described. Typically a few dollars per sample or less is tolerable. And as numbers get higher for the cost of each sample to be dealt with, it

becomes more and more challenging for newborn screening programs to address that.

There are a lot of complex reasons for that, including the fact that most newborn screening labs are not in a position to increase the cost for their revenue stream without either legislative or regulatory action in their state.

There are others who may be more able to comment about that.

(Crosstalk)

NED CALONGE: I'm sorry. Go ahead, Jennifer. Please go ahead.

JENNIFER KWON: I just had one comment about the treatment. And I agree; there probably are better people to comment on the cost of adding a test, which is an excellent question.

I think, Jannine, if that's okay if I call you Jannine, that treatments are different in different newborn screening disorders. And I think what we wanted to emphasize is that all treatments do have risks. But stem cell transplantation, the risks of stem cell

transplantation are somewhat different as opposed to treatments that have risks that are often smaller. They're often not quite as serious.

And many of the newborn screening disorders I feel have treatments that may not be that helpful, but are not necessarily overtly harmful. And I think that was part of what we wanted to bring out, just the sort of difference there. Thank you.

NED CALONGE: I did want to just say that in other screening evidence-based framework, like USPSTF, which deals for, again, screening tests for infants, children, adolescents, adults. But in pregnant women, the harms of treatment are included in the harm. Because without the screening, there wouldn't have been the treatment.

Not that that needs to inform our therapy. But I would want to point out that in other frameworks, that is common.

I have not been involved with the cost of newborn screening for about 11 years. But when I left, the state health department in

Colorado, seven dollars was the entire cost of newborn screening. If we kind of inflate that to nine dollars over the 11 years, this would be a significant increase that needs to be passed on in our state.

So, I don't know if that helps at all, but so that's one state. Other states it will be completely different.

Thanks, Jannine.

Jane.

(No audible response)

JENNIFER KWON: Muted.

NED CALONGE: Jane, are you having microphone trouble?

JANE DeLUCA: How about now?

NED CALONGE: Yes.

(Inaudible conversation)

JANE DeLUCA: Thank you. Just takes a few tries.

Thank you, Ned, and thank you, Jennifer and Shawn, for your presentation. And I want to especially thank the evidence-based group

for their very hard work.

I have two questions. So, I might be frozen, but you can still hear me, correct?

NED CALONGE: That is correct.

JANE DeLUCA: So, there were other tests that were performed after a baby has been identified, such as MRI and an LP. And I wanted to know if you could speak to which of those actually gives the most value or it's efficacious in terms of diagnostics for Krabbe disease.

And my second question is, do you know about the states that are actually in waiting right now to rule out Krabbe screening? And I was curious about that.

JENNIFER KWON: So, I'm happy to -- I don't know about the states that are ready to rule out. So, if somebody else -- if Shawn wanted to address that? Okay.

And then in terms of what testing is the most helpful, I think that neonatal LPs and MRIs can be very difficult to interpret. And so, one process to consider as a best practice perhaps

for early infantile Krabbe disease would be to identify a transplant center and a transplant specialist that you are comfortable with and trust, whose judgment you trust. Because you will not be able to interpret either testing on your own.

And ultimately, much of that testing and the value of that testing in determining whether or not a baby needs transplant will be in the domain of the transplanter.

And so, I think that my own bias is that a neurologist like me, who is very good at interpreting MRI and LPs and neurophysiology, probably isn't the best person to use those pieces of information to determine whether or not a child really needs transplant.

And I think that's part of the challenge with this disorder. We're not just saying, "Oh, now you need treatment. Here's the person to treat you."

We're saying, "Okay. Your biochemical testing is concerning. Your

psychosine level is high. And I know that the testing that I can order is not going to be that helpful. So, I'm going to confer with somebody I trust whose judgment I trust and look through the testing that needs to be done."

I hope that's helpful.

JANE DeLUCA: Thank you, Jennifer.

And can I ask the other question to the group, Ned? Is that appropriate?

NED CALONGE: Yes. Is there anyone, say Susan, or any organizational member who has the information on the states that are ready for their -- poised, I guess is what they said -- to start screening for Krabbe? If you raise your hand, I can -- yep.

(Pause)

NED CALONGE: Susan? Thank you.

SUSAN TANKSLEY: I'm just raising my hand to say I don't know. I'm sorry. I wasn't on all the calls with APHL to talk to states that are in that, in kind of that waiting stage. I don't know if Scott or Michele may be aware of anyone

else.

SCOTT SHONE: Thanks, Susan. Scott Shone, ASTHO org rep.

So, I will say I don't know a specific list of those who are waiting except we've had presentations for this body on what has been called RUSP alignment legislation. So, there are many states that have laws in place that require initiation of screening for conditions that are on the RUSP within a certain timeframe, between two and four years it seems to be.

So, those states, like ours here in North Carolina, would be if you would determine in waiting of the decision of whether or not to go. But that is different from, I think, the question of, Are they waiting for a RUSP decision because of a law or because they were already in process of adding it separately? So, I don't know if I actually added anything; I apologize.

JANE DeLUCA: You did. Thank you, Scott.

SHAWN McCANDLESS: Jane, how is that

-- can you just sort of share with me how that impacts the decision-making around this question?

JANE DeLUCA: You know, there are already 10 states that are screening for this. And I guess for me, you know, I was just wondering who else is poised to roll out screening for Krabbe regardless of RUSP? So, that was my thinking.

NED CALONGE: Kyle.

KYLE BROTHERS: Great. Thank you.

I don't know that I have a question. But I just think it's important when we have discussions like this that those who are voting put our thoughts on the record. Because the public deserves to hear that, not just a vote. So, I'm just going to talk a little bit and give you some thoughts.

First of all when you think about a follow-up plan, it's based on expert opinion. And there is absolutely no doubt that any plan that involves follow-up, including MRIs, travel hours to a specialty center, et cetera, is going to

carry harms.

But I think it is incumbent upon those providers and experts who are making recommendations for follow-up plans to recommend a follow-up plan where the benefits at least outweigh the harms. So, if the harms outweigh the benefits for the follow-up plan itself, we need to change the follow-up plan, right? It's a bad plan.

So, I'm not saying we need to. I'm just saying if the harms do in fact outweigh the benefits, it needs to be modified.

I do very much worry myself about the harms created by uncertainty, living with uncertainty. And I'm deeply troubled by families that receive a false positive through newborn screening and then may live, you know, months to years with the anxiety that something might be wrong, when in fact there's nothing wrong.

So, I think it's important to separate out the inherent risk and the uncertainties of information from the harms and

benefits of a follow-up plan, which is a manageable kind of harm.

I think it's a very good thing, from my perspective as an ethicist, that some parents are choosing not to pursue treatment. Because it implies that families are getting good information, they're engaging in forms of decision making, and that their decision making reflects their values. As we know, families' values differ from one another. So, I think that's a very good thing that that's happening.

And I think Shawn did a really nice job of addressing this issue, but I just want to repeat. We know there's good evidence that's probably speaking -- members of the public, health care providers, really the entire population tend to under-value the lives of persons who live with disability in ways that we often ourselves don't recognize.

So, I admit to working actively in my life to recognize if I am inadvertently under-valuing the lives of folks who live with

disability and trying to straighten out, you know, the way that I think about that. So, perhaps even more important, there's strong evidence that health care providers tend to overestimate the burden that families experience when taking care of a special-needs child.

So, again I'm not implying any of that was going on with the report today, because I think Shawn handled that really very nicely.

But I just think it's a really important point to keep in mind that there's evidence that hemopoietic stem cell transplant is life-saving, and it leads to the lives of children and families that live with disability. But we know that those lives are better than maybe our knee-jerk reaction would be to assume.

So, in any case, that's where my thinking is. In summary, I disagree with the classification of low net benefit. I think it's closer to moderate net benefit simply because I think some of the harms can be managed or should be managed by the health care system.

Okay. Thank you so much for the opportunity to talk.

NED CALONGE: Thanks, Kyle.

Michele.

MICHELE CAGGANA: This is Michele Caggana. I'm a member.

I'd like to just take up and follow up on what Kyle was saying. When we're talking about Krabbe, it was said many times today that Krabbe is a rare condition. So, we're actually dealing with very small numbers overall over a period of a year or so. I mean, we've been looking at the numbers that were in the evidence review and the number of babies that have been screened.

There was a lot of discussion about the lost to follow-up pieces. And most of those were in the places that do not do psychosine as a second-tier test. And one of the states is also in a pilot mode as well.

And I believe that the Committee -- you can correct me if I'm wrong being a brand-new

member. But I believe we can make it such that we ask states to do psychosine as part of the newborn screening before we contact families.

This Committee has done something similar when, on the SMA, decision was made saying that we are screening for specific -- you know, being very specific about what we're screening for.

And the other thing I'll add is that part of the newborn screening community, that we are definitely a community. And we spend a lot of time with APHL and amongst our individual state leaders in sharing best practices and doing quality improvement.

So, that people who have experience with Krabbe screening would be very, very happy to help other states in doing the best screening they can.

And in our experience looking at the use of GALC and then psychosine and CLIR, and we also look at a panel of other lysosomal enzymes, the referral rate is quite, quite well overall.

And in New York State compared to the early days when we had very few tools to work with.

Also, stem cell transplant is used for a lot of conditions, and it's used for the newborn screening conditions. So, you know, I know you can weigh mortality versus benefits. But it's not a unique, new treatment for a condition.

The other thing about the harm about inappropriately treating I think is maybe based on either older data or older discussions. Because we have not seen any evidence of that. And treating someone before or too early is also not new to Krabbe.

This is often parent-driven. Sometimes parents make a decision to treat too early in the mind of the expert. And in other cases, as we saw, sometimes parents have autonomy and decide not to treat at all. So, whether that's a harm or not I think is somewhat debatable.

I'd just say I have a baby who as a child that was talked about with the low

psychosine, was referred by the newborn screening program for follow-up. So, it wasn't a false negative uniform screening in our case.

The other thing I'll talk about a little bit is equity. Having a care network, having experts who can help people go through the process is truly a benefit, I think, in the medical community and in the newborn screening community.

And we also benefited from having that capacity when we began ALD screening. New York began ALD screening first, and we benefited from experts in the field who helped us get started. And so, I think there is a wealth of knowledge with the experts and the Leukodystrophy Care Network now that we would be able to manage newborn screening for Krabbe.

So, thank you.

NED CALONGE: Jennifer, did you have a response?

JENNIFER KWON: I just wanted to say, and I had neglected to bring it up in the liaison

talk. And I'm just sorry.

The point about stem cell transplantation and Krabbe disease is that even though there are other disorders where we use stem cell transplantation, in SCID, for example, none of the transplant centers in the SCID consortium would consider transplanting an infant under eight weeks of age. And it used to be 12 weeks.

And that has to do with -- and again it's a somewhat different situation. But it has to do with the neurologic, the perceived neurologic harms of the conditioning therapy that infants receive.

Now, for infants with early infantile Krabbe disease, those harms seem somewhat negligible compared to the impact of the disease. And I do understand that. But the other conditions that have stem cell transplantation, even like SCID where it's done in infants, are not done in infants this young.

And in XALD, which is the other example we have or that I can think of that I'm

used to -- I know that there are other conditions out there as well -- tend to focus on older children.

NED CALONGE: Thanks.

Ash.

ASHUTOSH LAL: Thank you.

My first understanding of the evidence is that it felt like there were two levels of psychosine elevation. And what is probably the thing that's driving it most is newborns will have levels over 10.

And that's informing at least my take on the evidence and my decision-making is, What is the benefit of stem cell transplant when somebody is identified with very high psychosine levels, or above the threshold of 10?

And what is the harm of missing a potentially treatable disorder? Where things have in some ways become diluted, I think, is the intermediate levels of psychosine, less than 10, more than 2.

And patients who likely will become

symptomatic later on, in these cases both the benefit of the treatment are missing, the patients who could be treated and missing that opportunity, as well as diagnosing late, I think they are much less intense compared to the former group.

But during the discussion of the potential harms, then we considered the harms from the diagnosis potential screening parts that the cases with later onset, along with the infants who really needed to be taken to treatment way early in life.

In my view, the degree of benefit/harm in the two groups are a little bit separate. The problem with the second group that's been obvious is the uncertainty because of the tremendous genetic heterogeneity of the disease itself. And I feel that this is something that the medical system will gradually have to come to grips with because this isn't the only example.

There are many other examples where pre-symptomatic genetic traits are identified,

either based on family history or for some other reason. And we have to understand how to counsel the families in a compassionate way, be realistic, and also modeling what we are learning. And that is something that we as the physicians and caregivers have to figure out.

Thank you.

NED CALONGE: Thank you.

Melissa.

MELISSA PARISI: Thank you. Melissa Parisi, NIH.

I want to thank all of the presenters today and really acknowledge just how challenging this is. I think if it were easy, we wouldn't be having such heartfelt and difficult conversations and really trying to grapple with the data as they exist, recognizing that perhaps what is available for us in making the decision is not ideal.

I think for me what is important to keep in mind and has had an influence as I've been struggling with this decision is the fact that the current screening approach involving psychosine

seems to make a significant difference in the number of newborns that are referred for additional evaluation.

And in the pre-psychosine era, clearly the creation of patients-in-waiting or individuals, babies that were being followed who may have had really low risk of developing severe manifestations requiring treatment was considerably higher.

And that as we consider this nomination, I think we need to ensure that whatever decision is made is made on the presumption that the addition of psychosine would be a requirement for a screening paradigm.

Having said that, I think trying to weigh the relative risks and benefits is very hard. And I do think that there is a degree of subjectivity in the face of all of the data that are presented in how one interprets net benefit relative to harm.

I think for me, you know, I also think about some of the paradigms that have been

presented before to this Committee and decisions that have been made. And there are certainly, as just described, other conditions in which stem cell transplantation has been the modality of treatment.

As just discussed very eloquently by Dr. Kwon, SCID and XALD, although the parameters for doing the transplantation are a little bit different in those disorders, it's certainly been the treatment for other conditions that have come before the Committee.

And I think also the uncertainty about the long-term outcomes has also been a component as well. You may recall that SMA was voted to add to the RUSP even with somewhat shaky evidence of relative benefit over harm and some uncertainty about long-term outcomes. And, you know, we're still gathering the data.

I guess although I wish there were better data, I guess I feel that there will be more data that will come forward. But I wonder if we were to say no to adding Krabbe to the RUSP,

what would be the clearcut advice that we would give to the nominators about what would be necessary to consider this more positively for addition?

In my mind, it feels to me like I would tend to put this in the category of moderate benefit rather than low net benefit. But that's again my subjective view at this point, and I'd like to hear what other folks think about what would be necessary to move this into that higher category of classification.

Thank you.

NED CALONGE: Thanks Melissa.

And, Gerry, I just want to say that this session and the comment session is for members. And I appreciate you being here.

Could I ask if there are other questions from members of the Committee?

Chanika.

CHANIKA PHORNPHUTKUL: Again I just want to thank Melissa and Kyle's comment that I think a good reminder about longer-term follow-up

and the subjectivity of the net benefit is something that we really need to think about.

You know, certainly I agree with you that we as health care providers tend to over-interpret or misinterpret or interpret incorrectly the burden to the family. And I think that is something that is very hard to be objective.

I also agree that if we were to move forward, a more specific testing, psychosine, will have to be part of it. Because the evidence is quite clear.

And last but not least, I may again want to really, you know, I really appreciate all the families that have come to this meeting. And we really appreciate your thoughts and inputs. And I just want to -- you know, I think this is why it's such a hard decision for all of us to think through what evidence do we have.

And if we were not to move forward, we definitely have to come up with a path forward that is objective. Thank you.

NED CALONGE: Thanks, Chanika.

I think when I hear phrases like "subjective" I have trouble balancing. That is always translated as a need to an increased level of uncertainty. And so I would just offer that.

Jannine.

JANNINE CODY: Jannine Cody, member.

You know, just to build on that point, it's how you interpret it. And I interpreted the intermediate levels to mean families are told, "You know, we found out your child is at risk. We're going to monitor them. So, if they really just start to have first signs, we're going to be on it like that instead of waiting for them to deteriorate beyond help."

And so, to me, being intermediate wasn't such a giant negative. So, it's very subjective in how you view this. So, I appreciate that it sounds like everyone else is having as much, I don't know, anxiety over how to vote as I am. So, I appreciate the discussion very much. Thank you.

NED CALONGE: Shawn.

SHAWN McCANDLESS: Thanks. Michele, I didn't mean to jump ahead of you in the line. I just want to respond to what Jannine said.

The comment about intermediate being a good thing and not that big of a deal, it has not been my experience with other conditions that that is how families perceive it. But I understand that there's room for different experiences and different interpretations of that. But that has not been my personal experience as a clinician of how families interpret that.

It's often that those calls have resulted in -- those identifications have resulted in very unhappy families who spend a lot of time on the phone yelling at me for ruining their life. And so, I feel where you're coming from.

I also wanted to just respond -- first off, I also -- several of you have said this is really hard. And I agree with that completely. I do want to be clear, though, to Kyle's point about valuing life and not weighing sort of the burden of what it means to any individual family

to care for a child with special needs. I'm fully onboard with that, and I agree.

And I want to be clear that Jennifer and I did not -- we did not take that into any consideration in our recommendation. So, I just want to be really clear about that.

For us, the benefit is these kids live longer. Now, how that gets weighed in terms of the balance is up to each person to determine individually. But we see that as the benefit. And that having your baby with you every day, regardless of how much work they are or work they're not, there's value in that for families.

So, I want to be really clear about that, that our assessment did not in any way incorporate a value judgment about what it means to a family to live with a child with special needs.

NED CALONGE: So, we're about out of time.

Michele, I think maybe you have the last comment.

Sorry, Dr. Warren.

Michele first.

MICHELE CAGGANA: Oh, okay.

So, with regard to sort of this intermediate assessment, we do -- you know, we have this category and we have -- it's in the consensus guidelines.

But states have the ability to set their intermediate or their infantile cutoff for psychosine wherever they deem it good for their population. So, they're still using psychosine, but can make a decision whether or not they want to do infantile-only screening or have these, quote, "patients-in-waiting," that population.

And I'll just add that with Pompe disease, we've been screening for that now for many years. And we have a huge proportion of families that are in that boat as well. And so, you know, learning how to deal and deliver that news I suppose is something that we'll continue to get better at.

The other thing is that it was

mentioned during the presentations earlier today that these kids, the kids who answer that later onset, actually have a higher net benefit than even the infantile cases in some cases. And so, if the discussion is that, you know, we can't deliver that news appropriately or be able to deal with that group of children, we're actually losing some kids who will have the most benefit overall.

NED CALONGE: Thank you.

Michael.

MICHAEL WARREN: Thank you.

I just want to share a few thoughts, and I'm comforted to know that others are struggling with this as well. I think sometimes these decisions are very clearcut or presumed to be clearcut, and I appreciate the candor.

So, I want to thank the evidence review group and Dr. McCandless and Dr. Kwon for their incredible work and for really trying to better understand where we are, particularly in places where the answers aren't clearcut.

I also want to thank all the families

who have been engaged. And we've got family members who are on this Advisory Committee. And I think it speaks to the importance both in terms of the process of having public comment, and also having membership on the Committee, of keeping families as an integral part of this conversation. And I think that's been an important value for this Committee, and I appreciate that.

Several colleagues have raised this notion that it's important we recognize disability is not the same thing as quality of life and continuing to make sure that we don't conflate that. And I think it can be really easy for all of us -- and I say "us" and include myself in that -- to be ableists. And so, I think to the extent that we can continue to understand those perspectives, it's incredibly important.

And we need to do better in understanding the impact of newborn screening on quality of life. And so, for those of us who fund research and fund projects, it's important for us to think about how we advance our knowledge in

this space.

(Pause)

NED CALONGE: Thanks, Michael.

There were --

(Crosstalk)

SHAWN McCANDLESS: I'm sorry to interrupt, Ned.

But I think you were still talking, but your sound went off.

MICHAEL WARREN: Yeah, sorry. Can you hear me now?

SHAWN McCANDLESS: Yes.

MICHAEL WARREN: Okay. Sorry about that.

So, I think also what I was saying, being sure that we understand the impact on the system overall, we've heard about the availability of providers, availability of treatment. As we think about, you know, if this were to move from 10 states to all the states, the question of equity becomes very important.

I think one of the things that we

often think about is where you live, where you were born, should not influence how long you live and how well you live. And yet we know there are real questions of equity.

And lastly, I'll just say as we move forward, we're likely to be continued facing these conditions that are incredibly rare or very rare. And I think it's important for this Committee to continue to think that the question is the framework for our decision making that has served us well for conditions of a certain prevalence, the framework that's the best moving forward.

And I'm not saying it is or it isn't. But I think it's important periodically to ask that question. So, thank you all.

NED CALONGE: Thanks.

I heard two Committee members express a feeling that the net benefit was or might be considered moderate instead of low. And as that has ramifications for where the condition is in the matrix, I think I will take the prerogative for asking for a motion to upgrade the net benefit

to moderate.

I need a motion in order for us to vote. So, that's why I'm saying it the way I'm saying it. So, we would need a motion and a second to change that.

Is it a comment or a motion?

SHAWN McCANDLESS: It's a comment. And the comment is that the -- just to be clear and maybe I'm misinterpreting the matrix. The decision matrix is significant benefit versus small-to-zero benefit. Those are the only two choices. The moderate rating is the rates to certainty of the net benefit.

Jennifer and I -- I can tell you we struggled with this. And if we could have said "moderate benefit," we would have. So, if that's what we're saying, I'm fully supportive of that. And I don't want to speak for Jennifer. But we struggled with that when we tried to put this onto the matrix.

JENNIFER KWON: Yes.

NED CALONGE: I appreciate that. Of

all the things I didn't have in front of me, it was the matrix. So, I sent a quick message to ask if that would change us from a C1. And with the current matrix, that would not change that and I think points to something that the Committee will want to look at and to think about changing the matrix going forward.

Thanks, Kyle. I knew you were ready.

KYLE BROTHERS: I want to be clear, though. I'm not opposed to changing the classification to B1. I just think that it's the interpretation of the matrix as it's written is that it's significant benefit versus small-to-zero benefit. Those are the two choices. And that's why in the slide I specifically circled that component on the matrix.

If somebody wanted to move to make the recommendation B1 as opposed to C1, I'm not opposed to that. But I just want to be clear what the terms actually say on the matrix.

NED CALONGE: Jennifer.

JENNIFER KWON: I was going to

reiterate that point. But also, in the interest of transparency, I think, as Kyle stated, I think it's important to sort of talk about where we're at.

I think that for me the most difficult part of this particular newborn screening program is how people react to the fact that they're told this information. And to me it's one of those programs that really reminds you that this is an unconsented activity. And this is something that we're imposing on families. And certainly, the number of families we're imposing on is lower with psychosine. But it is still an imposition.

And I think what I'm hearing from people who care for patients is what I feel as well. I feel like we can work this follow-up into our routines. We can counsel families and give them care through the process.

But the program itself, newborn screening itself, is an unconsented tax, basically, that people having babies are paying.

And so, I think that that is sort of the background that I haven't heard in these discussions. And I guess I just wanted to bring that up.

NED CALONGE: Thanks.

Kellie.

KELLIE KELM: Hi. I guess I wanted to talk a little bit about deciding that it was definitely a 1 or a -- that the readiness level was ready.

And I guess two things that I wanted to make a comment on that is that it's not just adding the first tier Krabbe test, which I think, depending on, you know, the platform that people use may itself not be a big addition. And I think it probably depends on the state to assess that.

You know, obviously there also is the addition of psychosine testing. It's not clear to me and we didn't really discuss why there are two states screening without psychosine and also without, you know, the sequencing component as well -- is one that is also potentially an added

item that not all states may be doing in-house. And it's unclear about how they might add that in all cases.

And to be clear, you know, I worry sometimes that we -- and the statement here talks about the public health department. And I'm going to put my Susan Tanksley hat on and say that it's also a system. And depending on the state, you know, some states also include in their system out to follow-up to a certain point. Each state is different.

And it's not clear to me about how all states will be including with this added screening, you know, whether some of this is -- and I think some of the barriers were things like adding psychosine testing, seeking out specialists, you know, setting up the specialists, and all the other steps as well. And so, I just wanted to add that as an item.

And I know it also talked -- Michele talked a little bit about using CLIR. So, it's obviously some software and some other -- some

other assessments that are being done to put people in different sort of areas.

And I realize that there's a lot of sharing, but I just also wanted to add that, that this is actually multiple steps. So, I don't know if I would say that states are ready. And that's just one thing I wanted to add.

NED CALONGE: Thanks, Kellie.

I wonder if we could stop the screenshare now.

(Pause)

NED CALONGE: Are there any additional comments from Committee -- oh, thank you, Shawn.

SHAWN McCANDLESS: Jennifer, I see your hand up freshly or is that old?

JENNIFER KWON: No, it's up freshly because I was going to tell Kellie that was Shawn's idea.

(Laughter)

SHAWN McCANDLESS: Yes, that was. I take the blame for that.

Because technically, according to the guidelines that we discussed in the past, development or readiness for this test based on the reporting back from the labs that responded to the survey would be in developmental assessment because the largest category of states said that it would be one to three years, which is how I believe developmental readiness is defined for this purpose as it goes to the readiness, which would be prepared to implement within one year.

I actually said I feel like it's ready because I think that most states now have already started. And your point about it being a system implementation, not just a lab implementation, is a really good point. I don't know that we're as confident of our ability to even assess that.

But it seemed to me that with most labs screening now for some sort of lysosomal storage disease, adding this with a reference lab to do that psychosine would not be a heavy lift.

And so that would really -- you

called me out completely correctly. It's not -- technically doesn't meet the criteria for readiness. But from a lab perspective, which is I think how I was interpreting it for this purpose, I think most labs could get this up and running in a year if they needed to.

NED CALONGE: Michael.

MICHAEL WARREN: Okay. So, I wanted, Dr. Calonge, to revisit your question about, Does this move? Because I think it's helpful for us to think about, to my knowledge, again we're likely to face conditions coming down that are more and more rare, and this is not -- conditions that are murky.

And given the framework that we've got now, I don't think we have moved the condition forward to date that has had a C rating. So, I am curious where the Committee is on moving from a C to a B. So, to your point, I would move that we raise that for a vote.

NED CALONGE: So, let me interpret your motion as changing the rating to a B1?

MICHAEL WARREN: Correct.

NED CALONGE: Is there a second from a Committee member?

I see a second from Kyle and from Lal and from Michele.

All right. It's been moved and seconded that we change the rating of screening for Krabbe from a C1 to a B1.

VOTE ON MOTION TO CHANGE SCREENING RATING

NED CALONGE: And I will do a roll call vote, starting with Kyle Brothers.

KYLE BROTHERS: Approve. Agree.

NED CALONGE: Yes. Say "I approve of the motion," or "I approve," or say "in favor" or "not in favor." That's what can be said. So, that would be an "in favor"?

KYLE BROTHERS: In favor.

NED CALONGE: Michele.

MICHELE CAGGANA: In favor.

NED CALONGE: Jannine.

JANNINE CODY: In favor.

NED CALONGE: Carla.

CARLA CUTHBERT: Not in favor.

NED CALONGE: Jane.

JANE DeLUCA: Not in favor.

NED CALONGE: Kellie.

KELLIE KELM: Not in favor.

NED CALONGE: Jennifer.

JENNIFER KWON: Not in favor.

NED CALONGE: Michael. Michael.

MICHAEL WARREN: In favor.

NED CALONGE: Ash.

ASHUTOSH LAL: In favor.

NED CALONGE: Shawn.

SHAWN McCANDLESS: Not in favor.

NED CALONGE: Kamila.

KAMILA MISTRY: In favor.

NED CALONGE: Melissa.

MELISSA PARISI: In favor.

NED CALONGE: Chanika.

CHANIKA PHORNPHUTKUL: In favor.

NED CALONGE: And my vote is not in favor.

The motion passes eight to six.

That's correct, isn't it, Leticia? Just to get my counting right.

LETICIA MANNING: Yes. Yes.

VOTE ON MOTION TO RECOMMEND KRABBE DISEASE FOR INCLUSION IN THE RUSP

NED CALONGE: So, given that, I would like to see if someone would like to make a motion to add screening for -- sorry.

To make a recommendation to the Secretary to add Krabbe disease to the Routine Uniform Screening Panel.

MICHELE CAGGANA: I'll make a motion to add.

NED CALONGE: Thank you, Michele.

Is there a second?

KYLE BROTHERS: Kyle Brothers.

I'll second.

NED CALONGE: It's been moved and seconded. I'll pause for any further discussion.

(Pause)

NED CALONGE: And again we'll have a vote -- sorry. I was just corrected. It's the

Recommended Uniform Screening Panel.

So, given the motion to make a recommendation to the Secretary, I will call roll again. And say, "I approve" or "I don't approve."

Kyle Brothers.

KYLE BROTHERS: I approve.

NED CALONGE: Michele Caggana.

MICHELE CAGGANA: I approve.

NED CALONGE: Jannine Cody.

JANNINE CODY: I approve.

NED CALONGE: Carla Cuthbert.

CARLA CUTHBERT: I do not approve.

NED CALONGE: Jane DeLuca.

JANE DeLUCA: I do not approve.

NED CALONGE: Kellie Kelm.

KELLIE KELM: I do not approve.

NED CALONGE: Jennifer Kwon.

JENNIFER KWON: I do not approve.

NED CALONGE: Michael Warren.

MICHAEL WARREN: I approve. Approve.

NED CALONGE: Thank you.

Ash Lal.

ASHUTOSH LAL: I approve.
NED CALONGE: Shawn McCandless.
SHAWN McCANDLESS: I do not approve.
NED CALONGE: Kamila Mistry.
KAMILA MISTRY: I do not approve.
NED CALONGE: Melissa Parisi.
MELISSA PARISI: I approve.
NED CALONGE: Chanika Phornphutkul.
CHANIKA PHORNPHUTKUL: I approve.
NED CALONGE: I vote to not approve.
Leticia, my count is eight to six in favor.
LETICIA MANNING: We did not hear CDC's vote.
NED CALONGE: I apologize.
Carla Cuthbert.
CARLA CUTHBERT: I do not approve.
NED CALONGE: The vote is seven to seven. Following Robert's Rules of Order, the motion does not pass.
NED CALONGE: I want to recognize that this has been a difficult decision, a

difficult and complex consideration of a very serious condition. But without a majority vote, it signals that we will not move Krabbe forward as a recommendation for addition to the RUSP today.

I want to thank everyone who's been involved in the nomination, everyone who was involved in the evidence-based review and decision-making process. Members of the Committee, the ERG, the Technical Expert Panel, people who have shared their stories with us today.

I need to acknowledge that for the nominators and advocates, I realize this is a disappointing outcome. Moving forward, the Committee will prepare a letter summarizing the evidence that we believe will be helpful to have in the future should a renomination come before the Committee.

(Pause)

NED CALONGE: Just taking a long breath. Sorry.

ORIENTATION TO WORKGROUP SESSIONS

We've come to the end of today's agenda. What we're going to do is break and assemble our three workgroups. I want to start by telling folks that in discussion with the workgroup chairs and with my colleagues at HRSA, and others, we've decided to change the approach and the structure of the workgroups.

We believe that we can have a more effective approach if we create groups that are going to review specific topics and who will be able in a more program-oriented or project-oriented approach to provide recommendations to the Committee that help support newborn screening and the newborn screening system.

We think that those topics can be identified by the priorities that the workgroups, the current workgroups, have been suggesting and working on already. So, over the last two meetings, we've asked for prioritized lists. And the charge to the Committees today is, as your last ask as these workgroups, to please bring forward prioritized topics that we can arrange

group work on moving forward.

I think the other advantage to doing this is an acknowledgement that if it is a discrete issue that a group is working on, it's very possible that HRSA can bring to bear resources to move those topics forward. So, it is for those reasons why we've decided to take a new approach to the process.

I realize that there are members of the public and the advocacy community who have worked on the workgroups. It is our intent to assure that any topic-related group includes input from the public, from advocates, and from families that they're interested in the specific topic.

I'll just pause to see if Committee members have any questions or comments.

(Pause)

NED CALONGE: So, I believe that we're going to put a link that you can go to that will give you a Zoom link to join a workgroup.

We have a pause in the time now before the workgroups start. They will convene at

3:45 and work through the charges as I've given to the Committee chairs.

ADJOURNMENT

NED CALONGE: And with that, I'm going to adjourn the Committee meeting for today and remind everyone we will resume via Zoom tomorrow morning at 9:30 Eastern Time.

And again, it's been a long and, I would say, arduous day. I want to express my appreciation to all attendees, to the Committees, and the people who worked so hard on moving newborn screening and supporting this system forward.

And with that, unless, Leticia, you have any other announcements, I'll adjourn the meeting.

LETICIA MANNING: No other announcements. Thank you.

NED CALONGE: Thank you all.

(WHEREUPON, THE MEETING WAS ADJOURNED AND WILL CONTINUE ON FEBRUARY 10, 2023 AT 9:30 A.M.)