BCKDK Deficiency Legislative Report- DRAFT

Table of Contents - TBD

Kelly Oshiro, Board Sponsor Letter-- TBD

Executive Summary

Newborn screening helps detect treatable conditions early in life through blood tests. The State Board of Health (Board), with the support of the Department of Health (Department), evaluates potential new conditions through a defined process and criteria involving evidence, ethics, equity, and cost-effectiveness.

During the 2024 legislative session, the Legislature passed, and Governor Inslee signed Senate Bill (SB) 6234, screening newborn infants for branched-chain ketoacid dehydrogenase kinase deficiency. SB 6234 directed the Board to consider adding Branch-Chain Ketoacid Dehydrogenase Kinase (BCKDK) deficiency to Washington's mandatory newborn screening panel and submit a report to the Governor and the appropriate committees of the Legislature by June 30, 2025.

BCKDK deficiency is a rare genetic disorder that impairs the metabolism of branched-chain amino acids, potentially causing neurodevelopmental issues such as autism spectrum disorder, seizures, and developmental delays. It may be detectable via newborn bloodspot testing using tandem mass spectrometry, which is part of the state's existing newborn screening technology. BCKDK is not included on any universal screening panel in the United States or abroad.

The Board convened a multi-disciplinary Technical Advisory Committee (TAC) to evaluate whether BCKDK deficiency should be added to the state’s newborn screening panel. The TAC considered key factors such as the availability of screening technology, diagnostic tests, treatment options, prevention potential, public health rationale, and cost-effectiveness. The TAC noted that while screening technology exists, there is currently insufficient evidence regarding the condition's

prevalence, treatment outcomes, and cost-effectiveness. As a result, most TAC members voted against adding BCKDK deficiency to the panel, due to limited data and the lack of available information to complete a cost-benefit analysis.

On March 12, 2025, the Board reviewed the TAC's findings and unanimously accepted the recommendation. The Board does not recommend including BCKDK deficiency on the newborn screening panel at this time. Both the Board and TAC agreed to not re-review the condition until more data and research are available to complete a comprehensive evaluation.

Background

RCW 70.83.050 authorizes the State Board of Health (Board) to adopt rules for screening Washington-born babies for hereditary conditions, including the list of conditions on the mandatory newborn screening panel. Chapter 246-650 WAC is the Board's rules for newborn screening and WAC 246-650-020 lists conditions for which all newborns must be screened.

Newborn screening is a public health system that universally tests newborn babies to identify serious, but treatable, conditions. The Department of Health (Department) houses the state's Newborn Screening Program. Shortly after birth, the attending health care provider collects a newborn screening specimen by obtaining drops of blood from a baby's heel on a filter paper card. Each newborn screening specimen is submitted to the Public Health Laboratories where it is tested for 32 conditions that are currently on the mandatory newborn screening panel.

To add new conditions to the panel, the Board and the Department have developed a process and criteria for evaluation that focuses on evidence, ethics, equity, and the balance between cost-benefit and cost-effectiveness. To determine whether a condition should be added to the panel, the Board convenes a technical advisory committee (TAC) to evaluate candidate conditions using guiding principles and established criteria [Appendix A]. The multi-disciplinary TAC includes representatives with expertise and experience related to the candidate conditions including clinicians, academia, insurers, public health, and families of those with rare conditions.

During the 2024 legislative session, the Legislature passed, and the Governor signed SB 6234 (Chapter 105, 2024 Laws), which directed the Board to consider adding branch-chain ketoacid dehydrogenase kinase (BCKDK) deficiency to the mandatory newborn screening panel.

The Board convened a TAC to evaluate BCKDK deficiency in January 2025. The TAC consisted of seventeen multi-disciplinary members, representing public health, public and private insurance organizations, healthcare providers and facilities, state ethnic commissions, specialty care clinics, and parent advocates [Appendix B].

Branch-Chain Ketoacid Dehydrogenase Kinase Deficiency

BCKDK deficiency is a rare inherited genetic disorder that leads to a deficiency of branched-chain amino acids. There are approximately 21 cases of BCKDK deficiency identified worldwide, with no

reported cases in the United States. BCKDK deficiency is caused by changes in the BCKDK gene, which produces the BCKDK enzyme. The BCKDK enzyme regulates the metabolism of branched-chain amino acids. Mutations with the BCKDK enzyme cause an overactive breakdown of branched-chain amino acids. As a result, proteins can't form properly, which impairs neurodevelopmental growth and development.[1,2]

Signs and symptoms for BCKDK deficiency can vary but may include autism spectrum disorder (ASD), language impairment, seizures, and microcephaly. Low levels of branched-chain amino acids can be detected via newborn screening of a dried bloodspot using tandem mass spectrometry. Newborns that have an out-of-range screening result for BCKDK deficiency should have DNA testing to rule out of confirm the diagnosis. BCDKDK deficiency can be treated with a high protein diet and supplementation of branch-chain amino acids.[2]

[1] Novarino, G., et al. Mutations in BCKD-kinase lead to a potentially treatable form of autism with epilepsy. Science 338: 394-397, 2012. [PubMed: 22956686]

[2] Tangeraas, T., et al. BCKDK deficiency: a treatable neurodevelopmental disease amenable to newborn screening. Brain 146: 3003-3013, 2023. [PubMed: 36729635]

Technical Advisory Committee Review

The TAC convened on January 14, 2025, to evaluate BCKDK deficiency against an established set of criteria: Available Screening Technology, Diagnostic Testing and Treatment Available, Prevention Potential and Medical Rationale, Public Health Rationale, and Cost-benefit/Cost-effectiveness. To help inform this criteria review, the TAC heard from Michelle Whitlow, Executive Director of the Lewis County Autism Coalition. While BCKDK deficiency does not cause all cases of autism spectrum disorder (ASD), it is associated with epilepsy and certain forms of ASD. M. Whitlow provided insights on the broader connection between ASD and branched-chain amino acid disorders [Appendix D].

Philip White from Duke University and Beth Ogata from the University of Washington Medical Center (UWMC) provided subject matter expertise regarding the natural history, diagnostic testing, and treatment for BCKDK deficiency. P. White explained how the BCKDK enzyme is involved in the breakdown of branched-chain amino acids (BCAA), and how a deficiency of this enzyme limits protein synthesis and growth. P. White noted that in the limited number of studies, all BCKDK deficiency cases showed global developmental delay at diagnosis. In these studies, clinical outcomes were shown to be improved in patients when BCAAs are supplemented, with a greater improvement of developmental delay if treatment was initiated before two years of age.

Beth Ogata, a registered dietitian at UWMC Metabolic Clinic, reviewed what a potential treatment plan would be for any patients that might be identified with BCKDK deficiency. Treatment recommendations for patients could include: increased dietary protein intake, BCAA supplements of an oral powder or tablets taken 4-7 times per day, plasma BCAA monitoring, developmental surveillance and referral, and regular clinic visits for monitoring, education, and adjustment of plan. B. Ogata explained that branch-chain amino acid supplements are not always reimbursed by

insurance or readily accessible. B. Ogata advised some patients may experience treatment fatigue and may not adhere to their treatment plan over time, due to the high burden of the lifelong treatment.

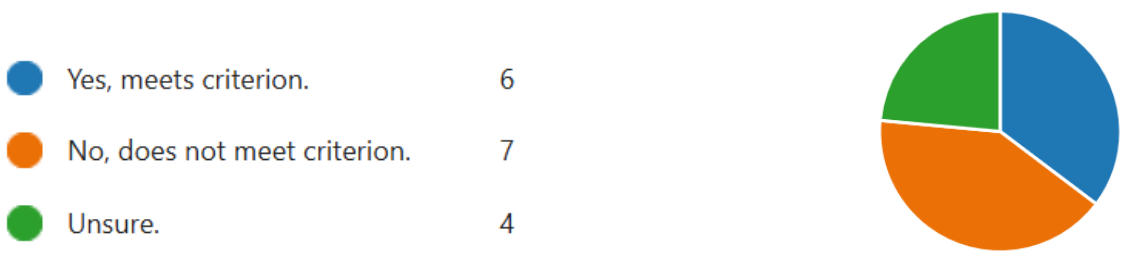
The Department's Newborn Screening Program shared the available screening technology and provided a cost-benefit analysis for Washington if BCKDK deficiency was to be added to the mandatory newborn screening panel. A cost benefit analysis is a part of the newborn screening evaluation process because adding a condition to the newborn screening panel would be considered a significant legislative rule change under the Administrative Procedures Act Chapter 34.05 RCW. BCKDK deficiency may be detected from a dried bloodspot by testing for low branch-chain amino acids using tandem mass spectrometry; the Newborn Screening Laboratory currently analyzes specimens for the inverse by detecting abnormally elevated branch-chain amino acids to screen for another condition on the panel. The cost-benefit analysis compares the status quo (no universal screening of a condition) versus a screening model. This analysis includes data from primary literature, states conducting screening for a condition, and expert opinion. Newborn Screening Program staff consulted with the Department's health economist who recommended against generating a benefit/cost ratio or cost-effectiveness estimate because of the lack of robust data to inform the economic model.

After the presentations from subject matter experts and the Department, TAC members were given the opportunity to vote anonymously via Microsoft Forms. Members voted on each criterion and provided an overall recommendation on whether BCKDK deficiency should be added to the mandatory newborn screening panel. For each criterion, TAC members could vote 'Yes, this condition meets the criterion,' 'No, this condition does not meet the criterion,' or 'Unsure.' Additionally, TAC members had the option to leave anonymous comments for each criterion and the overall recommendation.

Criterion 1: Available Screening Technology

The TAC evaluated BCKDK deficiency against Criterion 1: Available Screening Technology, in which sensitive, specific, and timely tests are available that can be adapted to mass screening. BCKDK deficiency can be detected from a dried bloodspot using tandem mass spectrometry, which is technology that has been utilized by the Newborn Screening laboratory since 2008. BCKDK deficiency would be screened for by looking for low branch-chain amino acid levels in a baby's blood.

Out of seventeen total TAC members, 6 voted 'Yes, meets criterion', 7 voted 'No, does not meet criterion', and 4 voted 'Unsure'.

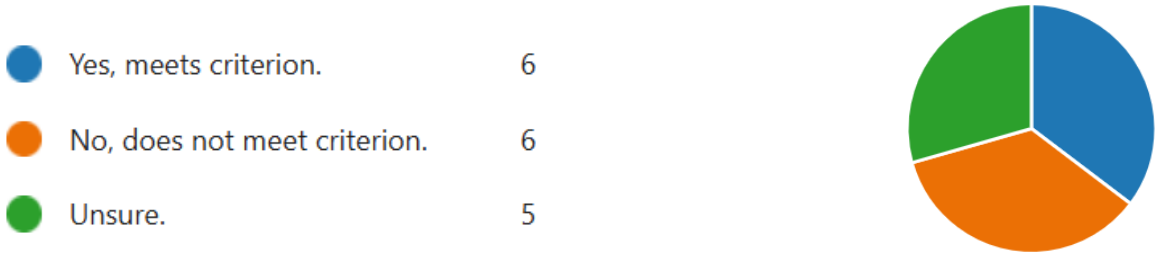


TAC members commented that screening technology is available to detect low branch-chain amino acids, but the actual test performance, such as the sensitivity and specificity, is unclear. Establishing a cutoff to determine a 'low' value for branch-chain amino acids for a newborn would need to be estimated from a population study as no other newborn screening program in the United States is currently screening for BCKDK deficiency.

Criterion 2: Diagnostic Testing and Treatment Available

Criterion 2: Available Diagnostic Testing and Treatment Available considers the availability of accurate diagnostic tests, medical expertise, and effective treatment for evaluation and care of all infants identified with the condition.

Out of seventeen total TAC members, 6 voted 'Yes, meets criterion', 6 voted 'No, does not meet criterion', and 5 voted 'Unsure'.

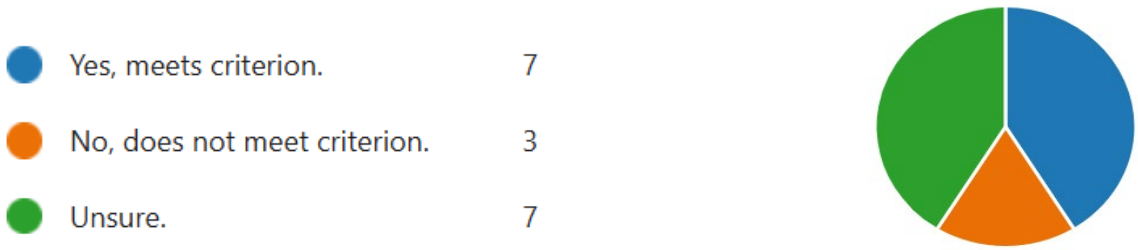


TAC members commented that there is very limited evidence available for this disorder, making it unclear whether the diagnostic criteria are met. Additional comments included the data on prevalence, long-term outcomes, false positives/negatives, and treatment effectiveness is insufficient, and the small sample size makes it difficult to verify the disorder's validity.

Criterion 3: Prevention Potential and Medical Rationale

Criterion 3, Prevention Potential and Medical Rationale: The newborn identification of the condition allows early diagnosis and intervention. Includes considerations: there is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention; the benefits of detecting and treating early onset forms of the condition (within one year of life) balance the impact of detecting late onset forms of the condition; newborn screening is not appropriate for conditions that only present in adulthood.

Out of seventeen total TAC members, 7 voted 'Yes, meets criterion', 3 voted 'No, does not meet criterion', and 7 voted 'Unsure'.

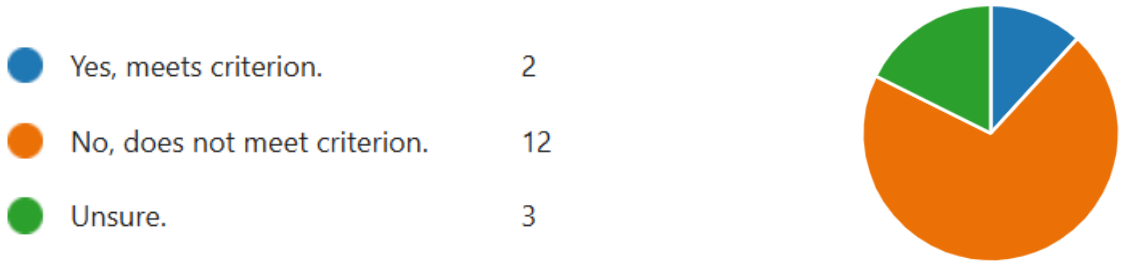


TAC member comments cited a lack of sufficient data on the prevalence, long-term outcomes with early treatment, and few number of patients in the literature. These limitations make it difficult to assess the relevant criteria.

Criterion 4: Public Health Rationale

Criterion 4, Public Health Rationale: Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.

Out of seventeen total TAC members, 2 voted 'Yes, meets criterion', 12 voted 'No, does not meet criterion', and 3 voted 'Unsure'.

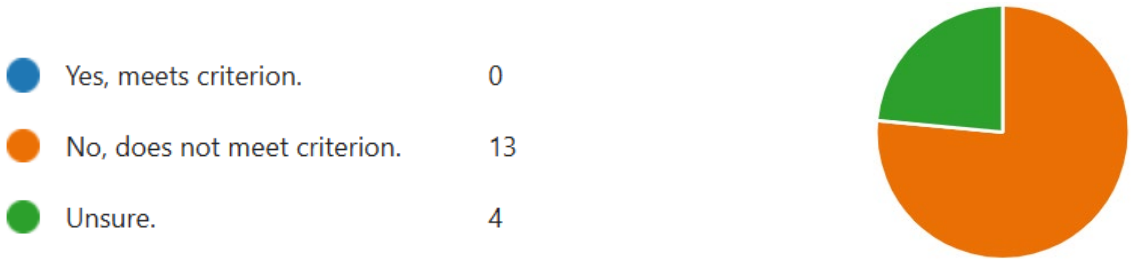


TAC members who commented again cited the limited data, making it difficult to properly assess whether the criterion has been met.

Criterion 5: Cost-benefit/Cost-effectiveness

Criterion 5, Cost-benefit/Cost-effectiveness: The outcomes outweigh the costs of screening. All outcomes, both positive and negative, need to be considered in the analysis. Important considerations to be included in economic analyses include: the prevalence of the condition among newborns; the positive and negative predictive values of the screening and diagnostic tests; variability of clinical presentation by those who have the condition; the impact of ambiguous results such as the emotional and economic impact on the family and medical system; and adverse effects or unintended consequences of screening

Out of seventeen total TAC members, 0 voted 'Yes, meets criterion', 13 voted 'No, does not meet criterion', and 4 voted 'Unsure'.



TAC members commented that due to the limited data on BCKDK deficiency, the Department was unable to generate a benefit-cost ratio or cost-effectiveness estimate from the existing cost benefit analysis model.

Overall TAC Recommendation

Out of seventeen TAC members, all but one member voted to recommend that the Board not include BCKDK deficiency on the newborn screening panel. One member voted in favor of recommending the inclusion of this condition to the panel. Comments from TAC members further emphasized concerns about the lack of evidence for BCKDK deficiency to make an informed decision. Many TAC members noted that the Board may want to consider re-evaluating BCKDK deficiency for the newborn screening panel if more evidence becomes available.

Board of Health Review

At its March 12, 2025 meeting, the Board reviewed the TAC recommendation regarding BCKDK deficiency and unanimously accepted the TAC's recommendation to not include BCKDK deficiency at this time. The Board could, as more evidence becomes available, review the condition at a later date.

Appendices

A. WSBOH Newborn Screening Process and Criteria 2015-2024
B. TAC Membership
C. BCKDK One-Pager
D. Lewis County Autism Coalition, letter
E. Duke University- Natural History, Diagnosic Testing and Treatment of BCKDK Deficiency
F. University of Washington Medical Center- Treatment of BCKDK Deficiency
G. Department of Health- Cost Benefit Analysis
H. TAC Voting and Comments Summary