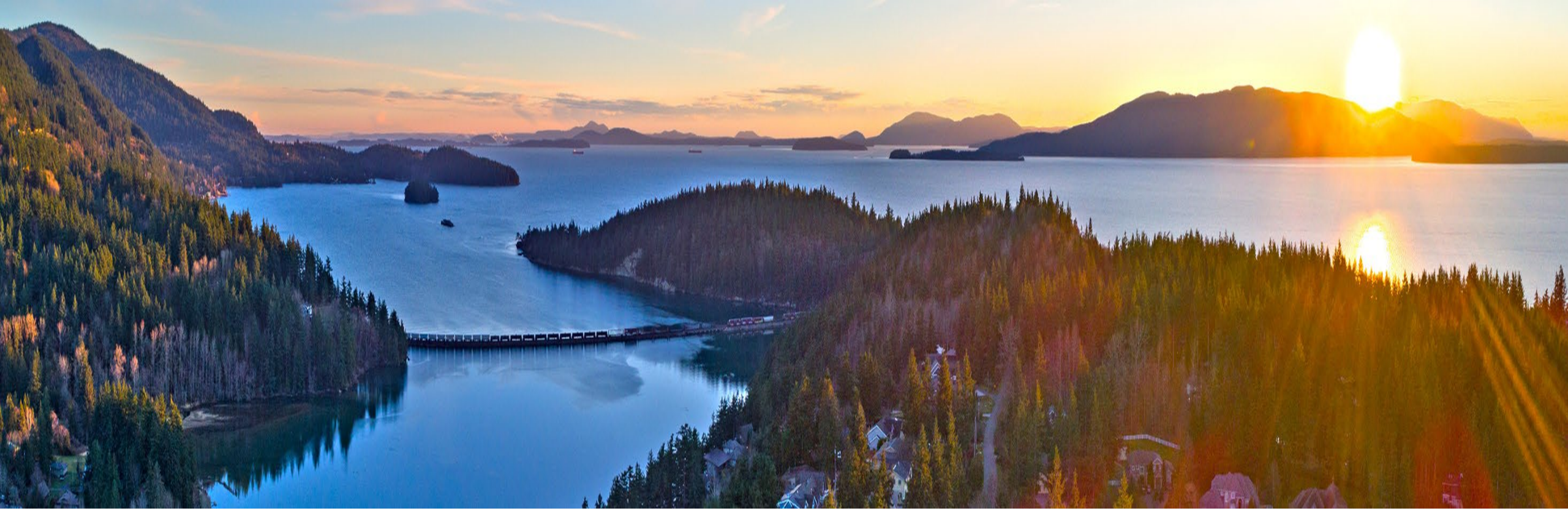

Washington State Board of Health

Petition for Rulemaking – chapter 246-650 WAC, Newborn Screening, Guanidinoacetate methyltransferase (GAMT) deficiency

March 8, 2023

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Director, Department of Health (DOH) Newborn Screening Program

Molly Dinardo, MPH
Health Policy Advisor, Washington State Board of Health (SBOH)

Board Policy for Newborn Screening Criteria

Three guiding principles govern all aspects of the evaluation of a candidate condition for possible inclusion in Washington's Newborn Screening 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 or condition should outweigh harm to families, children, and society

Newborn Screening Criteria

- Available screening technology
- Diagnostic testing and treatment available
- Prevention potential and medical rationale
- Public health rationale
- Cost-benefit/cost-effectiveness

GAMT Qualifying Assumption

- Petition - Guanidinoacetate methyltransferase (GAMT) deficiency
  - Submitted February 24, 2023, requesting to add Guanidinoacetate methyltransferase (GAMT) deficiency to chapter 246-650 WAC as a condition for newborn screening
  - In January 2023, the Secretary of Health and Human approved the recommendation to add GAMT deficiency to the federal Recommended Uniform Screening Panel (RUSP)
- Preliminary review of five criteria
  - John Thompson – DOH
  - Molly Dinardo – SBOH

GAMT Deficiency 101

- Inherited amino acid disorder
  - Autosomal recessive inheritance pattern
- Prevents the body from producing creatine
  - GAMT is an enzyme that helps make creatine from guanidinoacetate (GUAC)
  - Without enough creatine, organs in the body do not get enough energy (primary impacts on brain and muscles)
  - Elevated GUAC in the body has neurotoxic effects
- Signs and symptoms include:
  - Intellectual and developmental disabilities, delayed sitting or walking, delayed or limited speech ability, muscle weakness or low muscle tone, behavioral issues (anxiety, aggression, self-injury, hyperactivity), seizures, uncontrollable movements
- Children can begin showing signs and symptoms from early infancy to early childhood

GAMT and Newborn Screening Programs

- States that currently screen for GAMT deficiency
  - Utah (since 2015)
  - New York (since 2018)
  - Michigan (since 2023 – validation took 3 years)
- Other population-based screening programs
  - British Columbia, Canada
  - Victoria, Australia

Available Screening Technology

- Tandem mass spectrometry
- Measures guanidinoacetate (GUAC) and sometimes creatine in the blood
  - Utah, New York, British Colombia (Canada), Victoria (Australia)
  - Could be multiplexed with current testing in WA
- Prevalence: ~1:540,000 births (U.S. data)
- Test performance (~1.1 million screened in the U.S.)
  - Sensitivity: 100% (no known false negatives)
  - Specificity: 99.998%
  - Positive Predictive Value: 7.1%

Diagnostic Testing and Treatment Available

- Diagnostic tests
  - Guanidinoacetate (GUAC) and low creatine in the blood after a positive NBS
  - Molecular testing can be helpful
  - Testing available at Seattle Children's or other reference labs
- Treatment
  - Lifelong treatment with dietary supplements and a low-protein diet
  - Management requires support from multidisciplinary biochemical genetics team
  - Infrastructure and treatment available at Seattle Children's hospital
    - Current staffing levels are low with recruitments in progress

Prevention Potential and Medical Rationale

- Published evidence regarding early treatment outcomes is limited
- Case series and case reports suggest pre-symptomatic or earlier initiation of treatment is associated with better neurological outcomes
    - Federal review identified 6 publications and abstracts that looked at treatment initiation for children under 12 months
    - Case reports based on sibling pairs where the younger sibling is diagnosed at birth because of known family history of GAMT deficiency in an older sibling
    - Reports indicate reduced risk of intellectual disabilities and less frequent seizures
- Low risk of harm from treating patients that will not benefit from treatment

Public Health Rationale

- Rarity of GAMT deficiency
  - Individuals that carry a nonworking GAMT gene may never receive a diagnosis
  - Gaps in data related to the epidemiology of GAMT, including the birth prevalence and whether there are higher risk populations
- Autosomal recessive inheritance pattern
  - Carriers of a nonworking GAMT gene can pass down a nonworking copy to their children
  - If both parents are carriers, there's a 1 in 4 chance their child will have GAMT deficiency
  - If parents have a child with GAMT deficiency, they still have a 1 in 4 chance of having another child with GAMT, and chances stay the same for future children

Cost-Benefit/Cost-Effectiveness

- Federal Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)
  - Limitations from evidence review report (6/2/2022):
    - "Limited data were available for many parameter inputs. Insufficient data were available to project long-term outcomes for GAMT deficiency, either through newborn screening or clinical identification."
    - "Given the rare nature of newborn screened conditions, data are typically scarce for conditions being considered for addition to the recommended uniform screening panel. Compared with other conditions that have been nominated and considered for addition to the panel, data for the consideration of GAMT deficiency were considerably sparser."
  - Without additional published data, any formal cost-benefit analysis would rely solely on expert opinion
  - Other, non-quantifiable considerations could be reviewed and discussed
    - Psychosocial benefits/harms including impact of ambiguous results
    - Adverse effects/unintended consequences of screening

THANK YOU

WASHINGTON STATE BOARD OF HEALTH

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Resources from Federal Review of GAMT deficiency for the RUSP:

- Evidence-Based Review of Newborn Screening for Guanidinoacetate Methyltransferase (GAMT) Deficiency: Final Report. Prepared for the Maternal and Child Health Bureau. June 02, 2022.
  - Final Report
  - Available Under Recommendations to HHS Secretary
- Recommendations to the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) for Newborn Screening of GAMT deficiency. May 12, 2022.
  - PowerPoint Presentation for the ACHDNC Meeting
  - Available under ACHDNC's May 2022 Meeting Materials