WASHINGTON STATE BOARD OF HEALTH

HEALTH PROMOTION COMMITTEE
SPECIAL MEETING SUMMARY NOTES

What: Newborn Screening Technical Advisory Committee - Ornithine Transcarbamylase Deficiency

When: June 16, 2021

Participating by Zoom: Technical Advisory Committee (TAC) Members: Dr. Tom Pendergrass, Dr. Scott Lindquist, Joan Chappell, Trish Anderson, Dr. Krystal Plonski, Maria Siguenza, Shari Maier, Kristine Alexander, Byron Raynz, Victoria Raynz, Dr. Ben Wilfond, Dr. Sihoun Hahn, and Peggy Harris; Presenters Dr. Angela Sun, Dr. Anna Scott, Dr. John Thompson, Reesa Reonal; Board of Health and Department of Health Staff and six members of the public.

Summary Notes:
Co-chair Dr. Scott Lindquist welcomed TAC members, staff, and members of the public and provided a brief introduction of the members and purpose of today's meeting. Sam Pskowski, Board Staff, provided an overview of the virtual meeting functions and expectations. Co-chair Dr. Tom Pendergrass reviewed the purpose of the meeting, outlining the Board's authority to determine which conditions are included in the newborn screening (NBS) panel, and how the committee will use the Board's five criteria and guiding principles to make a recommendation on whether or not to add Ornithine Transcarbamylase Deficiency (OTCD) to the NBS panel. He noted the fifth criterion discussion was deferred to a possible future meeting.

Reesa Reonal, Department of Health Staff, provided a presentation on the Department's Newborn Screening Program. She described the Department's newborn screening program, timelines, current screening panel, and follow-up processes. Co-chair Pendergrass emphasized the challenge for the state in getting every child screened and how the time between testing and appearance of signs or symptoms can affect whether a screen is effective. Co-chair Lindquist commented on the NBS lab's success following up with families identifying infants who do not have a sample, success in getting second specimens, and the NBS program reporting results to providers.

Co-chair Lindquist then reviewed the Board's five criteria for assessing a condition for inclusion on the NBS panel. The four criteria considered at the day's meeting were; (1) available screening technology, (2) diagnostic testing and treatment available, (3) prevention potential and medical rationale, (4) public health rationale. The fifth criteria, cost-benefit/cost-effectiveness, was deferred to the next meeting, if the proposal for OTC Deficiency met the four criteria reviewed today. Co-chair Pendergrass again emphasized that screening only is appropriate when testing can be completed in time ameliorate the disease and promote better outcomes. If children become ill before the

test result is available, the time between a child's birth and when they can receive treatment can make testing inappropriate.

Co-chair Lindquist then introduced Dr. Angela Sun of the Biochemical Genetics Program at Seattle Children's Hospital. She provided a review of the natural history and treatment of OTCD. Dr. Sun reviewed the impact of OTCD, including the organ systems impacted, the variation in levels of severity, and the treatments available. Co-chair Pendergrass asked whether chemical markers exist that predict whether outcomes will be poor or very poor. Dr. Sun noted that some OTC deletions are more severe than others. She pointed out that glutamine levels can be helpful in predicting severity in some cases. John Thompson, Department of Health Staff, asked about the percentage of diagnoses which can be found through screening. Dr. Sun stated that this information is not known with certainty. Dr. Thompson reported that screening programs in other states see lower prevalence of affected infants and asked about data on values for markers that may be too low to identify some babies. Dr. Thompson asked about outcomes when babies are diagnosed at birth versus those who show up clinically. Dr. Sun shared that outcomes are better when the diagnosis is done prenatally or in the first days of life. TAC member Dr. Sihoun Hahn asked Dr. Sun to comment about ongoing clinical trials for treatment of OTCD. Dr. Sun reported that Seattle Children's is not a participant in current clinical trails, but she has seen information from those doing the trials showing improvement in outcomes when ammonia levels in the baby are kept low. Co-chair Pendergrass reported that the new therapy studies he has seen appear to be most effective in infants with less severe presentation of OTCD. He followed up with a question about other causes for high levels of ammonia, a symptom of OTCD, in newborns. Dr. Sun responded with the following list: sepsis, conditions causing seizures, and birthing stress or other conditions producing elevated ammonia levels. These other conditions may be more common and influence healthcare staff considering their being present before considering OTCD. Co-chair Lindquist asked Dr. Sun if she had any concerns about screening for OTCD. She responded that she has no clinical concerns but is interested in the diagnostics presentation to better understand gray areas. TAC member Peggy Harris suggested that the signs and symptoms of OTCD are similar to those from isovaleric acidemia.

Dr. John Thompson, Department of Health Staff and Director of the Newborn Screening Laboratory, presented findings on newborn screening for OTCD. Dr. Thompson reviewed screening programs in other jurisdictions (Massachusetts, California, and Puerto Rico) and how their experiences could affect how OTCD could be screened in Washington State using citrulline levels. Co-chair Pendergass asked whether the NBS program knows how many infants with low levels of citrulline are picked up currently. Dr. Thompson stated he did not have that information on hand but would look into it. Co-chair Pendergrass asked if there was data on ways to quantify the experiences of difficult birth and the risk of high ammonia levels. TAC member Dr. Ben Wilfond appreciated the data from the other jurisdictions and was curious if there was anything to learn regarding communication to physicians and families about screening results from those jurisdictions. Dr. Thompson stated that the NBS Program could follow-up. It was his impression that communication issues are similar to other conditions where the baby is likely already very sick in the hospital. Based on the timeline presented on the rate of elevation of ammonia levels, it is likely babies with higher levels would already be showing up sick in the hospital by the time screening results are available. TAC

member Dr. Krystal Plonski asked if Washington would consider moving toward Massacheusetts's or California's approach is setting levels of concern for citrulline . Dr. Thompson noted that Washington follows more closely to the model that Massachusetts has taken for the panel overall. He is concerned about the workload for follow-up staff given the likelihood of many false positives. Co-chair Pendergrass noted there appear to be two groups that will be identified, babies with severe illness and those who have sufficient function and develop disease later in life. TAC member Wilfond noted that providers are often asked to convey information to families indicating possibility of disease without confirmation. He wondered if the NBS program was the best place to address this particular condition. TAC member Harris noted that false positives can be stressful, but it is more stressful to have a symptomatic baby and no understanding of possible causes.

Co-chair Lindquist introduced Dr. Anna Scott, Seattle Children's, to provide information on the diagnostic testing for OTCD and invited Dr. Angela Sun to provide information on treatment availability in Washington state after the diagnostic testing presentation. Co-chair Lindquist asked if Dr. Scott had any concerns around the possibility of including OTCD in the NBS panel. Dr. Scott's biggest concern is the lack of sensitivity for testing low citrulline levels. She reported that an approximately 10% of cases have diagnostic testing that does not come up with conclusive findings. The diagnostic error tends to appear more in late-onset cases or cases who have an altered enzyme, but the disease does not appear at all. Dr. Sun discussed the treatment available in Washington, indicating that care can be provided at Seattle Children's Hospital, Mary Bridge Children's Hospital in Tacoma, and some services available at Sacred Heart Hospital in Spokane. She admitted that Seattle Children's sees patients from all over the state in Seattle.

Dr. Thompson followed up on Co-chair Pendergrass's earlier question and noted that if Washington used the California model, there would be approximately 3 positives/day while using the Massachusetts model would result in 2 positives/week. These rates of positives and the urgency in care results in a high caseload. TAC Member Hahn believed that this would be a significant burden to the lab and care teams. He urged that consideration of approaches to reduce false positives be included in the cost analyses.

The meeting broke for lunch from 12 – 12:30 p.m.

When the TAC reconvened, Co-chair Lindquist introduced Byron and Victoria Raynz and asked that they share their family's experience with OTCD. The Raynz's son was born with OTCD, following a healthy pregnancy, and without any signs of illness in the mother. By the time of diagnosis, their son was extremely ill and subsequently died before they had received a diagnosis. Mr. Raynz noted that it is not just the infant but the asymptomatic mother who benefits from screening, which could help with future family planning. Mr. Raynz acknowledged that the test and system are not perfect; we will not be able to help 100% of babies with OTCD, but maybe we could help half of them. TAC member Harris noted that she appreciated the inclusion of the parental perspective on the TAC. She also supported the benefit of having information gained from newborn screening. Members discussed the benefits of families having information and the issue of receiving false positive information. Dr. Scott repeated that genetic screening can be useful for diagnosing and ruling out OTCD.

Co-chairs Lindquist and Pendergrass then led the TAC in discussion applying each of the four criteria to OTCD. They explained the voting processes.

Available Screening Technology
TAC Member Raynz asked in the case where there was not a straight-forward answer, how could a TAC member convey their concern in their response. Ms. Pskowski clarified there is an 'unsure' option included on the ballot and also a place to write comments. Dr. Thompson noted the best data on screening technology is out of California showing 87% sensitivity, while Massachusetts and Puerto Rico assume 100% sensitivity. He stated that the best number is probably someplace in between. He reported that specificity is 99%. TAC Member Plonski asked if there are any conditions currently on the panel with lower sensitivity and specificity than OTCD. Dr. Thompson while sensitivity for most tests in the NBS program is pretty good. For instance, with cystic fibrosis the sensitivity is around 95%. For comparison, Dr. Scott asked about the numbers for very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, another condition with spectrum of disease symptoms and age of onset. Dr. Thompson reported that there have been no known missed cases but the positive predictive value for that condition is not high. TAC Member Kristine Alexander asked if a disorder had ever been removed from the panel due to a lower than expected benefit. Dr. Thompson reported that in Washington State, no test has been removed, but Iowa did recently stop screening for short-chain acyl-CoA dehydrogenase (SCAD) deficiency because of too many false positives. Co-chair Pendergrass noted that the State Board of Health would use this TAC process to consider removal of any poorly performing screening test.

Diagnostic Testing and Treatment Available
Co-chair Pendergrass noted that something the Board of Health considers is the issue of accessibility and provision of care for all who screen positive for a test and monitors for patients not picked up in the screens (false negatives). It was noted that if the NBS Program were to identify 2-3 patients a week with presumed OTCD, the resources currently available would be overwhelmed. Thus, the false positive rate is important to consider when we talk about the availability of testing and treatment.

Prevention Potential and Medical Rationale
Co-chair Pendergrass noted that timing of testing and results can be an issue for or against adding a test to the NBS. He raised concern about complete loss of the OTC enzyme since around half of babies with severe OTCD would be in the hospital or have passed away by the time a result is available. Co-chair Lindquist noted that even following a death, the information can be beneficial to the parents. Since OTCD has variation in presenting in infancy and through the first year of life, there may be value in testing. In addition, the individuals who have partial deficiency that produces onset in adulthood may not be detected in the newborn screens. The group discussed genetics as a field generally and the importance of it in medicine overall. TAC Member Harris noted that if the treatment is not detrimental to the baby, it would be beneficial to start treating while awaiting a test result.

Public Health Rationale
Co-chair Pendergrass asked if this screening will result in a changes to the care of patients and their outcomes. He also asked the TAC to consider whether population-

based screening for this condition is better than risk-based screening, screening families who have an affected child to help make decisions for future pregnancies.

Co-chair Lindquist asked for final thoughts or questions about the criteria or their meanings prior to voting. TAC Member Shari Maier asked what the risk of treating false positive cases while a family waits for a test result would be. Dr. Sun said the risk is not significant in the short-term. Restricting the diet to the level that is needed to manage OTCD for the short-term is not harmful. There are therapies to decrease ammonia levels that have no or minimal risk. Because a mainstay of treatment is dietary, some babies may develop an oral aversion to certain foods. Co-chair Lindquist clarified that the committee is not considering cost-benefit/cost-effectiveness today and that folks will now vote on the four criteria discussed today.

Ms. Pskowski provided a brief overview of the electronic ballot and directed TAC members to find a link in their inbox. The meeting took a short recess for voting and tally.

Co-chair Lindquist shared the vote tally with the group, there were no “no” votes.

Criteria	**Yes**	**No**	**Unsure**
Available Screening Technology	12	0	1
Diagnostic Testing and Treatment Available	12	0	1
Prevention Potential and Medical Rationale	11	0	2
Public Health Rationale	12	0	1

Ms. Pskowski clarified that based on the vote, the committee would proceed with the second meeting scheduled for July 7, 2021 to consider the cost-benefit/cost-effectiveness analysis.

Co-chairs Lindquist and Pendergrass closed the meeting at 2:10 p.m.