THE ADVISORY COMMITTEE ON

HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Advisory Committee Meeting - Day 1

November 3, 2022

9:30 A.M. to 3:00 P.M.

HRSA Headquarters

5600 Fishers Lane

Rockville, Maryland 20857

In-person and via Webinar

Attended via Zoom Webinar

C O M M I T T E E M E M B E R S

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 Professor of Family Medicine
University of Colorado School of Medicine

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

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

C O M M I T T E E M E M B E R S

(continued)

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

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

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

C O M M I T T E E M E M B E R S

(continued)

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

E X - O F F I C I O M E M B E R S

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

Health Resources & Services Administration

Michael Warren, MD, MPH, FAAP

Associate Administrator

Maternal and Child Health Bureau

E X - O F F I C I O M E M B E R S

(continued)

National Institutes of Health

Diana W. Bianchi, MD

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

ACTING DESIGNATED FEDERAL OFFICIAL

Soohyun Kim, 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

Marc Williams, MD, FAAP, FACMG

Director, Genomic Medicine Institute

Geisinger Health

American College of Obstetricians & Gynecologists

Steven J. Ralston, MD, MPH

Chief of Obstetrics

Howard University Hospital

ORGANIZATIONAL REPRESENTATIVES (continued)

Association of Maternal & Child Health Programs
Karin Downs, RN, MPH
MCH Director
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
Board Director
Vice President, Research Officer
University of North Carolina Health

ORGANIZATIONAL REPRESENTATIVES (continued)

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

March of Dimes

Siobhan Dolan, MD, MPH

Professor and Vice-Chair for Research

Department of Obstetrics & Gynecology and Women's Health, Albert Einstein College of Medicine

ORGANIZATIONAL REPRESENTATIVES (continued)

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

C O N T E N T S

P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks, and Committee Business

NED CALONGE: Welcome to the 4th meeting of the Advisory Committee on Heritable Disorders in Newborns and Children in 2022. As we are gathered in-person for the first time since August 2019, I would like to open this meeting by taking a moment to acknowledge the land we gather on today.

We acknowledge that the land and water on which our meeting is taking place was, and is still, inhabited and cared for by the Susquehannock tribe, and Piscataway Peoples, including the Piscataway Conoy Tribe and Choptico Band of the Piscataway Indian Nation. We are grateful for their past and continued stewardship of this land and pay our respects to Maryland's Indigenous community and their elders, both past

and present, as well as future generations.

We are excited to welcome two new Committee members. Dr. Jannine Cody is currently a Professor of Genetics in the Department of Pediatrics at University of Texas Health San Antonio. In 1985, her daughter Elizabeth was born with a rare chromosome abnormality called 18q-. This was a condition that was easily diagnosed, yet there was virtually no information on medical management or on maximizing the potential of individuals living with 18q-. In 1990, Jannine founded the Chromosome 18 Registry and Research Society as a way to bring affected families together and to learn from each other. In 1997, Jannine earned a Ph.D. in human genetics at University of Texas Health San Antonio. While pursuing her Ph.D., she developed the multidisciplinary Chromosome 18 Clinical Research Center, the goal of which is to make the chromosome 18 conditions the first completely treatable chromosome abnormalities. The center's longitudinal study that includes over 700

participants has generated over 60 peer-reviewed publications. Jannine has testified twice before the US Congress and has served on a variety of national committees and organizations related to genetics.

Dr. Ash Lal is an attending Physician in Hematology/Oncology at University of California San Francisco Benioff Children's Hospital, and in the and then the Division of Hematology, Blood, and Marrow Transplant Cellular Therapies at the UCSF Medical Center. He's the Director of the UCSF Benioff Children's Hospital Oakland Comprehensive Thalassemia Program and the Iron Disorders Program and is Co-Director of the Hemoglobinopathies Diagnostics Laboratory. Ash serves as a member of the Medical Advisory Board for the Cooley's Anemia Foundation, as well as the Coordinator and Principal Investigator of the Thalassemia Western Consortium.

His key areas of interest are thalassemia syndromes, iron overload, iron chelation, clinical gene therapy, nutrition,

erythropoiesis modulation, blood transfusion, global hematology, access to care, prenatal screening, newborn screening, and medical records portability.

And I wonder as we welcome you, Dr. Lal, if you'd like to make a comment or two.

ASHTOUSH LAL: I definitely feel very much honored to be asked to participate in the Committee, and this is my first time. So, I hope to learn and to start making contributions as soon as I can and as much as possible.

NED CALONGE: And we're sure you will, and we're so pleased you're joining us. Thank you. So next slide.

So, last month, the Maternal and Child Health Bureau welcome Dr. Jeff Brosco as the Director of the Division of Services for Children with Special Health Needs. Dr. Brosco is a historian and physician who teaches and practices general pediatrics and developmental behavioral pediatrics at the University of Miami's Miller School of Medicine. He's directed the MCHB

directed leadership education in neurodevelopment disabilities, training program at the Mailman Center for Child Development since 2010 and has served as the Director of Population Health Ethics at the University of Miami's Institute for Bioethics and Health Policy. In the past year, he was named Associate Chair of Population Health for the Department of Pediatrics.

His research focuses on history of policy and ethics regarding child health. He has authored fifty peer-reviewed publications and over ninety other publications.

For more than two decades, Dr. Brosco has held a series of leadership positions for the Florida Department of Health's Children's Medical Services, which seeks to improve the health of children with special care needs and did this from 2017 to 2019. During that time, he was Florida's Deputy Secretary of Health for CMS and he just stepped down after four years as the state's Title V Director for CHHCN.

He's also been active in National Health

Policy programs, including the Advisory Committee on Heritable Disorders in Newborns and Children and the National Workgroup on Standards for Systems of Care for Children and Youth with Special Health Care Needs.

And I wonder if I could ask him to come up and just make a few comments. Thanks, Jeff.

JEFF BROSCO: Thank you so much, Ned. It's great to be among friends again. As you heard, I'm completely new to HRSA. It's been like week five or six, but I'm certainly not new to newborn screening and have been part of this group in one way or another for two decades now.

So, what does this job mean? My kids keep asking me, what do you actually do, Dad? And I think the way that I think about it is families sometimes have trouble getting what their -- what their children need, and it's basically our job to make sure that families can get everything that their child needs so that they can play, go to school, and grow up to be healthy adults. That's basically it. And the way we're going to get

there's the blueprint. There is a series of publications in pediatrics that came out in June. Tomorrow, you'll hear from our colleague, Dennis Kuo, a little bit more about the blueprint and basically, it's the framework for how we get there. How do we get every child to be able to play, go to school, and become healthy adults? How does the Committee fit in?

Actually, this Committee is an essential part, it's a critical part of the system of care for children with special health care needs and, in particular, for both equity, equitable distribution, and for fairness.

So, the fair part, I think, is one of the really wonderful things about this Committee is that it's an example of how health policy should be done, right? We have community involvement, we have stakeholders who say here are important issues, here are conditions that need to be addressed. We have an evidence review process, it's transparent. We have the public voice, and then we have a decision based on the evidence and

the values of our society. There's not a better way to do health policy or a fairer way.

There's also an equity component, right? And that is when it's universal, when every child goes through newborn screening, we make sure we're not missing out on kids. And a few of us published something a couple years ago, and one of the examples that I particularly remember is in California, before and after screening for SCID. And I think all of you know, for severe combined immune deficiency, if you do a bone marrow transplant early enough, the child has much better outcomes than if it's clinically determined. And for years, using California as an example, most of the children who got transplanted were white, non-Hispanic. In fact, it was such that we thought population genetics kind of determined who had SCID and who didn't.

And in the first two years after universal newborn screening, about eighty percent of the kids who got a bone marrow transplant were Black, Hispanic or Asian. It suggested that this

really was about access to care, and that equity could be changed if we have universal approaches to what we do.

So, I want to, in particular, thank Jannine and Ash for joining us, for all of you guys for the hard work you do. This has a lot to do to go through, and it's really important. So, thank you.

NED CALONGE: We really appreciate the addition of Jeff's leadership as somebody knows the Committee well from his time spent with the Committee and I think both HRSA and the Bureau are so lucky to have him join us.

I was remiss, sorry, in not also acknowledging a new organizational representative. Karen Downs is the new organizational representative for the Association of Maternal and Child Health Programs and is joining us virtually today, I believe.

She worked for the Massachusetts Department of Public Health since 1999, and then retired in 2022. She was the MCH Director for the

Title V Program and Director of the Division of Pregnancy, Infancy, and Early Childhood within the Bureau of Family Health and Nutrition. DPIE promotes physical, social, and emotional well-being and resilience by fostering healthy environments in pregnancy, infancy, and early childhood. Ms. Downs provided oversight for maternal mortality reviews, perinatal home visiting programs, maternal and infant mental health programs, developing early childhood systems of care, and programs focused on addressing inequities and birth outcomes.

Prior to her work, at the end, MDPH, Ms. Downs worked in Cambodia, Laos, Thailand, and Nepal, providing emergency relief and reconstruction and working with rural communities to address family health and nutrition and enhance women's economic capacity. Ms. Downs received her BA in anthropology and sociology from Charleston Carleton College, an MS in nursing from Pace University, and an MPH from Boston University with an MCH concentration and certificate in MCH

leadership.

So, we welcome you, and Ms. Downs, if you'd like to make any comments, and it's certainly okay if you don't. But I do wish to recognize and thank Sabra Anckner for serving as the interim org rep over the last couple of meetings until Ms. Downs was able to join us.

So, with that, I'm going to turn things over to Soohyun for the roll call and some announcements.

SOOHYUN KIM: Thank you, Ned. I will now do roll call. For Committee members, as I call your name, please also report any new conflict of interest since the last meeting. If you respond no, we will record your attendance as well as no new conflict of interest.

Kamala Mistry, from Agency for Health care Research and Quality.

KAMALA MISTRY: Here, no conflict. Thanks.

SOOHYUN KIM: Thank you. Kyle Brothers.

KYLE BROTHERS: No.

SOOHYUN KIM: Ned Calonge.

NED CALONGE: Here and no conflicts.

SOOHYUN KIM: From Centers for Disease Control and Prevention, Carla Cuthbert.

CARLA CUTHBERT: I'm here. No conflicts of interest.

SOOHYUN KIM: Thank you. Jannine Cody.

JANNINE CODY: Here and no conflicts.

SOOHYUN KIM: Thank you. Jane DeLuca.

JANE DELUCA: Present, no conflicts.

SOOHYUN KIM: From the Food and Drug Administration, Kellie Kelm.

KELLIE KELM: Present and no conflicts.

SOOHYUN KIM: From Health Resources and Services Administration, Michael Warren.

MICHAEL WARREN: Here, no conflict.

SOOHYUN KIM: Jennifer Kwon.

JENNIFER KWON: Here, no conflicts.

SOOHYUN KIM: Ash Lal.

ASHTOUSH LAL: Here, no conflicts.

SOOHYUN KIM: Shawn McCandless.

SHAWN MCCANDLESS: Here, no conflict.

SOOHYUN KIM: From the National Institute of Health, Melissa Parisi.

MELISSA PARISI: Here, no conflicts.

SOOHYUN KIM: And Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Here, no conflicts.

SOOHYUN KIM: Thank you. I will move on to our organizational representatives. Please let me know if you are present or not.

From American Academy of Family Physicians, Robert Ostrander.

ROBERT OSTRANDER: Here.

SOOHYUN KIM: From the American Academy of Pediatrics, Debra Freedenberg.

DEBRA FREEDENBERG: Here.

SOOHYUN KIM: From the American College of Medical Genetics, Marc Williams.

We will not have a representative from the American College of Obstetricians and Gynecologists at this meeting.

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

KARIN DOWNS: Here.

SOOHYUN KIM: Welcome. From the Association of Public Health Laboratories, Susan Tanksley.

SUSAN TANKSLEY: Here.

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

SCOTT SHONE: Here.

SOOHYUN KIM: Shakira from the Association of Woman's Health, Obstetrics and Neonatal Nurses will be joining us tomorrow.

From the Child Neurology Society, Margie Ream.

MARGIE REAM: Here.

SOOHYUN KIM: From the Department of Defense, Jacob Hogue.

JACOB HOGUE: Present.

SOOHYUN KIM: From the Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Here.

SOOHYUN KIM: From March of Dimes,

Siobhan Dolan.

SIOBHAN DOLAN: Here.

SOOHYUN KIM: From the National Society of Genetic Counselors, Cate Walsh Vockley.

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

GERARD BERRY: Here.

SOOHYUN KIM: Thank you, everyone. I will continue with a few standard members for the Committee. As a Committee, we are advisory to the Secretary of Health and Human Services, not the Congress. For anyone associated with the Committee or due to your membership on the Committee, if you receive any inquiries about ACHDNC, please let Ned and me know prior to responding.

I also must remind 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 that organization or unless you have received a waiver from HHS authorizing you to participate.

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.

So, according to the Federal Advisory Committee Act, 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 Notice. For the November meeting, there will be a public comment period. Public participants may also submit written statements. As a reminder, public participants should be advised that the Committee members are given copies of all written statements submitted by the public and these public comments become part of the official meeting record. Any further participation will be solely at the discretion of the chair and the DFO.

So, we have not been in this building for a while. So, as a reminder, visitors only

have access to the pavilion which is this space, the cafeteria, and the restrooms, which are right outside this door to the left and the workgroup meeting rooms. All the other areas are restricted, and you require an escort by a HRSA staff member and there are no exceptions.

If you need to leave the building and reenter, you will be required to go through security screening again and will require an escort to meet you at security to escort you back here. Fifteen minutes prior to and after the lunch break ends, HRSA escorts will be at the main entrance for those who need to leave and return. If you need to leave and reenter at any other times, please notify a HRSA staff member. They all have escort badges or the registration team outside this room. We also ask that you do not take any pictures or videos in this building.

If we do have an emergency, and hope that we do not, and need to exit the building, we will go out the front door where you came in through and turn left, and we're going to gather

in the parking lot area. HRSA staff escorts will have a roster and they will make sure that everybody is accounted for. So, please note that you will have to reenter the building and go through security. So, please leave any non-essential items. Here is the map where we are going to be gathering, where the trees are.

Let's see, all right. So, for all attendees here, here is the Wi-Fi network information if you need to connect. We will have closed caption displayed on this screen. We're working on that. For Committee members and organizational representatives, if you are able to, we ask that you join the Zoom meeting with your video on, but please make sure that your microphone and speakers are off. Audio will come through the room speakers as they are right now. When you speak, please remember to turn on your microphone and speak into the microphone and please speak clearly and state your full name for ensuring proper recording.

For joining us virtually, members of the

public, audio will come through your computer's speakers. If you can't access audio through your computer, you may dial into the meeting using the telephone number in the email with the Zoom link. This meeting will not have a chat feature.

For Committee members and organizational representatives joining us virtually, audio will come from your computer speakers, and you'll be able to speak using your computer microphone. If you have any issues, you also have the call-in information sent via Email.

In order to better facilitate the discussion, Committee members and organization representatives should be using the raise hand feature when you would like to make comments or ask questions. As a reminder, the Chair will call on Committee members first and then organizational representatives. Same here, please speak clearly, and remember to state your name first to ensure proper recording for Committee transcripts and minutes.

Finally, to enable closed captioning,

please select the closed captioning icon on your Zoom taskbar. From the menu that appears, select show subtitles.

And with that, I will turn things back to Ned.

NED CALONGE: I hope you can all excuse the formality of the podium today. It helps with the Zoom, and since I'm on camera for those folks who are joining us virtually, it just makes it a little bit easier. So, you'll see a little bit of shuffling back and forth and just bear with us.

I'm going to start with Committee business real quickly, starting with a GAMT Deficiency. You'll remember at the May 2022 meeting, the Committee voted in favor of recommending adding GAMT Deficiency to the RUSP. Following the meeting, Dr. Powell, chair at the time, sent a letter to Secretary Becerra with the recommendation from the Committee, a copy of which you can find on our website. Please remember that the Secretary makes the final decision on whether or not to accept the Committee's recommendation.

And when we receive it, the decision will be posted on our website.

I'd also like to inform the Committee that on June 29th, Parent Project Muscular Dystrophy submitted a RUSP nomination package for Duchenne muscular dystrophy. The Nomination and Prioritization Workgroup has begun reviewing the nomination and has been in communication with the nominators and we'll continue to keep you updated on next steps.

The Committee had an initial discussion at our February meeting on the capacity to review multiple nominations per year. In August, I mentioned that we intended to form a workgroup comprised of current and former Committee members and other subject matter experts to look at the capacity of the Committee and the NBS system, and to develop criteria and a process for prioritizing the review of nominated conditions. We expect to convene this workgroup and begin work shortly after this meeting, and we'll keep you advised on our progress. Next slide.

Thank you to all for reviewing the August 2022 meeting summary. I would ask, are there any corrections to the meeting before we vote to approve? Seeing none, we'll vote to approve. And I'll just read down through the name and Soohyun will record the vote on our voting sheet.

I'm going to start with Kamila. And if you're joining by Zoom --

KAMILA MISTRY: Yes.

NED CALONGE: Thank you. Did you hear her, Soohyun? Okay. Then I have Kyle.

KYLE BROTHERS: Approve.

NED CALONGE: I vote yes. Carla.

CARLA CUTHBERT: Approve.

NED CALONGE: Jannine.

JANNINE CODY: I'll abstain since I wasn't present for the meeting.

NED CALONGE: Thank you. Jane.

JANE DELUCA: Approve.

NED CALONGE: Kellie.

KELLIE KELM: Approve.

NED CALONGE: Michael.

MICHAEL WARREN: Approve.

NED CALONGE: Jennifer.

JENNIFER KWON: Approve.

NED CALONGE: Ash.

ASHTOUSH LAL: I would abstain.

NED CALONGE: Thank you. Shawn.

SHAWN MCCANDLESS: Approve.

NED CALONGE: Melissa.

MELISSA PARISI: Approve.

NED CALONGE: And Chanika.

CHANIKA PHORNPHUTKUL: Approve.

NED CALONGE: With that, the minutes are approved. I appreciate your attention. Next slide.

NED CALONGE: This talks about our topics for this meeting today. We're going to have a presentation by the Department of Defense on the Newborn Screening and Genetic Services System, followed by a roundtable on State Implementation of Conditions Recently Added to the Recommended Uniform Screening Panel. We'll have

lunch, and after that, we welcome public comment. And then we'll have a Phase 2 update on the Krabbe Disease Evidence-Based Review. Next slide.

For those of you coming back tomorrow, we're going to have a presentation on the Blueprint for Change for Children and Youth with Special Health Care Needs and their Families and the Implications for Newborn Screening. We'll then have workgroup updates from this afternoon's meetings from Follow-up and Treatment, Laboratory Standards and Procedures, and Education and Training. And then we'll have a discussion on the action items to advance newborn screening. Next slide.

I want to talk just a moment about the workgroup meetings this afternoon. You remember at the meeting in August, the workgroups convened to discuss successes and challenges in implementing conditions added to the RUSP and potential solutions or resources that could address factors that contribute to the variability of implementation, status of conditions added to

the rest of across the country.

The charge I have for the workgroups this afternoon, is to start with some of the solutions and ideas that the workgroups identified and identify the top three priority solutions that the Committee can consider in supporting state implementation of conditions added to the RUSP. Also, how to better strengthen the Newborn Screening System. I would like to ask the workgroups to focus on actionable solutions and think about concrete next action steps.

Then tomorrow, each workgroup chair will present a summary of their identified solutions and the Committee will have a discussion session to consider what was generated. You can access links to each workgroup meeting at this link on the slide or using the QR code. We will also display this at the end of the meeting later.

So, we're going to move into items for today and we're going to start our day with learning more about the Newborn Screening System within the Department of Defense.

We know that many military families rely on state newborn screening programs for testing and follow up, while others may use a private laboratory and internal resources. We've invited Dr. Hogue, our organizational representative for the Department of Defense to provide us an update on how newborn screening and genetic services are delivered for military service members and their families.

By way of introduction, Dr. Lieutenant Colonel Jacob Hogue is currently the Chief of Genetics at Madigan Army Medical Center, which is located on Joint Base Lewis McChord in Tacoma Washington. Madigan serves as the referral center for complex medical needs for military service members and their dependents throughout the Pacific Northwest. In this role, Dr. Hogue is responsible for the medical care of individuals of all ages with suspected or confirmed genetic conditions throughout the region. Prior to his time at Madigan, Lieutenant Colonel Hogue served as the Chief of Genetics at Brooke Army Medical

Center in San Antonio, Texas.

In addition to his role as clinician and subject matter expert on genetics in the military, Commander Hogue currently serves as the Chief of the Department of Clinical Investigations and the Chair of the Ethics Board at Madigan. Lieutenant Colonel Hogue graduated summa cum laude -- cum laude from Valparaiso University, then earned his medical degree from the F. Edward Herbert School of Medicine at the Uniformed Services University of Health Sciences. He completed his pediatric residency at Madigan Army Medical Center, and his genetics residency at the University of California, San Francisco. He's board certified in pediatrics and medical genetics, and I feel lucky that we have his representation to the Committee and would like to invite him to the podium.

Dr. Hogue.

Department of Defense Newborn Screening System

JACOB HOGUE: Great, thank you. It's always fun to hear myself referred to as the Chief

of Genetics. It's just me there, so I always like to -- it's fun to say I'm the chief of myself, I am in charge of myself. I do have two genetic counselors that I'm now in charge of, but mostly, it's just me, so.

And I know you were curious who was going to speak on behalf of the Department of Defense today. My uniform kind of gives me away in that respect.

They asked me to speak today, I think, primarily related to newborn screening and the context of discussions we've been having at these meetings since I've been a part of these meetings related to variability between states related to adding conditions more recently added to the RUSP. And we certainly bridge across multiple states and regions, and then also related to access to certain services and the availability of services, particularly follow-up services for newborn screening conditions. And so, I'm going to speak both on how we approach newborn screening in the Military Health System, as well as the

availability of genetic services, since that's what I most directly am aware of, but I can give other information as well.

Okay, I don't have any conflicts of interest. Even though I'm speaking on behalf of the Department of Defense, I do have to tell you that these are my own opinions rather than necessarily the official policy of the Department of Defense, or the Defense Health Agency.

In order to understand what I'm talking about today; I think you have to understand a little bit about what our health system is. So, I'm going to give you probably more background than you all want to know about the Military Health System.

The Military Health System is the title that we use for all components related to health in the military, sort of the overarching system that's led by the Assistant Secretary of Defense for Health Affairs, responsible not only for health care delivery, but also medical education with the Uniformed Services University of the

Health Sciences, my alma mater, is right down the street, public health, private sector partnerships, as well as medical research and development.

In total, we serve about 9.6 million beneficiaries, have a budget of about 50.5 billion as of last year, which makes up seven percent of the total DoD budget.

The Defense Health Agency is a fairly new organization that you can kind of think of it as the health care delivery arm of the Military Health System. It was just formed in 2013. Congressional mandate to do that. Prior to 2013, military hospitals, also known as military treatment facilities or MTFs, and their personnel were under the control of Individual Services. This Congressional mandate led to the formation of the DHA and gradually have been transitioning to all MTFs going under the control of DHA rather than under the Individual Services. That was actually just completed this last summer. Currently, the director is Lieutenant General

Ronald Place. The goals of DHA are to integrate health delivery under both direct care and indirect care, and so, I'll speak to that in a little bit. It manages all the MTFs, coordinates management of the health care markets within regions, and some of the goals are to allow for rapid adoption of best practices, reduce unwanted variation across the Military Health Care System.

One of the early pushes of DHA was the creation and deployment of what's called MHS Genesis MHS. MHS Genesis is the new electronic health care system within the military. It doesn't want to tell you about MHS Genesis. Oh, there we go. So, MHS -- we've had an electronic health care record systems going back to 1996 within the Military Health System, a number of iterations of that. Prior to MHS Genesis, all of that was kept specifically at different military treatment facilities or regionally. It was not shared across the entire Military Health System. And importantly, it was not integrated with the VA system. So, there was a Congressional mandate

with the National Defense Authorization Act of 2008 that mandated that the Department of Defense and the VA create a joint use of an electronic health system so that data was better transferred as service members moved out of the military into the VA system.

As you will see, with some things related to newborn screening, while the military can rapidly deploy and meet those needs, some things move very slowly in the military, and so that from 2008, the contract for creating that system was awarded in 2015 on a Cerner based platform. 2017, at Madigan Army Medical Center, we were the first system to go live, and it's been a slow process expected to be completed in 2023. The importance of that is that it should have shared access to information to include information about newborn screening test results as our servicemembers and their families move from location to location, which is a very integral component of what happens in the Military Health System.

What most people are familiar with when they think of the Military Health System and don't work directly in our system is TRICARE. TRICARE is more generally thought of as a health insurance-like program that pays for care delivery by civilian providers. It does have some components as it relates to the direct care, which is what we provide in military treatment facilities, but a large component of the care that is provided to military beneficiaries is provided by civilian providers and covered by TRICARE.

There is always this balance of what we call make and buy decisions within the Military Health Care System of what do we provide directly and what do we contract and send outside of our direct system, and this is a component of that.

TRICARE contracts with third-party administrators divided by regions. So currently, the administrators for that are Humana and TRICARE East and HealthNet and TRICARE West. And there's also an overseas component.

The initial name TRICARE was -- there

were three plans that people could choose from. Those have actually changed over time. So, they've retained the name even though there's more than three plans now.

As I alluded to, there's this push and pull back and forth between direct and contract care in the Military Health Care System. So, the direct care system is what we provide at military treatment facilities or clinics. Currently, there are forty-nine inpatient hospitals and medical centers within the Department of Defense, thirty-two of those being within the continental United States and 465 clinics. You can see the numbers that we have for active duty and civilian personnel who work in those military facilities.

On the contrast is the amount that is done in the purchased care system, and you can see the large number of network providers and hospitals that are there within that system.

I would note that if you look at the most common procedure that is done in the MHS that's billed is childbirth, and so, that kind of

reflects the age of our population and the frequency that we care for mothers delivering and newborns as well.

This is a map showing where military treatment facilities are in the background. The green represents the numbers of beneficiaries. So, that includes not only active duty, active-duty families, as well as retirees, and their families, and individuals that are in the reserves. When they're activated, they are able to access these services as well. It's small for you to see, but all of the red spots are where there are military clinics and the H's blue -- H's are where there's hospitals.

In terms of the direct care system, there are priorities for care at military treatment facilities. The priority is -- the first priority is taking care of active-duty service members. That's the primary mission of the Military Health System is ensuring that we have a ready military force -- a medically ready force. And so, that does -- they do have the

first priority for care where that's available. The second priority is for family members of those active-duty individuals, and then you can see that the priority goes down.

So, what this means is that if there's a limited amount of space for care at a military treatment facility, as you get further down the priority, those are more likely to be pushed to the network to be cared for by civilian providers utilizing the TRICARE benefit.

What do our eligible beneficiaries look like? This was as of 2021 TRICARE evaluation report. In the maroon is the active-duty service members, 2.3 million active-duty service members within the Military Health Care System. The largest piece of this pie is the blue, which is the family members of the active duties. You can see what a large chunk of that is, with a large percentage of those being children under age four. The next largest piece of the pie would be retirees and their family members making up fifteen percent and seventeen percent. They

divide it by age sixty-five, because that's where they turn over to what's called TRICARE for Life when individuals are eligible for Medicare.

There are a total of about 120,000 births per year in the Military Health System. About half of those occur at military treatment facilities, with the other half occurring at civilian hospitals.

Where our service members are located. I couldn't find better breakdown of where all of our beneficiaries are. So, this is just the active-duty service members themselves. Eighty-seven percent are located within the US and territories, but we have a substantial proportion of active duty that is stationed at places outside of the United States, which is an important component of the medical care that we provide and how we design that medical care.

Another program that I thought I would share with you that people may not be familiar with, but I think is important related to conditions identified by newborn screening, is the

Exceptional Family Member Program. This program was established in the early eighties. It covers all of the services of the Department of Defense. Spouses, children, and dependent adults are included in the system, and really, individuals are required to be enrolled in the EFMP program if they have any special medical -- any condition that requires special -- specialty medical care for a chronic condition where those specialty services may not be available everywhere. Also for significant behavioral health concerns and for children receiving early intervention or special education services. And what the EFMP System primarily does is it controls assignments. So, the goal is to only station individuals at locations where their family member's medical needs and educational needs can be met. So, it will control and not allow someone to go to a location where those needs cannot be met. About ten percent of military families are enrolled. So, a substantial proportion of the military have at least one family member who's enrolled in the

EFMP program.

We have a long history of providing care for dependents, including children, in the military. In terms of laws covering that, that goes all the way back to 1884.

The military service members would bring families with them. There wasn't really any other medical care available and the medical care that was available through the military was often seeing family members and charging them for that. So, it was actually more of a response where they didn't want them to be charging those service members for that. But that was the first law mandating military to take care of dependents' medical care.

As World War II winded down, and we kept the larger standing military force than we had previously done outside of any active military conflict, there became quite a need to take care of service members, families, family members. And so, in 1943, Congress approved funding. Initially, it was only to care for maternity care

and care for children who were under one that were in the lowest four ranks. That actually first occurred at Fort Lewis. There was a major need for that care that was not being addressed and that was brought to the State Health Officer, who then pushed for that to occur. And 1956 is when the Dependence of Military Care Act was first passed by Congress, which allowed for the military to provide for all of the dependents. And then in 1966, that it was expanded to what is now TRICARE, the CHAMPUS System.

We have a long history of having -- training military pediatricians and providing direct care for children. Pediatric residency training in the military goes back to 1947. The first program was at Brooke Army Medical Center in San Antonio. Prior to that, there was a ninety-day course at Walter Reed, which was not down the road at the time, it was further into DC because of that major need for providing that care and the general medical officers did not feel comfortable providing that care. So, there was a ninety-day

course to try and get people up to speed for providing that care. At the time that they first started doing residency training in the military, there was actually only two pediatricians in the military.

We have a long history of providing care for military dependents and also a combat sport role. So, many of us are called on to deploy as general medical officers and on a number of humanitarian missions. So, a large component of pediatric care as a component of the humanitarian missions, the military medical services called on to provide them.

This is a picture of somebody I did residency training with Katy Gibson, while she was deployed to Iraq, taking care of a local child who was injured in an explosion just outside the base.

Our current strength, I couldn't find good numbers for the number of general pediatricians I could find in the army there are currently. There's over two hundred general pediatricians who are an active duty. I couldn't

find numbers for how many civilian pediatricians there are. In total, across all the services, there's about two hundred pediatric subspecialists, including all the pediatric specialists. So, a fairly small, small number, but it gives you an idea of how much direct care we're able to provide for pediatric patients.

That's a lot of background for you to kind of talk relatively quickly about newborn screening in the Military Health System. I took the timeline that is on the ACHDNC website and put that on the bottom of this related to important time points related to this Committee and Recommended Uniform Screening Panel. And on the top, I put some timeline related to policy and contracting issues that have arisen in the -- in the military related to that.

So, the first actual policy related to newborn screening in the military was an Army Policy in 2002 that required military treatment facilities to provide newborn screening. At the time, the policy required a total of four tests --

at least four tests had to be -- that had to be done. That obviously became an issue through the subsequent following years with the formation of this -- this Committee and ACMG Expert Panel and the recommendation for twenty-nine primary conditions and twenty-five additional secondary conditions, and there became quite a disparity between states. And because we have babies in the Military Health Care System across all of those states, there became a major concern that there was a major difference in what we were providing from one location to another across the military.

There was a TRICARE Management Agency requested study for this in 2005, and there was a recommendation to make sure that there was adoption of expanded screening. As I said, sometimes things move quickly in the military, sometimes they move slowly. And so, you can see the first time that actually led to any policy change was in 2011. And at that time, there was actually a central contract that was put into place that was with PerkinElmer Genetics. And the

intention of that contract was to move all newborn screening in the military to that contract. So, rather than utilizing state laboratories, it was a move to using one central laboratory. The intention of that was to ensure that babies across the Military Health Care System were having the same screening. So, as children moved from one location to another, that we would ensure that everyone was getting the same screening and that information on the results would be available, regardless of where someone moved.

That contract expired in 2016. A number of concerns arose during that time period that led to allowing that contract to expire. Some of the main ones were the implementation of a broader set of tests across multiple states. So, the major disparity from one state to another of what testing was done was reduced during that time period.

The other issues were related to, as we've talked about many times in this Committee, the newborn screening follow-up and subsequent

treatment is a major component of what occurs in a Newborn Screening System, not just the testing. And the contract with PerkinElmer covered the testing. It didn't really cover follow-up. And so, particularly in remote locations where there was not pediatric specialists available in the direct care system, some challenges of ensuring appropriate follow-up testing and subsequent required care when it was not done as a part of the state system. And primarily for those reasons, the decision was made to move newborn screening back to the state programs with the expiration of that contract.

So, as it relates to current newborn screening policy in the Military Health System, I would say, there is currently, again, we just transitioned to the Defense Health Agency very recently. So previously, there's policies that are under the Army, the Air Force, and the Navy. They're separate policies. There's been no pooled-together unified policy under Defense Health Agency. That is a discussion that's

happening right now within the DHA Women and Children's Clinical Support Group of DHA. The policies are essentially the same. There's some minor differences, but essentially, with the expiration of the central contract, CONUS is continental United States. So, that's a term that gets used within the Defense Health within the Department of Defense for OCONUS is out of the continental United States and CONUS is within the continental US.

MTFs are strongly encouraged to utilize their State Newborn Screening Program. And if they continue to use the central contract, they had to establish a formal plan for confirmatory testing, follow-up, and specialty care referrals. A little bit more vague as it relates to OCONUS sites. So, they were encouraged to contract with state programs, but were able to still utilize the central PerkinElmer contract. So, that's where things currently stand.

I thought I'd give you a couple examples of sites that are considered OCONUS by the

military and what is currently happening at those locations. I pulled Alaska first. So, while, you know, Alaska is a state, it's considered OCONUS by the military. In Alaska, I put the locations of military treatment facilities here in red is Coast Guard and blue is Air Force and the green are where Army sites are. There's two major military treatment facilities that care for children within Alaska and Bassett Army Hospital is in Fairbanks and JBER is outside of Anchorage. They utilize the state program within Alaska currently, and Alaska is sending their newborn screening to the state of Iowa at this time. So, that is what is happening within the Alaska military treatment facilities.

Their newborn screens are going to Iowa. They get recommendations back from the Iowa program. I would say that they then often contact -- so a couple of examples. More recently, we had identification of a child with cystic fibrosis that was in Alaska. That child received care through a pulmonologist who was in Anchorage, we

provided telemedicine genetics for that child, and that was all in the terms of getting EFMP started, and then that child was subsequently moved to a different location.

Similarly, the last one we had that turned out having to get transferred down to Madigan from Alaska was a child who had SCID that was identified by a newborn screen, got transferred down to Madigan, confirmatory testing done at Madigan, and then went to Seattle Children's for a bone marrow transplant as a part of the care there. So, those are a couple examples from Alaska.

Within the United Kingdom, mostly we have Air Force Bases within the United Kingdom. The main Air Force Base that cares for children, there is RAF Lakenheath. It's outside of Cambridge. They are contracted with the state of Wisconsin. So, they send their newborn screens to the state of Wisconsin, and when they get abnormals, they get recommendations back from the Wisconsin Newborn Screening Program. When they

have to then access care for follow-up or for treatment, mostly they're able to do that through specialists in Cambridge, but occasionally have to go to Great Ormond Street Hospital in London. And then they've also had some children that were identified that then were enrolled in EFMP and then were moved back to the to the United States.

They do have a couple of children, they told me, that have stayed there who have MCAD Deficiency that has not required substantial treatment, and they're cared for by specialty providers at Great Ormond Street.

And lastly, in Germany, we have a number of centers in Germany. The main one that provides direct care for children is Landstuhl. There is still a small NICU and neonatologist at Landstuhl. They also have they call it stork nesting where mothers who are pregnant and are set to deliver but are stationed at other more remote locations will be brought to Landstuhl and live in that region and then deliver at Landstuhl. The baby receives care there for a period before they go

back to where they're -- where they're living. So, they have those come in as well.

Landstuhl has continued to utilize the PerkinElmer contracts. So, their newborn screening is occurring through PerkinElmer, and they get results back through them. They then have to access care in the in the German medical system for follow-up. So, those are a couple examples related to how that's occurring.

And Korea is another location we have a large -- I didn't -- I felt like you saw enough maps of locations that I didn't need to include more -- but Korea is another one that's still continuing to use the PerkinElmer contract. I was actually contacted about a positive screen for galactosemia there yesterday that we're working through follow-up for.

I'm going to shift a little bit just to kind of tell you about what do we have for direct care as it relates to genetics. Again, I'm at Madigan Army Medical Center. So, you can see the one there. That's where I'm the chief of myself.

These are the locations where we have a genetics provider. Currently, we have a total of eleven geneticists within the Military Health System and fourteen genetic counselors. Now, not all of these are full time genetics providers. Keesler, I'll talk about in a little bit, has -- we have a genetics lab that that does a lot of the genetic testing within the direct system within the military. And there are three geneticists primarily, our molecular and cytogeneticists.

These are the locations, kind of the same map, just kind of showing where we all are. So, we're mostly where we have the major treatment facilities within the Military Health Care System. I would say that these are similar locations where other pediatric specialists are. So, in terms of the other specialists that we've discussed in these meetings of there being shortages of related to newborn screening, follow-up, pediatric endocrinologist, child neurologist, these are all the same locations where we have those specialties within the direct care system as well.

Questions I'm frequently asked about when I see -- when I meet with people outside the military and they're asking about how they've navigated TRICARE related to the coverage of genetic counseling and genetic testing within the TRICARE system. So, I thought I'd touch on that real quick and some challenges that arise related to that.

So, this is from the TRICARE manual, what TRICARE lists as authorized providers. And I would just say, genetic counselors are currently not considered authorized providers within the TRICARE system. Again, TRICARE is closely aligned to Medicare. And so, Medicare does not consider genetic counselors to be authorized providers, and so, TRICARE follows that policy. What that means is some challenges related to when we don't have those services directly available at military treatment facilities and people are sent to the network. It's very challenging to actually access care through a genetic counselor in the system because they can't bill TRICARE for that.

In terms of genetic testing, this is what's in the TRICARE policy as it relates to genetic testing. I hear from lots of individuals outside the military about challenges that they've had with trying to get genetic testing covered for TRICARE patients. So, this is -- it's, you know, TRICARE says it covers genetic counseling, again, provided by an authorized provider. So, it's written in the TRICARE policy is basically anyone who's an authorized provider, which could be a physician, a nurse practitioner, a PA, those are authorized, right, are the people that TRICARE says should be providing the genetic counseling, and that's a circle that we go into not uncommonly.

So, I feel fortunate that we were able to have some genetic counselors within the direct care system that kind of fall outside of this policy that we're able to utilize for that. But it's a challenge for -- for access for areas that don't have that directly available.

We do have the ability to add a military

treatment facility. I'm not really bound by the rules of TRICARE, nothing that I do actually gets TRICARE approval. So, it's a little bit outside of the insurance access component of that. So, it's a matter of my hospital paying for things. We actually have a reference laboratory that does genetic testing, that anybody -- anyone who's at a military treatment facility can use. Unfortunately, civilian providers are not able to send to this, even for TRICARE patients.

They have a fairly broad genetic testing menu, actually, so cytogenetics and broad number of next-generation sequencing panels like some sequencing, and a number of other things that have come up as it relates to newborn screening are included in newborn screening to include spinal muscular atrophy that are covered there.

With the formation of DHA, I am hopeful that we will get some traction with making some changes both in policy and expanding the services that we're able to provide directly for families and within the military. This year, DHA created a

Clinical Genomics and Precision Medicine Clinical Support Service, that we're outlining some goals over the next few years.

Some of those near-term goals are to expand the laboratory services for direct testing that we're able to do, addressing issues related to the clinical genetics workforce and genetic counselors in particular, some issues related to pharmacogenomics and how that information is put into MHS Genesis and translated across the system. And then we're working some -- there's some unique issues related to policy as it relates to genetic testing and active-duty service members that we're trying to address as well.

So, in summary, so I would say, another thing I'm asked about not uncommonly is how much is the military going to continue to provide medical care for -- For pediatrics? How much are we going to send out to the -- to the community versus providing direct care, and I think everything right now is we're continuing to train the same number of pediatricians, we're sending

the same number of people to pediatric specialty care, we're continuing to provide really the same amount of direct care for complex specialty needs within the military system. And I think that, at least in the near future, is going to continue to be the case. There are a number of changes related to the DHA transition, both in terms of this push/pull between direct care that we provide and the contract care, and that does relate to where children are -- where babies are born, and then therefore where their newborn screening is done.

The MHS Genesis transition and how that information will be seen visible across the DHS, Department of Defense, as well as some issues related to newborn screening are related to that. I've had a request to try and work towards electronic order entry and results return within MHS Genesis since we have a single system with newborn screening labs. The current priorities as it relates to MHS Genesis changes have to align with both a VA and DoD goal, and the VA does not

provide care for newborns. So, it is not an early change that will occur. But it's something that I'm hoping we can get.

As of right now, the Newborn Screening Program is primarily aligned with states. There likely will be a DHA policy update related to newborn screening within the next year. I expect that it will align with that. And I've given you some information both about clinical genetics, availability, and genetic testing coverage within the Military Health System.

And that's all I have. Any questions for me?

NED CALONGE: Thanks so much, Lieutenant Colonel Hogue. That was a great presentation and very informative. And I'm wondering if maybe I could ask you to stay at the podium while we have questions and discussion?

JACOB HOGUE: Sure.

NED CALONGE: That would be great. So, I'm looking at the room and reminding you that we're going to talk to Committee members first, as

far as questions and discussion, and then we'll ask our organizational representatives for additional comments, discussion, and questions. I realize that there are folks on the phone. I'm going to ask you to use the raise hand function on your Zoom screen. For those folks in the room, you'll notice you have a microphone in front of you, and there's a little button on it. So, if you're not using the microphone, could you push the button so that it's not red? And Dr. Lal, I'm going to ask you to unmute, or mute your -- yours, and then when you speak, unmute, and we'll kind of go from there.

The last thing for people in the room is if you have a question, if you could let me know by just putting your name card on it's side, that would be most helpful.

So, I'm going to start Lieutenant Colonel off, if that's okay, and just ask a couple of questions. So, we know there is variation by State Newborn Screening Programs, in terms of implementation on conditions added to the RUSP,

and I wondered how that shows up across the active-duty families. Does that influence what families are screened for on items of the RUSP?

JACOB HOGUE: Absolutely. I mean, so most of them are aligned with the state where they're born. So, an example would be between Washington state where we have added some of the newer disorders to include XALD and MPS 1 versus a child who's born in Hawaii, that we then have moving, where they have not added those disorders. So, there are some differences absolutely state to state, and those are reflected in the newborn screening that's occurring, I think.

How does -- how will that influence how we move forward as it relates to policy? I think it's unlikely that we move back to a centralized contract. While those differences are important, I think the other differences or the challenges that we saw arise from moving to a centralized contract kind of balancing the issues related to follow-up and treatment versus the differences of what is tested from one state to another will be

how that is looked at is looking at that balance. And I foresee that those differences will not outweigh the challenges related to follow-up and treatment to change that policy back to what it was.

NED CALONGE: I appreciate that. And I understand that, you know, it's a -- it's a current hot topic here for the Committee and for, I think, newborn screening across the country and appreciate you kind of highlighting the reason that's an issue.

The other question has to do with, I would think that DoD and the military families system would be an ideal place to think about quality improvement metrics, specifically thinking about the time to screening positivity, time to confirmatory testing, and time to treatment. I'm wondering if -- if -- if you have, I guess the way I'd say, the resources, and the direction to kind of do that quality improvement for newborn screening, across the DoD?

JACOB HOGUE: I would say it would be a

very good place for us to look because we're so broad on what we collect or where we're treating children. But I would not say that we have any unified policy or place to look for that. It's been very -- examples would be where we've looked closer into newborn screening sent from OCONUS regions with concerns that there might be delays in those coming and there have been some challenges related to both timing and then issues getting through customs actually where newborn screens and had to be repeated.

So, I think kind of looking at where we think the most substantial challenges will be, is where we've been able to put some priorities, but you're kind of looking at the -- the newborn screening. Anybody who's looking at the newborn screening system in a particular way, I would not say that that's been a, you know, a major centralized plan for addressing that in a way that that would be better addressed.

NED CALONGE: Well, I have to say I appreciate that. I guess it's also important to

tell you, I appreciate that you're there and taking on the service responsibility and I just -- I'm always looking for, you know, what -- what folks in general could do to make things better, and I think when you're -- when you're a department of only one, your personal resources, especially if it's spread over so many other duties, I think is tough. I hope you hear that we're very appreciative you're there.

JACOB HOGUE: Thank you.

NED CALONGE: I'm going go next to Kyle.

KYLE BROTHERS: Yeah. I just wanted to ask about timelines and turnaround time. I just know in Kentucky, we have, you know, a few-hour drive, and that creates all kinds of barriers and sending samples across the Atlantic Ocean seems like it could really create remarkable delays. I'm just curious about that.

JACOB HOGUE: Yeah. So, that was when I was speaking to the people in Korea, Germany, and England that I've spoken to recently about this. It's -- so, this kind of comes a little bit to the

direct and indirect system and what happens kind of uniquely in those situations, because they're actually not delivering many babies at those military treatment facilities anymore. So, what frequently happens in Korea is -- and Germany other than Landstuhl, most of the babies are actually born out in the network here, and they have a newborn screen that is there that is in the Korean system or in the German system. So, they may get that back. And then it's actually only on their follow-up, they come a few days after, or they will then send the screen to the state of Wisconsin or PerkinElmer genetics. And so, where they will often get the screen back, they'll be contacted by the German or the Korean hospital letting them know that they had this abnormal around the same time that they're getting a result back.

My understanding is that the turnaround has been fairly good for those. I mean, they go overnight, the same way as they often go other places and the turnaround -- the challenges have

really been those smaller numbers that get held up in some way by shipping problems or customs problems. Those have been the ones that really are a holdover for what the difference is. But otherwise, I think it's not been as much of a challenge. But again, in a lot of those places, it's actually -- it's actually a second screen that's occurring that's going there and sort of ensuring that that's done within the auspices of the US health care system, I guess is the goal from that rather than having those contracts be with health care resources within another country.

NED CALONGE: Thanks. I just thought I'd just take one second to talk about social issues. So, the National Academies, a long time ago, abandoned the use of honorifics or degrees and calling on people thinking that from an equitable standpoint, not using the doctor, or designation was something that made communication a little bit more easy flowing. I do think Lieutenant Colonel is one I'd like to keep, if that's okay with Lieutenant Colonel, but if I call

you by your first name, I hope that's acceptable. And I would kind of like that to be the norm for the Committee moving forward, unless someone has a strong objection. And given that preamble, I'd like to call on Michael.

MICHAEL WARREN: Thank you. The question I had was related to timeliness. So, it's been covered. Thank you.

NED CALONGE: Thank you. I'm going to go to Jennifer.

JENNIFER KWON: Thank you so much. I have to say, Lieutenant Colonel, I have a hard time picturing sort of what short-term follow-up looks like. You've done a really nice job talking about newborn screening and the identification maybe of screen positives. But I was wondering if you could share an anecdote maybe about how short-term follow-up works. I think you touched upon it by talking about your call. But let's say you want to initiate treatment or want to do confirmatory testing, I was wondering how that works within the military system.

JACOB HOGUE: It's really going to depend on where you are and what resources are there. So, I think there's -- there's no unified answer to that. So, if someone -- if a baby is born at Madigan Army Medical Center, where I am, it's going to occur very similar to how it does at your hospital. So, they have me there, we have a pediatric endocrinologist, we have hematology oncology, we have all the ability to send any confirmatory testing. Often, we turn out sending that testing through the same laboratories as the state of Washington Newborn Screening Program is recommending so that it's aligned with that program as compared to where I would otherwise send genetic test results or metabolic tests to provide confirmatory results. So, that part will look very similar to any other particular location.

Where that becomes more unique is in locations where there are no pediatric specialty providers related to follow-up. So, a lot of that falls harder on the general pediatrician, and it's

part of why we try to have general pediatrics providers at many of those locations. And that's one of the goals of having that aligned with the state programs is they often will facilitate earlier access to specialty care providers. Within state programs, that works fairly well. Overseas, it's more of a challenge, and I think it's kind of -- what frequently happens is reach backs to those of us that are at military treatment facilities. So, all of the pediatricians that are in those locations trained at facilities where they have all those pediatric specialists, and they reach back all the time so that I might get contacted from -- even though I have no control, I'm directly responsible for the care that occurs in Korea -- they will reach back to me as soon as I get that abnormal and we'll work together to work towards a follow-up.

JENNIFER KWON: And just to follow with a question to that, so how are treatments reimbursed? Like, are -- do you feel like that's a challenge through TRICARE? Do families have to

use, let's say, State Medicaid as a secondary for reimbursement?

JACOB HOGUE: I would say that I probably don't have as much of a direct eye on how TRICARE provides coverage for pharmacy benefits. It's similar to any other insurance plan. So, there is coverage for those. I know that we've had challenges with quick, particularly newer, very expensive treatments. I'm assuming that SMA treatment is on your -- your mind, as it relates to that. And we've seen that be a challenge that I've seen come up. We have a challenge, you know, often that is an example of something that even though we might have providers to care for in the acute time period, our hospital has a budget that it has given us. There is no special pharmacy budget, for example. So, if there's something that arises, that's over a million dollar- treatment that comes up as a one time, we would have to come up with that out of our hospital pharmacy budget, which is relatively small, in order to get that in the short term. So, that

would be example even where I am located, where we might have the individuals available to provide that treatment. That might actually go out to the network to be able to get that care on a quicker access. But, in general, that's not the case. We usually -- I don't usually have to. Again, what we do at a direct care facility doesn't have to get TRICARE authorization in the same way that you were if you were taking care of a TRICARE patient. So, it's really just internal, within the hospital decisions about how the budget is utilized. And usually, that's not a challenge for me, as it relates to pharmacy. The one offs are the ones where the pharmacy doesn't have the budget to get that in the short term. If that answers your question.

JENNIFER KWON: It does, thank you.

NED CALONGE: Chanika.

CHANIKA PHORNPHUTKUL: Thank you very much. I have a question about how can we at the medical facility -- I'm practicing in Rhode Island -- so, Newport is a big Navy station, and we do

see patients that have TRICARE. And how -- and the family moved, and I always have a hard time trying to connect the patient back to the community of, you know, where I could, you know, send them back. That's sort of, how can we help? And how can we -- where's the access to that?

And sort of a follow-up to that, the situation that I have dealt with is the shortage of metabolic formula that happened, you know, in the last six months or so. And what we have found is that working with TRICARE specialty pharmacy was really challenging. It's, I think, it's challenging all over the country, but I need some guidance so I can take that back home. Thank you.

JACOB HOGUE: I wish I could provide you with more specific guidance on how to navigate TRICARE. I would say I've heard similar things from a variety of civilian providers of challenges navigating TRICARE, both in terms of specialty pharmacy and genetic testing is probably where I hear about that the most where people run into challenges with coverage of that through TRICARE.

Again, those -- TRICARE itself is administered through the secondary contractor. So, that's -- while we may have some influence over what is in TRICARE policy, and therefore how that comes through related to how the contractors interpret that, you know, we don't actually have any control over what -- what is covered necessarily beyond our influence on policy. So, I don't know if that gives you a very clear answer for how to get things better covered through TRICARE and to navigate discussions with the TRICARE administrators to ensure that coverage occurs.

I think in terms of connecting with military specific resources, I think usually having contacts with the closest pediatrician is probably the best contact. And so, we're a fairly small system, and they often will have broader context. And so, you know, an example would be when I was a fellow at UCSF, Travis Air Force Base frequently referred patients to us to San Francisco for specialty care. We had challenges with navigating TRICARE as well, that they were

able to navigate better from inside the system for testing that we wanted to do or follow-up and those sorts of things. And really, maintaining a good relationship with the active-duty Air Force pediatricians who were at Travis Air Force Base, who were the referring providers and reaching back to them and having a direct discussion, rather than just sending my note, they were frequently able to facilitate getting care, ensuring that they're connected internally to the special systems within the military is usually the best way to do that. People are certainly welcome to reach out to me as well. But I probably don't know the direct contacts there, as well as a general pediatrician that who's stationed there.

NED CALONGE: Ash.

ASHTOUSH LAL: Thank you. I'm also from UCSF, and in hematology, we have also seen some patients from Travis. I appreciate what you have presented. My question is, it's really a follow-up to some of the other discussions that have taken place. For some of these rare disorders,

the centers that excel in those conditions or are doing active research maybe just in a few places around the country, how do you view -- is there support for families to form some relationships with those centers so they can both obtain current advice on standard of care as well as be eligible for any advances in management that may happen in the future?

JACOB HOGUE: Yeah. The short answer is yes. It depends on regionally and what the goals of care are. So, similar to -- so, there are abilities to provide for both travel as well as insurance authorization for children within the Military Health System to travel and be seen by specialists and receive treatment that is uniquely available at certain locations. So, the short answer is yes, absolutely.

What happens sometimes is where, you know, a family identifies, and they say I want to go see this expert on this disorder and trying to convince TRICARE that that's really a need that needs to be addressed versus a want or a desire

because they don't just provide insurance authorization, they provide travel for both that individual and their family members to that location for a period of time. And so, the short answer is yes, absolutely, if it's -- if it's a fair need that truly needs to be addressed, that happens fairly regularly.

The -- again, some of that goes through TRICARE and the regions get involved in that issue as well. So, they try and say, is there someone who's regionally able to provide that care rather than traveling from where I am to, you know, Duke or to Children's National, or whatever the case may be? Is there somebody who's on the West Coast? Can we send them to Seattle Children's? Can we send them to OHSU? Can we send them down to San Francisco for that care? So, there are some components of the logistics. But the short answer is, yes, that can occur.

Now, they won't send for clinical trials, for example, right? So, if it's for clinical treatment, the same as any other insurer,

clinical trials are not inherently a part of clinical treatment that insurance is covering. And so, that comes up sometimes where people say I want to go to UCSF to be a part of this clinical trial and TRICARE Insurance won't pay for someone to travel there to participate in a clinical trial, if that answers some of your question.

NED CALONGE: Thanks. I'd like to now turn to our organizational representatives. I'd like to ask those org reps on the phone, if it's possible to turn your camera on, it helps us see your hands a little bit better, and I'm going to start with Cate.

CATE WALSH VOCKLEY: Hi, thank you. Cate Walsh Vockley, National Society of Genetic Counselors. First of all, thanks for the great overview and for your acknowledgement of some of the challenges related to access to genetic counseling services. I think it's important to acknowledge that the members of the National Society of Genetic Counselors have been working diligently for quite a number of years to try and

become approved providers or recognized providers by Medicare, Medicaid, and that if that happens, that will improve some of your access issues.

My question relates to whether or not -- you mentioned that APPs, nurse practitioners and others, it's okay for them to provide genetic counseling, and I'm wondering whether or not they're actually doing that? And if so, have you looked at what the genetic counseling licensing laws say in the states where they're practicing in terms of who is able to provide genetic counseling?

JACOB HOGUE: An answer to the first question of whether we've looked at that, or I would say, anecdotally, we've looked at it many times, there have been some more different ways to look at that as well. There was actually a study the group was involved in related to a formal program of trying to train primary care providers to provide some basic genetic counseling surrounding genetic testing that was being performed. And that essentially worked okay, in

the short term and not well, in the long term, even with substantial training for those providers. So, and in terms of a more objective, formal way of studying that, I would say, limited, I'd say my, my incidental experience -- so what -- what frequently occurs is that that those providers don't feel comfortable providing that. So, that's sort of a TRICARE ask them to provide that genetic counseling. That is not something that they feel comfortable doing most frequently. So, it's not so much a situation where we have individuals who are PAs or nurse practitioners, particularly and specifically put in places to provide genetic counseling in place of genetic counseling. I didn't want to give you that as the impression because that is not at all the case. It's more than the circumstances where providers are in a place where they feel genetic testing is warranted and they don't really feel that they have access to reach out to someone or to get genetic counseling in some other ways. And so, they provide the best counseling that they can

surrounding that is what I've seen more commonly.

But I think, particularly where I where I am, where we have genetic counselors and where I'm there, people reach out to us all the time and would like us to serve that function as much as we possibly can. So, I would say, in general, people are not comfortable providing that. I think the situations surrounding the policy doesn't -- doesn't really match where people's knowledge and comfort level is providing that care.

CATE WALSH VOCKLEY: Well, and as genetic counselors become acknowledged providers, there's so much access to virtual genetic counseling that might be able to support your patient population. Thank you.

NED CALONGE: Debra.

DEBRA FREEDENBERG: Hi. Thank you for all of the work you're doing on behalf of newborn screening in children. My question really relates to continuity in short-term follow-up. As part of my -- I'm also in Texas State Newborn Screening Program, and we have a large number of military

facilities within the state, and we've had challenges on continuity in which when we do the screens and our follow-up folks are trying to call back the person, we identify someone within the facility as a contact, but they've been transferred or deployed or whatever, and then there appears to be no one that can do that follow-up, and we spend hours trying to figure out how to get the child appropriately cared for and I was wondering if there was any overarching within those providing those services, the pediatric services, to have some sort of continuity, because it seemed like there was very, very limited continuity happening.

JACOB HOGUE: I'd be curious to know what your experience is, you know, navigating that for other facilities outside the military. We certainly have that as a challenge. We have -- at Madigan, we have -- the goal is we have one person who's in charge of all the -- and so, what happens frequently as compared to services provided outside the military, is that it's a large system

and people are sort of assigned their pediatrician or that -- but they are not able to do that -- or pediatrician or family medicine provider to care for the baby after birth. And that's not really done until the baby's enrolled in the system. The baby can't be enrolled until the baby's born. So, as compared to where individuals might identify who's going to be the care provider for their baby before they're born and then, that can be written on the newborn screening card. So, that's the person that they have a contact for an abnormal result. Our system inherently creates a challenge related to that, I would say.

The ways that we've tried to address that are probably different at every facility. So, it may be a facility specific challenge that you're dealing with there. It's absolutely, it's certainly a problem. We have mobility of our providers, as well as our families that move, and I think that does create certain challenges and that would relate to that as well. We've tried to address that at certain facilities by having one

number for the state screen lab to call. So, that's what we have at Madigan, where regardless of who the baby is, or who their primary care provider is, it all filters through that individual, who then establishes the follow-up care to do that. And so that's what we've -- again, as we move to DHA, and we're trying to push out best practices.

Right now, it's -- what happens at each military treatment facility as it relates to something like this, is going to be individual to that particular military treatment facility, similar to the way it's going to be at any other hospital that's inside or outside of the military. And so, I would imagine that there's many challenges at specific facilities of navigating that type of situation.

I think the best practice is to have, again, given those inherent challenges with who the babies are seeing after birth and not having continuity to that it's established before the baby is born, is having one sort of in-road to the

system that then can push that. But there is no unified policy related to that or particular something that would push that to be a requirement at all military treatment facilities.

NED CALONGE: Thanks. I want to ask our organizational reps in the room to -- I know you have to share microphones, but the closer you can get to it, the better folks, especially online, can hear. And Natasha, you're next.

NATASHA BONHOMME: Hi, I'm Natasha Bonhomme with Genetic Alliance. Do you have any policies or recommendations around education either on the front end in terms of having people be aware that this is going to happen and how it will happen, depending on their location, or on the, I guess you could say, back end if there's a diagnosis and more condition-specific education or resources? Or is that then kind of just out of your hands?

JACOB HOGUE: I would say that there is policy surrounding one, the requirement to perform newborn screening and what the approach is if a

family is declining newborn screening, there's some policies surrounding that. In terms of other components, the policy is really to align with the state programs. And so, there is some reliance in that some of the benefit of aligning with the state programs is relying on those programs and the components of follow-up related to those programs in terms of what is -- what is both required at the front end about counseling surrounding newborn screening, as well as education surrounding conditions that are -- that are identified. And so, that's one of the goals of aligning with those with those state programs. I would not say that there's any broader DHA or Department of Defense Policy surrounding those -- those requirements.

NATASHA BONHOMME: Okay. So, does that mean there's any education coming from your huge team of one out to those families about newborn screening, or is that -- is that meant for them to get that information in other ways?

JACOB HOGUE: I'd say there's a large

amount of care that's provided that is not necessarily captured by policy. And so, yes, there's lots of education and follow-up that occurs for children, and I think we do -- I like to think that we do a very good job of providing education for families after we identify some of the conditions and get them into care and those kinds of components. But is that covered by policy? No, that's just providing good -- what I would think of as being very good medical care as it relates to follow-up for substantial disorders.

NED CALONGE: So, we just have a couple of minutes left. I'm going to go to Marc on the phone.

MARC WILLIAMS: Thank you, Marc Williams representing ACMG. Thanks very much for the presentation. I have two brief questions just to follow up and expand on some prior questions that were asked, the first relating to acute care with a positive newborn screen. I'm curious, in military facilities, whether there is access to the ACMG Newborn Screening Act sheets for the

providers to kind of assist with that.

And then, the second question is specific to treatment, which is if you're aware of whether or not TRICARE covers medical foods. This is unfortunately, as this group is well aware, a very common exclusion in most commercial insurance plans, and so, I was just curious to see if TRICARE is essentially the same as other commercial insurers or whether they have a specific policy on them.

JACOB HOGUE: The first answer, yes, absolutely. We have access to the to the ACT sheets to the ACMG and would say they're regularly utilized, probably depending on which state and how to get results back through PerkinElmer, for example, are more reliant on those versus reliant on the program to give them the follow-up information.

As it relates to the medical foods, I don't know that I know the specific details related to that. I know that there were major challenges a few years ago when there was a change

in the TRICARE contracts with coverage, particularly even if formulas for inborn errors of metabolism and medical foods were captured as a component of that. I believe that there is some coverage, but I know that it is imperfect and incomplete. That would be my short answer to that.

MARC WILLIAMS: Thank you.

NED CALONGE: And Margie, you have the last question.

MARGIE REAM: Margie Ream with Child Neurology Society. There are some situations with private or state-insured individuals that need out-of-state subspeciality care, particularly, you know, maybe very urgent, but getting approval for payment for out-of-state care can be a delay. Has TRICARE or the Miliary Health Service come up with a way to provide timely approval or very quick approval for out-of-system or network care in those sorts of situations that maybe the outsider military system might learn from?

JACOB HOGUE: I think the short answer

is yes, but it's inherent to our system being a federal system. We're actually -- that kind of aligns with some of the questions earlier related to some policy components where we aren't necessarily obligated to follow the state regulations or how that works within states. We, in general, try to follow those, but there's times where the federal rules might be a little different than the state rules in some way or what is mandated through the DoD. We are not -- the DoD is not at all bound by state boundaries. So, we -- we -- I would say that wherever the specialty care needs to be for follow-up and treatment is not really a challenge as it relates to approval. I would say more of the -- the -- the little line that showed the regions between the TRICARE regions is probably more of a challenge than the state-to-state lines more just navigating payment, and who's going to pay for that, and how does it actually shift over to this other, or can we pay for something that's occurring in that region that's occurring here.

But in general, that is not an issue that arises in the DoD system.

NED CALONGE: I hope everyone can join me in thanking Lieutenant Colonel Hogue for an excellent presentation and standing up there in the hot podium for a good discussion and it's very useful. Again, thanks for all you do for our active-duty military and their families. Thanks a lot.

JACOB HOGUE: Thank you.

Implementation of Conditions Recently Added to the Recommended Uniform Screening Panel

NED CALONGE: You'll remember that we had what I thought was a rich discussion, talking about the enabling factors and challenges to implementation of conditions added to the routine screening panel across the country. And we also discussed the complexity of the system, as it varies as well.

So, for this roundtable session, we've invited, and we'll hear directly from states that range in size, location, program structure, and

legislative requirements about their processes and experiences and implementation.

I'd like to introduce the panel now and then we'll get started. So, the first one I'm going to introduce is Lisa Caton, who is the Director of Screening and Special Services at the Oklahoma State Department of Health. Here she oversees the Newborn Screening Program, the Newborn Hearing Screening Program, the Pediatric Audiology Program, the Birth Defects Registry, and the Oklahoma Childhood Lead Poisoning and Prevention Program. She received her Bachelor's in Nursing from the University of Oklahoma in 2002, and a Master's in Science from Southern Nazarene University in 2014.

Early in her career, she worked as a charge nurse in a Level 2 Nursery, a quality improvement nurse, and a public health nurse. In 2009, she accepted a position in the Oklahoma Newborn Screening Program as the Newborn Screening Quality Assurance and Education Coordinator. Here, she had the opportunity to lead quality

improvement initiatives, add conditions to their newborn screening panel, implement pulse oximetry screening for critical congenital heart disease, provide education to various health care providers, and collaborate with stakeholders. In 2015, she became the administrative program manager for the Newborn Screening Program, and in 2017, she transitioned to being the director of the service area, where she continues to strive to improve the lives of infants and families throughout Oklahoma.

Next, we have Dr. Richard Olney, who has been the Division Chief for the Genetic Disease Screening Program at the California Department of Public Health since 2015. He's currently also the Director of the CDPH Genetic Disease Laboratory. He's board certified in pediatrics and clinical genetics and has had a career in the Division of Birth Defects and Developmental Disabilities at the Centers for Disease Control and Prevention that has spanned more than twenty years. He was previously the Medical Director for the Emory

University's Genetic Counseling Training Program.

Joining us in the room is Dr. Susan Tanksley, who is the Deputy Laboratory Director in the Laboratory Services section of the Texas Department of State Health Services in Austin, Texas. She manages the day-to-day operation of Texas Public Health Laboratory, which encompasses the state newborn screening, clinical chemistry, microbiology, environmental chemistry, and emergency preparedness laboratories. These high-volume testing areas process 4,500 to 5,000 specimens per day. Dr. Tanksley's focus has been on Newborn Screening Program expansion and improvement, including implementation of evidence-based performance measures in the preanalytical and postanalytical phases of screening.

She chaired the APHL Newborn Screening and Genetics and Public Health Committee from 2011 to 2017, co-chaired the Newborn Screening Workgroup for Mountain States Genetics Regional Collaborative Center from 2009 to 2015, and has served on the Advisory Committee for Heritable

Disorders in Newborns and Children as an organizational representative for APHL since 2013, and served as a member of the Condition Review Workgroup for the acting since 2012. Dr. Tanksley received a PhD in Genetics from Texas A&M University in 2000 and has been certified as a high-complexity laboratory director to the American Board of Bioanalysis since 2005.

Dr. John Thompson received a bachelor's degree from Brigham Young University in molecular biology and then received graduate degrees in public administration and public health genetics at the University of Washington. Here, he focused on newborn screening policy. Dr. Thompson has worked for the Washington State Newborn Screening Program since 2003 as a follow-up consultant, the short-term follow up supervisor, and most recently as the office director. He oversees all operations for bloodspot screening in the Regional Newborn Screening Laboratory screening babies born in Washington, Hawaii, and Idaho. He has had very rewarding opportunities to co-chair the NewSTEPs

Short-Term Follow-up Workgroup and contributes as a member of the advisory -- of our Advisory Committee's Cost Analysis Workgroup.

And last on the list but certainly prominent as well is Dr. Roberto Zori, who is the Chief of Clinical Genetics and Metabolism at the Department of Pediatrics and Director of Cytogenetics and Interim Medical Director at the Department of Pathology, Immunology and Laboratory at the University of Florida. Here, he received his medical degree at Odense University and completed his pediatric residency at the Bay State Medical Center and the University of Florida. Dr. Zori is a clinical geneticist and cytogeneticist, as well as a consultant to the Craniofacial Clinic for Clinical Genetics, Diagnostic and Counseling Issues. In addition to his chief and other directorship duties, Dr. Zori is interested in clinical syndromes, especially neurogenetic syndromes. He has served on the Florida Genetics and Newborn Screening Advisory Council since the 1990s and as chair of the Advisory Council since

2021.

So, I have a set of questions that I hope the panelists can identify, and we'll try to work through you as we go. But let's start with what does the process look like for your state to implement a new condition or add a new condition to your state screening panel, and what additional steps or requirements do you have to take or meet to implement the condition? And since Susan has stepped up, I'm going to start with you.

SUSAN TANKSLEY: All right. Thank you. Could I have my slides, please. I'll go ahead and get started while they're looking for those.

So, obviously, it takes a lot to implement a new condition in any state, and those are John's. So, in Texas, we have -- part of our statute actually states that we will screen for conditions on the core and secondary conditions on the RUSP, basically, as funding allows. So, if we have funding available, then we are expected and required to screen for those conditions.

So, in some cases, that has worked out

very well, and in other cases not so well. So, for -- in the in the case of Pompe, MPS I which have been on the panel for an extensive period of time, we have not had funding to implement those and so, that's one of those situations where we haven't been able to implement yet, but we're in the works for that. So, oh, there we are. All right, next slide.

The next slide is from our Health and Safety Code, and so, that's the statute that exists pertaining to screening for conditions on the Recommended Uniform Screening Panel. And then, in addition to those on the RUSP, the Newborn Screening Advisory Committee can also make recommendations for additional conditions to screen for. So, next slide, please.

So, as I mentioned, we haven't been able to start screening for Pompe or MPS I yet, and that's been contingent upon funding, whereas XALD and SMA, because they built on existing technologies, we were able to add those more rapidly because (1) there's less expense and (2)

it didn't require additional lab space.

So, because of the additional lab space required for Pompe and MPS I utilizing tandem mass spec, but not the existing tandem mass spec, we needed more space in the lab and we also needed the additional funding.

So, I can just go through a few of the things before the slide comes up that we have to consider. So, first of all is the financial aspect. Okay. I have power, excellent. Maybe. All right, no worries. So, one of the first things we have to do regardless, is to determine what it's going to cost us to add a condition. And so, we prepare a cost estimate that's inclusive of both the laboratory costs as well as the follow-up costs for that. And, if -- at this point, we have a law in place, which is amazing that actually establishes a Newborn Screening Preservation account. So that's in statute and it's been in place now for, I think, three years. Unfortunately, the source of funding, which is leftover Medicaid funding, hasn't been there. So,

even though it's been in law for three years, we have $0.00 in that account, which makes it pretty hard to implement a new condition. Previously, we received funding through legislative appropriation requests. So, specific requests for those -- for the addition of conditions, which is how we got money for XALD and for SMA.

But this law was put into place in hopes that it would solve that problem. So far, it hasn't. But we have hope, and we've been told that November 1st, which is supposed to be the transfer date. So, our fiscal year ends August 31st. So, after the end of the fiscal year, if there's money left over, we're supposed to be able to receive this money. So, this will be the first time we have money left over, and that process is being worked through with the comptroller's office right now, but we do anticipate a sizeable deposit sometime in the next few months that will enable us to implement Pompe and MPS I, and my slide is up there. So, okay. Well, I'll just talk through it.

So, if you're in the room, you can see behind Dr. Calonge that there's a slide that -- it's basically just a blip from our project management schematic, our plan for implementing Pompe and MPS I and MPS II, and it just gives some of the steps that are required -- high-level steps that are required in the implementation of basically any disorder and as well as the projected timeframe for that.

So, and I'm still not able to project it in here, but so that building retrofit piece looks -- it's that really, really long top line. And so, we have been in planning phases, because we haven't had funding. We've still been in planning phase for a very long time. We developed a cost estimate quite a while ago. We have all the building plans in place. But we are regulated, our -- our buildings are managed by a different agency. And so, we've been working with them to try to get that retrofit in place so that we can add all of the exhausts needed, basically for the tandem mass specs. So, that is in progress.

We have one -- another thing that has to be determined is which method will you use. And so, we did spend time researching the various methods that were available. When MPS II was added to the panel, that sealed the deal on which method we would use. And so, our plan is to use LC tandem mass spec for that screening.

We also have to evaluate first and second tier and whether those will be added as part of our screen or not. In Texas, we tend to utilize a lot of second-tier screening as well. And we do intend to move to next gen sequencing for our second tier. It'll actually be like a third tier as part of Pompe, MPS I and MPS II implementation as well.

So, you have to do -- you do your method development, you'd have to do validations, verifications, those sorts of things, which take a tremendous amount of time. I keep trying to let everybody see it, but you're not going to. All right, I'll just keep talking.

So, for those of you who can see the

little schematic, the actual process of the method development, the doing -- we don't do true pilot studies, but we do an extensive validation study to develop, not just looking at the performance metrics, but also developing our reference range, because of our large population, and we do two screens in Texas. We have to evaluate both on first screens, second screens, and look at all the things that might have had an impact on the assay as well. And so, that's part of that.

We have to determine how that's going to work into our workflow. So, we process about 2,500 specimens a day, six days a week. And so, how will that fit in? Even looking at like the plate punches, and how are you going to integrate that into the existing screening? What's time critical. So, where is it going to fit in the workflow? Obviously, we have to develop follow-up protocols and so, we have a lot of specialty centers in Texas and so, we like to meet with our specialists and have their input on the development of those, go ahead and develop those,

and then meet with them again, and have a final verification.

Yay, we have a slide. Okay, so another thing that takes a lot of time in our implementation is actually the health information technology component of this. So, not just the integration of the testing and the workflow in our LIMS and the follow-up processes in our LIMS, our Lab Information Management System, but we also do have a considerable amount of electronic test orders and results in Texas. And so, about twenty-five percent of the babies that are born, we have the information coming in, and the results going back out to the EHRs, and surprisingly, that takes a considerable timeframe. Maybe it's surprising, maybe it's not. But for instance, when we implemented cystic fibrosis, we had a nine-month timeframe that was completely dictated by the ability to have that testing done with the hospital systems, in order to actually be able to make sure that not only could we send the results, but they could receive them, and they were

actually, you know, the right things. So, there's a lot of testing that's involved in that.

For staffing, we have to obtain FTEs, or positions, as well as fill them. And this Committee, and a lot of others, have talked about workforce issues. It's definitely an issue in state programs.

And then finally, communication and education are a big thing that we try to improve upon each time. You know, Natasha always has questions about education and our communications with others, and it's critical not only for the health care providers to know that we're going to be screening for something new, and what they need to do if they receive those results, but also, we have that education out to families as well. And so, we try to integrate that into our communications for families.

One of the things that we've been doing, probably since cystic fibrosis in 2009 when we added it finally, is that we have a grand round with medical providers. And so, that's very

helpful to know from a program perspective, what they would expect to get and what they should do, but also from one of the specialists talking to them specifically about the disorder, and what it does, and things like that. So that's been very helpful. That's all I have. Thank you.

NED CALONGE: Thanks so much, Susan, and thank you for going first.

I do want to say that it's my understanding, this is the first major Advisory Committee meeting in this building for more than a couple of years, and I'm not trying to make excuses, I'm just asking for some forgiveness as we get our technology of the challenges of the hybrid meeting down. And I appreciate the work of staff, who's really working hard in the background to make this successful. So, I hope -- I hope folks appreciate that as we move forward. And Lisa, I wonder if I could call on you to talk about Oklahoma. And I think you may not have any slides, so it may be easier for you.

LISA CATON: Yeah, I think it will be

easier. Can everyone hear me okay? Excellent, okay. So, first I'd just -- go ahead.

NED CALONGE: I was just wondering if we -- oh, okay. Go ahead, Lisa.

LISA CATON: Okay. So first, I just want to thank the Committee for allowing Oklahoma the opportunity to share our process and our perspectives on adding conditions to our newborn screening panel. And as far us, the first question is a little, it's not necessarily tricky, but our process has changed. So, from the last time when we added conditions to the next time will be different. And the reason for that is, in this past year, our state legislator actually passed and statute language updates, which requires Oklahoma for our newborn screening panel to be consistent with the RUSP to the extent practicable. And so, for us, that means moving forward, when we add conditions, the first thing that we're going to need to be a little more proactive than what we've been in the past when conditions are being reviewed by the Committee and

it looks like they're possibly going to be added. So, we need to kind of get out of the gate a little bit quicker, if that makes sense, than what we have in the past.

And so, we'll do is we'll go ahead and start looking at kind of doing like a feasibility and a readiness assessment in Oklahoma. That'll be both from the public health lab side, and also from the follow-up side. So, very similar to what Susan and I'm sure most everybody else will kind of talk about, is looking at the methodology that's available and looking at our lab processes, and how does that fit in, and looking at staffing and cost and CPT codes, because we would need to work with our Health Care Authority to be able to increase our newborn screening to see just a whole multitude of different things that would need to be looked at and making sure we have specialists in the state that are willing to accept these referrals and what does that referral process look like and just a variety of different things from there.

And once we kind of complete that, and if we do feel confident that we can, you know, move forward with that, then at that point, what we do is we take that information, kind of compile that into a presentation, and we still will present that to the Infant and Children's Health Advisory Committee, which is who we go through in Oklahoma, to receive support to add a condition to the newborn screening panel. And what that Committee does is they make a recommendation to our Commissioner of Health and then at this point, when our Commissioner of Health signs off on it, then we can begin work to actually start adding a condition with that. But we will start that kind of in tandem with you guys looking at conditions and adding them, we need to go ahead and start that legwork for ourselves upfront as well. So, that's where it is different than what it was before, because before, we actually would have to go through a role change process, which took about a year and a half to two years, depending on timing of when it was added when we could get into

our advisory committee, and when we could get our file to be able to change our ledger -- our roles within Oklahoma. And so, that is a bit of a process and that will no longer be required, which is great. But the downside is we need to be more proactive and be more ready and prepared to do it quicker than what we have in the past.

NED CALONGE: Thanks, Lisa. Next, I wonder, Richard, if you could talk about California.

RICHARD OLNEY: Yeah, thanks also for inviting me and if we could pull up my slides at this point. I have a few slides. That's great to talk about the process in California and see everybody on the webinar. Thank you for the invitation.

We, in California, I believe were the first state to have RUSP alignment legislation such as we've heard about with Texas, and now Oklahoma. You can go to the next slide.

So, our statutes were modified in 2016, with the passage of what then was Senate Bill

1095, and that -- you can see the language there. An excerpt from the language is that it sets a two-year implementation phase for adding conditions to our newborn screening after they're adopted by the Federal RUSP. And so, this is not only after your Committee has recommended them, but the Secretary has formally signed off on those. There was sort of a grandfather clause because there were conditions on the RUSP at the time this legislation was adopted, such as Pompe. So, it gave us two years after the act was or the statute was amended in order to add it.

So, you can see below the statutory language there, that we did add Pompe and MPS I in 2018, and then SMA was added in 2020, and all of these were added almost exactly two years after the mandate was enacted, or they were added to the RUSP. Next slide, please.

So, as in Texas and Oklahoma, as we've heard, there are, you know, many steps involved with expanding and adding conditions to the panel, and this sort of shows how all the puzzle --

puzzle pieces are fit together and obviously, laboratory method development verification, built out of the laboratory, as needed with new instruments and so forth is central. But we, as in Texas, have fairly elaborate with, so many results, elaborate procedure for getting the laboratory data interpreted and turned into actual results that can be reported out, and that's done through a network of state case coordinators and there's also a collection of both short-term and long-term follow-up data that's at the bottom of the puzzle there. Unlike some states, we do, for the newer disorders in particular, we have developed contracts with commercial labs for confirmatory testing. So that's -- that's also part of the process of implementation. And then obviously, we never want to forget the educational materials and then coordinating with specialists, and sometimes coordinating with specialists has been more challenging such as SMA, bringing in a new group of neuromuscular specialty centers that were not part of the newborn screening before --

Newborn Screening System.

And finally, all of this is tied together by we have an online screening information system, or SIS, that puts all of these pieces together electronically and that also is a process of developing and testing that system that does take almost that full two years of time that we have, by our legislation. Next slide, please.

So this, sort of lays out how it worked for Pompe and MPS I. August 2016 was when the Act was passed that amended our statutory authority. And unlike some other states, we don't have an Advisory Committee. So, in essence, the-- your Committee's recommendations have become, you know, our roadmap, and there are no further internal approvals after they're added to the RUSP because it just becomes automatic because of the legislation.

We do, like everybody have a budgetary process, I didn't mention that in the previous slide, but that's always at the beginning, and our budgetary cycle is set according to the calendar.

And so, when the condition is added to the RUSP is important, you know, especially if it's added in the summer, that's when the gears start going for putting together cost estimates and figuring out about how many new staff we're going to need and all that sort of thing, and that's basically a year-long process that starts, in this case with Pompe and MPS started that in that summer of 2016.

And then all the other pieces that I mentioned with the puzzle are sort of laid out here. Some of them occur simultaneously. But they do sort of go along this line of, you know, starting with the information technology part, thinking about how we're going to modify our screening information system, and the lab processes at the same time really. Sometimes that involves, you know, actually building out new rooms in the lab and that sort of thing and then all the procurement and contract processes, as anybody who works in state government knows can be quite prolonged. So, once you decide what you need, it takes a while.

Staffing is definitely a major, major impediment, as was mentioned previously, not only getting approval for new positions, but recruiting, hiring, the whole process of human resources can be quite convoluted and difficult, especially when we have a limited pool of people, as per the workforce discussions mentioned previously.

And then what we found is, when we get towards the end of this timeline, the crunch time is with end-to-end testing of all the information, technology, and capacity testing for the lab. You know, we do need to do quite high throughput with our volume in California. We've really come down to the wire with that towards the end with but with Pompe and MPS and also with SMA, we were able to go live within that two-year period. So, it all worked out for us in the end.

So, I'll stop there. I know we're going to go a little bit more with additional questions later about special challenges, and I'll talk about that when we get to that.

NED CALONGE: Thanks. Thanks so much, Richard. Now I'd like to move to Washington State and hear from John.

JOHN THOMPSON: Great. Thank you very much to the Committee for inviting me to join this great discussion.

Washington state is a little bit different than the three states that we've heard from already, because we do not have any specific rules that tie our newborn screening panel to the RUSP. The State Board of Health has the rulemaking authority for newborn screening in Washington State, and that's a partner agency to where I work at the Department of Health. So, we have lots of good communication between the two groups of people who have newborn screening responsibilities. Next slide, or advance if you could.

So, the way this works is the board convenes an ad hoc Newborn Screening Advisory Committee as is needed, and that can happen in several different ways. Typically, in the past,

we've had either parent advocates or specialty care physician advocates who have recommended a any evaluation of a candidate condition for inclusion into our screening panel. It can also happen through the spring boarding off the work from the Federal Advisory Committee and the recommendations for adding to the RUSP. So, it happens both ways.

For example, a few weeks ago, when MPS II was signed by the Secretary, I sent an email to my liaison at the board and said, "Hey, this is, you know, this is now part of the RUSP and to get on to the agenda for our consideration, within our -- at least put it on the radar for the board, who has the authority for the rulemaking, and then also alerted our internal policy people at the Department of Health in my division that this is happening." If you could advance.

The board has five criteria to evaluate candidate conditions. And so, they're listed here. Available screening technologies. So, there needs to be a sensitive specific test that

can be done for the whole population.

The next is that diagnostic testing and treatment is available. So, once they're tested, is there infrastructure to take it to the next step for a diagnosis and treatment.

Prevention potential and medical rationale. That identification in the newborn period provides benefit to the baby.

Public Health rationale is that the -- like, the condition is, like something that all babies should be screened for rather than targeted screening.

And then the final is cost benefit/cost effectiveness, and the benefits need to outweigh the costs. And that's a real interesting challenge to quantify.

And so, I think this is a part of what's unique about Washington's process is that there's formal economic analyses that are made for any candidate condition. This dovetails the last -- advance please.

This dovetails with a separate

requirement. If you can advance the slide, please. Washington has an Administrative Procedure Act. And so, I'll just read what a portion of that says. It says "before adopting a rule, an agency shall determine that the probable benefits of the rule are greater than its probable costs, taking into account both the qualitative and quantitative benefits and costs and the specific directives of the statute being implemented." So, we have a process in which the condition will be evaluated. We'll take a look at -- we basically do a decision tree analysis where we compare the outcomes for no screening model, which is the status quo, with a screening model. And so, we look at the differences in mortality and morbidity, the differences in the costs of treating, and costs of screening and diagnostic testing, and make a final determination in the form of a benefit cost ratio and then net benefit for the screening programs, and those are helpful information for the Advisory Board to understand when they make recommendations to the Board of

Health.

So, what's difficult and, well, impossible to do in the in the system that we have currently is to evaluate some of the intangible challenges and both benefits and costs of adding new conditions. Like, how do you measure the, like, how do you put a dollar figure on the confusion and stress that's caused by a diagnostic odyssey, for example, compared with perhaps a screening test that doesn't perform super well, and creates a large number of false positives? Like so, how do you compare those, and how do you put a dollar figure on those? So, there's some things that just can't be done, but they are part of the discussion amongst the Advisory Panel, and amongst the Board of Health when making decisions.

Let's see, in this, kind of from an overall perspective, from the time that a condition is either brought to the board's attention from, like, wherever this process starts to actual implementation usually takes about two to three years, which is similar to what we've

heard from our other states today. And one of the big pieces, as Susan mentioned, is, can you piggyback this technology? Like, can you add this to an existing infrastructure in our laboratory, and if not, that adds time.

For our standpoint, as a fee for service setup that we have in Washington, we need to have legislative approval to increase our spending authority. So, anytime that we need to increase our fee, it needs to be approved by the legislature. And so, as you can imagine, with them meeting only once each year, the timing of that request and whether it's granted, will play significantly into how quickly we can implement screening for a new condition. Thank you.

NED CALONGE: Thanks so much, John. And now if we could turn to Roberto and Florida. And you're on mute, Roberto. Oh, he's coming up with slides.

ROBERTO ZORI: Sorry, yeah, thank you. So, thank you, more than thank you, I need to say. This is a bit apprehensive. I'm very apprehensive

of this in order to be able to do justice to the Florida Screening Program, and at the same time, give you information that might be useful.

So, I thought I'd start with the Commandments, which we live under. This is the Florida Statutes, and it really says a couple of things. It really says that as soon as a condition is approved by the Federal Advisory Program on the screening panel, the clock starts. So, the Newborn Screening Committee -- Newborn Screening Section has then a year to prepare to present to the Advisory Council, and I'll go into what that means in a minute.

The second part of this gives the role of the Advisory Council, which looks at that -- at that work done by the Section, and then gives the up or down or I need more information answer. So, at that point, if it's approved, like most of them are immediately, then there's a year and a half before the screening is mandated to start. So, there's a two-and-a-half-year maximum -- two and a half year max time, unless the Advisory Committee

sends it back for more information. So, if I could have the next slide. Next slide, please.

Yeah. So, here is the -- here's the roadmap for this. So, we've divided it up just in like four quarters. But the first is that a condition is on the screening panel and added to the RUSP. That sets in play -- in motion to mainly two people, the coordinators of the Newborn Screening Plan, Emily Reeves and Dusty Stern. They are the heart and brains of the screening program. I don't know how they stay sane in getting this all together and getting everyone to work together. But they do an incredible job. So, it is very operator dependent. That then has to be presented. They also do the budget. So, they do budget and assessment of what's needed. They start drafting the budget, and that's in the second quarter. And then in the third quarter, then, we say that that's when it's presented to the Advisory Council, that's within a year. At that point, the Advisory Council, if they approve it, then they have another year and a half to

start screening, and so, screening is mandated to start within that -- after the approval, within a year and a half. And that sort of ensures at one point that that there is immediacy, that this is taken and done as quickly as possible. The problem with this is that we, in doing so, we have to maintain precision and accuracy, and it feels frequently like that scene in Home Alone where everyone is running to get on the bus in a certain amount of time. And I feel frequently that I may end up as the boy that's left behind because there's so many moving parts done within that timeframe.

So, if I can just tell you what that timeframe is just give me a second there. All right. So, when that goes into effect, the Secretary recommends two routes that this will be done, and the Newborn Screening Program starts. And what they do evaluate is the cost per screening tests, methods, compatibility with LIMS, space, staffing, data system updates, contracted providers that may be needed, provider education

that has to be done for the specialists and for the individuals, technical assistance needed for the birthing facilities, follow-up process, updated rules, website updates, updated education material, and then complete the framework for the added newborn screening conditions in Florida that we have to fill in and send to us.

Now, so, that's all done within a year and even the budget. The legislature budget request begins also during this period for a vote. So, within one year of the action by any routes, the program presents the framework for added newborn screening conditions to the Florida Advisory Council for an official vote.

Now, again, there is an enormous push to get this approved at that level. The Advisory Council can request additional information if they're uneasy because all this is presented at that one meeting when meetings are held twice a year. So, there's a lot of information to present, and if the council doesn't feel that this safeguards all accuracy, they could theoretically

send it back for new information, and this has been done recently twice for MPS I and Pompe. And then we re-reviewed it at six months, the information was given. Again, the people in counsel are not always -- usually, most of them don't know what MPS I is or Pompe. They're not geneticists, and so that has to be presented in the assessment done during that meeting. And in each of these two cases, we sent it back for a vote. And on the other hand -- and then we voted on it after six months. So, in essence it delayed this process.

If the Advisory Council votes favorably, then the clock starts again at eighteen months, then implements -- then screening must be implemented within the eighteen months. During those eighteen months, the legislature budget has to be submitted during the appropriate legislative cycle to ensure that funding is available. Nothing can be bought or done until that money is in place, and that has to also be done within the eighteen-month framework. And so, and until the

funding is received, the isn't able to procure any resources, reagents, equipment, staffing contracts, until that's done. All right. And that's again within the eighteen months.

And really, that is the program. The problem has been recently that the push to get this moving faster and faster is there. There are four lobbyist entities that have made this sometimes difficult. The -- it's not that their reasons for lobbying are well understood and appropriate. So, parents, the researchers, the companies involved with a screening program, a screening reagent for testing, and then the legislators themselves, they all feel strongly that this should be done and have been lobbying for this process to go faster and even faster than we're able to do. The problem with that is appropriate, to go as fast as possible. Our concern at the Advisory Council is we're all physicians is, as you know, we swear by the same thing, first do no harm, and that this procedure is done with minimal risks to patients. In other

words, that patients be identified positively and correctly with treatment, that's appropriate. And secondly, that stress is caused by the parents by being screened with waiting for confirmatory testing, and we're afraid that we miss someone. So, all of those three things have to be considered. They're in the process and that's where the delay comes in if we do not think that the conditions are in place, as presented, that safeguard those three risks. And I think that's all I've got for now.

NED CALONGE: Thanks, Roberto, and I want to thank each one of the speakers for such great outlines of your program overall. I think maybe one more question before we open it up for discussion and that's to see if there is like a certain step or part of the process that was the most challenging or takes the longest to get over, and if there are resources or strategies that help your program get past those most challenging steps. And Susan, I'm going to turn to you again to lead us off.

SUSAN TANKSLEY: All right, thanks. Giving kind of the overview, funding really has been the biggest issue for us. So, when we do the cost estimate and, you know, looking -- so, I gave Pompe, MPS I, and MPS II as an example. And so, our cost to implement is on the order of like $7 million. It's a lot of money. And our annual ongoing costs are expected to be over that. So, you know when we get seed funding from grants, it's very helpful. But unless we have funding already in the works, there's no point in even applying for the seed funding, because 300,000-400, you know, that's not going to get us anywhere in implementation.

We were able to apply and we're very thankful to get some of the funding through CDC through the latest round of funding. And we wrote it up as implementing or developing our second tier and third-tier testing. So, it's not nearly enough to do all the work on like the tandem mass spec piece. But it's enough for us to be able to do some of that work that's going to take longer.

So, the development of a second tier LCMS, MSSA, and the development of that third tier, as I mentioned next gen sequencing of a panel, essentially, of all of the genes for all of the newborn screening disorders. And so, you know, the seed funding is definitely helpful. I'm not saying don't do that, please continue to do that. Because I think that's helpful for a lot of states.

But that really has been our issue is funding. And as I mentioned, we do have, I call it a Newborn Screening Savings Account, and I know there are some states who have that. It's a valuable asset. When we get a deposit, it will be nice, because that should set us up for the future to be able to not have that as an impediment.

NED CALONGE: Thanks, Susan. Lisa, could I ask you to go next?

LISA CATON: Absolutely. So, I would say previous to our statute language being updated, the most timely thing that took for us as far as the length of time, would have been going

through the role change process, because that would take us a year and a half to two years just to get through that. So, that was a barrier and that's been removed, which is -- that is one very positive thing.

I think moving forward, what's going to be most likely going to be our barrier is going to be the lab capacity to be able to add those conditions depending on the methodologies available, the equipment, is it included, and, you know, can we run it with another condition that we're testing for? Those factors can be very complicated if you're talking about bringing on an entire new equipment because you need space to do that. And it's also getting the staff and getting staff trained to proficiently be able to run the tests and reduce false positives and stuff like that. So, I think previously, it was the roles was the most challenging part. Going forward, I think it's going to be just the implementation in the lab. It's going to be more challenging for us if I had to rank it right now.

NED CALONGE: Thanks, Lisa. Thank you. Richard, could you go next?

RICHARD OLNEY: Yeah. I mentioned before that staffing is a major challenge for us and as many programs, not just, you know, getting money for a position, that takes time, but the actual hiring process and in finding people to do that. When we implemented screening for adrenal leukodystrophy, we did get over some of that by doing a contracting process to hire contract staff. That, in itself takes time, but that that was one solution we had.

Funding is not as much of an issue apparently, as in Texas. And in fact, the mandate and statute has been kind of, I think, accelerates or puts more weight on our requests for funding just because, you know, we have to do it and so, that allows us to do it.

And finally, I just wanted to mention, I noticed in the in the Florida statute, that there's a mention of having an FDA approval of an assay. And, of course, laboratory developed

testing can be a prolonged process, and not just capacity for the lab, but, you know, developing new processes, and having that available would certainly facilitate things in California, but that's not part of our statute.

NED CALONGE: Thanks, Richard. John.

JOHN THOMPSON: Yeah. So, I think, from our standpoint, the part of the process that takes the longest time is the budget piece and that's sort of tied, like the rulemaking won't start until the budget is approved. So, put together those are the longest. But the budget is definitely the longest.

So, for example, our Advisory Committee last year considered ornithine transcarbamylase deficiency as a candidate that was recommended, put forward by a family who lost a child to OTC deficiency. And so, the Advisory Committee met last summer, early fall, and then I think in November of last year, the Board of Health approved OTC deficiency for our adding to our panel.

And so, immediately, I started the internal policy process for greasing the skids, so to speak, because I knew that we needed to increase our fee in order to be able to do that. And so, I started talking with our divisional management team and saying, okay, next May when we do our proposals to the Governor's office, we need to add OTC deficiency and then, this is what that looks like. And so, we're in that process. It's going -- so far, we're in good shape and there have, like, in that process, like internally, there's always chances that it might not be approved, or it might be delayed and then once it gets to the governor's office, it needs to show up in his budget and then when the session starts in January, it needs to show up in both the House and the Senate budget. So, there's all these hurdles that need to happen in order for that fee increase to move forward.

And so, the like there's a pretty decent amount of preparation and communication that goes into making that happen so that when the

legislators or the staff for the Senate contact our DOH policy person, they'll say, well, why do you need to do this, and they'll have an answer. That's ready. So, that's what we're facing.

NED CALONGE: Thanks, John. And Roberto.

ROBERTO ZORI: Yes. So, like anyone else, it's money, and in Florida, there's money and time. And so, setting a time clock may actually force legislators to approve it since there is a time clock. But there is nothing in place that says if they did not approve it, what do we do then because the time clock doesn't stop. So, that's sort of an intrinsic problem with the system. Though, the problem is that there's a lot of work to be done in one year. Everything's prepared, including the budget within the year. The Advisory Council then doesn't have like a lot of time to assess their preparedness, and they're pushed very hard to, because of the time, to approve it. There is -- how could you deal with that? I mean, one, I think it would be helpful if

we had guidelines at the federal level for what needs to be in place for each condition or suggestions, so they'd have something to work with. Because we -- this is all new to us. We're building a cathedral without ever haven't built a church.

And so, the other thing is that it's very important to get it right the first time despite the low amount of time we have to do it. If there was the ability to review this so there would be a second review, to pick up the things or go back and pick up the things we forgot, or there are new things done. So, there's no automatic review process for the individual conditions where you could go back and say, well, we did things quickly, forgot about this. For example, with CF, we passed it for CF, but there is no provision for genetic counseling, and I think that should have been considered. You know, there is no re-review. There -- we can sort of go back to the legislative too, but that's a difficult issue, because it's for extra money.

So, I would really appreciate, when we have the accepted condition, that we go back and review it in terms of is it doing what we presumed or are there risk factors, like I said before, too many false positives, false negatives, prolonged wait for parents that make the system not optimal, so we could optimize the system in place. You know, we declared victory as soon as we put this on the list. But there's, you know, I don't know if the casualties are too high that I don't think that this should be a victory. So, I think that a review process has to be in place with the automatic review for extra legislative -- legislative monies to be released to fix what we didn't do, because of the timeframe.

Anyway, that's really all I got. Oh, yeah, like I said, if it's not approved, the budget, then we don't really know what would happen next.

NED CALONGE: Thanks. Thanks, Roberto, and thanks to all the panelist members. I'm going to open it up. We have about a half hour for

discussion, starting with questions and comments from the Advisory Panel. I do really appreciate Roberto for reminding us, and Susan, you did at the very beginning, that there's a lot more to the implementation of a new condition other than the laboratory. So, we talked a lot about laboratory challenges in terms of equipment, space, personnel, reagents, tests, but the issues about the other parts of the system like counseling, treatment, confirmatory testing, diagnostics, especially at the molecular level, where does that occur, in the state lab, outside of the state lab, who interprets those? The complexity of the system is great, and funding will always, I mean, it's interesting to say, well, that's not so much of a problem. It's almost inconceivable for me to think about that, as the general fund dollar is the most precious dollar in Colorado, because it's the only dollar that one hundred different legislators trying to control.

So, with that kind of preamble, I wonder if we could start with Michael.

MICHAEL WARREN: Thank you all for these insightful comments. I just wanted to make folks aware, we're going to be releasing a funding opportunity that's forecasted to release on November 10th. That is subject to change. But, Susan, to your point, it won't be $7 million. It's $345,000 per state, but we're anticipating funding twenty-five states. That's new for us and it's to be able to support states really wherever they are, as we think about that continuum newborn screening, whether you're focusing on quality metrics, whether you think about building state capacity to be able to bring on some of these new conditions that are added. And so, I hope we will have more than twenty-five applications and can later make the case for more funding, but excited to have that 345 a year for five years.

NED CALONGE: Thanks, Michael. Shawn.

SHAWN MCCANDLESS: Thank you. I'd like to thank all of the speakers as well. That was really fascinating and insightful. And it points -- it points to something I think is really a huge

problem for newborn screening as a system, and that is that people do things with the very best of intentions, advocacy groups, state legislators, but without understanding what they're actually doing and the unintended consequences of the decisions they make. For instance, we've heard about today in Texas a mandate to screen for, not just the RUSP, but the secondary conditions, which, if anybody had even looked at the website for ACHDNC, they would recognize that they are specifically not intended to be targets of newborn screening. They're intended to be reminders for clinicians that these are other conditions you may encounter when you're working up a kid for one of the primary conditions or Washington state where Dr. Thompson told us that you have a mandate to screen for OTC in spite of the fact that the data show that we don't have an appropriate screening test for OTC and that the test that's available is neither sensitive nor specific.

So, we're going to be spending a lot of money for a completely ineffective program. And

as somebody who has spent the last ten years researching that particular question, how do we screen for OTC deficiency, I'm particularly perturbed by that. And there have been other examples. And so, I have three questions for the speakers related to this, and the first is a simple one. Should this Committee consider eliminating the terminology around the secondary screening panel? Should we just get rid of the secondary? Would that be helpful in any way? The second question, so first question is should we eliminate the secondary panel?

Secondly, the second question is what would be the impact on state Newborn Screening Programs if this Committee were to make a recommendation to the Secretary for a -- to add a condition only if an appropriate secondary tier test was required to be available to minimize false positives? And I don't know that this Committee actually has the ability to do that. But what would be the impact on states if there were a mandate to -- if we're going to implement

testing that you implement a second-tier test to minimize false positives?

So, the first question is eliminating a secondary panel and the second question is a mandate to do second-tier testing.

And the third question is recognizing the limited options for action that are available to this Committee, what can we do to improve your state's ability to implement recommendations regarding newborn screening? Thank you.

NED CALONGE: So, I'm going to take the same order if that's okay, and if any panelist wants to defer, just let me know. But I'm going to see if Susan has an answer she'd like to offer to Shawn's questions.

SUSAN TANKSLEY: All right.

SHAWN MCCANDLESS: And you can answer any or all of the questions.

SUSAN TANKSLEY: Okay. Thank you, Shawn. Those are really great questions. So, I have -- in regards to your first question, so, I have been chairing a condition counting task

force, through Association of Public Health Labs for the last about a year and a half. And at the Newborn Screening Symposium two weeks ago in Tacoma, I gave the recommendations from that Committee, one of which includes an evaluation of the secondary conditions, perhaps to see if they need to be on the core, or if it needs to be eliminated altogether. And so, I do think that that needs to be evaluated and considered. It does have unintended consequences, and there's a lot of confusion over the intent of the secondary targets. And you're correct, it's absolutely spelled out in the ACMG paper. It's absolutely spelled out on the website. There's not conflicting information there, but it has been interpreted differently, and it's not just in Texas that it's been interpreted differently. Ours just happens to be in statute.

In regard to the impact on state Newborn Screening Programs, if it was required to have a second-tier test. So, I think, as we -- as the Committee has considered new conditions, since the

original conditions from ACMG, I think there's been a lot of emphasis on minimizing false positives, and, you know, it has to -- there has to be a really good test. And a lot of programs tried to implement that second-tier testing or some way to reduce false positives. So, moving forward, and even in the existing ones, I don't know how big of a problem that would be in in Texas itself, just speaking for Texas, that's something we seek to do. Unfortunately, the same cannot be said for the original panel. And, you know, that's really, if you look at the endocrine disorders in particular, that's where most of the false positives are coming out of, I would say, most Newborn Screening Programs. Even if you look at the disorders coming out of tandem mass spec in comparison, so many more disorders, but so many fewer positives reported out with much better positive predictive values. And so, one of the things that we've talked about on the lab workgroup, over the years even has been improvement of existing, you know, the conditions

on the panel, and we really haven't gotten much traction there or moved forward with that. But that's another thing is just looking at what we're already doing and quality improvement opportunities there.

So, as Dr. Warren spoke about the additional funding coming out, you know, something at the top of my mind is, is there something quality improvement related that might fit in there that we could definitely use that funding for? I'm going to think more on your third question.

NED CALONGE: Thanks. Lisa.

LISA CATON: Yeah. So, I would probably echo a lot of what Susan said as well. I think there's a lot of confusion between the primary and the secondary panel and what that really means. Even though we understand it, the general public does not. For our legislation, or our statute that was updated, it does not differentiate. It just says it will align with the RUSP. And so, that makes it challenging because there are a

couple of conditions on the secondary panel that we do not screen for. So, then the question was, well, when are you adding those? And it's like, I don't know if we are. And so, then it goes back to looking at that. So, I think definitely reevaluating that is great.

I think as far as the second-tier testing, I love the idea of second-tier testing to reduce false positives. But we also need to make sure that that first-tier testing is still a really good solid test as well, because the costs that can incur if you're spending a lot of specimens for second-tier testing can be a huge burden for the program as well. So, that's a, I don't know, that's a double-edged sword. I don't know quite the answer to that on that one.

And, I would say things to pay -- and this is -- this is really out there and stretching a little bit, but, you know, the -- what the Committee has seen and been going through over the years has changed, and you're getting more and more conditions quicker and quicker and getting

added in the capacity for the lab to be able to do that is challenging. But if we're so busy doing that, we can't go back and refine and even make improvements on what we've already been screening for, and we're just caught in this vicious cycle. So, I would almost consider maybe adding like, maybe when conditions get added, they're not necessarily added to the RUSP, but they're in like a trial period, like a holding period, where we're gathering data from states that are expanding long-term data, it's contributing, really what the feasibility is that's appropriate to truly go on to the RUSP, and then it can get slid on to the RUSP or something. And then, it's not so much a state just trying to scramble and add if they have a statute or some kind of requirement to align with the RUSP. That gives some time to those states that can move forward that do not have maybe as many challenges with funding or something else or the expertise within the laboratory or specialist within your state, whatever the error may be. It provides a little bit of, I guess, a

little bit of cushion to try to figure that out and to see really what a screening for that condition look like long term. Just a suggestion.

NED CALONGE: Thanks, Lisa. Richard.

RICHARD OLNEY: Yeah, I also would really support reexamination of the secondary conditions on the RUSP and that term and what it means and what it means for RUSP legislation in particular. And I know that Susan will be coming back to you with the recommendations from APHL and I would listen closely to those because they've been vetted quite a bit among many of us.

I'm going to skip over the second question but go right to what the Committee can do. And I already mentioned, in California, we pay a lot of attention to FDA approval and availability of test kits because we use regional labs for a lot of our first-tier screening, and with the neuro conditions, we've not been able to do that. The laboratory developed them and that means, you know, hiring in-house resources, hiring and other resources for in-house testing, which is

a bit burdensome. And then, I would -- I know, it's been talked about in the past about reexamining conditions that are already on the RUSP as to whether they are -- and really should stay on there, what's -- what's the data after in the real world, and we've heard about states that have dropped conditions that they were previously screening for. And it seems like once they're on the RUSP currently, they haven't been dropped. So, you know, I think it's important for the Committee to think about a reevaluation process for existing conditions. I'll throw it over to John.

JOHN THOMPSON: Thanks. Great advise from everybody so far. I'll jump to the second question. I think that having a requirement for only if a second-tier test is available would be great for some programs. I think that not all of our newborn screening laboratories have the capacity or expertise or space in their laboratory to do second-tier testing. A lot of the tests that are being done as second or third tier are

molecular, and I just was on a webinar yesterday talking about the, like, the status of, like, very not many Newborn Screening Programs have a strong molecular component to them currently. So, that might tie in to your third question.

But also, like, we were taking advantage of an opportunity from the Association of Public Health Laboratories. We have a fellow. That was the first time we've been able to host a fellow and we are doing -- like, his job is method development and we've got a tandem mass spec that we purchased just for this project and it's not going to be borrowed for regular testing, like every other time we've ever had to bring on a new test. Like, we're really focusing on, like, what can we do to better improve what we're already assigned to do with the work that he's doing? And second-tier testing is part of what we're hoping he can do during his two-year tenure with us.

The -- your third question, the funding that was mentioned by Dr. Warren, like, I could think of so many different ways that we could use

that type of funding, especially since it's a significant amount per award over several years' time. That's really critical for us. A lot of the funding opportunities seem to be either smaller dollar figures or for shorter durations, and it's been difficult for us to justify the amount of time and energy to get a contract established, wherein we've used a lot of the resources just in establishing that. So, the long-term piece is really helpful for states. So, we appreciate that level of support. And building infrastructure, quality improvement efforts, health information exchange, data analysis, education, follow-up, like, there's so much that we could use that type of funding to do over a period of five years. So that's really exciting to us. Thank you.

NED CALONGE: And Roberto.

ROBERTO ZORI: Yeah. The problem with being last is I don't remember the questions, but I'm going to try. But the first one has to do with the secondary criteria, and that's a big

problem. In our state, we tried to be more involved with decision-making and the information we need to approve a program. I think the results of that may have been negative because we saw in the last recently, one SMA, we had a year and a half, but legislature decided that we should move faster on that and so, not slower, so we had less time to review.

The other thing is that CMV, since it was a secondary criteria -- fit the secondary criteria, they just went around -- they went straight to the legislature. But there's nothing in the statute that says other things can't be taken up. So, it wasn't presented to the Advisory Committee, it went straight to the legislature for funding. And so, that's another door that's open now that we had never seen before.

So, I think with the effectiveness of the lobbies, again, they all have good intentions, but they're starting to make work difficult if you want to be analyze -- do a fair amount of analysis on precision, and again, not doing any harm.

I think that I don't -- the second question was the -- the removing the -- oh, the second tier. Now, you know, a tent is not a tent. I think there's too many places where the devils can hide in those details. So, I think that that's not going to work, and there are ways to get around it.

Finally, the third one, you know, I don't understand how we have a program, that's -- you know, when you make a comment or put down some roots, then that's done. That's sort of where states have to be mobilized. But there's nothing at the end of it to say, a quality improvement program, I mean, there's no analysis of are we doing the right thing, are we actually doing what we intend to do, to improve the health of our infants, and not cause too many issues with that.

So, I would say that it's time to, like I did once in the Advisory Council I voted for, that we stop adding new things unless we fix what we have. There are too many holes in our -- in our present screening systems that we should fix.

And in fixing those systems, we make things better for the next one.

So, I think it's time to have a Quality Improvement/Quality Assessment Program, and that should be maybe at the federal level that does and says -- that makes a comment, and that would allow us to have some ammunition with legislatures that we can make the arguments that precision and accuracy matters. Because at the moment, there's no way for us to actually -- not -- very little way for us to convince anyone to take this up seriously. But again, the quality that each state sort of reports back.

In terms of the twenty-five grants, I don't get it, why not fifty. I would say that shouldn't be based on a number of competition. All the states have problems. Some of us are more awake than others. But it should be based on a good project. So, there should be fifty of them, and what you could do is reject the ones that don't seem to have -- to have enough teeth and help them get to a better project so they get that

money. So, the incentive should be that each state comes up with a good project, not that we award the twenty-five. I mean, come on. It's not a race. We're all -- so, yes, I need more money, and I think it needs to be in place.

I need some guidelines. I mean, again, these are so complicated. You know, the rare diseases, we have guidelines. We create guidelines for rare diseases and what we should do A, B and C. Why shouldn't there be a guideline for any condition you have and then have a Committee set up what is the optimal guidelines so that we have something that the Advisory Committees has some push and say that these guidelines aren't met, and we believe in those guidelines.

NED CALONGE: Thanks. I appreciate your passion. Okay, I'd like to turn now -- oh, I'm sorry, Jennifer.

JENNIFER KWON: Hi, Jennifer Kwon. I -- just a quick comment. I was just thinking for those states where RUSP recommendations are sort

of a requirement for adding to their state newborn screening panel, I was wondering if there was a way that the Committee could phrase a recommendation in such a way for quality evaluation or quality improvement or review of some past added condition so that that would -- that state -- that same state language could push those recommendations through as quickly as nominated conditions are pushed through. It was just a thought as a way to help states like Oklahoma and Florida institute some of the looking back quality improvement measures without having to scramble to just introduce a new condition.

NED CALONGE: Thanks, Jennifer. I think it's a really interesting, great discussion. I will say that in our last letter, for me, it would be my first letter from the Secretary accepting the last condition we added, not the one that's still pending, that the charge back to the Committee was to report on kind of the quality improvement finding and what happened after we implemented it. And so, clearly, that's an

expectation of the Secretary moving forward, and I think thinking about how to make sure that we're thinking about quality improvement and quality assessment at the state level is key.

Let me turn now to our organizational representatives with Debra going first.

DEBRA FREEDENBERG: All right, thank you. So, I'm really -- my comment is really related more as a state newborn screening program, then from the pediatrician aspect and when you start thinking about secondary conditions, we're an integrated program, but you need to be cautious about what you're going to do. For instance, in our state, we can't provide resources or benefits, clinical help, to any child unless it is a screened condition. So, for instance, if you were to look at secondaries versus primaries, we could provide services to a child with cobalamin A or B but not C or D. So, I think you need to -- there may be unintended consequences you need to think through what that might mean. And I don't know if we're unusual in that, but that's the way it is

for us.

And then the other comment that I have is, you really need to be careful in defining what secondary conditions are. Because we have heard that there are some state programs that would consider a late onset of a screen condition a secondary condition, because it doesn't happen in the newborn screening period. And so, I think those are challenges, you know. For me, as a geneticist, it doesn't make much sense to think of it in that form. But there are -- that is one of the thought processes that's out there around the country. And so, I think you really need to be very careful in your definition of what you're calling and what your aims are.

And then my last comment is, we are, I think, one of the few programs that's really an integrated program in both the laboratory and follow up component. And within that -- even within that, although we're one integrated program, we do have challenges between the two parts of it. Susan's laughing continuously. And

so, there are a lot of Ying and Yangs and pressures within programs in terms of their abilities to both implement, you know, educational aspects of it. And so, I think you kind of -- there's nothing that's perfect and that there are, in theory, we're a model of an integrated program, but in reality, we have lots of holes in it. So, I just wanted to put that out there.

NED CALONGE: Thanks, Debra. Natasha.

NATASHA BONHOMME: Thank you. Natasha Bonhomme of the Genetic Alliance. I have a couple of things.

One is, you know, I understand and hear the call for wanting the public to be better informed and more aware and act accordingly to that. But, I mean, we can't even decide amongst experts around these things. So, I think we have to kind of pivot that a bit. You know, I think about some of my very early conversations with Susan fifteen or so years ago about counting conditions, and we are now having a workgroup after a year and a half thinking about that. And

so, we all know, I'm going to, you know, stand up for parents and the public, and I think, yes, there's a lot to be learned, but we have to be better communicators. If we can't even agree, you know, how can we expect that from families and advocates and clinicians, right? It's not just families who are advocating for the addition of these conditions.

Also, to go along with that, newborn screening is the only system that catches at this level. You know, I think back to the work that Don Bailey did when he was on this Committee really asking the question around, what would it look like if we had pediatric screening just as a way to try to take -- I don't think he would necessarily frame it this way -- but take some pressure off of the Newborn Screening System. We had those activities. They were very interesting presentations, and then that was that. So, I think there are lots of reasons why people may be adding conditions or wanting to add conditions at a level that may not necessarily fit what some in

this room think is appropriate, but it's what's there. So that's one.

Another piece is, and this has come up a bit in some of the responses, which I'm really happy about is, you know, as there's all this attention to adding conditions, I think it would be really helpful to hear, you know, clearly, from state programs, what they are not able to do because of this. And again, that's come up a bit in some of these responses. I think that would be really helpful for the larger Newborn Screening System stakeholders to really understand. You know, there have been mentioned around QI, there's been mentions about just reviewing what we're already doing. I really encourage, if that is a pressure that states are feeling, which I know it is, because I hear it in conversation, but to think about how to communicate that out. All stakeholders want to have a sense of what's really going on.

And lastly, with all these pressures, I think really thinking also about what are the

things that can be done across states, not just every state having to reinvent its same wheel. I think about that, particularly around education. I mean, it still really surprises me how often I'll hear from three states who are building the same educational materials, and, you know, asking us to review them at the end of the process, and I say, you know, you could have saved a lot of time coming either to us or to a patient advocacy organization or some other group because that information is eighty to ninety percent the same. So again, just really encouraging to use the resources that that are there. Thanks.

NED CALONGE: Thanks, Natasha. I appreciate your comments. And I want to be really clear, I'm -- it was not my intention to criticize parents or advocacy groups or say that they need to be doing better. And certainly, it's not my intention to say that any group of parents or advocates or researchers should be an expert in how the Public Health System of newborn screening works. My point is a little bit more directed

towards legislators. I do think legislators and state legislations have an obligation to have their staff dig into the -- to the implications of what they're proposing, and I've seen several examples where that has specifically not happened, and that's not the fault of the advocates who are bringing it to the attention of the legislators. That is a fault with the legislators. And so, I speak only for myself when I say this, but I think that there is a real responsibility that is often neglected on the part of state legislators to do their due diligence before bringing these things forward. I think that your -- I think you very eloquently stated what I feel, which is that we all need to work together, and the point that you made at the end about programs developing the same tools independently, that's exactly the point I'm making about making these decisions about how to move forward. We just -- if we don't act together, public health people, clinical specialists, advocacy groups, if we don't act together, if we don't listen to each other, the

system is going to collapse. The Newborn Screening System will collapse under its own weight and under the problem -- the unanticipated problems that we create if we don't work together. So, we all have to take advantage of opportunities like this, to listen to each other, to talk to each other, and to understand the realities of the situation. So, thank you for your comments. Roberto.

ROBERTO ZORI: Yeah. Just quickly, during expanded screening, we were in bad shape, we were not ready at any level for a metabolic disease. And so, what we did was exactly what I think Lisa's referred to is we went to three states, and we brought three states in and looked at their program and presented. Our workgroup worked over a year, we looked at every aspect, and actually the end result I sent to you. So, I'd like you to, maybe if you have time, to look at that. I think that's what should be done, that sort of that sort of detail for every newborn screening. It took a while. But we had a

workgroup, and we went to other states, and we put together, I think, the only document out there for how to do expanded newborn screening, first.

The second is I agree about the lobbyists. I've got my good friend. His -- his child has Pompe. We were on the other sides of the -- of the -- of the argument in this and he was a lobbyist also. I understand why he did that. I would do the same thing. But again, there are priorities, and we have to sometimes make them, and it's his job to lobby for institution of Pompe today, and it's mine to see whether that can be done safely, and we don't agree on a timeframe, but we did have a conversation over time. And I think that lobbyists of any sort, we need to engage them with an advisor counselor or something to put that in perspective. I've found that all the lobbyists have good points, but at the -- actually, the timeframe and what we need to be in place, that may differ in terms of what their timeframe is.

NED CALONGE: Thanks, Roberto.

So, I want to make sure that I respect the time of the panelists and recognize you may have something that follows on quickly if you need to drop off. I understand that I have two more comments from organizational representatives, and if we can be brief, that would be great. I'm going to start with Marc Williams.

MARC WILLIAMS: Thank you. Yes, this will be brief. First of all, I want -- I share everybody's dismay and despair about the inclusion of secondary findings. We've tried to be as clear about that as we can, and that's not working, obviously.

I wanted to extend, though, on what Roberto had recommended about quality improvement, and I think that the point I would bring up is that we really need more than that. I think we need to begin to look at implementation of science frameworks to evaluate the implementation of these Newborn Screening Programs, and the reason I say that is because, as we've heard this morning, there's been so much -- there is so much

heterogeneity about the conditions and the individual states and territories that are implementing them, that using a formal framework to gather the information is going to be much more successful than quality improvement, which tends to really work much better in more homogeneous types of settings. So, I think that's a really exciting thing to do. It's something I'm very interested in, and I hope we can pursue that at some point in the future.

NED CALONGE: Thanks, Marc. Gerry.

GERARD BERRY: Yes. Gerry Barry, I'm representing the Society for Inherited Metabolic Disorders, and my home is Boston Children's Hospital and Harvard Medical School.

I'm usually a very positive person, but I think there's a need here to be really transparent and I have to say that, at this point in time, our individuals who are caring for patients with positive newborn screens are really struggling, and this is not even with the addition of new materials. Part of this has to do with the

with the pandemic and the changes that have occurred. But this is really a very dicey situation right now, in terms of providing adequate care. It's a real struggle. So, I think -- I think we have to keep this in mind with these discussions.

NED CALONGE: Yeah, Gerry. I really appreciate your comment. I think as Natasha was talking, I was thinking about state labs do things other than newborn screenings. So, you took us up a level and I would take us up even a level higher and recognize that state labs responding to COVID testing and Monkeypox testing plus other additions to their strategies and things they have to do all have to work within the same physical environment and the same budget and the same legislative priorities. And so, always keeping in mind that we are looking at a very important part of a very important part of public health is important, and now it's interesting because I think we are now competing for the same workforce amongst several different programs in state laboratories and

health care delivery systems and in public health. And so, it doesn't mean we need to take our eye off of our focus, and I do think trying to be understanding and look for ways that we can facilitate, and support implementation will really be key to the success. And I take Shawn's warning about collapse about Gerry's comment very seriously because I think we want to be very careful as we move forward and add conditions always with the concept of how do we improve implementation, long-term follow-up, and contribute to the health of the population moving forward. So, with that, I know we're over time, but I'm going to hold us to just a shorter lunch break, if that's okay, and ask you all to come back at 1:30. I'm going to turn things over to Soohyun who is going to say even though it's a lovely day in Washington, all the doors lock behind you. So. I'll turn that over to Soohyun.

SOOHYUN KIM: For our virtual attendees, I just want to let you know we will be restarting our meeting to help us troubleshoot some of our

technical difficulties. So, please rejoin the meeting before 1:30 using the same link that you used to join this morning.

And then, for our in-person attendees, just a gentle reminder that you only have access to the pavilion area and the lovely cafeteria. If you are going to leave the building, you are going to have to come to security, so please plan accordingly. With that.

NED CALONGE: We'll see you all at 1:30.

SOOHYUN KIM: See you at 1:30. Thank you.

Lunch Break

NED CALONGE: This afternoon, we have our usual public comment period, and then we're going to have our first Phase 2 to update on Krabbe Disease Evidence Review. That will kind of close out our all-person meeting, and then we're going to end the day with workgroup meetings in the three standing workgroups, and I'll give you more information about that later. Do you have any other announcements, Soohyun? She says no, so,

let us please turn to our comment period.

Public Comment

We received eleven requests for public comments. We received two written versions of the oral testimony that was shared with the Committee in the meeting materials, and I know that we read those and look forward to those comments from their authors. And I have a list, and I'll just proceed with the list as we go. And my request is that you come up and speak at the podium.

So, Marianna Raia from Expecting Health will be first.

MARIANNA RAIA: Can you hear me okay? Great, thank you. Thank you, Dr. Calonge and thank you to the Committee for the opportunity to share with you today three key updates related to our Newborn Screening Education and Engagement Initiatives. My name is Marianna Raia and I have the privilege of working as the Associate Director of Programs at Expecting Health. Our programs are driving by clear vision that the fear and confusions individuals and families face during

pregnancy and parenting is replaced by confidence in agency to make the best health care decisions for their lives. We do this through a variety of programs that center around education, engagement, and partnership with key system stakeholders.

The Newborn Screening Family Education Program is a HRSA-funded program dedicated to developing opportunities for all families to learn about newborn screening and to develop training and education resources that build confidence for families to become leaders in the Newborn Screening System.

As this Committee knows well, newborn screening is more than just a screen at birth, but a complex system with many stakeholders. We believe that families are integral to driving system change and supporting positive family experiences within the Newborn Screening System. We focus on supporting families through their newborn screening journeys and create tools and resources that support families before, during, and after screening.

We would like to take a moment to thank HRSA for their partnership and support to fund this work.

To date, we have engaged over 18,000 families through a combination of efforts including online training and education modules, which are available in both English and Spanish, online video education, and targeted initiatives to raise awareness and knowledge of newborn screening during the prenatal period specifically.

Additionally, the program has developed an extensive partnership network of forty-five organizational and individual partnership relationships, which are integral to the dissemination and connection to families.

The network is invited to participate in biannual community of practice forums, where all have the opportunity to share more about their work, key problems, and the strategies to engage families in the newborn screening community.

In collaboration with the University of Texas Health Science Center at Huston, as well as

the Indiana Community Clinic, we conducted two pilot programs to increase awareness and knowledge of newborn screening during pregnancy among medically underserved populations. Through the initial success of this program, we've seen an increase in the number of states directly reaching out to us for technical assistance and support to develop and implement newborn screening education initiatives during pregnancy.

As a result, we have formed a workgroup including representatives from nine state laboratory and follow-up programs as well as family representatives from three different states. This group will meet four to six times between October of 2022 and July of 2023 with the aim to create and design a family-informed resource that will be shared with all state programs to support implementation of prenatal education at the state level.

Secondly, the Navigate Newborn Screening Ambassador Program, which launched in October of 2021, represents a network of trained family

leaders interested and engaged in the Newborn Screening System. Participating individuals commit to join a yearlong program, which includes online and virtual live training modules, quarterly group learning and discussion sessions, and various other opportunities to connect and share their stories with others in the newborn screening community. We successfully completed our first year of this program in August of 2022 and have ten ambassadors representing ten different states who received certificates of program completion and are actively working with other newborn screening stakeholders.

In an effort to quantify the impacts of this program, we asked ambassadors to share feedback through both a baseline and post-program evaluation and were able to measure noticeable increases in knowledge about the Newborn Screening System as well as confidence in their leadership abilities.

Since completing the program, trained ambassadors have provided input and support at

both the state and national levels including contributions to national survey designs, state advisory Committees, genetic counseling training, and most recently attendance in speaking opportunities at the APHL Newborn Screening Symposium.

We are looking forward to expanding this network of family ambassadors and launched a new cohort with thirteen new families, including diverse perspectives from a range of geographic locations, condition groups, and various perspectives.

We would like to take this time to share with the Committee and other attendees that this training network is available, interested, and eager to collaborate. We encourage you all to reach out directly to us if you wish to connect with this network of family leaders.

And finally, in partnership with the EveryLife Foundation, Expecting Health recently cohosted the 4th Annual Newborn Screening Boot Camp. This event is designed to educate and

engage participants on the latest newborn screening updates and best practices, and to build relationships between stakeholders from all aspects of the Newborn Screening System. We had over forty live attendees and roughly twenty-six virtual attendees with many more that have registered. The agenda included three key sessions, including a presentation and panel discussions regarding updates from this Committee, changes from the ACHDNC, data and patient perspectives, and equity in newborn screening. This event continues to support and validate the need for coordinated efforts across stakeholders to build relationships, increase communication, and generate opportunities for advocates to engage in the Newborn Screening System.

In closing, I'd like to thank the Committee again for allowing me the opportunity to share these updates in this important work with you all. Through these efforts and with the experiences of the families we have the privilege of working with, we've identified several helpful

strategies for education and engagement that we will apply to existing and future programs.

As this group knows very well, the landscape of newborn screening continues to evolve, and this work highlights the utmost importance of ensuring families are not just a part of the discussion but are given the opportunity to share their insights, experiences, and ideas for solutions to help improve the Newborn Screening System for all who are a part of it. Thank you.

NED CALONGE: Thanks, Marianna, and thanks for all the work at Expecting Health.

Next, I'd like to welcome Dylan Simon from the EveryLife Foundation for Rare Diseases.

DYLAN SIMON: Good afternoon and thank you all for having me today. My name is Dylan Simon and I serve as the Director of Policy for the EveryLife Foundation for Rare Diseases.

The patient community and the Committee here find strong alignment in our commitment ensuring the timely implementation of conditions

that have been nominated for addition to the RUSP. And while we appreciate the Committee's discussions in the previous two meetings on how to strengthen newborn screening, we feel that discussion may have conflated the many legislative approaches underway, and thus we feel it is important to provide some clarity into our legislative process and the legislation that we seek.

Since 2016, the EveryLife Foundation has been working with the rare disease community and state leaders to pass state RUSP alignment legislation to ensure that state health departments are resourced, implementation timelines are reduced, and patient access organizations can focus precious resources on community follow-up. Our collaborative and systemic approach has resulted in our community helping to pass legislation in eight states and consulting in two additional states to pass RUSP alignment legislation. Those states include California and Florida who you heard from today,

in addition, Georgia, Ohio, North Carolina, Arizona, Pennsylvania, Iowa, Mississippi, and Maryland. In addition, in Oklahoma, while Oklahoma does not meet -- does not have all the aspects of RUSP alignment legislation, which I'll go into momentarily, we did help to consult with both a state advocate as well as the state legislator and the legislation that was passed last session to help reduce the rulemaking process for the state.

When we begin RUSP realignment efforts in every state, we seek to engage newborn screening stakeholders including patient advocates, policymakers, public health labs and department officials. We work with these stakeholders to craft legislation or regulation that ensures that each state can successfully add new RUSP conditions within a predictable timeline. In every state we work in, we reach out to both the department as well as local advocates to ensure -- to aid in the development of the legislation to ensure the fact that that

legislation will work best for that state. We are also aware that we are not the only community members advocating for newborn screening legislation within states, which is why we think is important today to talk to you about what we consider state RUSP alignment legislation, and that contains three components.

The first component is auto-inclusion or vote for inclusion, either requiring the state to add a new RUSP condition or requiring the state's Newborn Screening Advisory Council or Department of Health to consider a new RUSP condition for their state panel. The bill does not name specific conditions, nor do they allow for conditions that have not met the evidentiary criteria of the federal RUSP to be required to be added by the state.

The second component of RUSP alignment is the timeline, which requires the state to add or consider adding a new RUSP condition within a stated period of time. Depending on the state, that period is typically two to three years.

Finally, the third component of RUSP alignment legislation is the allocation of resources. While different in every state, this typically includes the ability for the department or Public Health Lab to raise the fee as they see fit, or the creation of a newborn screening line item within the budget. Essentially, if we're going to ask the state to add a condition, we're going to ask them to in a certain amount of time. We want to make sure that the funding is that we want to make sure that the state has the resources to implement this condition properly.

We're committed to ensuring that the conditions which have been nominated for inclusion on the RUSP have pathways that are timely and resource implementation in all fifty states. As an organization, we are engaging with stakeholders every day to determine the best way to enhance policy efforts that improve and strengthen newborn screening.

Thank you again for the opportunity to speak with you today. I'm happy to answer any

questions about this at any time, so please do not hesitate to reach out and have a great rest of your day. Thank you.

NED CALONGE: Thanks to EveryLife Foundation for Rare Diseases for your work.

And now, Kim Stephens from Project Alive.

KIM STEPHENS: Chairman and members of the Advisory Committee, my name is Dr. Kim Stephens, and I'm pleased to offer comments on behalf of over thirty million Americans living with rare diseases as President of Project Alive, the co-chair of EveryLife Foundation Newborn Screening Diagnostics Working Group, and as a parent advocate.

The EveryLife Foundation for Rare Diseases is a nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community. Through our newborn screening efforts, the EveryLife Foundation works with many diverse stakeholders that comprise the newborn screening ecosystem every day. To ensure the Committee

remains representative of these stakeholders, we encourage the Committee to provide more formalized opportunities for engagement. To this end, we have the following suggestions for consideration of the Committee.

We recommend that as the composition of the Committee is considered, professional diversity among Committee members and representation of the ecosystem be reflected. We request that the Committee once again add a patient advocate as a Committee member so that they may properly represent the patient experience on the Committee.

We ask the Committee take time to respond to public testimony, to develop a deeper dialogue between the Committee and the various stakeholders that make up the Newborn Screening System, and we request that the Committee add a public comments section two their quarterly meetings dedicated to advocates speaking about conditions currently within the RUSP nomination review process.

And finally, we ask that the Committee include patient advocates and panel presentations to ensure presentations and subsequent conversations that occur at the Committee meetings are properly represented by the patient experience.

We ask that as you continue forward, you actively communicate your concerns regarding resources and other limitations with newborn screening, but not allow those concerns to dominate conversations.

In turn, as a patient advocacy community, we will continue to work with policy makers to provide more resources and reduce workforce barriers so that all know newborns may realize the lifesaving benefits of newborn screening.

Thank you for the opportunity to speak with you today.

NED CALONGE: Thanks, Kim. And also our thanks to Project Alive.

Next, I'd like to welcome Heidi Wallis

from the Association for Creatine Deficiencies.

HEIDI WALLIS: Good afternoon. It's nice to see everybody in person, not on a Zoom screen. It's great to be here. I'll be really brief. I want to leave this stand with everyone here remembering I'm representing GAMT Deficiency, GAMT. I hear people go that one deficiency, it's really rare. But I also want to bring up the patients that I'm talking about, and my kids are the poster kids. My nineteen-year-old daughter is severely intellectually disabled. She was diagnosed at five-and-a-half, and my son was diagnosed at birth, thanks to his big sister, and he is a typical fifth grader, doing fantastic. All of this because of a supplement they could get over Amazon and measure in the kitchen on a scale, and that's it.

So, you know, I've heard -- we first were here in May 2016, and I'll just say for the comments, we've kind of gone around about the advocates and they can be a real pain. We've waited six and a half years very patiently and you

know, heard from a lot of experts, this is the no brainer condition. This is multiplexed with amino acids, and acylcarnitines that the labs are already screening for, the treatment is safe, effective. There's just nothing holding us back. And so, I'm just here to say GAMT Deficiency Association for Creatine Deficiencies, we've got a strong network of researchers, we have expert panel meetings where we bring these rare disease folks together, and they talk about treatment and care, and they connect with each other and support each other. So, the follow-up piece is taken care of, and we've got a strong patient registry. We're developing core outcome sets where we're here and we're here for the patient. Please don't forget us. And if you're in a lab, reach out. We would love to share a presentation that we created with laboratorians and experts on the disease, how it manifests, how the treatment easily addresses those issues, and how this screening can be put into your lab.

I also want to throw out I spent three

years working in my home state's public health lab in newborn screening, and maybe unpopular to some of the advocates, I will say it's hard to add a disorder. I know that process. We added disorder while I was there, and it's not simple. So, this is a long, hard process, and I appreciate everyone's work. I appreciate the struggles to communicate things like primary conditions and secondary and this is hard. But I know that working together, we all are doing great things, and I appreciate your support. I am hoping in nine days or less, we've got a signature on GAMT from Secretary Becerra. And again, reach out. GAMT Deficiency, my name is Heidi Wallis, and I'd love to talk to you. Thank you.

NED CALONGE: Thanks so much, Heidi, and thanks to the Association for Creatine Deficiencies.

Next up, I'd like to invite Niki Armstrong from Patient Project Muscular Dystrophy.

NIKI ARMSTRONG: On behalf of Parent Project Muscular Dystrophy and the Duchenne

Patient Community, thank you for the opportunity to speak today. My name is Niki Armstrong. Are you guys getting that? Yeah. Better? Perfect, okay. And I am the Newborn Screening Program Manager for Duchenne Newborn Screening. I'm pleased to provide an update about our efforts.

As you know, because I've been telling you for the last few years that Nancy Kennedy told you before that, we have been working on Duchenne newborn screening and the infrastructure for more than ten years. The learnings from our efforts and the efforts of everyone that came before us, were compiled into a RUSP nomination package that is currently in review, and we look forward to discussions of that in future meetings.

Today, I wanted to give you a quick update of some of our efforts to prepare for Duchenne newborn screening and advances in Duchenne treatment. We understand, as we discussed at length today, that this is way more than just a lab test that needs to be validated. And so, one of the pieces that we wanted to learn

more about was how providers feel about Duchenne newborn screening and specifically the providers that would be seeing these kids in clinic. So, those are the neuromuscular physicians and the rehab specialists.

So, as part of that process, we developed a survey -- we used a steering Committee, developed a survey that was then sent out to the professionals that would be seeing these kids. So, we used our certified Duchenne Care Center Network and asked providers for their opinions on the benefit of Duchenne newborn screening and whether or not the care community was ready for Duchenne newborn screening, and then what they would do afterwards -- what they would do at those initial visits after those babies were diagnosed, and that work has now been published. So, I'm happy to share that publication. But today, I'm going to give you just some of the highlights.

So, our first question asked them for their view on Duchenne newborn screening, and

whether they thought the care community was ready for this, and the answer was a resounding yes. They felt that there was benefit to Duchenne newborn screening and the care community was ready.

We then asked what they would do with those initial visits when they saw the infants that were diagnosed with Duchenne because, of course, we want to make sure that there's something that we're doing for these babies. And the providers answered many, many different responses, things like genetic counseling, referral to early intervention services, screening siblings, maternal carrier screening, assessment of social and language developments, discussion of clinical trials, and, of course, initiating the FDA-approved exon skipping therapies. Overall, the physicians reported believing that the optimal time to start those exon skipping therapies was before age two, with the vast majority wanting to start them as soon as possible. But unfortunately, right now, Duchenne is not

typically diagnosed until after age four, and at that point, there is significant irreversible muscle damage that we do not have a way to fix or to change. And of our list of care recommendations that the experts endorsed, every single one of them is time sensitive with benefit to being initiated early, social and language skills, physical therapy and occupational therapy, even screening mothers and siblings. There is a benefit to doing all of those things earlier.

Right now, Duchenne has five FDA-approved therapies and two potential therapies, including gene therapy that are under FDA review. We expect responses on those two additional therapies next year. In addition, our research pipeline has more than twenty different potential therapies in clinical trials, and even more in preclinical research. But for the best outcomes, we have to identify these babies and treat these babies before there's irreversible muscle damage, and newborn screening will provide the opportunity to do that. Thank you.

NED CALONGE: Thanks, and, of course, thanks for the work of Parent Project Muscular Dystrophy.

I would now like to invite Amanda DeRossett up -- oh no, I'm sorry, she's virtual. So, Amanda.

AMANDA DEROSSETT: Can you all hear me?

NED CALONGE: We can.

AMANDA DEROSSETT: Okay. Hi, everybody. My name is Amanda DeRossett. My son, Ty, screened positive for Krabbe disease in 2016.

NED CALONGE: Amanda?

AMANDA DEROSSETT: Yes?

NED CALONGE: Is it possible for you to turn on your video?

AMANDA DEROSSETT: Oh, yes.

NED CALONGE: Thank you, go ahead. I'm sorry to slow you down.

NED CALONGE: You're good.

AMANDA DEROSSETT: So again, my name is Amanda DeRossett. My son, Ty, screened positive for Krabbe disease in 2016. On our second day at

home with our perfect newborn, we headed to his first doctor's appointment. He was just five days old. The doctor walked in with his assistant and sat down. He looked at us and said, I'm sorry to tell you, but your son has a metabolic disease. What does that mean? He proceeds to inform us that Ty has Krabbe disease, which is fatal and there is no cure. He did get us in contact with a specialist who explained to us he had a chance to be transplanted. My husband and I chose to transplant, and there's yet to be a day that we regret that decision. I can't imagine if we weren't given that option. Ty was the first child found on newborn screening in Kentucky and one of the quickest ever to be transplanted.

Fast forward to today. Ty will be six years old at the end of November. He embraces life and everything he does. Ty, just like most six-year-olds, he loves books, especially Pete the Cat, driving his jeep, playing his tablet, swinging at the park, and watching movies. We cannot imagine our life without Ty.

Sorry. What you aren't aware of is we actually lived in Tennessee when Ty was born. We chose to have Ty at a Kentucky hospital because we lived on the state line. We were unaware that every state did not test for all the same diseases. Had we have chosen for him to be born in Tennessee, he unfortunately would not likely be with us today because in 2016, Tennessee did not test for Krabbe disease. Today it does.

I believe that every parent regardless of their state should have the ability to choose whether or not they want their child to be treated for this vital disease.

The biggest thing I can ask each of you in deciding whether or not you will recommend Krabbe is to put yourself in our family shoes. Would you want that choice to save your child's life? Sorry, but I got it said. But thank you all so much for allowing me to tell our family story.

NED CALONGE: Thank you so much, Amanda.

I recognize these are difficult

opportunities and it means a lot to us all for you to have the courage and ability to present to us today. It's a gift that we appreciate. Thank you.

I wonder if we could now turn to Kelly Denora Bonacoursa.

KELLY DENORA BONACORSA: Good afternoon. My name is Kelly Denora Bonacorsa, and this is my daughter, and this is my daughter Sophia. Sophia has Krabbe disease. She was diagnosed in March at age six months, following back-to-back emergency room visits, invasive medical procedures, long hospital stays, and multiple misdiagnoses. Her diagnosis of Krabbe Disease blindsided us. Our lives have ended. Our active-duty military move overseas canceled, our careers halted, and our family plans extremely complicated. Sophia was born a seemingly healthy child, but in the months preceding her diagnosis, Sophia didn't reach important milestones, even losing some skills she once had. She became irritable and rigid. She plateaued in length and weight. Sophia spent five

weeks inpatient for failure to thrive and to understand why she stopped developing and started deteriorating. She saw countless physicians, underwent endless scans and tests, and even endured a failed gastrostomy tube procedure that required intensive wound care. Our situation went from devastating to tragic when we learned that the commonwealth of Virginia determines Sophia's chance at life. You see, we live in a state that doesn't screen for Krabbe disease at birth, largely because the disease isn't on the Recommended Uniform Screening Panel. Sadly, Sophia's diagnosis came too late, and treatment couldn't help her.

Sophia is one year old, and she is dying. Her life is limited. She's impacted by hearing loss, muscle weakness, difficulty swallowing, seizures, stiff posture, and significant developmental delay. She's legally blind. Sophia can't walk, sit, talk, or eat. She's unable to smile. She requires in-home nursing services and around-the-clock medications.

She's dependent on special equipment like a feeding pump and a suction machine since she can't safely swallow. She needs continual supportive treatments to help her perform functions that you and I take for granted like looking at an object or moving an arm. She receives hospice and palliative care for pain management and other physical symptoms.

In the seven months since Sophia's diagnosis, her medical care amounts to over half a million dollars in expenses. And as Krabbe progresses, Sophia's health will worsen, and her care will become more complicated.

Today, I want you to see Sophia -- really see her. She's a beautiful, sweet, little girl. She's fond of the outdoors and likes music. She loves to taste the apples. We tried to give her a full life even in the face of her disability and her very short life expectancy, including trips to the farm and daily walks and playtime with her cousins.

The Virginia Newborn Screening Advisory

Board voted against adding Krabbe to the commonwealth's panel of conditions in November 2020. My daughter was born ten months later.

I need you to remember Sophia and recognize that you, the Committee, can create change so that no other child suffers an early unnecessary death and no other family misses precious moments. Newborn screening for Krabbe disease is critical because early diagnosis and intervention make a difference in the life of the child and the family. And I know because it would have drastically altered the course of our lives. Thank you for your time today. Thank you.

NED CALONGE: Thank you, Kelly.

Next virtually, we're going to hear from Hema Rangarajan from the Nationwide Children's Hospital.

HEMA RANGARAJAN: Good afternoon, Chairman and members. Can you hear me okay?

NED CALONGE: We can indeed.

HEMA RANGARAJAN: Thank you. So, good afternoon, everyone. Obviously, I was very

touched by the last two comments, something that's very close to our heart here at Nationwide.

So, my name is Hema Rangarajan and I'm a physician who specializes in bone marrow transplant for children. I'm an Associate Professor of Pediatrics at Nationwide Children's Hospital, Columbus and the Ohio State University here in Columbus, Ohio.

So today, I would like to take this opportunity to briefly describe my team's experience -- the BMT team at Nationwide's experience in the care and transplant for newborns with Krabbe disease, and thereby demonstrate to you how transplant for these infants can actually be done within state without having to go out of state to another transplant center.

So, over the last five years, with the implementation of the newborn screening for Krabbe disease in Ohio, the bone marrow transplant team at Nationwide, we have the unique opportunity to take care of two infants with Krabbe, who are diagnosed by the newborn screening.

The first infant is -- was -- is a newborn girl who was diagnosed in April of 2017. Immediately following her abnormal screen, we were alerted, and she was seen by a multidisciplinary team comprised of ourselves, the BMT team, the genetics, neurology on day nine of life. So, her result came on day five or six, and we saw her on day nine as soon as we could.

As this was our first infant with newborn Krabbe that we were considering transplant, we immediately reached out to our colleagues at Duke University, because we knew they had vast experience in transplanting such infants and sought their guidance and collaboration, and this was a very successful partnership because with the team at Duke led by Dr. Joanne Kurtzberg, we immediately initiated the process of transplant for our patient.

We first had to work with the National Marrow Donor Program that is the NMDP, and we rapidly identified suitable cord blood units in a matter of just few days, like one or three days.

It didn't take us that long. And with the same help provided by Dr. Kurtzberg at Duke, we actually tested the levels of enzymes in the cords, and we chose the most suitable and appropriate cord. Usually, when we take patients to transplant using a cord blood, we cannot start chemotherapy for transplant until the cord blood arrives at the center. But that would have meant we would have lost some days.

So, again with Dukes guidance, we sought special approval from the National Marrow Donor Program to actually start chemotherapy even before the cord arrived at our center so that we could expedite the process of transplant in our patient.

We took our first patient to transplant in May of 2017, and we started therapy -- that is chemotherapy -- on day twenty-six of life -- of the child's life and did the transplant on day thirty-five. So, this was then followed surprising and a year and four months later, our team actually took another male infant with an infantile Krabbe disease once again diagnosed with

an abnormal newborn screen in August of 2018. This patient came to us after he was actually diagnosed at a local children's hospital, which was not transplant -- did not have a transplant team there. And therefore, we were alerted about him on day -- his day nineteen of life and the Nationwide Multidisciplinary Team immediately met with the family when the child was twenty-one days of age. I remember that distinctly because it was over a weekend, and we could not bring on Saturday and Sunday. So, we said please, please, come to us on that Monday.

And using the same steps I previously described, and because we've had the experience, we were able to expedite the process and this baby actually started chemotherapy on day twenty-nine of life and received his cord blood transplant on date thirty-eight of life.

So, during this entire process, we frequently communicated with our team at Duke to make sure we're taking the right steps and we also monitored the neurodevelopmental progress of our

patients posttransplant over several months and years.

As of today, both patients are alive, with the first patient being nearly five-and-a-half years posttransplant and the second patient being four years, two months posttransplant, and I'm happy to say that both are free from transplant-related complications. Both children are making steady developmental gains with strong cognitive, receptive, and expressive language skills, and as expected, their motor skills is a little bit lagging behind.

But to conclude, I think I would like to take this opportunity to say that our experience is actually an important and highly successful example of how in-state pediatric transplant centers are able to perform transplants for infants with Krabbe disease diagnosed by an abnormal newborn screen through an expedited process. And I can confidently state that this process was made possible because of our collaboration with our colleagues at a center

which had more experience in this area.

Thank you. I'm happy to take any questions.

NED CALONGE: Thanks so much.

Next, I'd welcome Stacy Pike Langenfeld from Krabbe Connect.

STACY PIKE LANGENFELD: Thank you so much for this opportunity to speak today. I am Stacy Pike Langenfeld, Co-Founder and President of Krabbe Connect.

I want to take a moment to review the 2009 RUSP submission that didn't get approved. Concerns around the disease not being well defined, concerns about the screening method, and uncertainty on the benefits of treatment. I'm going to take a moment to tell you about three -- those three items today.

The disease is broken down into four categories: early infantile, late infantile, juvenile onset, and adult onset. Truthfully, I knew these categories back in 2001 when my daughter was diagnosed. We've known for quite

some time the most severe forms are early infantile and late infantile subgroups. Many publications have identified early infantile as accounting for nearly ninety percent of the cases.

But to be clear, I want you to hear me out on how our community sees the subgroups of Krabbe disease. Early and late infantile, no chance of quality of life without access to newborn screening. Juvenile and adult onset have the option to treat with or without access to newborn screening, however, prefer to know sooner than later to have the ability to treat at the most optimal time.

Well, let's talk about screening method. Over the past three years or more, we've proven that if a low GALC enzyme activity is identified through an infant's dried blood spot, the sample is moved on to second-tier testing to test for the biomarker psychosine. Published studies have validated that the use of psychosine assay can identify a patient as having severe Krabbe disease with onset in infancy, or later onset variant.

Studies have also proven that psychosine can assist in monitoring the later onset subgroups. But to be clear -- oh, sorry about that.

Onto treatment. Today, the standard of care is transplant. Many stories exist on the internet on Krabbe disease patients living well with transplants. Transplant kids attend school and dress up for Halloween. Oh my gosh, you should have seen the photos this year. They were so cute. Eat on their own, manipulate objects, navigate their wheelchair, and so much more. The development of children post-Krabbe disease transplant is widely available through several peer-reviewed articles. When reviewing these publications, don't make the mistake of comparing them to normal children born without disease. The only fair and equitable comparison that should be made is between patients born with Krabbe disease who were transplanted, and patients born with Krabbe disease who were not transplanted. The difference between the quality of life for the transplanted versus the non-transplant patients is

crystal clear.

We also now have gene therapy clinical trials; however, only patients identified through newborn screening will have access to the current clinical trials.

Now let's talk about the other stories. A majority of the stories that exist on social media can be summed up by one father's statement in a todayshow.com article. Buying a 3'6" coffin is at the bottom of every parent's to do list. Five months ago, my kindergartner, Emmett, took his last breath. This is this is because only nine states currently test for Krabbe disease.

As I close out, I truly believe I'm very thankful for this opportunity to be in front of you today and you continue your evaluation of Krabbe disease. Please remember to keep the mission of newborn screening at the top of everything you discuss. The reason Dr. Robert Guthrie pioneered this health care program was to help identify disease at the earliest point to allow for early intervention and to decrease the

morbidity and mortality of infants born. I believe the mission remains the same today and I believe Krabbe disease can be safely screened. Thank you so much.

NED CALONGE: Thank you, Stacy. Again, we appreciate all the work by Krabbe Connect.

And next I have Lisa Brackbill from the Leukodystrophy Newborn Screening Action Network.

LISA BRACKBILL: Good afternoon. It is such an honor to be here with you today. My name is Lisa Brackbill, and I live in Hershey, Pennsylvania. My daughter, Tori, was diagnosed with Krabbe disease at six-and-a-half months and died at twenty months of age because she wasn't eligible for treatment. It is because of Tori and our great loss that I advocate. I advocate so that other parents can seek treatment or take advantage of gene therapy clinical trials, and not be told there's nothing we can do because those are the worst words a person and parent can hear on diagnosis day.

I have lived and breathed both Krabbe

and newborn screening for seven and a half years now, and I understand the disease, I understand the assay, and I understand the newborn screening system and the treatment options. In fact, I know more about Krabbe and newborn screening than I know about my daughter. I spent five years advocating in Pennsylvania for a stronger, more equitable newborn screening program, and if you have any questions, I'm happy to share our success because we took the legislature and funding out of the equation entirely, and I think our system is a great model, as a side note.

I saw great success with Act 133 of 2020. Because of the mounting evidence and my persistence as a member of the LSD subcommittee, the Pennsylvania Newborn Screening Advisory Board added Krabbe at that time and we found four babies in our first seven months of screening. Those parents were given an opportunity that we were denied, which is the opportunity to even try to save our child's life.

I have encountered many common

objections to screening for Krabbe and I've even created a frequently asked question/ objections document because there are scientifically backed answers to every question I've heard raised.

We as a community of scientists, clinicians, advocacy groups, and families are ready to see every baby screened for Krabbe disease. The ten states already screening paved the way and solved the problems. Those who know the disease best believe it is time for Krabbe to be added to the RUSP.

These babies will be born with Krabbe whether they are screened for it at birth or not, and it's time to give them the best possible opportunity to actually live, no matter where they are born. No parent should have to bury their child, especially when newborn screening gives them the opportunity to treat it. I've seen both versions of the Krabbe story, one of despair like mine, and one of hope, like Ty's. Let's give these families hope. Thank you.

NED CALONGE: Thank you, Lisa and thanks

for the Action Network.

I want to thank again and recognize the contributions of all our public commenters today and thanks for sharing your stories, your passion, and your worries, and life journeys with us. Thank you.

So, in July of 2021, the Committee received a nomination for Krabbe disease for inclusion on the RUSP. And you've heard, it was the second nomination that the Committee has considered. At the May 2022 meeting, the Nomination and Prioritization Workgroup presented an overview and the Committee voted to move Krabbe disease forward to a full evidence-based review. In our August meeting, the Committee reviewed the Phase 1 update on the evidence-based review, and today, Dr. Kemper -- Dr. Alex Kemper, lead for the Evidence-based Review Group, and Dr. Lisa Prosser, ERG member, will provide the Committee with the Phase 2 update.

Dr. Kemper is the Division Chief of Primary Care Pediatrics at Nationwide Children's

Hospital and Professor of Pediatrics at The Ohio State University College of Medicine. Dr. Kemper'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.

Dr. Lisa Prosser is the Maryland Fisher Blanch Research Professor of Pediatrics and Director of the Susan B. Meister Child Health Evaluation and Research Center. Dr. Prosser also holds an adjunct faculty appointment at the Harvard School of Public Health.

Her research focuses on measuring the value of childhood health interventions using methods of decision, sciences, and economics. Current research topics include newborn screening programs, vaccination programs, and methods for valuing family spillover effects of illness.

With those introductions, I'd like to ask Dr. Kemper up to the podium. Thanks, Alex.

Krabbe Disease Evidence-Based Review

Phase 2 Update

ALEX KEMPER: Good afternoon, everyone. I'm pleased to be able to present this interim summary of the Krabbe Disease Evidence-Based Review.

So, this is a list of the Evidence Review Group members. In the interest of time, I'm not going to read through them all. But I would like to thank Dr. Kwon and Dr. McCandless for their work serving as the liaison from the Advisory Committee to our Evidence Review Troup. Next slide, please.

As we do with all of our projects, we have a series of technical expert panels, panel members, these are experts in issues related to Krabbe disease, who we work closely with, and we'll have them evaluate the report before it's finalized and submitted to the Advisory Committee. Next slide, please.

We have had two group calls with the technical expert panel. Advance, please.

In addition to this, we've had a series of key informant interviews with experts and

advocates in the field. This is a really important part of our process to really make sure that we understand all the nuances and issues related to Krabbe disease newborn screening. So. I'd like to thank members of our TEP and the other individuals who participated in the interviews. Next slide, please.

So, this is obviously a very brief outline of what I hope to accomplish today. We're going to provide a very high-level summary of where we are with the evidence-based review, and I'm going to be highlighting our current progress in terms of talking about some particular studies and findings that I think are going to inform the final report.

Dr. Prosser will talk about the decision analytic modeling process, and I will follow up with where we are with the Public Health Impact Assessments, and then we'll end with next steps and open the floor to conversations.

So, you know, you heard just a few minutes ago about the 2009 review, and I just want

to highlight it again, although the summary of the issues was excellent.

So, it was not recommended in 2009, and there were several gaps that were identified at the time, including issues related to the definition of early infantile Krabbe disease. There were questions at the time about the screening and treatment algorithm. There were questions about the benefit of stem cell transplantation, including if there were subpopulations of infants with Krabbe disease that would benefit more than others. And then there was also concern about over-referral and potential burdens and follow-up for those infants who screen positive. Next slide, please.

So, there have been obviously a lot of advances since 2009, including psychosine testing, in addition to screening for low enzyme activity level, which can really decrease false positive referrals. Next slide, please.

So, the reported prevalence of Krabbe disease is on the order of about one per 100,000

with a fairly wide range based on different study types. It's lysosomal storage disorder and leukodystrophy, as you heard just a little bit ago, it's chromosome fourteen, it's an autosomal recessive disorder. There are more than two hundred variants of the GALC gene, the gene that's associated with Krabbe disease. Many of them are private, and not all of them are pathogenic. However, there are some specific variants that are predictive of the outcomes, including a specific thirty kilobyte deletion, which is associated with the most severe form of Krabbe disease. And then, it's associated with low glucocerebrosidase or CALC enzyme activity and we heard about that just before I came up, and elevated psychosine concentrations in early infancy, as I mentioned just a little bit ago as well. Next slide, please.

So, I do want to summarize the natural history of the disorder. For those who -- those infants who develop symptoms before the first six months of life, they present on average, around

four months of age. About half of them develop head control, but lose milestones like head control, within a very short period of time. There's spasticity, early onset of severe irritability, there are swallowing problems that develop, and then loss of fixation. Most infants who develop symptoms of Krabbe disease in the first six months of life don't develop any language, there's a loss of vision and hearing, there's seizures, but that could be more variable, and survival between ten and thirty-two months. Next slide, please.

For those who develop symptoms later, so six months to thirty-six months, those infants oftentimes present with irritability and developmental regression. They too have loss of milestones about fourteen to sixteen months later, and the median survival time is about six-and-a-half half years. Next slide, please.

So, I want to spend some time just talking about infantile Krabbe disease and some of the language that we're going to be using around

it. So, the term infantile Krabbe disease, it's a classification that's involved, and I think that reflects better understanding of the epidemiology and also have the term be used for different clinical purposes. Next slide, please, or advance.

So, I just want to -- I think it's helpful to put up different definitions that are used. So, in the article that was published in 2017, early infantile was described as less than six months, late infantile from six to forty-eight months, and the juvenile form that was about four years of age. Please advance.

And then in 2019, there was a study that described infantile as being less than six months, and then described late onset as being the late infantile form between six and thirty-six months, and the juvenile form between three and eight years. Next slide, please.

And then, more recently, there was a study that described the early infantile as those infants who, if untreated, would develop symptoms

within the first six months, late infantile between six to twelve months, and then they discuss in the article early childhood and adolescents and adults who can get affected in this late onset bucket. Next slide, please or advance.

So, the condition, as nominated for the Advisory Committee, really focuses on infancy developed Krabbe disease in the first thirty-six months, and that's how we're going to focus on it. I put these definitions up just so you can understand how there's, you know, the terminologies evolved and sometimes when we're looking at studies, things and terms can be slightly different. But what we're going to do in the evidence review process is to focus on the infants who would be expected to develop symptoms of the first thirty-six months of life. And obviously, as we go along, if we find, for example, from state newborn screening programs who have babies who might have developed even a later form of Krabbe disease, we'll summarize it. But

again, I just want you to understand that there's some variation in how the terminologies evolved. Next slide, please.

So, let's talk a little bit about screening. So, the Tier 1 screening -- the first tier for any newborn for Krabbe disease is with GALC enzyme activity. And then from there, there could be additional testing. So dried blood spot psychosine level can reduce false positives, and as I'll be talking about in a little bit, can also be helpful to stratify risk for those babies who are found to have low enzyme activity and an elevated psychosine level. Next slide, please.

There's also molecular analysis. So, as I talked about before, there are a large number of variants, but some of those variants can be predictive of the expected outcome. Next slide, please.

So, I want to summarize this one study, Expert Panel Recommendations for Follow-up After Positive Newborn Screening. It's called a study, but it's really a report, and it's really based on

dried blood spot psychosine levels.

So, dried psychosine level that's two or greater is typically considered to be abnormal, and if it's ten or above, that's strongly predictive of the early infantile Krabbe disease, and that's where the follow-up is time critical.

There are three different pathways that infants can fall under based on whatever the psychosine level is. Advance.

The first is the early infantile form, and those babies require immediate referral for diagnostic evaluation and treatment, and those are for the babies who are above ten. And then there's this at-risk for late onset Krabbe disease, and those are infants who are recommended to see a specialist within two to four weeks to follow up and see what needs to be done. And for those infants, this is, again, for the infants in the two to ten range, the genotype can be helpful. So, the genotype can help stratify infants into a high-risk group, where they need more frequent monitoring is listed on the slide or low risk,

where there's less need for intensive follow-up during childhood and up through to adulthood.

So again, the psychosine level is really the laboratory result that helps classify infants into needing an urgent follow-up with a specialist or if there can be a slight wait. Next slide, please.

And. of course, there's going to be some infants who are not going to expected to have Krabbe disease based on the psychosine level, and they're not going to have -- they're not going to need follow-up. So typically, that's less than two. Next slide, please.

And, again, I just want to highlight that using psychosine this way really does reduce referral from newborn screening. Next slide, please.

So, these are the states that are currently offering Krabbe disease newborn screening. You can see the one state in the light blue, Ohio bases screening on GALC alone, the other states use psychosine at some point during

the screening algorithm, and I'm going to be talking about that a little more in a second. Next slide, please.

So, I want to go back in time a little bit and talk about this report of the first eight years of newborn screening for Krabbe disease in New York. This is pre-psychosine. They describe screening from 2006 to 2004, there were essentially two million infants that were screened. Next slide, please.

And there were 620 of those infants had a low GALC enzyme activity, and there were ultimately 348 who were referred for follow-up with others assumed to have a negative screen based on the GALC polymorphisms that were found. Next slide, please or advance.

And based on the infants that were referred in these sort of early days of the New York Newborn Screening Program, you can see the distribution of finding including five infants who were confirmed to have infantile Krabbe disease. Next slide, please.

So, I now want to summarize a little bit of a later report. This is from Illinois, describing 2017 to 2020, where about half a million infants were screened, and this is a report of their two-tier screening. Next slide, please.

There were -- so they -- the way the program works is they looked -- they did repeat testing on infants who had GALC enzyme activities of sixteen percent or less, and that those on repeat testing were thirteen percent or less, were considered to be positive. So, there were 288 of those, you know, essentially half a million that were positive. Next slide, please.

And then they did second tier psychosine level testing and GALC sequencing. And from this, they identified two newborns with elevated psychosine levels, so ten to thirty-five -- ten and thirty-five, and obviously, that's, that's above ten, and they were referred to immediately. There were six newborns with psychosine levels between two and five, and 178 with pseudo

deficiency alleles and psychosine less than two. Next slide, please.

This is a summary of information that we've gotten back covering more recent period of newborn screening. The listed states were very kind to provide this data to us. In working with our partners at APHL, we're continuing to work with the states to better define this information. But you can see the referrals range from, what was it, like 0.6 per 100,000 up to a high of nearly 13.8 per 100,000. So, there's that bimodal distribution, and some of that has to do with how decisions are made about referrals. So, we're referring in as soon as a low GALC level is -- as soon as a low GALC level was confirmed on newborn screening while awaiting the psychosine or the molecular testing. So, you know, states vary in the point at which they make their referral.

You can see the range of infantile Krabbe disease per 100,000 infants that were identified and those who were, you know, at risk for late onset, so the ones that are still in

follow up there. The classification of infantile Krabbe disease and at-risk for late onset Krabbe disease was based on information that we received from the Newborn Screening Program, and we're working closely with the Newborn Screening Programs and their follow-up arms to really better characterize those infants who were referred including the status of this with Krabbe disease. Next slide, please.

So, the diagnostic evaluation includes GALC enzyme activity as a clinical test, so, separate from the newborn screening dried blood spot, psychosine concentration against a clinical test, and then molecular analysis that had not been previously done. And then, there's a lot of additional information that can be collected to help confirm the diagnosis. But this can be done in conjunction with the work that needs to be done to plan for a stem cell transplant so MRI, nerve conduction studies, EEG, evoked potentials, lumbar puncture for CSF, are all -- can be helpful in terms of confirming the diagnosis. But really,

babies with very high levels of psychosine and low GALC enzyme activities are the ones that need to be teed up for likely stem cell transplant. Oops, loo, it worked this time. There we go.

Now, in terms of where things are going -- I'll still play to you -- so, the treatment, as we've discussed, for Krabbe disease is a stem cell transplant with those with suspected early infantile Krabbe disease requiring urgent referral and transplant goal ideally of thirty days. I'm going to drill into that thirty days in a minute, and then for the other phenotypes, it's still stem cell transplant. But based on the development of signs or symptoms, as was talked about in the public comment period, there is gene therapy that's being evaluated in clinical trials right now, but that gene therapy isn't available for clinical purposes right now.

So, I want to go back to this thirty-day recommendation and talk about one of the studies that really gave rise to this. So, this is a study of nineteen subjects who received a stem

cell transplant for early infantile Krabbe disease diagnosed by -- or not diagnosed, treated with a stem cell transplant by two months of age, between 1996 and 2010, in a single center, and for whom at least five years of follow up was available. So, about sixteen percent of them were diagnosed based on newborn screening, the bulk were identified by family history, the median age at transplant was twenty-seven days with a range of nineteen to sixty-one days, and most, but not all, were treated with umbilical cord blood from unrelated donors. Next slide, please.

So, if you look at survival at five years, it was eighty-four percent, and at ten years, it was seventy-nine percent. And there is no difference in five- or ten-year survival based on if the transplant was done before thirty days or after thirty days.

But as I drill into these numbers, I'm going to remind everyone that, you know, we're talking about nineteen subjects, and so I put less value on the P value. Obviously, this isn't the

kind of thing that it's easily powered for statistical significance. Please advance.

But I want to summarize important points about the outcomes of the transplant against stratifying, based on whether the transplants occurred before thirty days or after thirty days. So, for those and, again, follow-up was up to five years, ninety percent were walking, although some did need an assistive device versus seventeen percent. All were "verbal", but I didn't have any additional information on what that was, versus about fifty percent who got transplanted after thirty days. Ninety percent could feed by mouth versus seventeen percent. And none of those who were transplanted before thirty days had seizures versus a third of those who had transplant after thirty days, that statistical significance value is listed as NS, not significant.

Again, you have to take caution when you interpret studies around just around nineteen subjects. Now what I can't do is go back and say, well, what if you'd moved things to thirty-five

days or forty days and look at the outcomes that way? When we talk to the experts, they really say that based on this and, and their expert experience, they would really like to get the transplants done by thirty days. But if you can get it to forty-five days, maybe that's okay. But certainly, once -- and from the expert opinion once you develop significant involvement, then the benefit of the transplant is not going to be as effective. Next slide, please.

So, I'm going to go back and talk about more recent information from New York. So, this is from 2016, where they had about two million newborns that were screened. 348 newborns were referred based on the screening with two lost to follow-up, and of these, five had infantile -- early infantile Krabbe disease, of which four retreated with transplant. Next slide please.

And these are the outcomes of those five infants. So, there was an infant who was transplanted twenty-four days who died at sixty-nine days of age, an infant who was transplanted

at thirty-one days who died at eighty-four days, an infant who was transplanted at thirty-two days who had follow-up to eight years, who had developmental delay and was non-ambulatory and did have some complications related to the transplant, and then another infant who was transplanted at forty-one days who at forty-one days who at five years of follow-up had developmental delay and failure to thrive. And then there was one infant where the parents refused transplant who died at eighteen months.

So again, these are small numbers. But I want to give you a sense of things. I want to be clear as we go about and talk about our analysis, we are going to be comparing outcomes of newborn screening for Krabbe disease to infants who were not detected through newborn screening. That's really the comparisons that we're going to be making. And I'm going to be visiting this again in a second when Dr. Prosser comes and joins us. Next slide, please.

This was a recent study, identifying the

age and of transplants and outcomes for infants with early infantile Krabbe disease. And so, each row represents a different infant, and I think this slide is particularly helpful just in understanding all the things that have to happen to be able to get a transplant by around thirty days of life.

So, the vertical kind of light blue line is thirty days. So, you can see the first infant in this study received transplant -- I can't remember -- it was like forty days, you know, after -- after the thirty-day mark, and you can see all the things that have to happen in order to be able to get the transplant done. The second baby had it before, the third one a little bit later, the fourth one right around the thirty-day mark, and the last two after the thirty-day mark. I highlighted on this slide, baby number 1 and baby number 4, because these were infants who had to go out of state for their -- for their transplant. Next slide, please.

This slide describes some of the

outcomes for those infants who were transplanted. Each colored bar represents a different infant and there was variation in terms of the length of follow-up, going from thirty to fifty-eight months after transplant. All the infants did have developmental delay, particularly related to gross motor deficits, but they were -- they were still alive at this thirty- to fifty-eight-month mark. Next slide, please.

So, our ongoing focus, as I alluded to before, was clarifying the screening results and digging more into the outcomes of stem cell transplant for early identification. And ultimately, what we'd like to do, although I'm not sure that we're going to be able to find the data this way, is to be able to stratify things by genotype and the initial GALC enzyme activity level and the psychosine level. But to the degree that we can put those three together that way, we will. Next slide.

So, I'm going to be quiet for a minute and have Dr. Prosser talk about the projecting

population health outcomes. So, Lisa, I hope you're there.

LISA PROSSER: I am here. Are you able to hear me?

ALEX KEMPER: Yes, we can.

LISA PROSSER: Terrific, great. And Alex, you'll advance the slides on your side?

ALEX KEMPER: I -- Alisha is.

LISA PROSSER: Excellent. Okay, great, because I don't see any controls on this side. Thank you very much.

On the next few slides, I'll be walking through the plan for evaluating population-level health outcomes for newborn screening for Krabbe disease.

So, using simulation modeling, the overall objective is to be able to project population-level health outcomes. So, modeling an annual US newborn cohort of 3.65 million, this analysis will project both newborn screening outcomes as well as outcomes under clinical presentation. So, under newborn screening

outcomes, those will include screening specific outcomes such as positive screens, cases of confirmed Krabbe disease, and importantly, as Dr. Kemper has walked through in the previous slides, the numbers of babies that will fall into the various at-risk categories following the newborn screening process.

We'll also include projections of the numbers of babies who receive transplant, as well as projected transplant outcomes within a short timeframe, and mortality.

Under clinical presentation, we'll be comparing these outcomes to identify cases of Krabbe disease without newborn screening as well as mortality without newborn screening. Next slide, please.

So, just a step back, just for a brief moment. So, the methodological approach that we'll be using is decision analysis, and I know this has come up a little earlier in the presentations today. It's a systematic approach to decision-making under conditions of

uncertainty, and the goal here is really to project ranges of short-term outcomes for newborn screening compared to clinical presentation given the scarcity of the data for newborn screened conditions, and particularly like for Krabbe. Our goal, again, will be to project ranges to give a sense of what those projected outcomes would be under a national newborn screening recommendation.

Decision analysis will then allow the decision maker to identify which alternative is expected to yield the most health benefit. And here, there will be a number of different outcomes which can be used to measure health benefits.

At the same time, it can also be used to identify key parameters and assumptions. So, it would be possible through sensitivity analysis to identify which parameters in the model are driving the results and where it would be important to have more information as we move forward. Next slide, please.

So, where we are right now, the model structure is in development and in the next two

slides, I'll walk through the current model structure.

The second technical expert panel focused on reviewing the model structure and the assumptions underlying the -- underlying the model, and the model went through a number of revisions following that process. The time horizon for the modeling analysis, right now we're anticipating a three-year time horizon for the overall analysis, depending on as we finalize on the parameter inputs and finish reviewing literature, that may only be two years, but right now we're anticipating we'll be able to project outcomes up to three years.

During the second expert panel, there was a very -- a very rich and important discussion about the classification and terminology of screening outcomes, which is reflected in the current structure of the model. That may be updated as we learn more in the coming months. And we've also refined the definition of the timing of transplant, as well as transplant

complications based on the expert panel discussion. Next slide, please.

So, this slide shows the schematic of the -- of the simulation model for the newborn screening arm. And so, starting on the left-hand side, the analysis will use a hypothetical -- a cohort of hypothetical newborns who are not at higher risk for Krabbe disease and model their pathway through a hypothetical screening program.

So, if you kind of walk through across the top of the diagram, and I won't go through all the detail here, but I do want to give a flavor of what will be incorporated into the simulation.

So, following newborn screening, the baby can either screen positive and be referred for further diagnostic valuation or screen negative. If they screen positive, it is assumed again and important to characterize here that the plan for the simulation modeling is to model a state that is using a screening approach that includes psychosine as second-tier testing or evaluating whether a baby should be referred for

transplant evaluation. So, that's what you'll see reflected here on the screen. So, important to note that the screening approach depicted here in this model will not match what's happening exactly in every single state. But we'll be able to use data from multiple states to inform this -- the data underlying this model.

So, following a screen positive and further referral for diagnostic evaluation, including the results of psychosine testing, a baby could then fall into one of four groups, either presumed early infantile, referred for transplant evaluation, at risk for late onset, and within that group, they would be identified as either following the low-risk follow-up pathway or the high-risk follow-up pathway. They could fall into the category of not recommended for regular follow-up, or they may decline follow-up, and we will be able to model the projected numbers that fall into those two categories as well based on current state level data that's been shared with us.

So, just following along through the top part of the model. So, for those that are referred for transplant evaluation, then there is a probability that there'll be transplanted within thirty days, and Dr. Kemper has characterized that this thirty days instead of thirty-ish days that there's -- that within thirty to thirty-five days, you may see that exact number change in the final version of the model. But looking to be able to identify where outcomes are likely to be different beyond a certain timeframe if transplant occurs after a certain timeframe, we want to be able to differentiate those two categories of outcomes. So, transplant either within that window or outside of that window are also to capture outcomes for babies that are either not recommended for transplant, or if parents elect not to not to follow a transplant recommendation.

So again, just following through the very top box, and then we'll move on to the next slide.

So, following transplant on the outcomes

that will be modeled here, as there's a probability of either surviving or potentially dying of transplant-related complications. Here, we'll be modeling outcomes within a one-hundred-day window following transplant. For babies that survived the transplant, again, we'll be looking at long-term outcomes, and looking to characterize short-term outcomes over a three-year time period, in terms of what their level of symptoms are at the end of those three years in terms of either no or few symptoms, moderate severe symptoms, or having died from Krabbe or from transplant complications.

So, I'm not going to go through any of the rest of this part of the model in detail. But let's move to the next slide and I'll walk through a comparison which is the clinical presentation arm.

So, here for this part of the model, the simulation will evaluate the same cohort of hypothetical newborns who are not at higher risk for Krabbe disease. They will have some

probability of presenting with Krabbe disease at some point due signs and symptoms that can happen either within the first year of life or beyond that. Here, we'll be comparing those infantile Krabbe disease and again, we're using here a definition of infantile Krabbe up to and through twelve months of life.

We'll be modeling similar outcomes as was seen on the previous slide. And then we'll be able to compare outcomes under a hypothetical newborn screening program compared to no screening. Next slide, please.

This slide shows a table of anticipated projected results from the model. So, we'll be able to project the numbers of positive screens as well as all the screening outcomes listed on this slide comparing newborn screening, and then compare it to clinical presentation just for the identified early onset Krabbe disease cases. Next slide, please.

This slide shows the anticipated health outcomes that will be modeled for longer-term

health outcomes. So, projecting the number of babies that receive transplant under newborn screening compared to clinical presentation, as well as longer-term projected outcomes related to symptom severity or death. And then being able to evaluate the number of cases or deaths that are averted in those different categories. Next slide, please.

So, in the next few months, we'll be continuing to update and finalize the model structure with continued conversations with experts in the field as well as our liaisons. The Advisory Committee will be finalizing the model input using data from states with screening programs that have very generously shared very detailed information on their screening outcomes to date, as well as incorporating additional literature from literature, and then filling the gaps with the with information and discussion with the technical expert panel. We'll be running analysis and sharing those preliminary results with liaisons, the Advisory Committee, and with

the technical expert panel as we finalize those results.

So, I will stop there. I'll turn it back over to you Dr. Kemper, and I would be happy to take questions at the end.

ALEX KEMPER: Okay, fantastic. Thank you very much.

So, I'm just going to summarize by talking about where we are with the Public Health Impact Assessment and I should really give credit to Elizabeth Jones and Jelili Ojodu, who are our partners at APHL, who really do a fantastic job with this part of the project and also collect those data like I showed you before from the newborn screening programs.

So again, we're collecting data from states that are offering Krabbe disease screening and they're conducting interviews with relevant individuals within those programs. You can see who's been completed by little asterisk there. Next slide, please.

As we've talked before, GALC enzyme

activity can be measured by tandem mass spec or fluorometry, and it can be multiplexed with other liposomal storage disorders and screening tests. Contracted labs are often used to measure the psychosine. Although it could be done within the State Newborn Screening Program, most people are sending psychosine out. Please advance.

And so, we're continuing with the usual Public Health Impact Assessment looking at the usual barriers to implementing newborn screening, as was talked about this morning. Next slide, please.

And we're just about to begin the survey of the newborn screening programs that are not currently offering Krabbe disease newborn screening. We held a webinar on October 13th to begin to allow those programs to prepare to respond to the survey, and the link was distributed at the end of October. It's going out as we speak. Next slide, please.

And so, with that, I'd like to stop and open things up for questions.

NED CALONGE: Thanks so much to Lisa and Alex and the entire team. I know you've worked hard on this presentation. I also want to thank the work of the Committee that signed on to provide comments and expert guidance. It's been a great experience. I apologize for having a question, because I've seen it several times, but it wasn't until I saw it big on the screen that it came up. But way back in the early slides, you were talking about the New York experience, and there were nine high-risk kids for infantile Krabbe and then five got transplanted or five were confirmed. I was just curious about how did the other four unruled out and what was there -- and was there any chance that one of them --

ALEX KEMPER: Yeah, yeah.

NED CALONGE: -- not being transplanted.

ALEX KEMPER: I'm going to sort of dance around that because we're still trying to collect all that information directly from the program. So, my guess is that there's probably --

it's been like -- this is a guess, but maybe three dozen children that have been transplanted related to early detection through newborn screening or other ways, and I really do want to just finalize it with a list and know like what happens to those with later onset. So, I'm looking at Dr. Kwon. She may have personal experience with some of those infants. But, in terms of summarizing it, I'm just -- I'm going to sort of plead the fifth until we have that all organized on one table.

NED CALONGE: Great answer. It makes me feel not bad about missing it before. Jennifer.

JENNIFER KWON: I'm a little removed from that report. But I think none of those needed to be transplanted.

KYLE BROTHERS: This is a somewhat related question but could you -- could you just confirm it sounds like with psychosine testing, we now believe that there were no false positives that are then making it all the way to transplant. But I mean, that would be a very difficult kind of thing to recognize if that was happening. But it

would just be good to know what information we have related to that.

ALEX KEMPER: Yeah, I think -- I'm going to turn your single question into two questions.

So, as we talk to the experts and we look at the data that we have, it's true that babies who have the early infantile Krabbe disease or the kind of Krabbe disease that you would want to move to transplant, they're all going to have elevated psychosine levels. It's just part of the condition.

Now there is, for example, a single case report of an infant who had a psychosine level that was close to two but not exactly two, who turned out to have the infantile form of Krabbe disease.

So, I think that, you know, the science has really gotten around psychosine in terms of when it's elevated, that it is associated with the kind of disease that you'd want to transplant. But one of the points that I didn't make during the presentation that I probably should have made

stronger is that, you know, these various cutoffs and stuff, to a certain degree, it's artificial, because these are all spectrum diseases and it's clear that there really is this spectrum of psychosine levels and that kind of thing. And, but I don't think that there's any infant with an elevated psychosine level that didn't turn out to have, you know, the kind of disease that would benefit from transplant.

NED CALONGE: Thanks. And Soohyun was reminding me just a couple of additional points. So, for Committee members in the room, if you do identify your first and last name, that helps with the recording and the minutes, and then if you're in the room, if you shut your video off, it keeps the screen a little less cluttered. Oh, video on? Well, I misunderstood that. So, if you'll turn your video on so that we can see whose --

ALEX KEMPER: I'm glad their video is on because it's unnerving to see a gigantic version of yourself on the screen.

NED CALONGE: Over and over again. So,

I'm going to turn next to Jane.

JANE DELUCA: Thank you, Dr. Kemper. That was a great presentation. I wanted to know a little bit more about the psychosine because it sounds like it's a really important measure. So, you had mentioned that it's actually sent out to some labs where it's performed and is it a simple analysis, or is this something that's complex?

ALEX KEMPER: Well, I'm not a laboratory person, so I sometimes think that it's all simple for me because I just circle the lab that needs to be ordered, and it comes back. But what I will tell you is that it's more complicated, from what I understand, than doing, for example, GALC enzyme activities, which can, you know, easily be multiplexed, and there are certain labs that are doing the analysis. So, a lot of people send them to Mayo. People are sending them to my home institution, Nationwide Children's, and I'm looking at Margie because I can't remember where the other places are. But there's a handful of places now that offer it.

NED CALONGE: Next, I'm going to Ash.

ASHTOUSH LAL: I'm unable to start my video. It's been stuck. Slightly unrelated question. My question is about late infantile and later onset Krabbe. In those cases where transplants are done, is the timing of the transplant decided by symptomatic disease, or is there pre-symptomatic MRI evaluation or other indicators to decide upon the optimal time?

ALEX KEMPER: Yeah, I can tell you that we're really, you know, all of our work so far is really focused on the very youngest children. So, I'm going to point to Margie, who helps me for the clinical side of things and is one of the members of our Evidence Review Group, that it's a constellation of findings in terms of if there is a, you know, change on MRI or nerve conduction, those kinds of things, tied off to clinical cases, clinical findings. But we've really been so focused on the early infantile one, I don't know if you want to add any color commentary, Margie.

MARGIE REAM: I was looking up the

other. The third lab is PerkinElmer. So, PerkinElmer and Mayo.

ALEX KEMPER: PerkinElmer, that's right.

MARGIE REAM: And so, in the process of looking that up, I didn't catch the beginning of the question.

ALEX KEMPER: The question is like when would you decide to do a transplant for somebody with later onset Krabbe disease?

MARGIE REAM: Based on the symptoms. So, seeing signs of active disease is usually when people would consider it time to transplant. So, the later onset the disease, the slower -- the more slowly progressive it is. So, with very early onset, it's very rapidly progressive, and so, then it's, you know, if it's by genotype, then we know they're going to have early infantile disease and then move quickly through that evaluation process. But if they seem to be late -- at risk of later onset disease, then we have a little more time to do the evaluations.

NED CALONGE: Shawn.

SHAWN MCCANDLESS: Thank you. Thanks, Alex, for the presentation and just a couple things. I want to -- I want to echo what one of the speakers in the public comments earlier noted about making sure that we're comparing -- using the right comparison group, and I think that -- I think the point was well made that, you know, the right comparison group for kids who are transplanted is kids who weren't transplanted, and so as much as possible, we would want to see those data.

Likewise, we would, I think, and this is not news to you, but I just want to make sure that everybody hears me say this, which is that we really, I think, need to know as much as we can in the kids who are transplanted. What was the evidence that points towards the severity of disease? And it comes back to that comparing apples to apples argument, that if we're going to compare people who were transplanted to people who are not transplanted, we need to be confident that the people that were transplanted have similar

genotypes and similar psychosine concentrations to the people that were not transplanted, so that we can compare the outcomes, because we've already seen today that if you transplant somebody who's going to present with symptoms at six months rather than one month of age, that outcome without treatment is going to be much different. And so, we want to be really confident that we know as much as we can possibly know with this very limited data set. So that's my comment.

My question is -- maybe there's more of a -- maybe this as a question, maybe it's a comment. What -- could you summarize, and maybe not today but next time -- could you summarize the data supporting the utility of psychosine? Is it -- is there -- is this like overwhelming data that psychosine is a really clean marker, or is it -- is that still in question?

ALEX KEMPER: So, I'll confess to you, when you said I could have this as a question or a comment, if it was going to be hard, I was going to take it as a comment, and if it was going to be

more straightforward, I was going to take his question.

What I can say is, from the evidence that I've looked at, that psychosine clearly reduces the number of infants that are referred, and it's really baked into the algorithms right now for classification of, you know, expected type and drives towards treatment as well.

So, psychosine, I think, is a real, if I can use this term, a game changer related to how newborn screening works for Krabbe disease, or at least you have to get it at some point along the way.

SHAWN MCCANDLESS: It's certainly impacted decision making.

ALEX KEMPER: Correct.

SHAWN MCCANDLESS: My question is a little bit different though, and that is how compelling is the evidence? Because I just can't find a lot of data on this.

ALEX KEMPER: Well, I'll take that as a comment.

SHAWN MCCANDLESS: That is a comment. There are -- I can't find a lot of papers and a lot of data. So, it's small numbers, and big decisions being made on small numbers.

ALEX KEMPER: But it's a condition that's, you know, rare to start with, so.

NED CALONGE: Kellie.

KELLIE KELM: Kellie Kelm, FDA. My first comment is, and looking at the entirety of what you presented today and seeing a number of things that I know is going to be very challenging for all of us, whether, you know, seeing the definitions of, I guess, onset change, in a very short number of years, small numbers of people, and I know you only really presented some, you know, the transplant data on the on the youngest kids, although I will say the nomination is for kids thirty-six months and younger. So, I'm assuming that means we may also get data not on those kids that would be in early infantile, but that we would have to consider larger than that unless we want to, you know, talk about how we

might, you know, consider this condition.

But, you know, I think all of that, and also looking at the difference in referrals in states and stuff and, as you mentioned, the use of psychosine, and we always have to deal with problematic data here. I think I will harken back to what Shawn said that the more that we can see of the data, and because I think we're going to, whether it's year-to-year, state-to-state, you know, what we're going to get from each kid is probably going to be very different. I think it's -- since we're talking about small numbers, it's going to be very important, it's going to be really challenging, but that's why they pay us the big bucks, right?

But, you know, I don't envy you. I don't -- I'm interested in seeing what numbers Lisa can actually plug in because I can't tell how many states have the psychosine data, and we'll be able to do that at one point, and how many kids we can't put in there that we have experience with. But that's what I'm interested in seeing in the --

in the final report and, I hope, more granularity I think is just going to be more helpful for us to get a bigger picture. Thanks.

ALEX KEMPER: Got it, we agree.

NED CALONGE: Thanks. Melissa.

MELISSA PARISI: Melissa Parisi, NIH. I have another psychosine question. I'm just curious about the stability of the measurement and whether it is considered a biomarker for progression of disease, or if you measured it in an infant with early onset disease at two weeks and at two months, assuming they hadn't gotten transplanted, it would be the same or if there's any -- if there are any studies that look at the progression of psychosine levels over the disease course.

ALEX KEMPER: Yeah, there are studies that look at changes in psychosine over time, I just don't have the date on the top of my mind, but I can get back to you even before the final report with that. But we'll make sure that we put that in there as well because there is a change

with psychosine over time.

NED CALONGE: I'm going to turn to our organizational reps now and Robert.

ROBERT OSTRANDER: Thank you. Robert Ostrander, AAFP. On these complicated cases, I'm very happy to be an organizational rep and not a voting member. And great presentation, Alex, it's good to be back. I'm going to step back a little bit from Krabbe and just talk about our process in general over the years. I'm not going to get too far into the weeds. But it occurs to me that much of today's conversation has been informed by states that have instituted universal newborn screening for Krabbe disease, and it's just fortuitous that this particular nominated condition has this wealth of data, relatively speaking, and others don't, because they only have pilot studies, and no one has done the mandatory universal newborn screening in a small number of states. I mean, if, you know, your disease has a famous quarterback whose kid gets it, you know, you get some early legislation, and you get this

raw data and this great source of data, and if it doesn't, you know, we're way behind the eight ball.

I wonder if it would be reasonable for the Committee to consider making a recommendation with some of these more complicated conditions. Would the Secretary consider advocating for funding a limited number of states to institute universal newborn screening about a condition? I mean, this is basic improvement science, you know, before you dive in all the way you do a PDSA cycle, essentially, do it, study it, and then move forward if it confirms. And so again, that's kind of my observation after having been involved with this group for more than ten years and watching our evidence review evolve and the difference between conditions where some states have instituted universal screening and other conditions where that has not been an opportunity.

NED CALONGE: Thanks, Robert. Shawn.

SHAWN MCCANDLESS: I want to respond to Robert. I think I love that idea except I would

tweak it a little bit in that first off, I'm not sure we're empowered to make that kind of recommendation. But if we were, I would say, based on what we heard from some of the parents and families today that it would be really uncomfortable to me to say we're going to do it in twenty-five states and not do it in fifty states. So, I love the idea of a limited introduction, collect data, and show that it -- show with confidence that it's an effective program. But I would be in favor of doing it in every state, which has its own set of complications, but.

ROBERT OSTRANDER: Just to finish, my -- just to throw out the rest of my comment was, I mean, the whole problem with doing that is that we don't dive in about something we're not sure of.

NED CALONGE: Alex.

ALEX KEMPER: Well, I just want to comment to something early on. So, you know, there no doubt that, you know, there was a famous football player who has, you know, had a personal family attachment to Krabbe disease, but we've

dealt with so many other advocacy groups and scientists in the field and stuff like that, I don't want -- I know, that's not what you intended, but for the message that it was -- that that's sort of what drove us to where we are, and I know you one hundred percent didn't want to say that, but I just wanted to clarify that.

NED CALONGE: Well, I want to again, give our thanks to Alex and the entire team. He's one representative of an army of people.

ALEX KEMPER: A fantastic, wonderful army. We're very lucky.

NED CALONGE: We want to make sure I recognize all of them, and thank you for the work today, and we look forward to Phase 3 presentations.

This brings us to the end of today's session, but not the end of opportunities to participate in thinking about the Newborn Screening System. So, we are going to adjourn here and then, I think, Soohyun is working on putting up the workgroup meeting locations for

people who are here physically and the webpage where you can Zoom into a workgroup if you so choose. Remember, the charge for the workgroups is to identify three top priority solutions and action steps that the community can consider on supporting state implementation of those conditions added to the RUSP, and overall strengthening the Newborn Screening System.

We'll adjourn for today. I'll tell you that same place, same starting time tomorrow, so 9:30, and I appreciate the work of everyone today and especially our folks providing public comment. It's greatly appreciated. And we'll see you tomorrow, I hope.

(THEREUPON, DAY 1 OF THE MEETING CONCLUDED AT 3:00 P.M.)