Newborn Screening Legislative Report

Branch-Chain Ketoacid Dehydrogenase Kinase (BCKDK) Deficiency

June 2025

WASHINGTON STATE BOARD OF HEALTH

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CO-CHAIR LETTER

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,

Nirupama (Nini) Shridhar, PhD, MPH
Washington State Genetics Coordinator
Technical Advisory Committee Co-Chair

Kelly Oshiro, JD
Washington State Board of Health Vice Chair
Technical Advisory Committee Co-Chair

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 an ultra-rare genetic disorder (it affects less than 1 in 50,000 people) 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 currently included on any universal newborn screening panels in the United States or abroad. In addition, there have been only 21 cases of BCKDK deficiency identified worldwide, with none reported in the United States to date.

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 not to re-review the condition until more data and research are available to complete a comprehensive evaluation.

BCKDK deficiency is an ultra-rare condition that has never been diagnosed in the United States. There is limited information on how common it is, how well treatments work, or whether universal screening is cost-effective. Washington residents who are concerned about BCKDK deficiency, for themselves or their children, should speak with a healthcare provider. The provider can help decide if genetic testing for BCKDK may be appropriate and recommend the next steps, including referral to a specialist if needed.

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 focus on evidence, ethics, equity, and the balance between cost-effectiveness and cost-benefit. 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 multidisciplinary TAC includes representatives with expertise and experience related to the candidate conditions, including clinicians, academics, insurers, public health professionals, 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 was comprised 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 (BCKDK) DEFICIENCY

BCKDK deficiency is an ultra-rare inherited genetic disorder characterized by 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 blood spot using tandem mass spectrometry. Newborns with an out-of-range screening result for BCKDK deficiency should undergo 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].

[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 C].

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 cases of BCKDK deficiency showed global developmental delay at diagnosis. In these studies, clinical outcomes were shown to improve in patients when BCAAs are supplemented, with a greater improvement in developmental delay if treatment was initiated before the age of two[Appendix D].

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[Appendix E].

The Department's Newborn Screening Program described the screening technology currently available; BCKDK deficiency may be detected from a dried blood spot 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[Appendix F].

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

TECHNICAL ADVISORY COMMITTEE REVIEW

status quo (no universal screening of a condition) versus a screening model. This model typically utilizes data from primary literature, states conducting screening for a condition, and expert opinion[Appendix G]. 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 using 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[Appendix H].

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'.

TECHNICAL ADVISORY COMMITTEE REVIEW

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 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

This criterion reviews if 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.

TECHNICAL ADVISORY COMMITTEE REVIEW

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

This criterion reviews if the 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

This criterion considers if 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

TECHNICAL ADVISORY COMMITTEE REVIEW

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'.

Yes, meets criterion.	0
No, does not meet criterion.	13
Unsure.	4

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, making it difficult 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, FINAL RECOMMENDATION, AND CONCLUSION

At the March 12, 2025, public meeting, the Board reviewed the TAC's recommendation regarding BCKDK deficiency.

Staff from the Board and Department presented a summary on the condition's natural history, diagnostic testing options, available treatment, the limited data available to support a cost-benefit analysis for universal screening, and an overview of TAC member voting.

After discussion, the Board unanimously accepted the TAC's recommendation not to add BCKDK deficiency to the state's newborn screening panel at this time. The Board agreed that there is currently insufficient evidence to justify including the condition in universal newborn screening.

The Board concluded that BCKDK deficiency could be reconsidered in the future if additional research and evidence become available.

BCKDK deficiency is an ultra-rare condition. There is limited information available on the prevalence of the condition, the effectiveness of treatments, or whether universal screening is a cost-effective approach. Washington residents concerned about BCKDK deficiency, whether for themselves or their children, should consult a healthcare provider. The provider can help determine if genetic testing for BCKDK is appropriate and recommend the next steps, including referral to a specialist if necessary.

APPENDICES

Washington State Board of Health

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

Last updated March 14, 2025

The Washington State Board of Health (Board) 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 (Department), and/or Board members can request that the Board review a particular condition for possible inclusion in the newborn screening (NBS) panel.
To determine which conditions to include in the NBS panel the Board convenes a newborn screening technical advisory committee (TAC) to evaluate candidate conditions using guiding principles and an established set of criteria.

This document describes the Qualifying Assumption, Guiding Principles, and Criteria the Board has approved to evaluate conditions for possible inclusion in the newborn screening panel. The Board and Department apply the qualifying assumption. The Board-appointed Newborn Screening TAC applies the following three guiding principles and evaluates the criteria to make recommendations to the Board on which condition(s) to include in the state's required NBS panel.

QUALIFYING ASSUMPTION

Before the Board convenes a TAC to review a candidate condition against the newborn screening criteria, staff should complete a preliminary review to determine whether sufficient scientific evidence is available to apply the criteria for inclusion, which is the qualifying assumption. If the candidate condition is on the Health Resources and Services Administration (HRSA) Recommended Uniform Screening Panel (RUSP), the Board and Department will consider the qualifying assumption met and convene a TAC.

***A note on the RUSP*:** The RUSP is a list of conditions that the Secretary of the Department of Health and Human Services (HHS) recommends states screen for as part of their newborn screening programs. Once the HHS Secretary recommends a new condition, the Board and Department will review it for possible inclusion in the Washington NBS panel within two years of the recommendation.
***Conditions pending RUSP Review or Previously Denied for the RUSP*:** RCW 34.05.330 of the Administrative Procedures Act (APA) allows any person to petition a state agency to adopt, repeal, or amend any rule within its authority. Agencies must respond to the petitioner within 60 days. If the agency accepts the petition, it must

initiate rulemaking. An agency can deny the request for rulemaking, and in doing so, it must explain its reasons and, if appropriate, describe alternative steps it is prepared to take.
If the Board receives a petition for rulemaking regarding a candidate condition currently under review for the RUSP, the Board will wait until the federal committee finishes its review and the HHS Secretary makes a final decision before convening a TAC. For petitions involving conditions that have already been reviewed and denied inclusion on the RUSP, the Board will instruct staff to work with the petitioner to determine if concerns raised during the federal review have been addressed before recommending the Board convene a TAC to review the condition.

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.
    - The sensitivity of the screening test is estimated to be ≥95%.
    - The specificity of the screening test is considered acceptable based on the estimated number of false positive results and their potential impact on the families, healthcare system, and newborn screening program.
    - A timely test is one that enables intervention before irreversible harm develops, within the current standard timeframes for specimen collection, receipt, testing, and reporting.
    - There is adequate peer reviewed evidence to evaluate this criterion.

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.

- A diagnostic test accurately identifies who needs treatment and is readily available to all newborns screened.
- The available treatment is effective in reducing morbidity or mortality and outweighs any risks or harms of the treatment.
- The medical expertise needed to diagnose and care for those with a positive newborn screen is reasonably available to all newborns screened.
- The appropriate consultants and treatment centers have been identified and have capacity for the expected increase in diagnostic testing and/or referrals.

3. **Prevention Potential and Medical Rationale**: The newborn identification of the condition allows early diagnosis and intervention.

- There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention.
- The condition must have an onset form that occurs in infancy (within the first year of life); newborn screening is not appropriate for conditions that only present after the first year of life.
- The benefits of detecting and treating infantile-onset forms of the condition (within one year of life) balance the impact of detecting later onset forms of the condition.
- There is adequate evidence of acceptable quality to evaluate this criterion.

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

- All available risk-based screening tools for the condition have been considered and are found to be inferior to universal newborn screening.
- There is adequate evidence of acceptable quality to evaluate this 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.

- The economic analysis considers:
    - 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.
    - Dollar values for costs and benefits of screening vs. no screening.

- The impact of ambiguous results, adverse effects, or unintended consequences of screening, such as psycho-social or economic impacts on the family and medical system, must also be considered.
- The results of the economic analysis shows that the outcomes, financial or otherwise, outweigh the costs of screening.
- There is adequate evidence of acceptable quality to evaluate this criterion.

6. **Public Health Infrastructure Readiness:** The Newborn Screening Program's capacity to implement screening within a reasonable timeframe has been considered.

- The systems and staffing necessary to perform the test and report screening results have been identified.
- Resources needed to implement short/long term follow up protocols by the newborn screening program have been identified.
- Accessibility to treatment for anyone diagnosed with the condition is considered acceptable based on the frequency of treatment needed.

Criterion	Opinion			Comments
	Meets	Does not meet	More info needed	
1. **Available Screening Technology** Sensitive, specific and timely tests are available that can be adapted to mass screening				
The sensitivity of the screening test is estimated to be ≥95%				
The specificity of the screening test is considered acceptable based on the estimated number of false positive results and their potential impact on families, the healthcare system, newborn screening program.				

A timely test is one that enables intervention before irreversible harm develops, within the current standard timeframes for specimen collection, receipt, testing, and reporting				
There is adequate evidence of acceptable quality to evaluate this criterion				
Overall impression of criterion 1:				
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				
A diagnostic test accurately identifies who needs treatment, and is readily available to all newborns screened.				
The available treatment is effective in reducing morbidity or mortality, and outweighs any risks or harms of the treatment.				
The medical expertise needed to diagnose and care for those with a positive newborn screen is reasonably available to everyone screened				
The availability and proximity to treatment for anyone diagnosed with the condition is considered acceptable based on the frequency of treatment needed				

The appropriate consultants and treatment centers have been identified and have capacity for the expected increase in diagnostic testing and/or referrals				
There is adequate evidence of acceptable quality to evaluate this criterion				
Overall impression of criterion 2:				
3. **Prevention Potential and Medical Rationale** The newborn identification of the condition allows early diagnosis and intervention.				
There is sufficient time between birth and onset of irreversible harm to allow for diagnosis and intervention				
The condition must have an onset form that occurs in infancy (within the first year of life); newborn screening is not appropriate for conditions that only present after the first year of life.				
The benefits of detecting and treating infantile-onset forms of the condition balance the impact of detecting later onset forms of the condition				
There is adequate evidence of acceptable quality to evaluate this criterion				
Overall impression of criterion 3:				

4. **Public Health Rationale** Nature of the condition justifies population-based screening rather than risk based screening or other approaches				
Any available risk-based screening tools for the condition have been considered and are inferior to universal newborn screening				
There is adequate evidence of acceptable quality to evaluate this criterion				
Overall impression of criterion 4:				
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				
The economic analysis considers: • 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. • Dollar values for costs and benefits of screening vs. no screening				
The impact of ambiguous results, adverse effects, or unintended consequences of screening , such as emotional or economic impacts on the family and medical system, must also be considered.				

The results of the economic analysis shows that the outcomes, financial or otherwise, outweigh the costs of screening				
There is adequate evidence of acceptable quality to evaluate this criterion.				
Overall impression of criterion 5:				
6. **Public Health Infrastructure Readiness** The Newborn Screening Program's capacity to implement screening within a reasonable timeframe has been considered				
The systems and staffing necessary to perform the test and report screening results have been identified				
Resources needed to implement short/long term follow up protocols by the newborn screening program have been identified				
Accessibility to treatment for anyone diagnosed with the condition is considered acceptable based on the frequency of treatment needed				
Overall impression of criterion 6:				

Overall impression of the condition:
Recommendation:

Washington State Department of HEALTH

WASHINGTON STATE BOARD OF HEALTH

Newborn Screening Technical Advisory Committee (TAC)

NBS TAC Membership

MEMBER	ALTERNATE	REPRESENTING
Kelly Oshiro, JD Board Co-Chair Assistant Attorney General		Washington State Board of Health (Board)
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Washington State Department of HEALTH

WASHINGTON STATE BOARD OF HEALTH

Newborn Screening Technical Advisory Committee (TAC)

NBS TAC Membership

MEMBER	ALTERNATE	REPRESENTING
Lisa McGill Vargas, MD Neonatologist	**Rucha Shukla, MD** Neonatologist	Pediatrics, Neonatal-Perinatal Medicine, Sacred Heart Medical Center Neonatology Intensive Care Unit (NICU)
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Taylor Kaminski, 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
Steve Kutz, BSN, MPH Chair, Washington State American Indian Health Commission		State Commissions, American Indian Health Commission

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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

- 1 Science. 2012 Oct 19; 338(6105): 394–397
- 2, 4 Spectrum News December 17, 2019
- 3 Science. 2012 Oct 19; 338(6105): 394–397, paragraph before Supplementary Material
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- 13 J Pers Med. 2021 Aug; 11(8): 784
- 14 MedIndia March 14, 2019
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DUKE MOLECULAR PHYSIOLOGY INSTITUTE

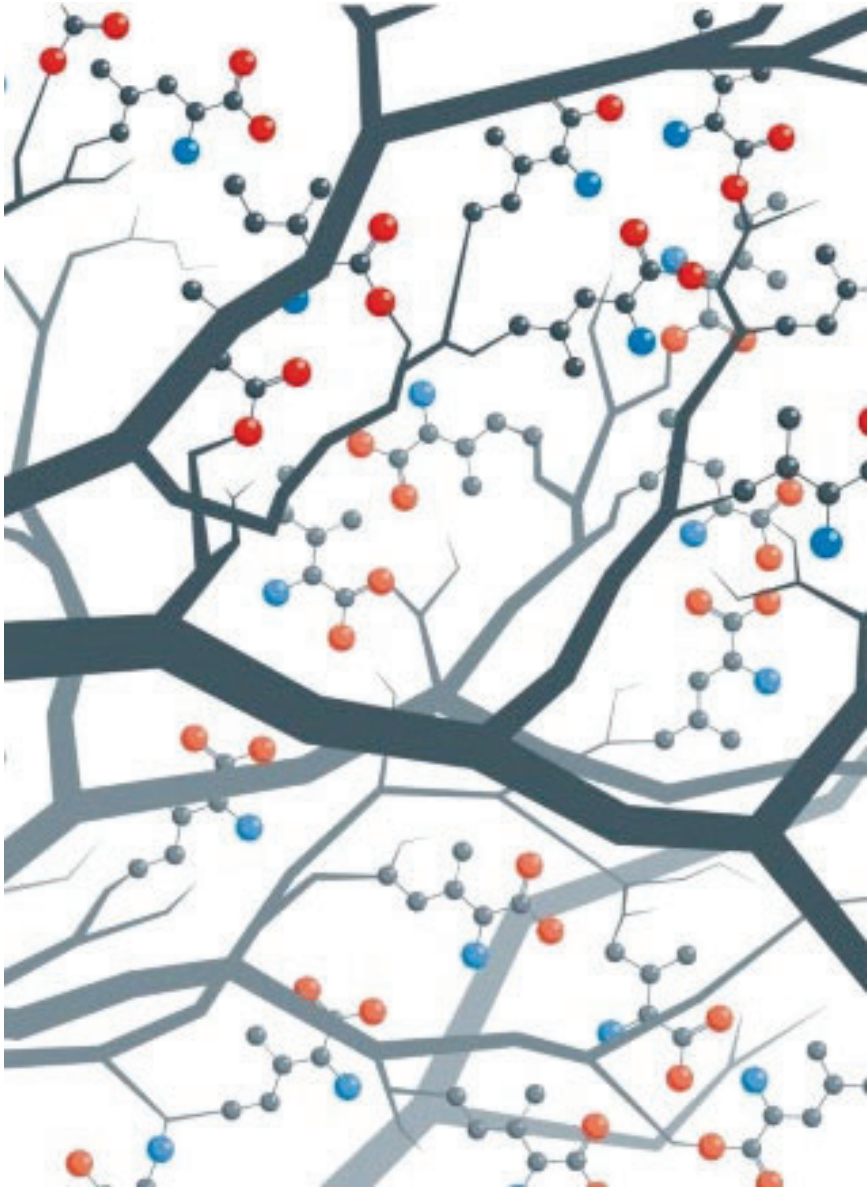
BCKDK Deficiency:

Natural History and Diagnostic Testing

Phillip J White, PhD

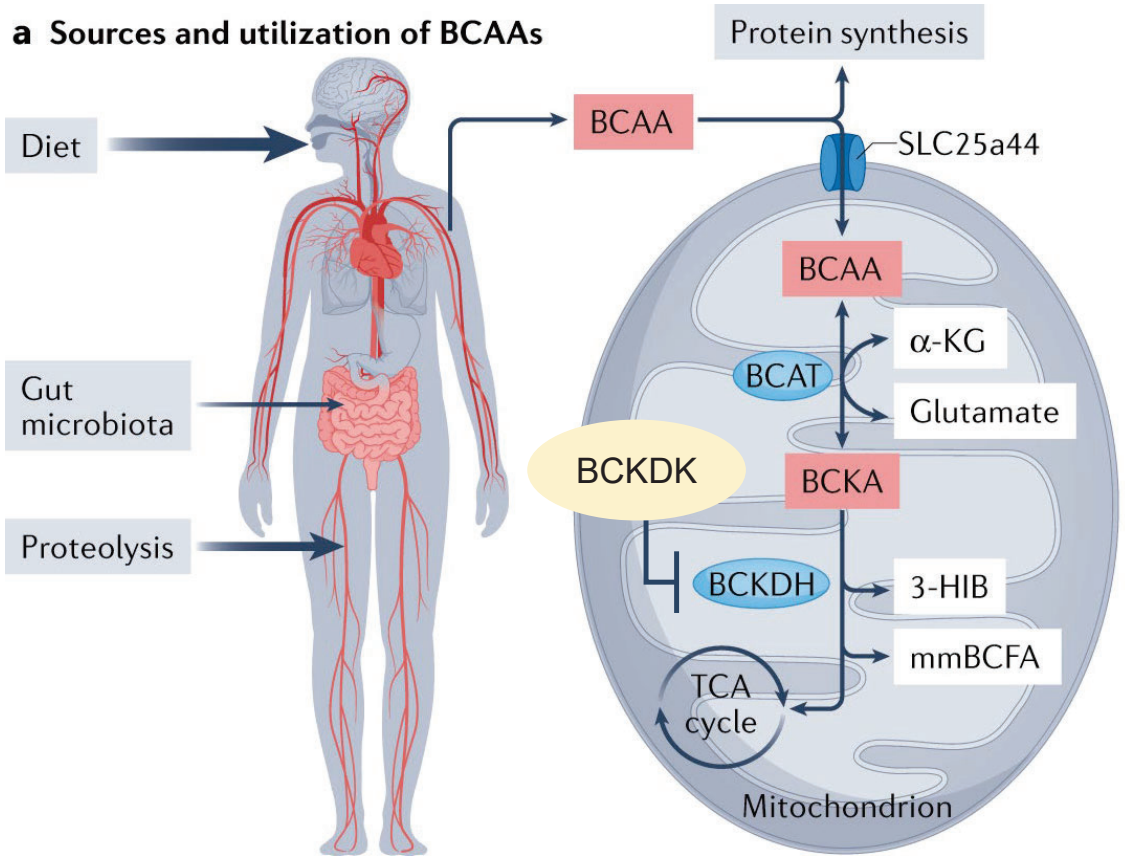
Associate Professor of Medicine

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



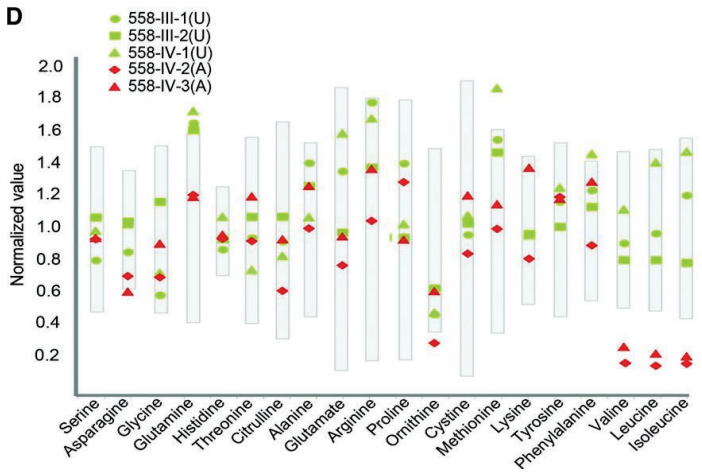
McGarrah & White, Nature Reviews Cardiology 2022

KEY POINTS

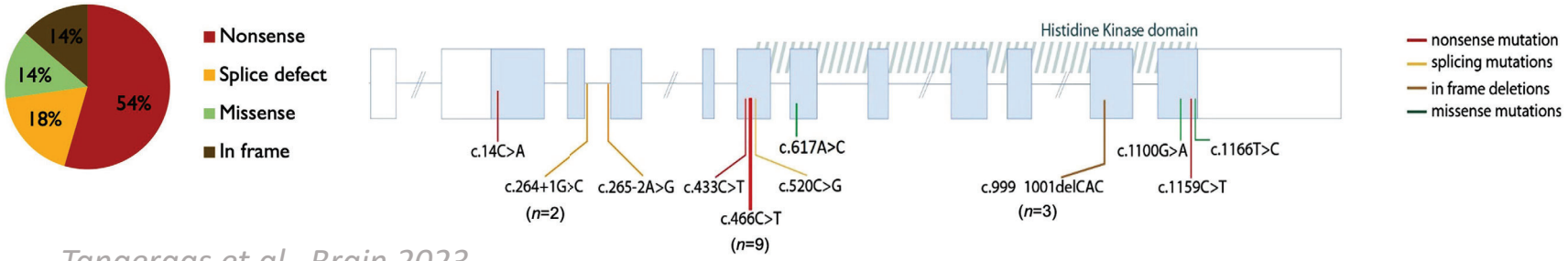
- The branched-chain keto acid dehydrogenase kinase (BCKDK) is an enzyme that controls the breakdown of BCAA by inhibiting the rate limiting step in the catabolic pathway.
- BCAA are essential amino acids that are required for protein synthesis and growth.
- BCAA play a major role in maintaining nitrogen 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.

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



Tangeraas et al Brain 2023

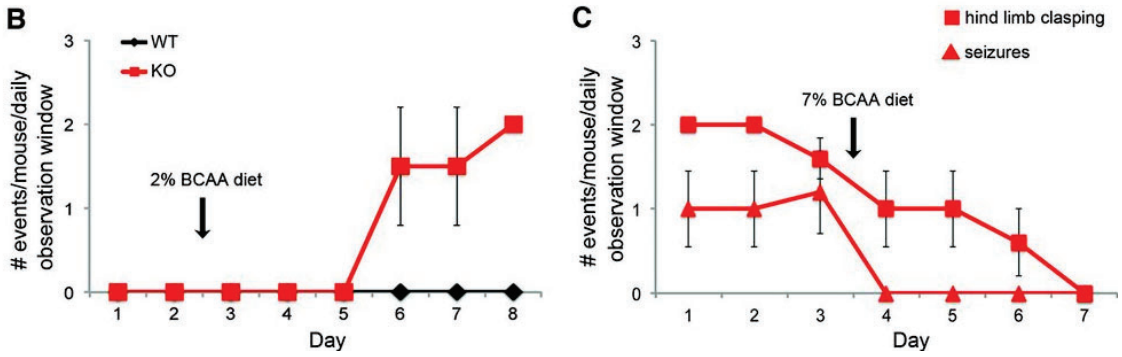
Natural History of BCKDK Deficiency

- 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.



Novarino et al Science 2012

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.

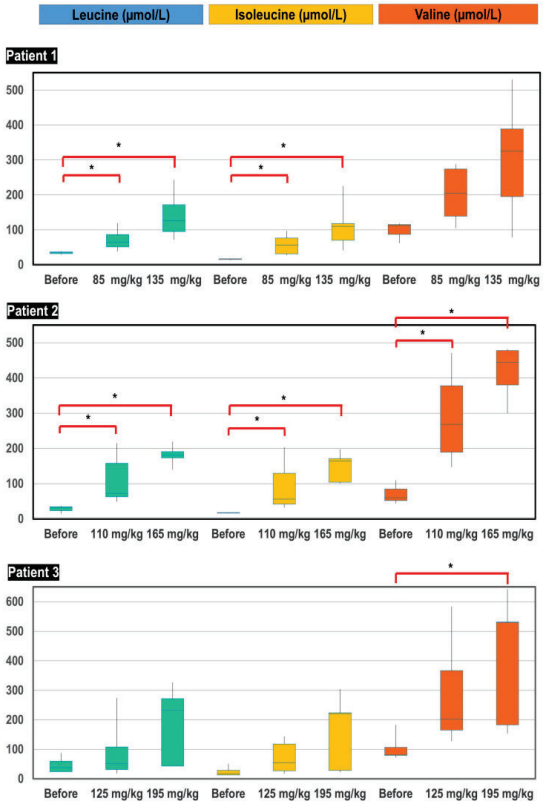
- Head circumference and motor function were the two main items that improved with treatment.

- 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.

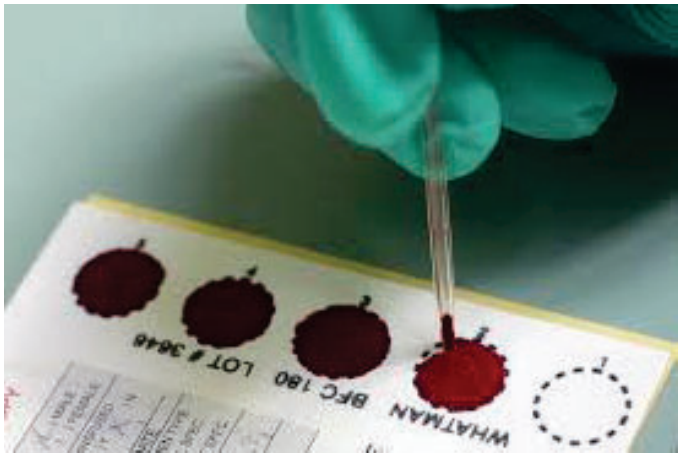
- BCAA treatment improved seizure control in 3 siblings with BCKDK deficiency (Boemer et al 2022)

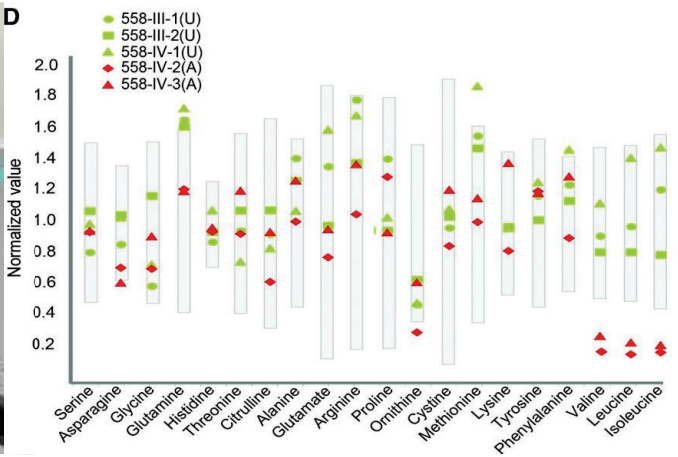


Boemer et al Int J Mol Sci 2022

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

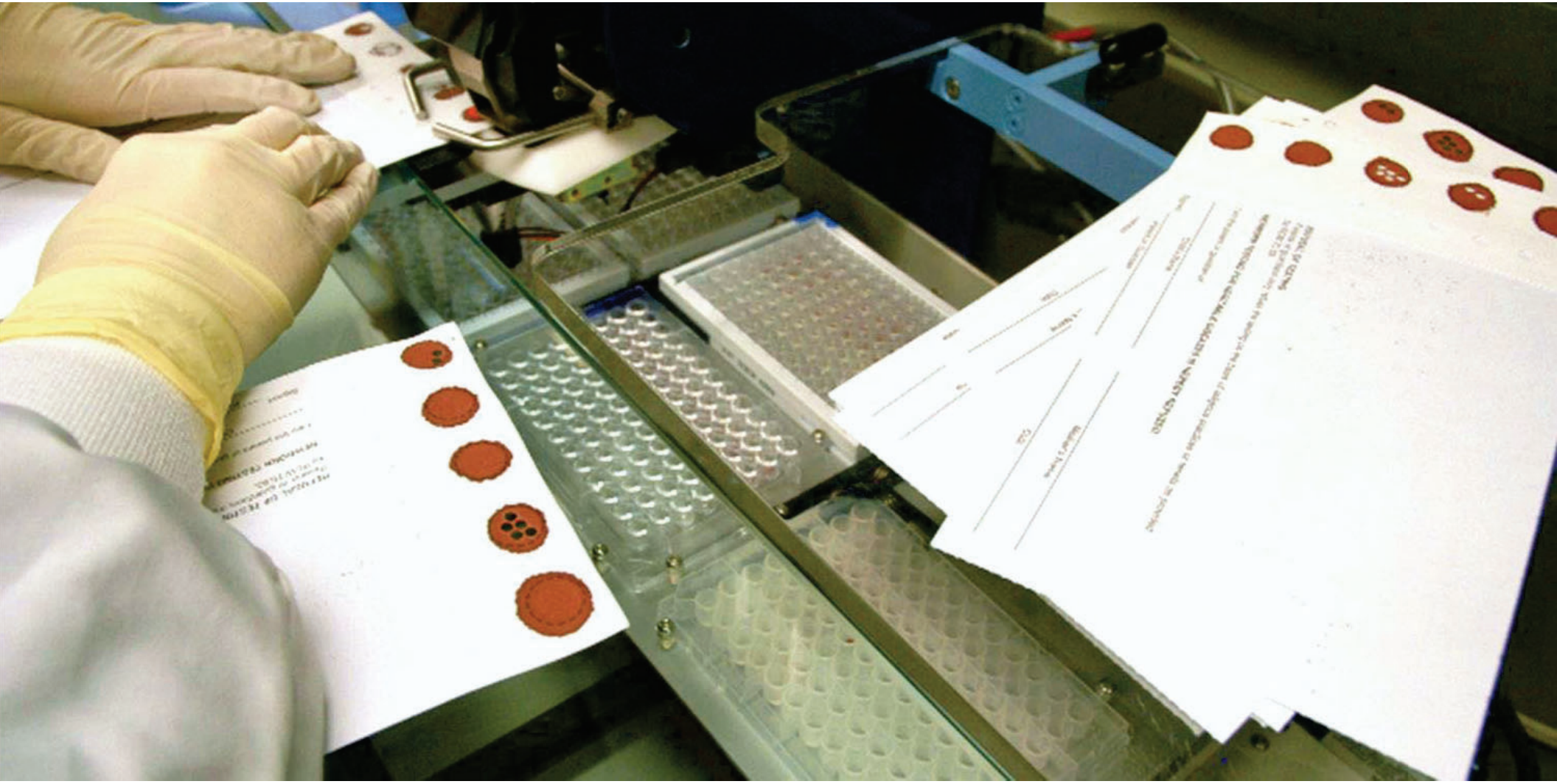
High protein diet + supplement BCAA
- ➢ Improved plasma BCAA
- ➢ Stabilization of head circumference (11)
- ➢ Language improvement (3)
- ➢ Motor function improvement (13)
- ➢ ≤2 yo did not develop autism (3)

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
  - 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



Washington State Department of HEALTH

AVAILABLE SCREENING TECHNOLOGY FOR BCKDK DEFICIENCY

Megan McCrillis, MPH

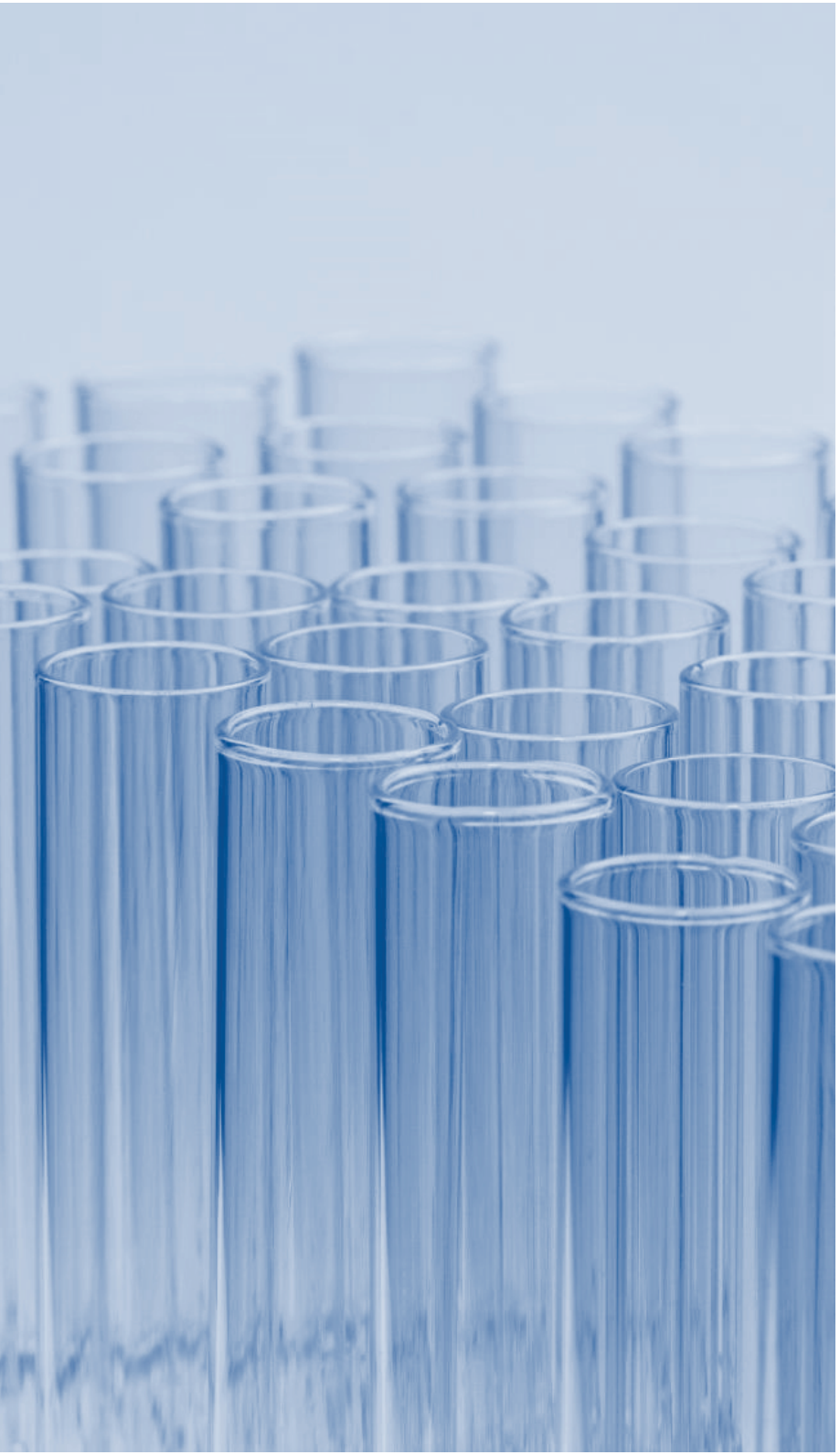
Policy Analyst, WA State Newborn Screening Program

Does BCKDK Deficiency meet the "Available Screening Technology" criterion for inclusion on the WA State Newborn Screening Panel?

Available Screening Technology Criterion

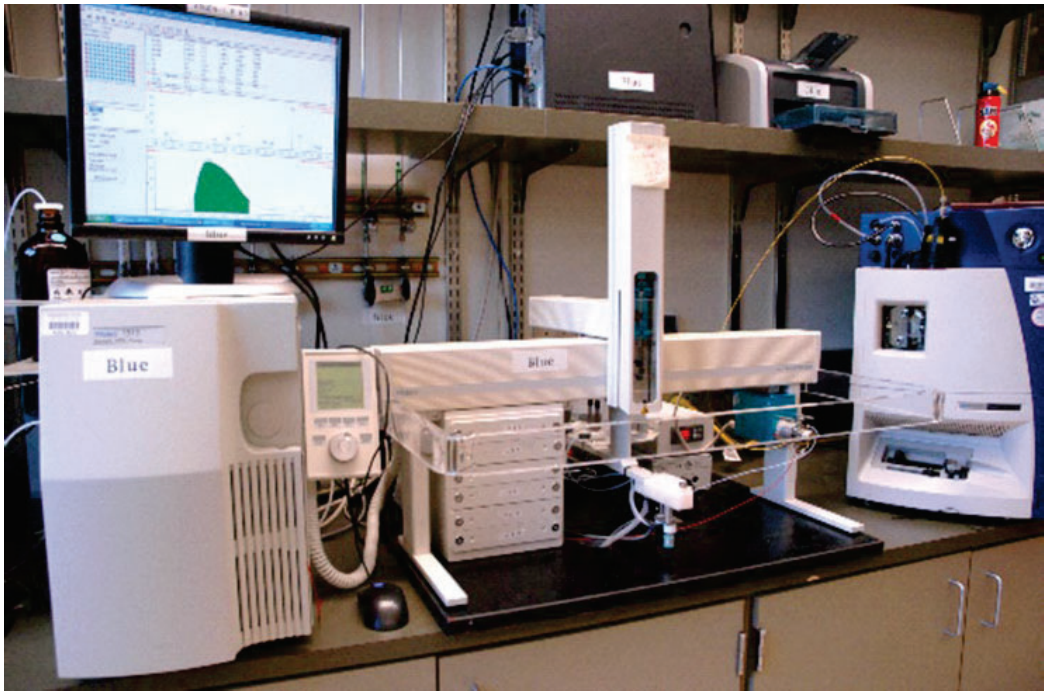
- Sensitive, specific and timely tests are available that can be adapted to mass screening

- No U.S. states or other countries currently screening for BCKDK deficiency
  - Possibly the autonomous region of Catalonia
- No prospective screening pilot studies



Available Screening Technology Criterion

- Sensitive, specific and timely tests are available that can be adapted to mass screening



- Screening test available that looks for abnormally low levels of branched-chain amino acids (valine, leucine, isoleucine) in dried blood spots
- Analysis done by tandem mass spectrometry (MS/MS)
- WA State already has this equipment and already tests for those analytes to look for other conditions on panel

- Unaffected newborns can have low amino acids for a variety of reasons (such as illness or diet) and may produce false positive results
- Post-analytical tools such as CLIR (Collaborative Laboratory Integrated Reports) can help to clarify NBS results by pooling data from many screening sites with values of confirmed BCKDK deficiency cases

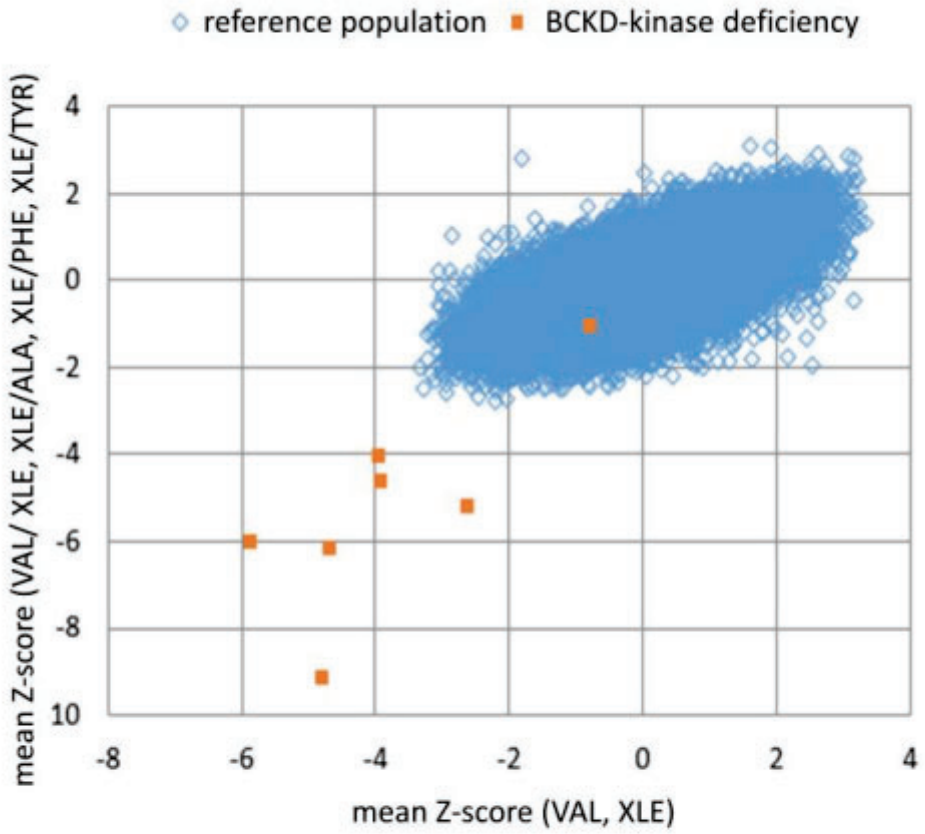
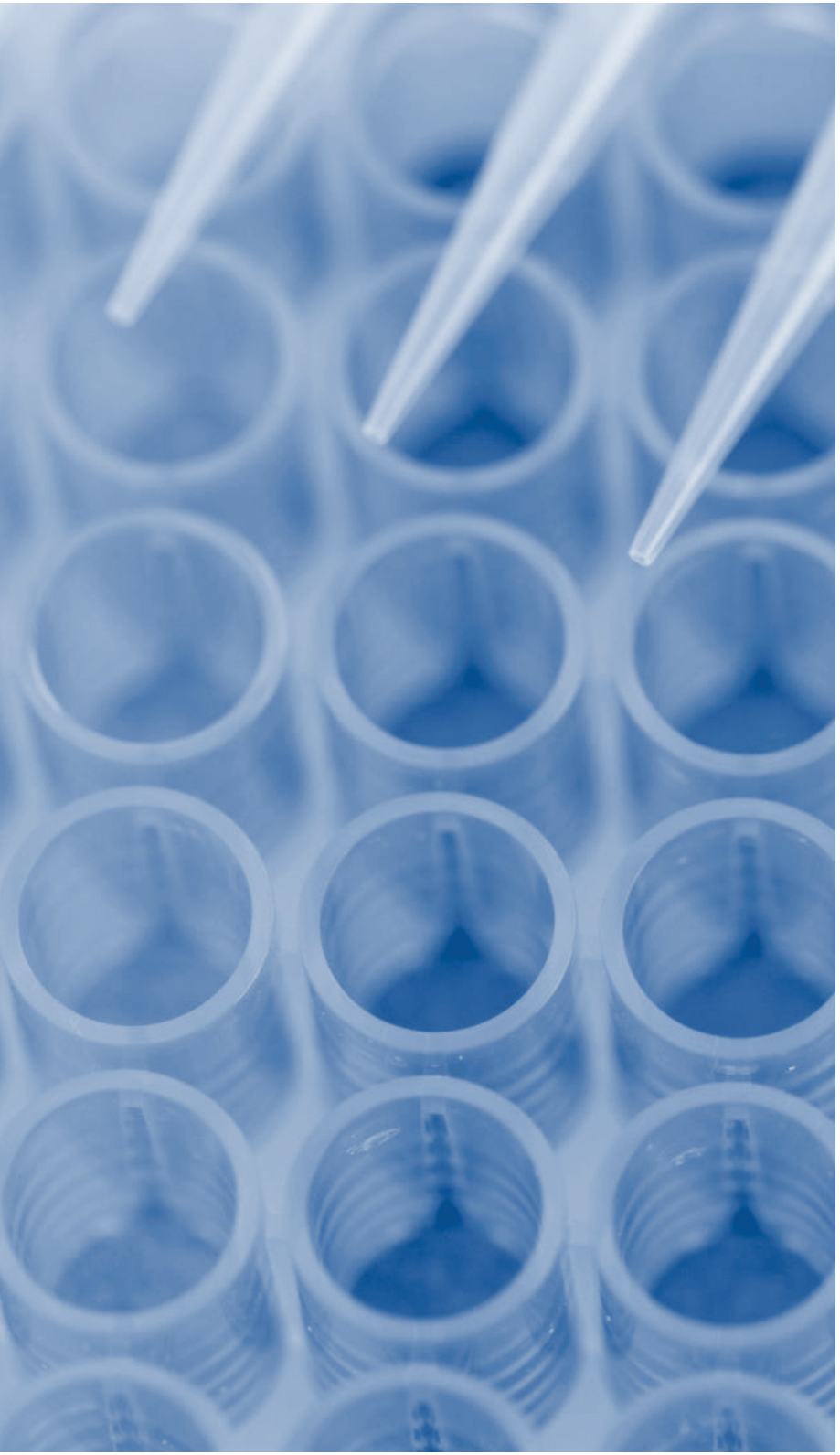


Figure 6 DBS newborn screening from BCKDK deficiency. Amino acid plot from seven newborns later diagnosed with BCKDK deficiency (orange squares) compared to a subpopulation of healthy newborns (blue diamonds). Algorithm by courtesy of Prof. Piero Rinaldo.



Available Screening Technology Criterion

- Sensitive, specific and timely tests are available that can be adapted to mass screening

- No prospective screening means no real-time data regarding sensitivity and specificity of test
- Sensitivity is unknown
- Specificity is unknown
  - CLIR tool is available, but nobody knows how many babies with positive CLIR results would need diagnostic testing or if they would be resolved by a normal second screen

Available Screening Technology Criterion

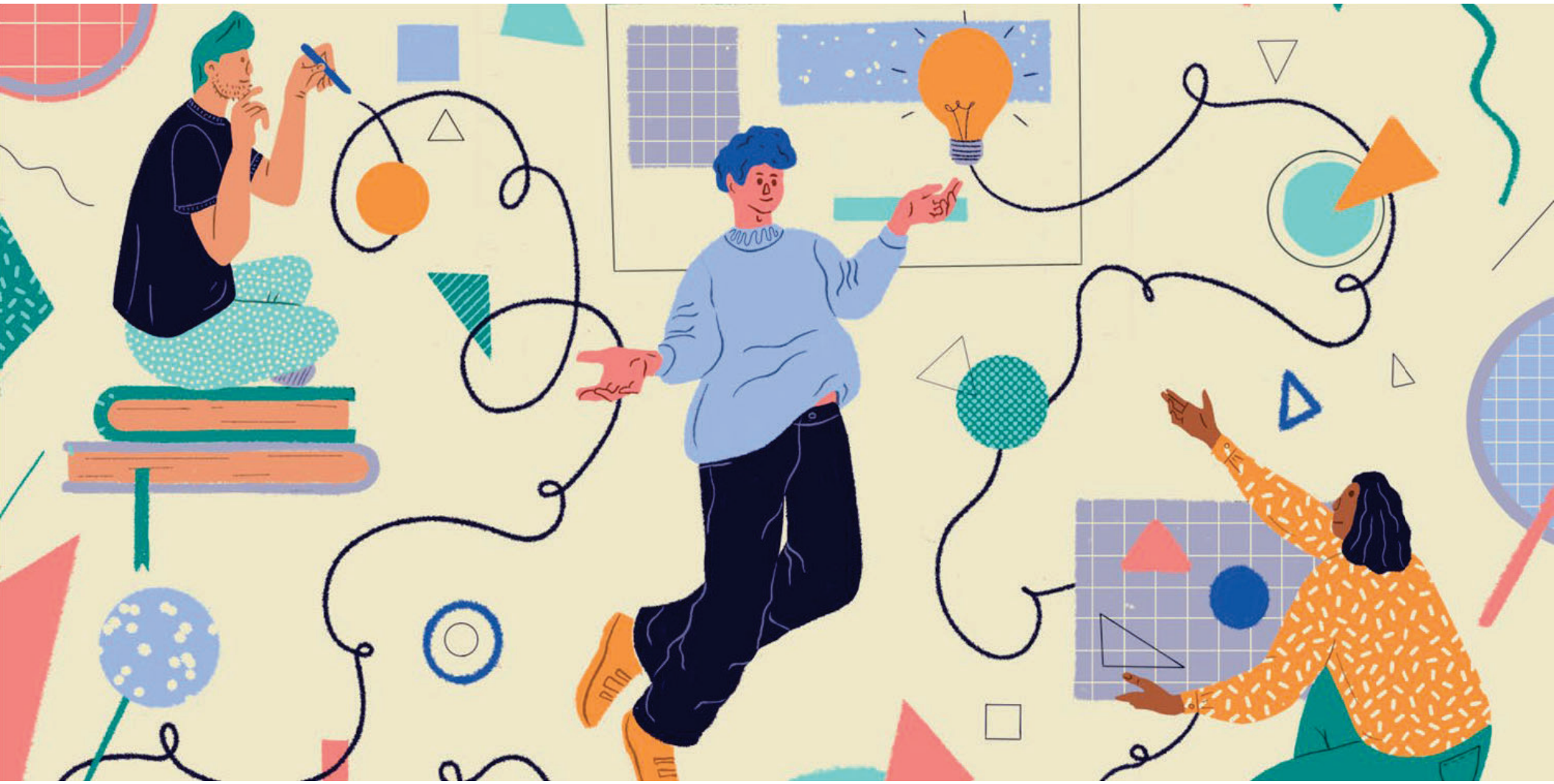
- Sensitive, specific and timely tests are available that can be adapted to mass screening

- Screening results for BCKDK deficiency would likely be available within one or two days of specimen receipt
- In one study, no BCKDK deficiency patients who initiated treatment before the age of 2 years developed autistic features (n=3)
- A MS/MS screening test for BCKDK deficiency would be timely enough to intervene before 2 years of age

Other Considerations

- Supplemental nutrition in NICU babies would be an interfering substance and require a repeat screen once off HA/TPN
- Babies may have low amino acid results for a variety of reasons which may result in false positive screening results

Questions?



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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

- Decision Tree
  - Compares status quo v. screening model
- Data from:
  - Primary literature
  - States currently screening or pilot studies
  - Expert opinion
- Sensitivity analysis – vary assumptions
  - High and low estimates for parameters

The cost- benefit model

- Decision Tree
  - Compares status quo v. screening model
- Data from:
  - Primary literature → extremely limited
  - States currently screening or pilot studies
  - Expert opinion
- Sensitivity analysis – vary assumptions
  - High and low estimates for parameters

The cost- benefit model

- Decision Tree
  - Compares status quo v. screening model
- Data from:
  - Primary literature → extremely limited
  - States currently screening or pilot studies → none
  - Expert opinion
- Sensitivity analysis – vary assumptions
  - High and low estimates for parameters

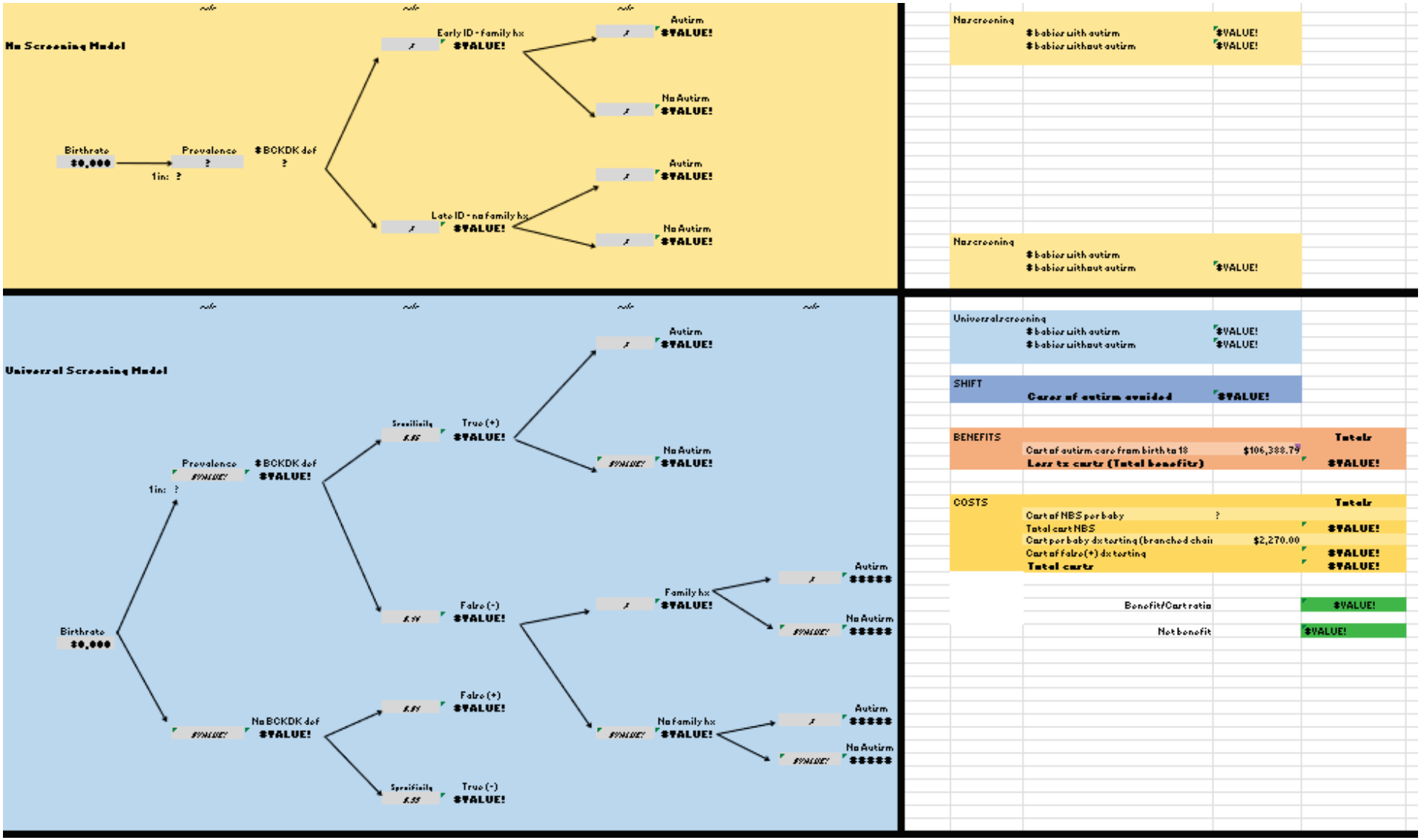
The cost- benefit model

- Decision Tree
  - Compares status quo v. screening model
- Data from:
  - Primary literature → extremely limited
  - States currently screening or pilot studies → none
  - Expert opinion → mostly not accessible
- Sensitivity analysis – vary assumptions
  - High and low estimates for parameters

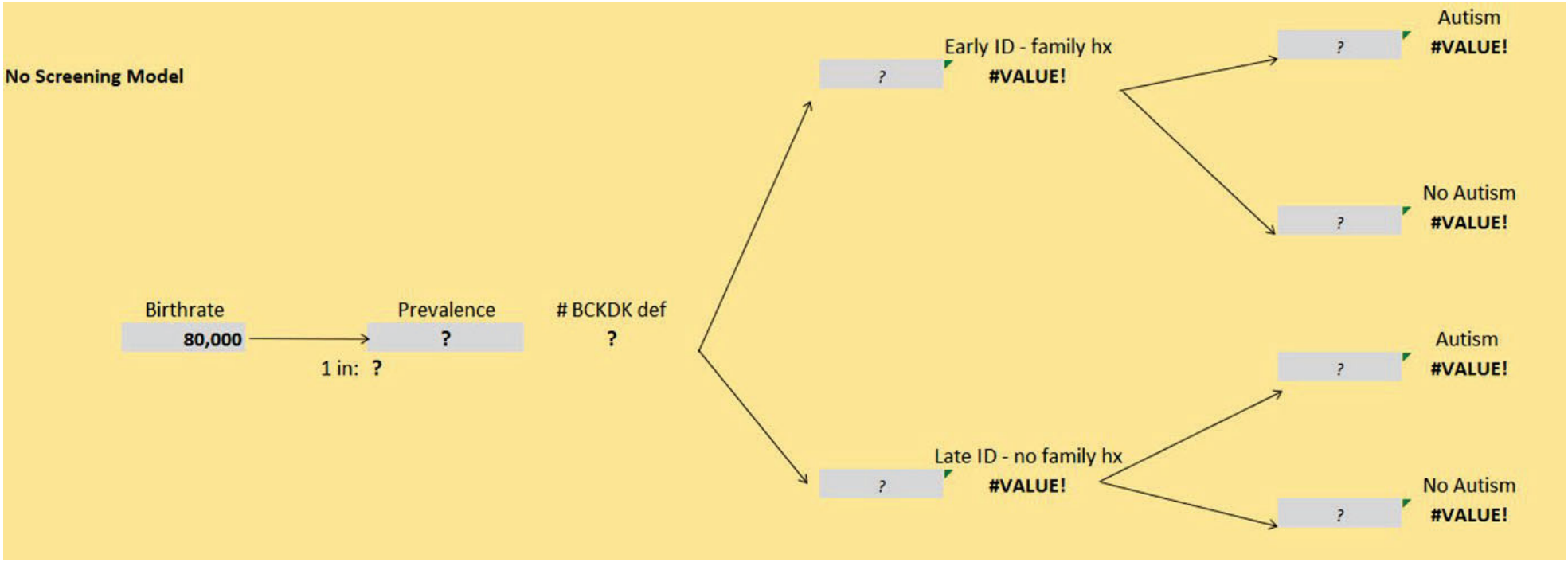
The cost- benefit model

- Phone-a-friend:
  - Insight from Anna Hidle, Public Health Economist, Washington Department of Health

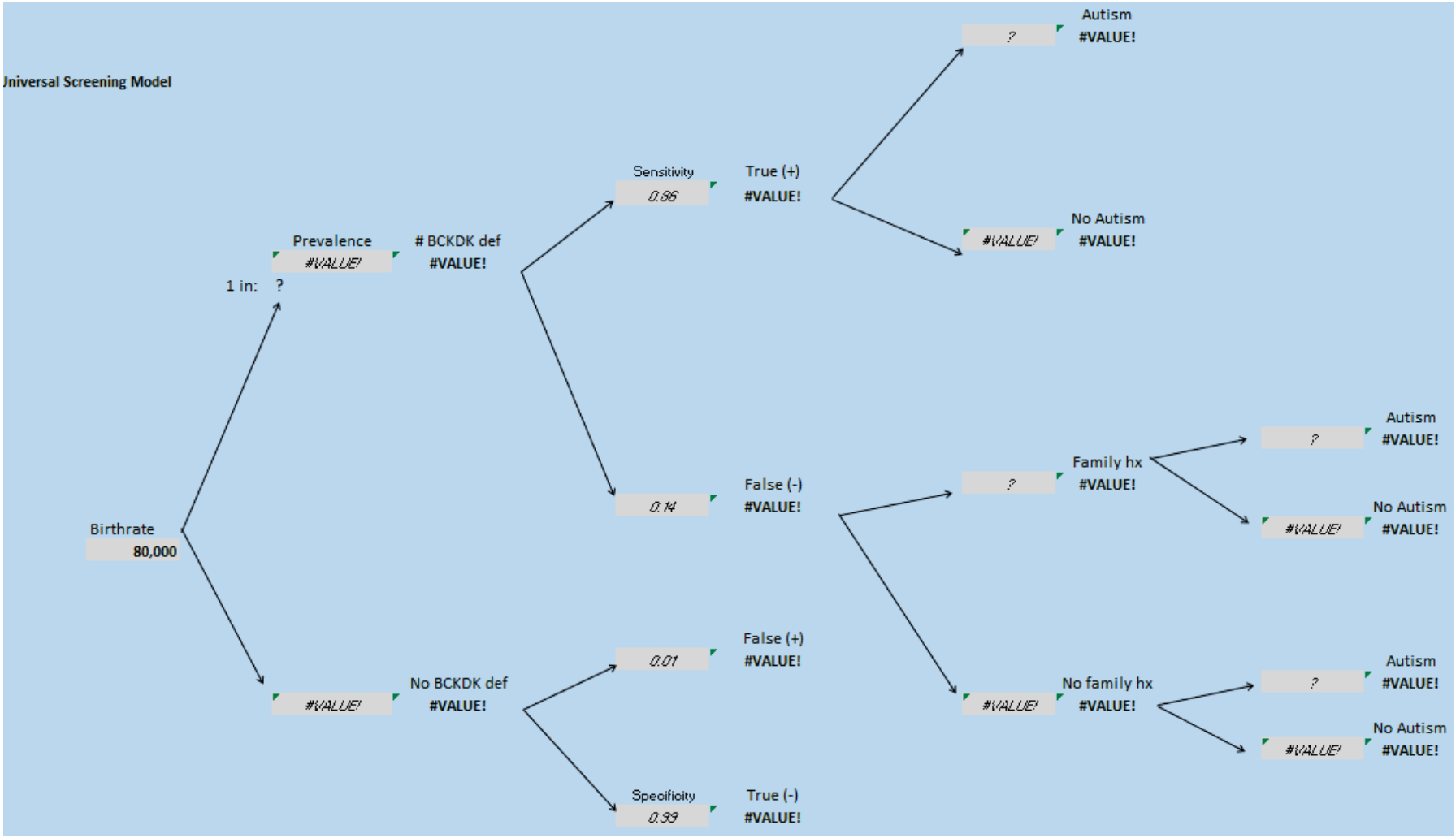
The cost- benefit model



Status quo: No screening model



Newborn screening model



Benefits and Costs

No screening			
	# babies with autism		
	# babies without autism	#VALUE!	
Universal screening			
	# babies with autism	#VALUE!	
	# babies without autism	#VALUE!	
SHIFT			
	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 chai	$2,270.00	
	Cost of false(+) dx testing		**#VALUE!**
	Total costs		**#VALUE!**
	Benefit/Cost ratio		#VALUE!
	Net benefit		#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.

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Newborn Screening Technical Advisory Committee (TAC)

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

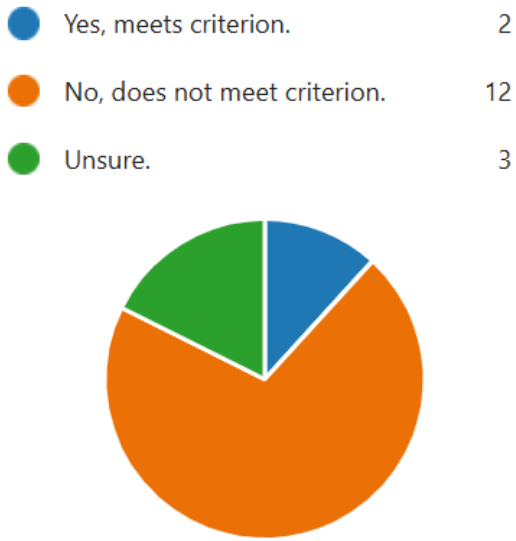
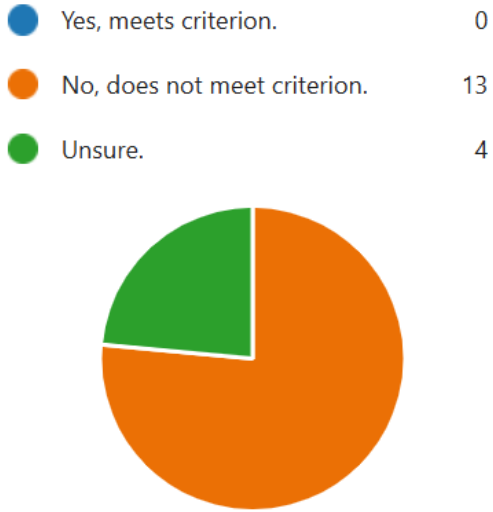
TAC Member Voting Summaries and Comments

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

(continued on the next page)

2. Diagnostic Testing and Treatment Available Yes, meets criterion. 6 No, does not meet criterion. 6 Unsure. 5 	• There is very limited evidence available for this disorder, making it unclear whether diagnostic criteria are met. • 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.
3. Prevention Potential and Medical Rationale Yes, meets criterion. 7 No, does not meet criterion. 3 Unsure. 7 	• There is a lack of sufficient data on the prevalence, long-term outcomes with early treatment, and the number of patients in the literature, making it difficult to assess the relevant criteria.

4. Public Health Rationale 	• Not enough information to assess this criterion. Rarity gives pause, but true prevalence is unknown.
5. Cost Benefit / Cost Effectiveness 	• There is insufficient data available to evaluate the condition, including the lack of BCA testing, limited prevalence information, and only 21 patients reported in the literature. • Screening is not being conducted, and there are concerns about unintended consequences for conditions on the newborn screening panel.

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Newborn Screening Technical Advisory Committee (TAC)

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[1]
- There are 21 cases of BCKDK deficiency identified worldwide, with no cases yet reported in the United States[2]
- BCKDK deficiency is caused by changes in the BCKDK gene, which produces the BCKDK enzyme[1]
- 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[1]
- Without enough amino acids, proteins can't form properly, which impairs neurodevelopmental growth and development[1,2]

SIGNS & SYMPTOMS

- Signs and symptoms can vary but may include autism spectrum disorder, language impairment, seizures, and microcephaly[2]

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[2]
- 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[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]

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 wsboh@sboh.wa.gov.

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WASHINGTON STATE BOARD OF HEALTH

This report was prepared by the Washington State Board of Health in partnership with the Department of Health's Newborn Screening Policy Team.

Kelly Kramer, Newborn Screening Policy Advisor
Molly Dinardo, Board Policy Advisor

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