# WASHINGTON STATE

Branch-Chain Ketoacid Dehydrogenase Kinase (BCKDK) Deficiency Legislative Report- DRAFT

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Date: April 2025

Dear Governor Ferguson and Committees of the Legislature,

As co-Chairs of the Newborn Screening Technical Advisory Committee, we present to you the Newborn Screening Branch-Chain Ketoacid Dehydrogenase Kinase (BCKDK) Deficiency legislative report as required by Senate Bill 6234. This report details the process undertaken by the Newborn Screening Technical Advisory Committee (TAC) review of BCKDK deficiency as a condition for inclusion on the state's mandatory newborn screening panel.

Each year, newborn screening in Washington helps identify hundreds of infants with serious but treatable conditions, allowing for early diagnosis and timely intervention. The TAC evaluates conditions to be included on the panel by reviewing data and considering the voices of interested parties, patients, and families affected by these conditions.

The Newborn Screening TAC is composed of physicians, scientists, public health experts, and community advocates who bring a diverse range of expertise. The role of this committee is to evaluate and make informed recommendations on conditions for inclusion in the Washington Newborn Screening Panel. We approach this responsibility guided by science, equity, and a commitment to the lifelong health of Washington's newborns.

This committee devoted their time and attention to the evaluation of BCKDK deficiency, a rare, autosomal recessive metabolic disorder associated with developmental delay and treatable forms of neurodevelopmental impairment. As part of the review, the TAC examined the available clinical evidence, assay feasibility, estimated incidence, and the potential benefits of early intervention through newborn screening.

We are proud of the work this committee has accomplished and grateful for the contributions of our members, partners, and subject matter experts. As we continue to evaluate conditions in newborn screening, we remain focused on ensuring that all children born in Washington have access to timely, equitable, and evidence-based screening services.

Thank you for your ongoing support and collaboration.

Sincerely, Kelly Oshiro Nirupama Shridhar Co-Chairs, Newborn Screening Technical Advisory Committee

#### **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 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 comprised 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 (BCKDK) 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 or confirm the diagnosis. BCDKDK deficiency can be treated with a high protein diet and supplementation of branch-chain amino acids.[2]

<sup>[1]</sup> 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]

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

#### 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 who 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 that 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 described the screening technology that is currently available; BCKDK deficiency may be detected from a dried bloodspot by testing for low branch-chain amino acids, quantified by 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 Department's Newborn Screening Program also provided a cost-benefit model that estimated how healthcare benefits and costs could shift in Washington if BCKDK deficiency was added to the mandatory newborn screening panel. The cost-benefit model compares the status quo (no universal screening of a condition) versus a screening model. This model typically utilizes data from primary literature, from states conducting screening for a condition, and expert opinion. Due to the rarity of the condition and lack of robust data sources, Newborn Screening Program staff consulted with the Department's health economist who recommended against using the model to generate a benefit/cost ratio or net benefit estimate. So, while a full analysis was not performed, the model is built and could be utilized in the future if additional data sources become available. 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.

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 the March 12, 2025, Washington State Board of Health (Board) public 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**

Appendix A. WSBOH Newborn Screening Process and Criteria 2015-2024

Appendix B. TAC Membership January 2025 TAC

Appendix C. BCKDK One-Pager

Appendix D. Lewis County Autism Coalition, letter

**Appendix E.** Duke University- Natural History, Diagnostic Testing and Treatment of BCKDK Deficiency

Appendix F. University of Washington Medical Center- Treatment of BCKDK Deficiency

Appendix G. Department of Health- Cost Benefit Analysis

Appendix H. TAC Voting and Comments Summary

# **Washington State Board of Health**

### PROCESS TO EVALUATE CONDITIONS FOR INCLUSION IN THE REQUIRED NEWBORN SCREENING PANEL

2015-2024

The Washington State Board of Health has the duty under RCW 70.83.050 to define and adopt rules for screening Washington-born infants for heritable conditions. Chapter 246-650-020 WAC lists conditions for which all newborns must be screened. Members of the public, staff at Department of Health, and/or Board members can request that the Board review a particular condition for possible inclusion in the NBS panel. In order to determine which conditions to include in the newborn screening panel, the Board convenes an advisory committee to evaluate candidate conditions using guiding principles and an established set of criteria.

The following is a description of the Qualifying Assumption, Guiding Principles, and Criteria which the Board has approved in order to evaluate conditions for possible inclusion in the newborn screening panel. The Washington State Board of Health and Department of Health apply the qualifying assumption. The Board appointed Advisory Committee applies the following three guiding principles and evaluates the five criteria in order to make recommendations to the Board on which condition(s) to include in the state's required NBS panel.

#### QUALIFYING ASSUMPTION

Before an advisory committee is convened to review a candidate condition against the Board's five newborn screening requirements, a preliminary review should be done to determine whether there is sufficient scientific evidence available to apply the criteria for inclusion.

#### THREE GUIDING PRINCIPLES

#### Three guiding principles govern all aspects of the evaluation of a candidate condition for possible inclusion in the NBS panel.

- Decision to add a screening test should be driven by evidence. For example, test reliability and available treatment have been scientifically evaluated, and those treatments can improve health outcomes for affected children.
- All children who screen positive should have reasonable access to diagnostic and treatment services.
- Benefits of screening for the disease/condition should outweigh harm to families, children and society.

#### CRITERIA

- 1. Available Screening Technology: Sensitive, specific and timely tests are available that can be adapted to mass screening.
- 2. Diagnostic Testing and Treatment Available: Accurate diagnostic tests, medical expertise, and effective treatment are available for evaluation and care of all infants identified with the condition.
- **3.** Prevention Potential and Medical Rationale: The newborn identification of the condition allows early diagnosis and intervention. Important 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.
- 4. Public Health Rationale: Nature of the condition justifies population-based screening rather than risk-based screening or other approaches.
- **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. For example the emotional and economic impact on the family and medical system.
  - Adverse effects or unintended consequences of screening.







Newborn Screening Technical Advisory Committee (TAC)

WASHINGTON STATE

#### **NBS TAC Membership**

MEMBER	ALTERNATE	REPRESENTING
<b>Kelly Oshiro, JD</b> Board Co-Chair Assistant Attorney General		Washington State Board of Health (Board)
<b>Nirupama (Nini) Shridhar, MPH, PhD</b> Department Co-Chair State Genetics Coordinator		Department of Health (Department)
Joan Chappel, RN, MSN Nursing Consultant Advisor/Supervisor	Sunpreet Bhangoo, RN Occupational Nurse Consultant	Washington Health Care Authority (HCA)
<b>Byron Raynz</b> Parent Advocate		Parent/Child Advocacy
<b>Emily Shelkowitz, MD</b> Pediatrics, Medical Genetics	<b>Christina Lam, MD</b> Medical Director, Biochemical Genetics	Pediatric Specialty Care, Seattle Children's Hospital Biochemical Genetics
<b>Eric Leung, MD</b> Neonatologist		Neonatology and Washington Chapter of the American Academy of Pediatrics (WCAAP)
Heather Hinton, MS Certified Genetic Counselor		Genetic Counseling, MultiCare Yakima Memorial
<b>Joon-Ho Yu, MPH, PhD</b> Pediatrics/Public Health Bioethicist		Bioethics, Department of Epidemiology, University of Washington Bioethics, Treuman Katz Center for Pediatric Bioethics and Palliative Care
<b>Kristine Alexander</b> Senior Medical Policy Research Analyst		Private Insurers, Regence Health Plans
Krystal Plonski, ND, LAc, EAMP, FABNP Naturopathic Pediatrics and Acupuncturist		Naturopaths, Seattle Children's Hospital, and Washington Association of Naturopathic Physicians (WANP)







Newborn Screening Technical Advisory Committee (TAC)

WASHINGTON STATE

**BOARD**OF**HEALTH** 

#### **NBS TAC Membership**

MEMBER	ALTERNATE	REPRESENTING
<b>Lisa McGill Vargas, MD</b> Neonatologist	<b>Rucha Shukla, MD</b> Neonatologist	Pediatrics, Neonatal-Perinatal Medicine, Sacred Heart Medical Center Neonatology Intensive Care Unit (NICU)
<b>Peggy Harris</b> Public Health and Children's Health Advocate		Parent/Child Advocacy, Save Babies Through Screening Foundation
<b>Priyanka Raut, DNP, MHS, RN</b> Senior Director of Nursing		Pediatrics, Yakima Valley Farmworkers Clinic
<b>Roberta (Bobbie) Salveson, ARNP, PhD</b> Pediatric Nurse Practitioner, Medical Genetics		Pediatric Specialty Care, Mary Bridge Children's Hospital Biochemical Genetics
<b>Taylor Kaminski,</b> Community Doula		Perinatal and Postpartum Care, Global Perinatal Services
María Sigüenza Executive Director		State Commissions, Commission on Hispanic Affairs
Molly Parker, MD, MPH Family Medicine Physician		Provider, Population Health, Jefferson Healthcare
Michelle Whitlow, M.S. Executive Director		Parent/Child Advocacy, Lewis County Autism Coalition
<b>Steve Kutz, BSN, MPH</b> Chair, Washington State American Indian Health Commission		State Commissions, American Indian Health Commission

#### NBS TAC Staff Support

Kelly Kramer, Board Newborn Screening Policy Advisor John Thompson, Department Director of Newborn Screening Megan McCrillis, Department Newborn Screening Policy Advisor Molly Dinardo, Board Policy Advisor **Crystal Ogle**, Board Administrative Assistant **Michelle Larson**, Board Communications Manager **Anna Burns**, Board Communications Consultant





#### Branch-chain Ketoacid Dehydrogenase Kinase (BCKDK) Deficiency Overview

Newborn Screening Technical Advisory Committee January 14, 2025

#### **ABOUT THE CONDITION**

- BCKDK deficiency is a rare inherited genetic disorder that leads to a deficiency of branched-chain amino acids<sup>1</sup>
- There are 21 cases of BCKDK deficiency identified worldwide, with no cases yet reported in the United States<sup>2</sup>
- BCKDK deficiency is caused by changes in the BCKDK gene, which produces the BCKDK enzyme<sup>1</sup>
- The BCKDK enzyme regulates the metabolism of branched-chain amino acids
- Mutations with the BCKDK enzyme causes an overactive break down of branched-chain amino acids<sup>1</sup>
- Without enough amino acids, proteins can't form properly, which impairs neurodevelopmental growth and development<sup>1,2</sup>

#### SIGNS & SYMPTOMS

• Signs and symptoms can vary but may include autism spectrum disorder, language impairment, seizures, and microcephaly<sup>2</sup>

#### DIAGNOSIS

- BCKDK deficiency may be detectable through a newborn screening blood spot using tandem mass spectrometry, although it is not a part of any newborn screening program<sup>2</sup>
- BCKDK deficiency can be confirmed with DNA testing

#### TREATMENT

• Treatment for BCKDK deficiency includes a diet high in total protein intake and branch-chain amino acid supplementation<sup>2</sup>

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

To request this document in an alternate format or a different language, please contact the State Board of Health at (360) 236-4110 or by email at <u>wsboh@sboh.wa.gov</u>.

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

### Comment for TAC Meeting January 14th, 2025

Good morning, members of the Technical Advisory Committee and the Board of Health,

Thank you for the opportunity to participate in this important discussion regarding the potential inclusion of branch-chain ketoacid dehydrogenase kinase (BCKDK) deficiency in Washington State's mandatory newborn screening panel. My name is Michelle Whitlow, and I am the Executive Director of the Lewis County Autism Coalition. Today, I hope to provide insights to support a thorough and thoughtful review of this issue.

First, I would like to acknowledge the complexity of this matter. BCKDK deficiency is an extremely rare metabolic disorder that affects amino acid processing, with only about 20 documented cases worldwide. This makes it significantly rarer than conditions like phenylketonuria (PKU), which is already included in the newborn screening panel. Although testing for both PKU and BCKDK uses a heel prick for blood collection, the clinical frameworks and cost-benefit implications for these conditions differ significantly. PKU benefits from well-established treatment protocols, while BCKDK's rarity has hindered the development of robust, evidence-based interventions.

Notably, research has shown a connection between autism and unusual amino acid metabolism. For instance, one clinical trial found that nearly 17 percent of autistic participants exhibited signs of unusual amino acid metabolism. Similarly, a 2012 study linked mutations in a gene involved in carnitine synthesis, a compound derived from amino acids to autism. Washington State already screens for several amino acid metabolism disorders, including PKU and maple syrup urine disease (MSUD), demonstrating the state's commitment to addressing rare metabolic conditions. These findings suggest that existing newborn screening efforts may already address related metabolic concerns, further illustrating the state's diligence in this area.

However, the extremely low prevalence of BCKDK deficiency raises questions about its inclusion in the panel. To provide context, the last condition proposed for inclusion—Ornithine Transcarbamylase Deficiency (OTCD)—has been put on hold due to a lack of funding. OTCD, which has a higher documented prevalence of approximately 1 in 14,000 to 113,000 live births, underscores the challenges of implementing new screenings without sufficient resources.

Adding to this complexity is Washington State's projected \$10 billion budget deficit. Expanding the newborn screening panel without a clear plan for sustainable funding risks straining an already underfunded system and diverting resources from existing public health priorities.

This discussion highlights several key considerations:

1. **Rarity of BCKDK Deficiency**: While early screening and intervention offer immense benefits, the extremely low prevalence of this condition raises questions about cost-effectiveness, particularly in light of the financial constraints demonstrated by the OTCD example.

- 2. Need for Additional Research: The need for further research and data collection to better understand the prevalence, long-term outcomes, and treatment efficacy for BCKDK deficiency. Without sufficient data, decisions may rely on incomplete information, leading to unintended consequences.
- 3. **Community Input**: As part of the autism community, we hold the principle of "Nothing About Us Without Us" as a cornerstone of our advocacy. While there is a connection between BCKDK deficiency and autism spectrum disorder (ASD), the broader ASD community's perspective on this specific condition has not been widely explored and may be worthy of consideration. This underscores the importance of meaningful engagement with individuals and families who may be directly impacted by this decision in the future.

In light of these considerations, my intent today is exploratory rather than declarative. I aim to raise critical questions and advocate for a comprehensive and inclusive review process. I encourage the committee to carefully weigh the costs and benefits, prioritize additional research, and ensure that any decision reflects the best interests of both individuals with BCKDK deficiency and the broader community.

Lastly, I deeply appreciate the Board of Health for including the autism community in this vital conversation. This inclusive approach ensures that diverse perspectives are considered, aligning with our coalition's mission to foster thoughtful, community-driven decision-making.

Thank you for your time and for allowing me to contribute to this discussion. I am happy to do my best to answer any questions or provide additional insights as needed.

Warm regards, Michelle Whitlow Executive Director Lewis County Autism Coalition

References

### Below are some sources/references that I accessed but did not include above via in-text citations because I figured it a less formal submission... I

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# BCKDK Deficiency: Natural History and Diagnostic Testing

Phillip J White, PhD

Associate Professor of Medicine

**Duke University** 



Washington State Board of Health, Newborn Screening Technical Advisory Committee Meeting, January 14 2025

#### **BCKDK Deficiency is a Disorder of Impaired Branched-Chain Amino Acid (BCAA) Homeostasis**



#### **KEY POINTS**

- The branched-chain keto acid dehydrogenase kinase (BCKDK) is an enzyme that controls the breakdown of BCAA by inhibiting the rate limiting step in the catabolic pathway.
- BCAA are essential amino acids that are required for protein synthesis and growth.
- BCAA play a major role in maintaining nitrogen balance.
- In the brain, BCAA are used to generate neurotransmitters.
- Loss of BCKDK results in BCAA wasting and extremely low levels of BCAA in blood, urine, and cerebrospinal fluid.

McGarrah & White, Nature Reviews Cardiology 2022

#### **Natural History of BCKDK Deficiency**

- BCKDK Deficiency was first described by Novarino *et al* in 2012 in a population of six patients aged 5-22 as a Mendelian form of Autism (100%), with Intellectual Disability (100%), and Epilepsy (50%).
- The disorder is characterized by low BCAA levels in blood and CSF.
- Additional cases have since been reported all are linked to genetic mutations that either alter BCKDK abundance or function
- The largest published study from Tangeraas et al describes 22 persons and provides the most insight into BCKDK deficiency.
- NOTE: No report on the condition to date has provided a complete natural history of the disorder.



Novarino et al Science 2012



#### **Natural History of BCKDK Deficiency**

- All BCKDK-deficient patients show global developmental delay at diagnosis.
- Seventy-five per cent present autistic traits or ASD
- Microcephaly is not present at birth in any of the cases, but appears postnatally in most patients.

Of the 22 cases in the Tangeraas study:

- All 17 patients older than 2YO had language impairment. 9 were non-verbal
- Delayed motor milestones present in all include: lack of head control, delayed rolling over, unsupported sitting and walking.
- 19/21 gross motor function impairment.
- 16/16 intellectual disability.
- 12/17 met DSM-5 criteria for autism spectrum disorder
- 9/20 had epilepsy
- All published studies show dietary modifications can raise BCAA levels to normal range in affected persons.



#### **Natural History of BCKDK Deficiency**

- The findings of Tangeraas, suggest there is a marked difference in clinical outcome depending on whether BCAA supplementation occurs in early development (before 2 years old) or at later stages (beyond 2 years of age).
- In the three patients where BCAA treatment was initiated <2 years of age, follow-up indicated amelioration of the developmental delay compared to older patients.
- Head circumference and motor function were the two main items that improved with treatment.
- Motor functions stabilized or improved in all patients
- Cognition and neuropsychiatric features did not improve after treatment. However, patients who initiated treatment before 2 years of age did not develop autism over time.
- P15, who had the earlier diagnosis and treatment (8 months), presented normal cognition and almost normal global neurodevelopment when evaluated at 3 years.
- BCAA treatment improved seizure control in 3 siblings with BCKDK deficiency (Boemer et al 2022)



Boemer et al Int J Mol Sci 2022

#### **Diagnostic Testing for BCKDK Deficiency**

- BCAA are measured in neonatal dried blood spots as part of standard testing.
- High BCAA are currently used to identify Maple Syrup Urine Disease.
- All cases of BCKDK deficiency have BCAA levels below the standard range.
- A lower threshold could be used to indicate a need for further genetic testing and evaluation.



# **BCKDK Deficiency**

Natural History, Diagnostic Testing, Treatment

# **Natural History**

Clinical features compiled from 4 reports:

- Novarino et al (2012) 3 families, 6 individuals
- Garcia-Carzola (2014) 2 families, 2 individuals
- Boemer (2022) 1 family,
   3 individuals
- Tangeraas et al (2023) 13 families, 21 individuals

↓ plasma/CSF BCAA levels

Global developmental delay Autism Seizures Progressive microcephaly Language impairments Intellectual disability Gross motor function impairments Epilepsy Skin issues

# **Diagnostic Testing**

Will leave this part to the testing experts, but it appears there are pilot studies that use existing NBS methods and confirmatory testing to identify individuals with BCKDK deficiency

# Treatment

Information compiled from 3 reports:

- Novarino et al (2012) 2 families, 4 individuals
- Garcia-Carzola (2014) 1 family, 1 individual
- Boemer (2022) -1 family,
   3 individuals
- Tangeraas et al (2023) 13 families, 19 individuals

#### Supplement BCAA

- Short-term ↑ in plasma BCAA
- No adverse effects

#### High protein + BCAA via tube feeding

- Improved communication, social
- Improved gross motor sills

#### Supplement BCAA

- Subjective behavior improvement; Vineland
- Improved seizures

#### High protein diet + supplement BCAA

- Improved plasma BCAA
- Stabilization of head circumference (11)
- Language improvement (3)
- Motor function improvement (13)
- $\geq$  <u><</u>2 yo did not develop autism (3)

# **Clinical Practice**

- → Referral to Biochemical Genetics Clinic
- → Confirmation of diagnosis, assessment
- → Individualized treatment plan might include
  - Increase dietary protein intake
  - BCAA supplements (oral powder/tablets taken 4-7 times per day)
  - Plasma BCAA monitoring
  - Developmental surveillance and referral
  - Regular clinic visits for monitoring, education, and adjustment of plan

### NBS - Related Treatment Considerations (Clinician's Lens)

- Access to treatment
  - "Increased natural protein" not covered by insurance
  - o BCAA supplements poorly reimbursed and/or not readily accessible
- Treatment burden and fatigue
- False positives
- "Mild" presentations
- Potential to improve lives and contribute to knowledge base





# COST BENEFIT ANALYSIS FOR BCKDK DEFICIENCY

Megan McCrillis, MPH Policy Analyst, WA State Newborn Screening Program John D. Thompson, PhD, MPA, MPH Director, Newborn Screening Program Does BCKDK Deficiency meet the "Cost-benefit/Cost-effectiveness" criterion for inclusion on the WA State Newborn Screening Panel?

# The 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. For example the emotional and economic impact on the family and medical system.
- Adverse effects or unintended consequences of screening.

# The cost-benefit model

O Decision Tree

Compares status quo v. screening model

OData from:

• Primary literature

- States currently screening or pilot studies
- Expert opinion
- Sensitivity analysis vary assumptions
   O High and low estimates for parameters

# The cost-benefit model

O Decision Tree

Compares status quo v. screening model

• Data from:

 $\circ$  Primary literature  $\rightarrow$  extremely limited

- States currently screening or pilot studies
- Expert opinion

Sensitivity analysis – vary assumptions
 O High and low estimates for parameters

# The cost- benefit model

O Decision Tree

Compares status quo v. screening model

• Data from:

 $\circ$  Primary literature  $\rightarrow$  extremely limited

- $\circ$  States currently screening or pilot studies  $\rightarrow$  none
- Expert opinion
- Sensitivity analysis vary assumptions
   O High and low estimates for parameters

# The cost- benefit model

Decision Tree

Compares status quo v. screening model

• Data from:

 $\circ$  Primary literature  $\rightarrow$  extremely limited

- $\circ$  States currently screening or pilot studies  $\rightarrow$  none
- $\circ$  Expert opinion  $\rightarrow$  mostly not accessible
- Sensitivity analysis vary assumptions
   O High and low estimates for parameters

# The cost-benefit model

### • Phone-a-friend:

 Insight from Anna Hidle, Public Health Economist, Washington Department of Health

### The cost-benefit model



# Status quo: No screening model



## Newborn screening model



# Benefits and Costs

No screening # babies with autism # babies without autism Universal screening # babies with autism # babies with autism # babies without autism # babies without autism # babies without autism # VALUE! Hobies without autism # VALUE!
# babies with autism       #VALUE!         Universal screening
Universal screening # babies with autism # babies without autism # babies without autism #VALUE! SHIFT Cases of autism avoided #VALUE!
Universal screening # babies with autism # babies without autism #VALUE! SHIFT Cases of autism avoided #VALUE!
Universal screening # babies with autism # babies without autism #VALUE!  SHIFT Cases of autism avoided #VALUE!
# babies with autism #VALUE! # babies without autism #VALUE! SHIFT Cases of autism avoided #VALUE!
# babies without autism #VALUE! SHIFT Cases of autism avoided #VALUE!
SHIFT Cases of autism avoided #VALUE!
SHIFT Cases of autism avoided #VALUE!
SHIFT Cases of autism avoided #VALUE!
Cases of autism avoided #VALUE!
BENEFITS Totals
Cost of autism care from birth to 18 \$106,388.79
Less tx costs (Total benefits) #VALUE!
COSTS Totals
Cost of NBS per baby ?
Total cost NBS #VALUE!
Cost per baby dx testing (branched chaii \$2,270.00
Cost of false(+) dx testing #VALUE!
Total costs #VALUE!
Benefit/Cost ratio
Benefit/Cost ratio #VALUE!
Benefit/Cost ratio #VALUE!

# Summary

- The quality of the results are only as good as the data in the model
- We don't have a benefit/cost ratio to share today
- The model is built
  - Parameters for missing assumptions could be entered in the future when data is available

# Questions?

**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. For example the emotional and economic impact on the family and medical system.
- Adverse effects or unintended consequences of screening.





WASHINGTON STATE

Newborn Screening Technical Advisory Committee (TAC)

#### Meeting to Review Branch-Chain Ketoacid Dehydrogenase Kinase (BCKDK) Deficiency for the Newborn Screening Panel

#### **TAC Member Voting Summaries and Comments**

The following is a compilation of comments from TAC members provided when voting on each individual criteria, and an overall recommendation. Comments have been summarized and are organized by each criterion and then overall comments provided.

Criteria		Major themes
1. Available Screening Technology		• Tests and technology are available for measuring BCA serum levels,
Yes, meets criterion.	6	but their performance, sensitivity, and specificity are unclear. • While the upper limits of normal BCA levels are defined, lower limits
No, does not meet criterion.	7	can be estimated from population norms, and tandem mass
Unsure.	4	spectrometry is already used to directly measure BCA plasma levels.

2. Diagnostic Testing and Treatment	Available	•	There is very limited evidence available for this disorder, making it
Yes, meets criterion.	6		unclear whether diagnostic criteria are met.
		•	The data on prevalence, long-term outcomes, false
No, does not meet criterion.	6		positives/negatives, and treatment effectiveness is insufficient, and
Unsure.	5		the small sample size makes it difficult to verify the disorder's validity.
3. Prevention Potential and Medical I	Rationale	•	There is a lack of sufficient data on the prevalence, long-term
Yes, meets criterion.	7		literature, making it difficult to assess the relevant criteria.
No, does not meet criterion.	3		
Unsure.	7		

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4. Public Health Rationale		•	Not enough information to assess this criterion. Rarity gives pause, but true prevalence is unknown.
Yes, meets criterion.	2		
No, does not meet criterion.	12		
Unsure.	3		
<ol> <li>Cost Benefit / Cost Effectiven</li> <li>Yes, meets criterion.</li> </ol>	ess 0	•	There is insufficient data available to evaluate the condition, including the lack of BCA testing, limited prevalence information, and
No, does not meet criterion.	13	•	Screening is not being conducted, and there are concerns about
Unsure.	4		unintended consequences for conditions on the newborn screening panel.

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