NEWBORN SCREENING TECHNICAL ADVISORY COMMITTEE SPECIAL MEETING SUMMARY NOTES

What: Newborn Screening Technical Advisory Committee Meeting: Guanidinoacetate methyltransferase (GAMT) Deficiency and Arginase 1 Deficiency (ARG1-D)

When: September 8, 2023

Participating:

- Technical Advisory Committee (TAC) Members Kelly Oshiro (State Board of Health Co-Chair), Nirupama (Nini) Shridhar (Department of Health Co-Chair), Steve Kutz, Dr. Tashi Gyaltsong, Joan Chappel, María Á. Sigüenza, Dr. Eric Leung, Thomas May, Krystal Plonski, Kim Tuminello, Christine Zahn, Dr. LuAnn Chen, Khim Shoenacker, Trish Anderson, Nancy Ledbetter, and Dr. Emily Shelkowitz.
- State Board of Health (Board) staff Melanie Hisaw, Michelle Larson, Molly Dinardo, and Michelle Davis; Department of Health (Department) staff John Thompson, Samantha Fuller, Kelly Kramer, Michael Katsuyama, Alexandra Montaño, and other Department staff.
- Other Guests Melanie Ogleton and Amanda Winters (Meeting Facilitators), Makena Chandra (University of Washington), Tami Berk and Wilkes (American Sign Language Interpreters), Fernando Rios and Nicolás Arizaga (Spanish Interpreters), and approximately 15 members of the public.

Summary Notes

Welcome and Introductions

- Michelle Larson and Molly Dinardo provided introductory remarks and overviews of the language interpretation channels and Zoom meeting functions; Melanie Ogleton asked TAC members to introduce themselves, their role and organization (if applicable), and to share their favorite summer treat.

TAC Overview and Meeting Norms

- TAC Co-Chairs Nini Shridhar and Kelly Oshiro discussed the scope and purpose of the meeting and plan for the day. Amanda Winters provided an overview of meeting norms.

Newborn Screening Program Overview

- John Thompson provided an overview of the Department's Newborn Screening (NBS) Program, noting there are currently 32 conditions that every baby in Washington is screened for. John T. shared information regarding the number of tests their lab completes each year, the number of newborns screened, and what happens when a baby has abnormal test results. John T. also discussed the

specialty care partners their program partners with and gave a brief overview of the Federal Recommended Uniform Screening Panel (RUSP).

Newborn Screening Criteria Review

- Molly D. provided an overview of the Board's three guiding principles and criteria for evaluating candidate Conditions for the state's newborn screening program.

Family Perspective – GAMT Deficiency

- Kim Tuminello, a parent of two children with GAMT Deficiency, provided a presentation on the impact of GAMT Deficiency on children and their families. Kim T. explained that GAMT Deficiency is a rare, recessive genetic disorder and that their child was one of the first in the U.S. to be diagnosed with this condition. Kim T shared that their son was not diagnosed until 10 months old but noted that once treatment began, they saw very fast progress in their child's development, despite some difficulties with their developmental skills. When Kim's second child was born, since they were aware of the GAMT diagnosis in their son, they were able to get an early diagnosis for their daughter and start treatment early on. Kim T. shared that the health outcomes for their daughter have been very good, with the daughter having normal development. Kim mentioned that although both children will be on treatment for their entire lives, early diagnosis and treatment at birth are imperative for better outcomes.

Natural History of GAMT Deficiency – Diagnostic Testing and Available Treatment

- Dr. Emily Shelkowitz shared a presentation on the natural history of GAMT Deficiency. Dr. Shelkowitz noted that GAMT Deficiency is very rare – about 130 people are diagnosed with the condition worldwide. Dr. Shelkowitz spoke about the age of onset and provided an overview of common and uncommon symptoms of GAMT, which range from mild to severe developmental delay to movement disorders and low muscle tone. Dr. Shelkowitz discussed the typical diagnosis of the condition, most commonly biochemical testing of blood or urine, and that treatment of the condition has two components, replenishing cerebral creatine stores or reducing guanidinoacetate levels (requiring close dietary monitoring).
- Dr. Shelkowitz shared outcomes in a case series of 48 individuals with GAMT Deficiency and the degree of disability correlated with the age of diagnosis. In the case series, the two individuals who were treated shortly after birth had normal development. Dr. Shelkowitz summarized that GAMT appears to be highly treatable if therapy is initiated early.

Available Screening Technology – GAMT Deficiency

- Michael Katsuyama provided an overview of available screening technology for GAMT Deficiency, which includes a bloodspot test adapted to tandem mass spectrometry (MS/MS) to test for elevated levels of Guanidinoacetate (GUAC) and low levels of creatine. Michael K. noted that this technology is already being used by the Newborn Screening lab and has been in the program since 2004. Michael K. also included information from current states testing for the condition, and based on

these data, indicated that the sensitivity of testing is 100% and the false positive rate (specificity) is 99.99%.

- Dr. Tashi Gyaltsong asked a clarifying question regarding when true positive cases could be expected and inquired if maternal circulation could affect newborn screening or create false negatives for those receiving early newborn screening. Dr. Shelkowitz responded that some disorders are affected by maternal diet; however, an amino acid profile in newborns collected at less than 24 hours of life is likely the newborn's own metabolism.

Cost-Benefit Analysis – GAMT Deficiency

- Makena Chandra provided an overview of the economic model and results of the GAMT Deficiency cost-benefit analysis. The findings of the analysis showed that the benefits of newborn screening outweigh the costs – each dollar spent has an expected benefit of $1.45.
- Steve Kutz asked if the costs in the model were based on lifetime costs. Makena C. responded that the costs in the model are through the age of twelve.

Application of Criteria and Discussion

- Melanie Ogleton and Amanda Winters gave TAC Members three minutes of individual reflection using a set of reflection questions related to the Board's three guiding principles. Melanie O. and Amanda W. then opened things up for a larger group discussion and had members add any comments they didn't want to share verbally to a virtual notetaking and discussion platform called Padlet. The meeting facilitators also read questions and comments out from the Padlet to help facilitate the discussion.
- Thomas May, Dr. Tashi Gyaltsong, Dr. Emily Shelkowitz, Dr. Eric Leung, Michael Katsuyama, and John Thompson discussed the available screening technology for GAMT Deficiency, the impact of ambiguous results, timing of testing, and the condition's low false positive rate compared to other newborn screening conditions, like Pompe disease.
- Dr. Shelkowitz emphasized that identifying GAMT early, specifically the period between 3 weeks to 3 months, is critical.
- Dr. Gyaltsong spoke about the experience of having gone through a false positive case of Pompe with a family and emphasized the trauma the family experienced while waiting for confirmation of a diagnosis.
- In response to a Padlet question, Joan Chapel shared information about Medicaid coverage for genetic testing and coverage of the newborn screening test. Dr. LuAnn Chen and Steve Kutz commented on insurance coverage for genetic testing and noted that any delays in coverage impacts children's health outcomes.
- Molly Dinardo responded to a comment in the Padlet regarding the RUSP recommendation for GAMT and clarified that while Washington reviews and takes the federal recommendations into consideration, Washington has its own process to evaluate conditions.

GAMT Deficiency Vote #1 – Criteria

- TAC Members participated in an anonymous, online vote to assess whether GAMT Deficiency meets or does not meet the five criteria established by the Board. *See addendum for vote summary and comments*.

GAMT Deficiency Vote #1 – Results and Discussion

- Melanie Ogleton and Amanda Winters reviewed the results of the TAC's vote and associated comments for each of the criteria established by the Board.

GAMT Deficiency Vote #2 – Recommendation

- TAC Members participated in an anonymous, online vote on an overall recommendation to the Board regarding the addition of GAMT Deficiency in the state's newborn screening panel. *See addendum for vote summary and comments*.

GAMT Deficiency Vote #2 – Results and Next Steps

- Melanie Ogleton and Amanda Winters reviewed the results of the TAC's vote and associated comments, noting clear consensus on the recommendation to add GAMT Deficiency. There were no additional comments or questions from TAC Members.
- Molly Dinardo described the next steps for the TAC, explained that the results of the committee will be shared at the October 9 Board meeting for further deliberation, and invited TAC members to attend.

Family Perspective – ARG1-D

- Christine Zahn shared the story of their granddaughter Willow, who was diagnosed with ARG1-D at age 5. Christine Z. noted that an early diagnosis for Willow would have been life-changing, as ARG1-D is a silent disorder that wreaks havoc on the brain and body, all from eating food that we all eat. Christine Z. also shared that with an early diagnosis, dietary restrictions can be started immediately and slow down the progression of the disease. Christine Z. added that anything that we can do to help prevent the buildup of Arginase in the bodies of affected children and make an early diagnosis can make an immense impact on the physical, emotional, and financial well-being of children and their families. Christine Z. then shared a video detailing the shared experiences of children and families impacted by ARG1-D.

Natural History of ARG1-D – Diagnostic Testing and Available Treatment

- Dr. Emily Shelkowitz shared a presentation detailing the natural history of ARG1-D. Dr. Shelkowitz noted that, like GAMT, ARG1-D is also rare, with less than 260 individuals having been diagnosed to date. Dr. Shelkowitz mentioned that newborns are typically asymptomatic, and symptoms of the condition are "insidious" and don't typically become apparent until a child is about 1 to 3 years old. Dr. Shelkowitz also shared common symptoms associated with ARG1-D and noted that because one of the most common symptoms is spasticity in the legs, ARG1-D can be misdiagnosed as cerebral palsy. Dr. Shelkowitz discussed the typical diagnosis of the condition, most commonly through biochemical testing measuring plasma arginine, and treatment of ARG1-D which entails reducing levels of arginine through low-protein diets and/or ammonia diversion therapy and monitoring arginine levels to avoid hyperammonemia.

- Dr. Shelkowitz shared that current treatment lowers but does not normalize arginine levels. Based on published literature, Dr. Shelkowitz summarized that ARG1-D is partially treatable with the clinical tools currently available, and even a partial reduction in arginine has clear and meaningful impacts on the disease course.

Available Screening Technology

- Michael Katsuyama provided an overview of available screening technology for ARG1-D, which, like GAMT, includes a bloodspot test adapted to tandem mass spectrometry (MS/MS).
- Michael K. mentioned that the Washington Newborn Screening Program is already running the ARG1-D test for Idaho babies, which has ARG1-D on its state screening panel. Michael K. also included information from current states testing for the condition, and based on these data, indicated that the sensitivity of testing is 100% and the false positive rate (specificity) is 99.99%.
- Kelly Oshiro asked how long Washington has been screening ARG1-D for Idaho babies, and if any cases have been identified yet. Michael K. responded that they have been doing this screening since 2021 and that they haven't identified any cases of ARG1-D to date.
- Dr. Tashi Gyaltsong asked if Washington had considered screening for ARG1-D prior to this meeting. John Thompson responded with some background history on the Board and the Department's condition review process, which was put into place once the lab started using tandem mass spectrometry (MS/MS), a technology that has the capability for screening many different conditions. John T. noted that when Idaho requested that the Washington lab support its newborn screening testing, this didn't have an impact on the conditions Washington screened for, since Washington has its own process for evaluating conditions.
- Nini Shridhar, Dr. Eric Leung, and Dr. LuAnn Chen asked questions about current screening technology and capabilities with tandem mass spectrometry and inquired about the differences between core and secondary conditions on the federal RUSP. John T. and Dr. Emily Shelkowitz responded to their questions.

Cost-Benefit Analysis – ARG1-D

- Makena Chandra provided an overview of the economic model and results of the ARG1-D cost-benefit analysis. The findings of the analysis showed that the benefits of newborn screening outweigh the costs – each dollar spent has an expected benefit of $2.03.
- Dr. Tashi Gyaltsong inquired if the Washington lab is already testing all specimens for ARG1-D. John Thompson responded that the lab is only testing specimens that come in from Idaho for ARG1-D.
- Steve Kutz, Nini Shridhar, and Dr. Emily Shelkowitz discussed that ARG1-D outcomes vary based on the accumulation of arginine, the timing of when treatment is initiated, and the dietary needs of people diagnosed with ARG1-D.

Application of Criteria and Discussion

- Melanie Ogleton and Amanda Winters gave TAC Members three minutes of individual reflection using a set of reflection questions related to the Board's three

guiding principles. Melanie O. and Amanda W. then opened things up for a larger group discussion and had members add any comments they didn't want to share verbally to a virtual notetaking and discussion via Padlet. The meeting facilitators also read questions and comments from the Padlet to help facilitate the discussion.

- The facilitators read a question regarding timing around confirmatory testing. Dr. Emily Shelkowitz discussed expected timelines and their specific variations.
- The facilitators read a question regarding who absorbs the additional testing costs. Dr. Shelkowitz stated that confirmatory biochemical tests would go through insurance, are not expensive, and do not require pre-authorization. Genetic testing would need to wait for pre-authorization but would still run through insurance. John Thompson added that for newborn screening testing, the panel is a fee for service testing and would be billed at the time of screening and would be one screening cost per baby.
- The facilitators read a question concerning challenges to children/families in trying to manage arginine levels. Christine Zahn responded that this could be very challenging, especially if a child is school-aged or has multiple caregivers – it can be difficult to get them to consume food, and it requires close monitoring and tracking.
- TAC Members also discussed equity considerations around whether universal screening allows for better access to a diagnosis and equity in care received. John Thompson stated that without universal screening, there isn't the opportunity to intervene or to get a diagnosis. Dr. Shelkowitz echoed John's point and agreed that while there are equity issues around care, universal screening allows for equity around screening and a potential early diagnosis.

ARG1-D Vote #1 – Criteria

- TAC Members participated in an anonymous, online vote to assess whether ARG1-D meets or does not meet the five criteria established by the Board. *See addendum for vote summary and comments*.

ARG1-D Vote #1 – Results and Discussion

- Melanie Ogleton and Amanda Winters reviewed the results of the TAC's vote and associated comments for each of the criteria established by the Board.

ARG1-D Vote #2 – Recommendation

- TAC Members participated in an anonymous, online vote on an overall recommendation to the Board regarding the addition of ARG1-D in the state's newborn screening panel. *See addendum for vote summary and comments*.

ARG1-D Vote #2 – Results and Next Steps

- Melanie Ogleton and Amanda Winters reviewed the results of the TAC's vote and associated comments, noting clear consensus on the recommendation to add ARG1-D. There were no additional comments or questions from TAC Members.

Meeting Closeout

- Kelly Oshiro shared more information regarding the upcoming Board consideration and voting on the TAC's recommendations on October 9 in Wenatchee. Kelly O.

thanked the TAC Members and families for sharing their stories and thanked the Board and Department staff, and the meeting interpreters. Nirupama Shridhar and other TAC Members echoed Kelly O's sentiments.

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PO Box 47990 • Olympia, Washington • 98504-7990
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