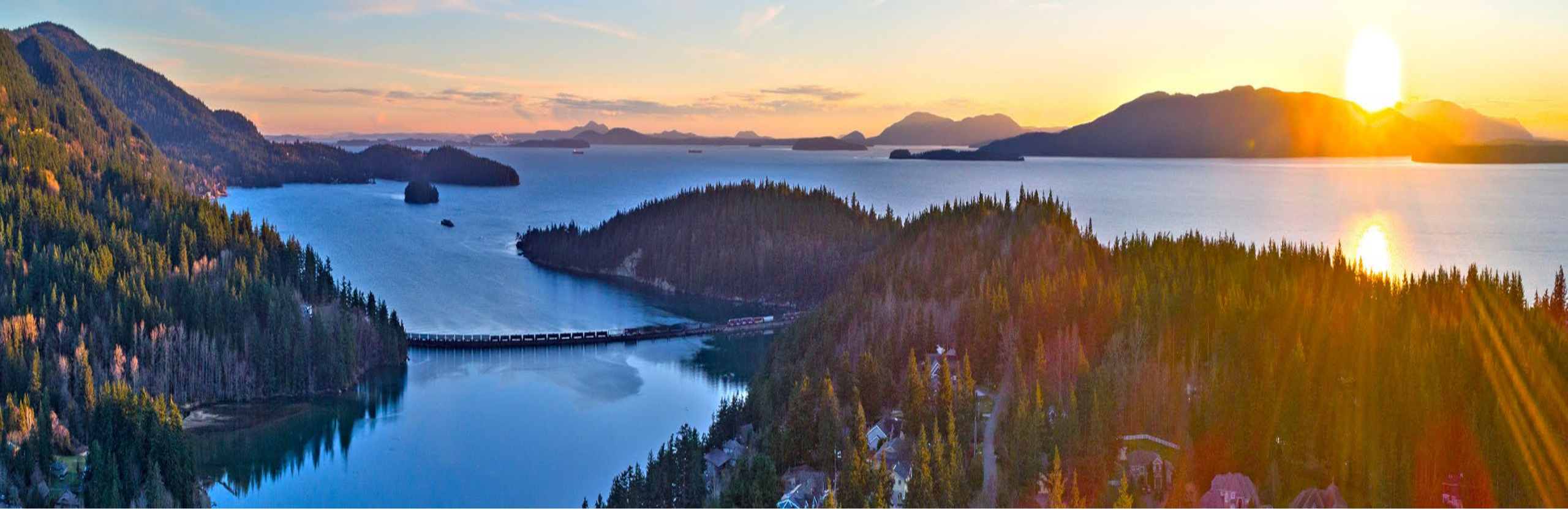


Washington State Board of Health

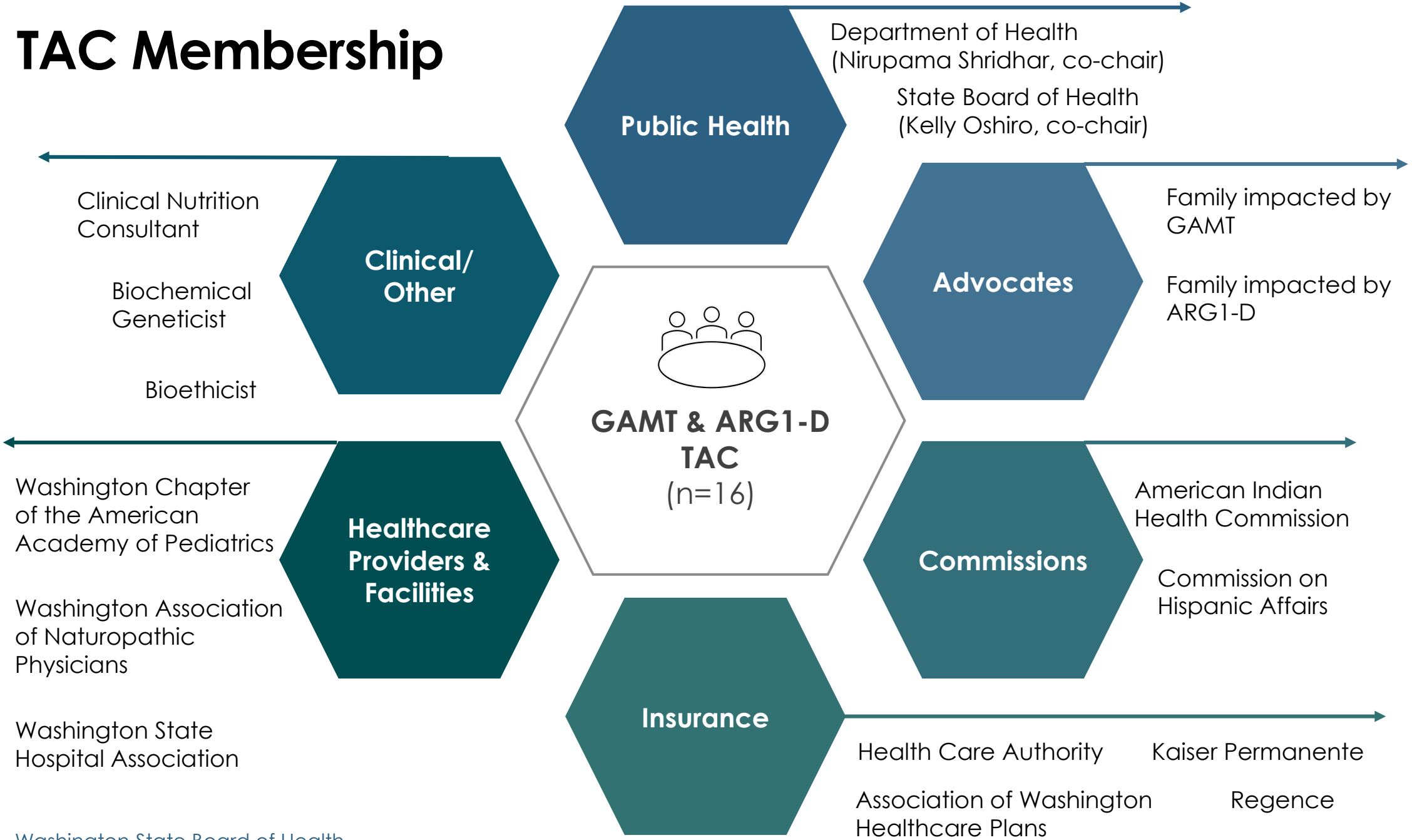
Newborn Screening Technical Advisory Committee (TAC) Recommendations on Guanidinoacetate Methyltransferase (GAMT) Deficiency and Arginase 1 Deficiency (ARG1-D)

October 9, 2023

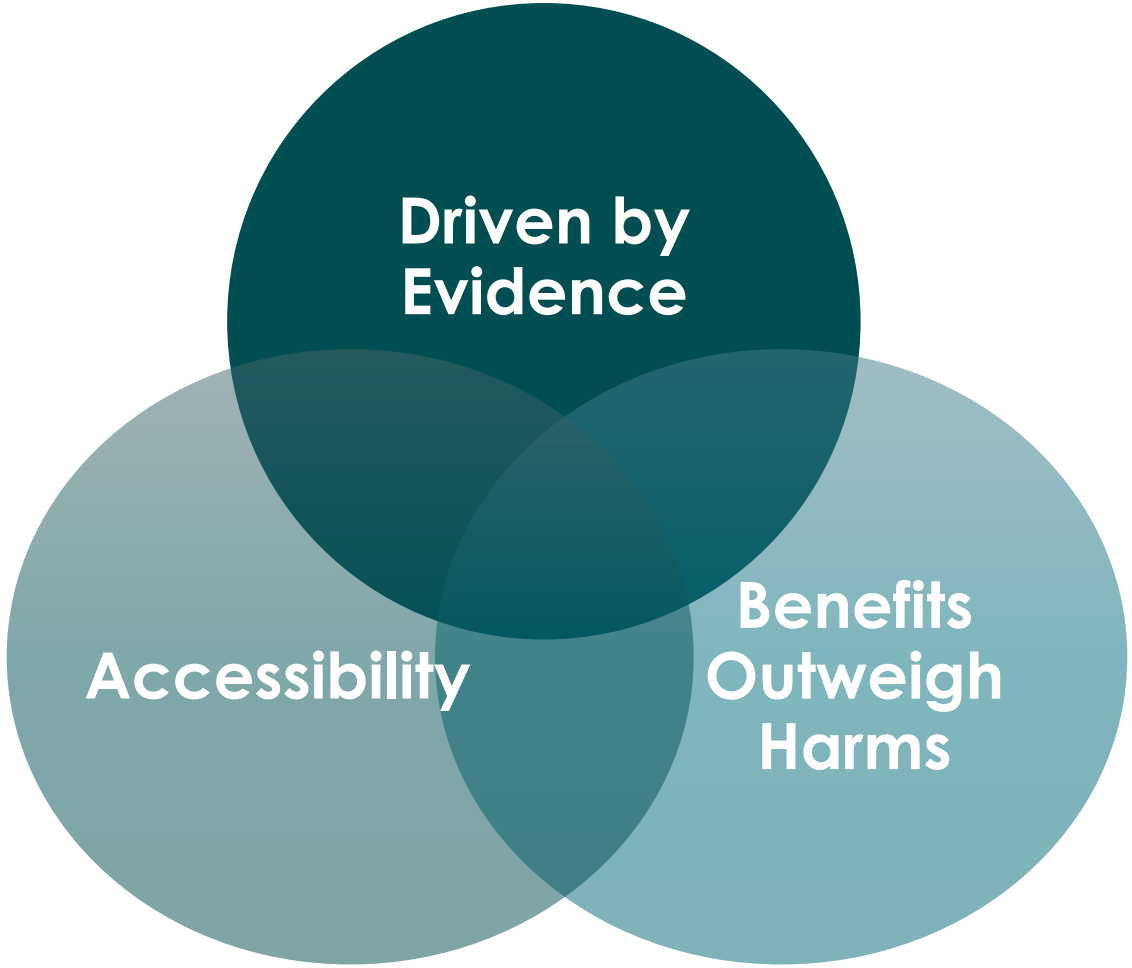
Technical Advisory Committee (TAC) Background

- The TAC met on September 8, 2023, to determine whether GAMT Deficiency and ARG1-D met the Washington State Board of Health's criteria for newborn screening conditions.
- Committee heard presentations from families impacted by the conditions, Board staff, Department staff, and subject matter experts to inform discussion and evaluation of the conditions.
- Reviewed GAMT Deficiency first, then repeated the process for ARG1-D.

TAC Membership

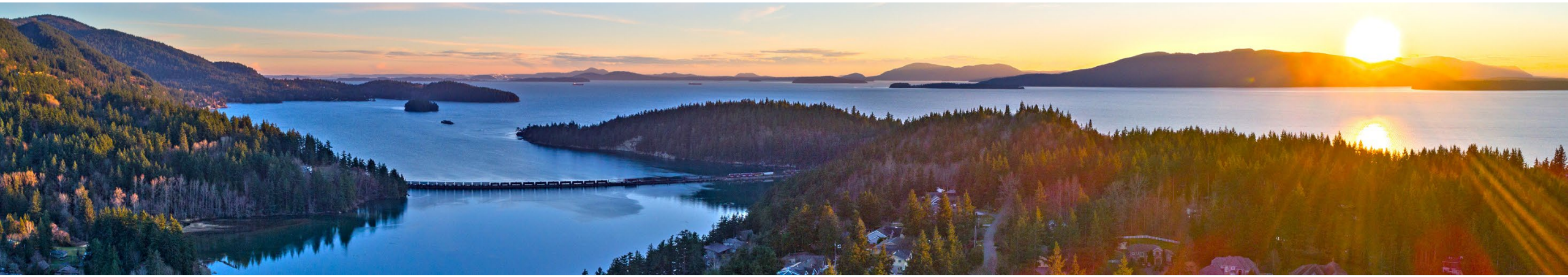


Guiding Principles & Newborn Screening Criteria



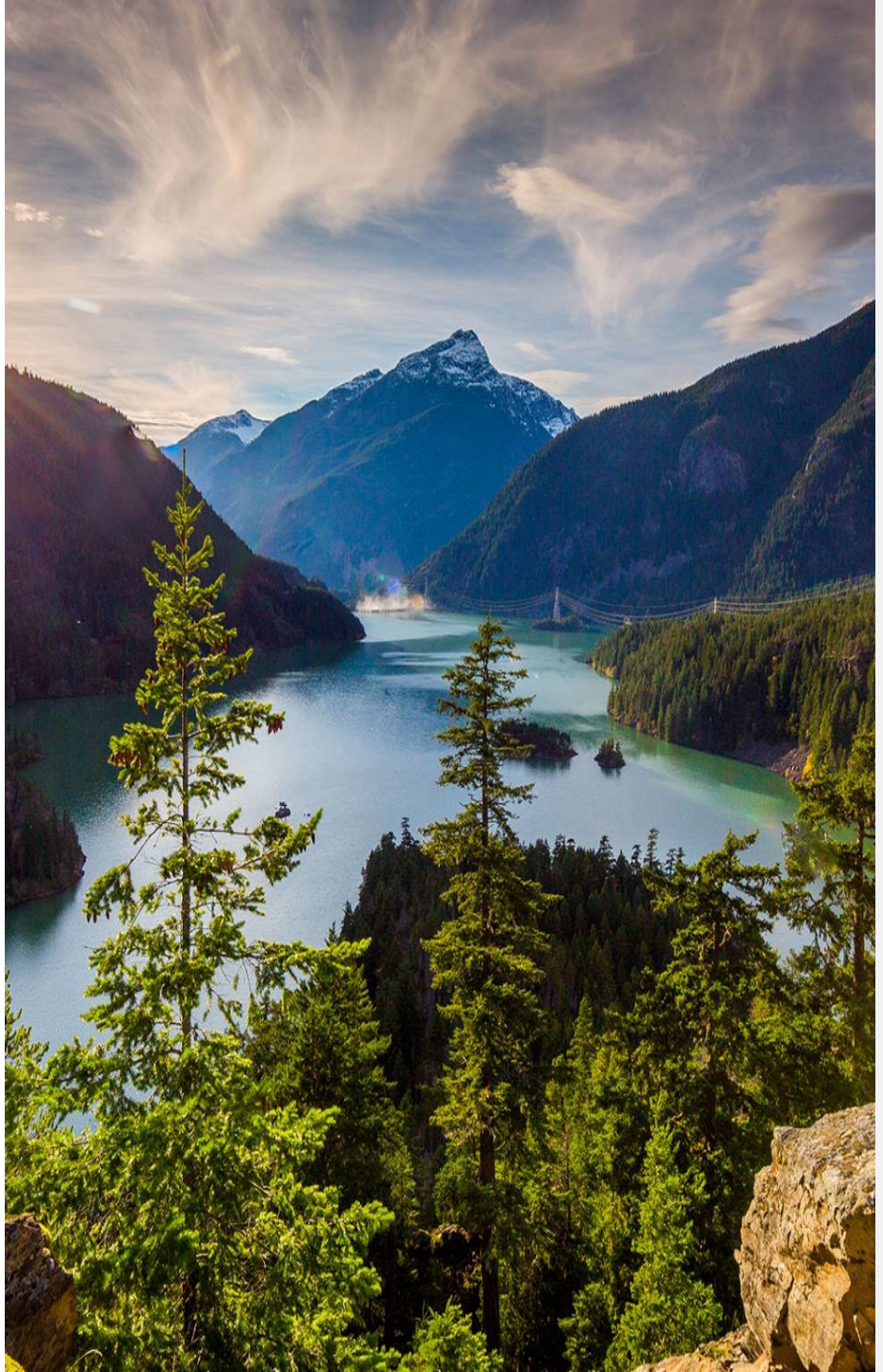
1. Available Screening Technology
2. Diagnostic Testing and Treatment Available
3. Prevention Potential and Medical Rationale
4. Public Health Rationale
5. Cost-Benefit / Cost-Effectiveness

GAMT Deficiency Background, Committee Voting, & Recommendation



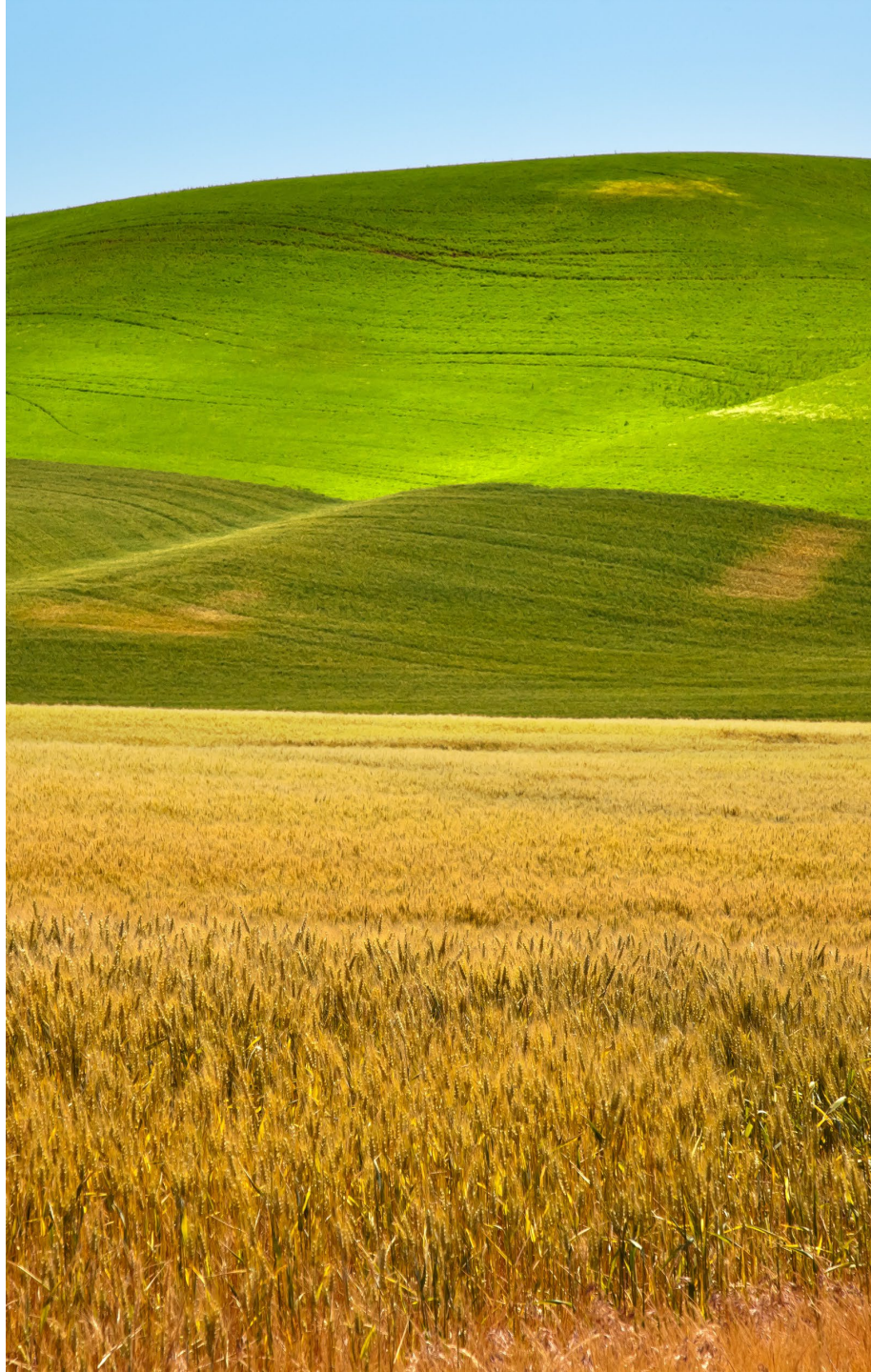
Background – GAMT Deficiency

- Rare, autosomal recessive disorder.
  - ~130 individuals diagnosed worldwide.
- It is among three types of inherited anomalies that impact the metabolism and transport of creatine in the body, also known as cerebral creatine deficiency syndromes (CCDS).
- If untreated, GAMT Deficiency leads to developmental delays and cognitive impairments (can be moderate or severe).
- Signs and symptoms of the condition vary and can start anywhere from 3 months to 2 years of age.



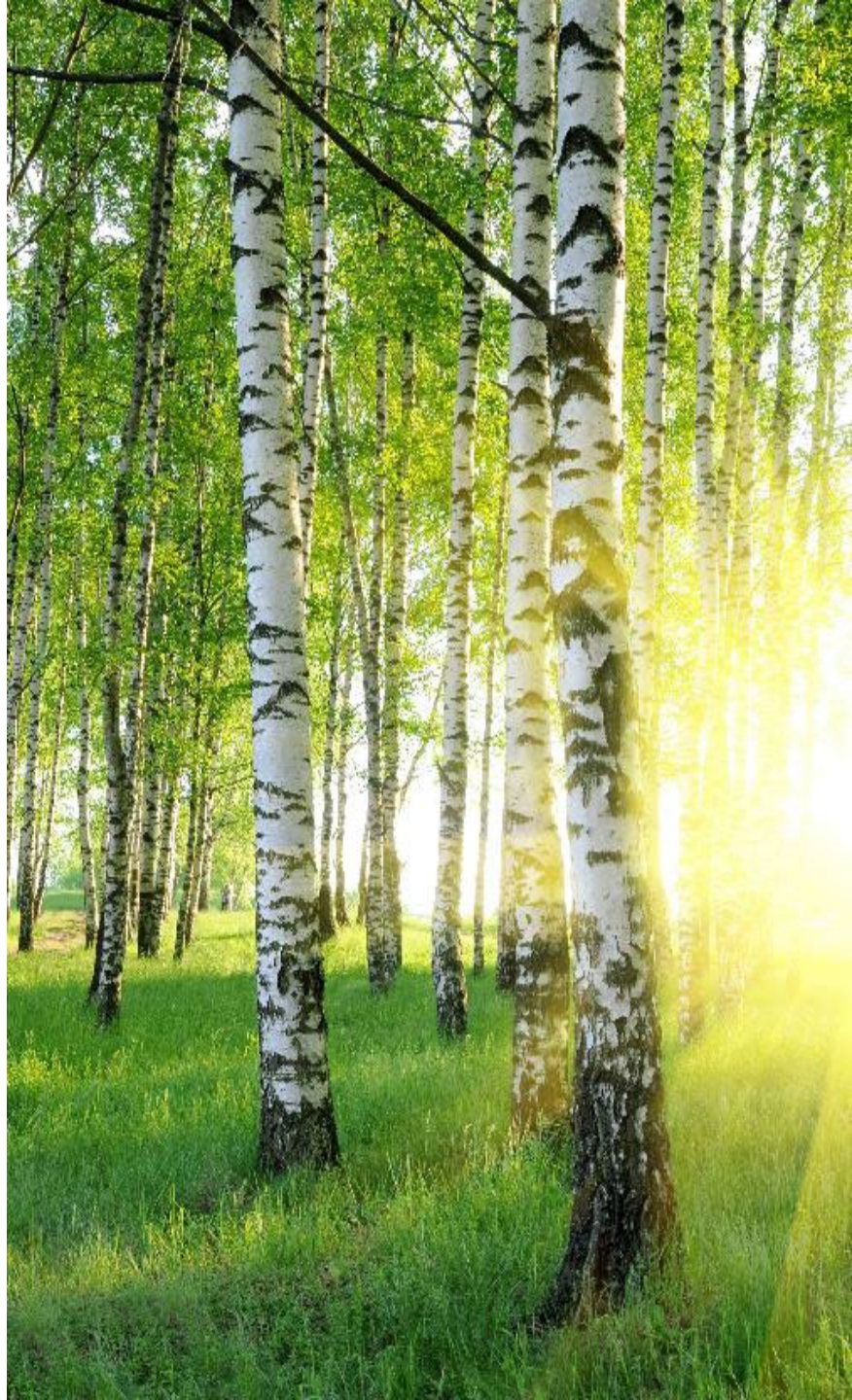
Available Screening Technology

- Technology – Tandem mass spectrometry (MS/MS)
  - Technology in WA NBS Program since 2004
- Measures guanidinoacetate (GUAC) and creatine in the blood.
- Currently, Utah, New York, British Columbia (Canada), and Victoria (Australia) have screening programs for GAMT.
- Across the 4 screening programs – 3.07 million babies:
  - 3 cases of GAMT (prevalence = 1:1,000,000 births)
    - 3 true positives (sensitivity = 100%)
    - 0 false negatives
  - False positive rate (NY+UT) 2.1/100,000 (specificity = 99.99%).



Diagnostic Testing & Treatment

- Testing includes:
  - Biochemical Testing: Measuring Guanidinoacetate (GUAC or GAA) and creatine levels in blood or urine.
  - Molecular Genetic Testing: Analysis of GAMT gene.
  - Brain magnetic resonance spectroscopy: May also be an option and would detect low-level cerebral creatine levels in the central nervous system (CNS).
- Treatment:
  - Oral creatine, sodium benzoate, and/or ornithine supplements.
  - Low protein diet and supplementation with a synthetic arginine-free formula.
  - Physical, occupational, speech, and behavioral therapy.
- According to the published literature, if treatment is started early, the condition is highly treatable.



Cost-Benefit for Adding Newborn Screening for GAMT

No Screening	Babies/Year	Value/Year
Severe Disability	0.0385	
Moderate Disability	0.0342	
No Disability	0.0083	
Early Treatment Costs		$93.85
Late Treatment (Severe) Costs		$68,495.18
Late Treatment (Moderate) Costs		$55,443.93
Total Costs		$124,032.96

Screening	Babies/Year	Value/Year
Severe Disability	0.00021	
Moderate Disability	0.00019	
No Disability	0.0806	
Early Treatment Costs		$1,045.88
Late Treatment (Severe) Costs		$376.05
Late Treatment (Moderate) Costs		$304.40
Total Costs		$1,726.33

Cost-Benefit for Adding Newborn Screening for GAMT

Benefits	Value
Shift in early treatment costs	-$952.03
Shift in late treatment (severe) costs	$68,119.13
Shift in late treatment (moderate) costs	$55,139.53
Total benefits	$122,306.64

Costs	Value
Costs of screening ($0.99 per baby)	$82,008.19
Cost of false positives	$2,178.75
Total costs	$84,186.94

Benefit/Cost ratio	**1.453**
Net Benefit	**$38,119.70**

GAMT TAC Voting Summary – Criteria

Criteria	Yes	No	Unsure	No Response
Available Screening Technology	14	0	0	2
Diagnostic Testing and Treatment	13	0	1	2
Prevention Potential and Medical Rationale	13	1	0	2
Public Health Rationale	14	0	0	2
Cost-benefit / Cost effectiveness	14	0	0	2

GAMT TAC Voting Summary – Overall Recommendation

Option	Vote
1. I recommend the Board add GAMT Deficiency to the list of conditions for which all Washington-born newborns must be screened.	16
2. I do not recommend the Board add GAMT Deficiency to the list of conditions for which all Washington-born newborns must be screened.	0
3. At this time, I do not recommend the Board add GAMT Deficiency to the list of conditions for which all Washington-born newborns must be screened; I recommend the Board revisit GAMT Deficiency at a future date.	0

Board Member Discussion & Next Steps

For discussion: Does the Board agree with the TAC's recommendation for GAMT Deficiency?

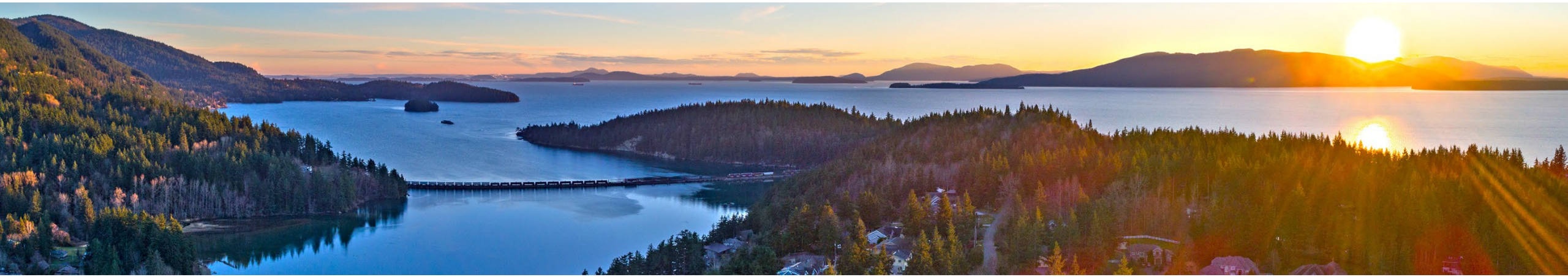
Possible Action: The Board may consider the following…

- Direct staff to initiate rulemaking to include GAMT Deficiency screening in the NBS panel.

OR

- Determine that GAMT Deficiency should not be considered at this time and revisit the condition in two years.

ARG1-D Background, Committee Voting, & Recommendation

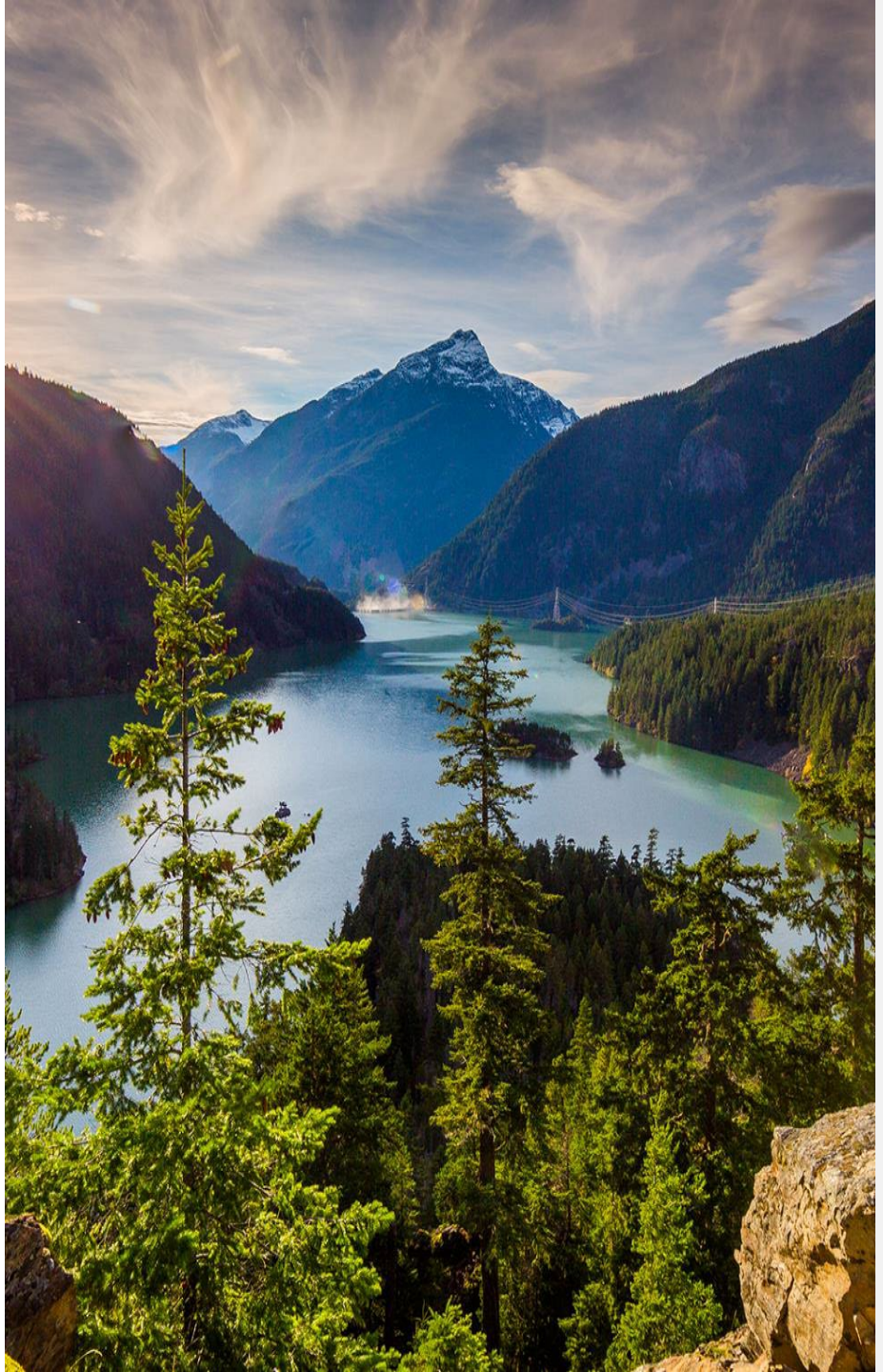


Background – ARG1-D

- Rare, autosomal recessive disorder.
- Causes the amino acid arginine and ammonia to accumulate in the blood.
    - When ammonia levels become too high, it has neurotoxic effects.
- Newborns are typically asymptomatic.
- Symptoms start off subtle, do not start to become apparent until early childhood (1-3 years of age), and are progressive without treatment. Symptoms may include:
    - Spasticity in lower extremities (most common, affects 80-90% of those diagnosed)
    - Impairments in cognitive development
    - Seizures
    - Stunted growth
    - Challenges with eating
    - Liver problems

Available Screening Technology

- Technology – Tandem mass spectrometry (MS/MS)
  - Technology in WA NBS Program since 2004
- Measures high levels of arginine in the blood.
- Over 30 states currently screen for ARG1-D either as a primary or secondary screening target.
- U.S. based Screening – 29 million babies
  - 22 cases of ARG1-D identified (prevalence = 0.75:1,000,000 births)
    - 22 true positives (sensitivity = 100%)
    - 0 false negatives
  - False positive rate (US) 5.0/100,000 (specificity = 99.99%)



Diagnostic Testing & Treatment

- Testing includes:
  - Biochemical testing: Measurement of plasma arginine level on plasma amino acid analysis.
  - Genetic testing: Analysis of the ARG1-D gene.
  - Measurement of ARG1-D Enzyme Activity Levels.
- Treatment includes:
  - Low-protein diet and supplement with synthetic arginine-free amino acid formula.
  - Ammonia diversion therapy: Nitrogen scavenging medications (sodium benzoate, sodium phenylbutyrate, glycerol phenylbutyrate).
  - Referrals to neurology, and physical, occupational, and/or speech therapy.
- Current treatments lower but do not normalize arginine levels.
  - According to the published literature, ARG1-D is partially treatable with current tools available.
  - However, even a partial reduction in arginine has a meaningful impact on disease outcomes.

Cost-Benefit for Adding Newborn Screening for ARG1-D

No Screening	Babies/Year	Value/Year
Deaths	0.0075	
Surviving with long-term disability	0.0637	
Surviving without long-term disability	0.0117	
Early Treatment Costs		$19,853.16
Late Treatment Costs		$114,264.14
Total Costs		$134,117.30

Screening	Babies/Year	Value/Year
Deaths	0.0000456	
Surviving with long-term disability	0.0095	
Surviving without long-term disability	0.0734	
Early Treatment Costs		$124,167.36
Late Treatment Costs		$679.41
Total Costs		$124,846.77

Cost-Benefit for Adding Newborn Screening for ARG1-D

Benefits	Babies/Year	Value
Deaths averted	0.00750	
Long-term disability averted	0.0542	
Value of long-term disability averted		$81,259.71
Value of a life		$11,600,000.00
Value of lives saved		$86,981.13
Less treatment costs		$9,270.54
Total benefits		$177,511.38

Costs	Value
Costs of screening ($0.99 per baby)	$82,008.19
Cost of false positives	$5,255.13
Total costs	$87,263.32

Benefit/Cost ratio	**2.03**
Net Benefit	**$90,248.06**

ARG1-D TAC Voting Summary – Criteria

Criteria	Yes	No	Unsure	No Response
Available Screening Technology	14	1	0	1
Diagnostic Testing and Treatment	11	1	3	1
Prevention Potential and Medical Rationale	14	0	1	1
Public Health Rationale	15	0	0	1
Cost-benefit / Cost effectiveness	13	0	2	1

ARG1-D TAC Voting Summary – Overall Recommendation

Option	Vote
1. I recommend the Board add ARG1-D to the list of conditions for which all Washington-born newborns must be screened.	15
2. I do not recommend the Board add ARG1-D to the list of conditions for which all Washington-born newborns must be screened.	0
3. At this time, I do not recommend the Board add ARG1-D to the list of conditions for which all Washington-born newborns must be screened; I recommend the Board revisit ARG1-D at a future date.	0

Board Member Discussion & Next Steps

For discussion: Does the Board agree with the TAC's recommendation for ARG1-D?

Possible action: The Board may consider the following…

- Direct staff to initiate rulemaking to include ARG1-D screening in the NBS panel.

OR

- Determine that ARG1-D should not be considered at this time and revisit the condition in two years.

THANK YOU

WASHINGTON STATE BOARD OF HEALTH

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