WASHINGTON STATE DEPARTMENT OF HEALTH

Significant Legislative Rule Analysis

WAC 246-650-010 & 246-650-020

A Rule Concerning Newborn Screening – Adding Ornithine Transcarbamylase Deficiency (OTCD), Guanidinoacetate Methyltransferase (GAMT) Deficiency, and Arginase 1 Deficiency (ARG1-D) to the list of screening tests performed by the Department of Health

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Washington State Department of HEALTH

WASHINGTON STATE BOARD OF HEALTH

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SECTION 1

A brief description of the proposed rule, including the current situation/rule, followed by the history of the issue and why the proposed rule is needed.

Proposed Rule and Brief History

The Washington State Board of Health (board) in collaboration with the Department of Health (department) is proposing amendments to the newborn screening requirements in WAC 246-650-010 and WAC 246-650-020. The proposed rule expands the Washington State newborn screening (NBS) panel of required tests by adding three new conditions: Ornithine Transcarbamylase Deficiency (OTCD), Guanidinoacetate Methyltransferase (GAMT) Deficiency, and Arginase 1 Deficiency (ARG1-D). To implement screening for these conditions, the board must amend WAC 246-650-010 and WAC 246-650-020. Early detection of OTCD, GAMT deficiency, and ARG1-D is critical for saving lives and improving long-term health outcomes for affected infants and their families.

The NBS program, operated by the department, tests all babies for rare but treatable health conditions using a dried blood sample. Washington State law (RCW 70.83.050) requires that the board create rules for newborn screening. These rules are found in chapter 246-650 WAC. Specifically, WAC 246-650-010 and WAC 246-650-020 define and list the conditions that the department must screen all babies for after birth.

Anyone may petition the board to review a condition for possible inclusion in the NBS panel, including members of the public, department staff, and board members. To evaluate candidate conditions, the board convenes a Technical Advisory Committee (TAC), which reviews evidence against guiding principles and established criteria. The TAC provides findings and recommendations for board consideration.

In 2021, the board formed a Technical Advisory Committee (TAC) to review OTCD following a petition from a family whose child had passed away from the condition. In 2023, the board formed another TAC to review GAMT Deficiency and ARG1-D after two parent advocates submitted petitions. After reviewing evidence, hearing from families, and consulting experts, both TACs recommended adding the conditions to the screening panel. The board considered these recommendations at its meetings in October 2021 and October 2023 and voted to proceed with rulemaking to amend chapter 246-650 WAC.

Through this rulemaking, the board proposes amendments to chapter 246-650 WAC to support the addition of three new conditions to Washington's newborn screening panel: OTCD, GAMT deficiency, and ARG1-D. These amendments include adding formal definitions for each of the three conditions and incorporating them into the list of newborn screening tests performed by the Department of Health.

In addition, the Board is proposing minor housekeeping changes. These include updating the definition of amino acid disorders and reclassifying relevant conditions under a new definition, “urea cycle disorders” as OTCD, ARG1-D and citrullinemia type I (CIT) are specific types or urea cycle disorders. The rulemaking also removes outdated language related to prior screening requirements that sunset in 2020 and are no longer applicable.

Adding OTCD, GAMT deficiency, and ARG1-D to the newborn screening (NBS) panel requires an increase in the NBS fee. This fee is not adopted in rule, and falls under the department’s fee authority established in RCW 43.70.250(2), which requires legislative approval to increase spending authority for department programs, permit fees, etc.

The department charges a one-time screening fee that covers all required newborn screens in Washington State, including repeat or follow-up screens when medically necessary. This fee, collected for each tested infant in Washington, covers the costs of laboratory screening, follow-up services, and coordination with specialty care.

The department bills the screening fee to the facility that collects the infant’s initial specimen. This is typically the birth hospital but may also include a clinic, birth center, or laboratory. Facilities can usually recover the cost through insurance reimbursement or patient billing. Medical facilities may charge their own administrative fees for collecting or processing specimens, which are separate from the department’s screening fee.

For specimens collected in an at home setting, the department bills the client’s insurance directly when the specimen is accompanied by the insurance information. If the patient is uninsured, they must pay the screening fee out of pocket via check or money order.

To implement screening for these additional conditions, the department secured increased spending authority from the Legislature during the 2025 legislative session. Beginning January 1, 2026, the screening fee will increase by $4.02 to cover the cost of testing for OTCD, GAMT deficiency, and ARG1-D. This increase is expected to be covered by public or private insurance, or by families directly.

This significant analysis (SA) outlines the department’s cost-benefit assumptions from 2021 (OTCD) and 2023 (GAMT and ARG1-D), which were used to evaluate these conditions for inclusion in the screening panel, in addition to the actual costs of screening implementation. In the initial analysis, the department estimated that the cost of screening would range from $8 to $12. These cost estimates influenced decisions made by both the Technical Advisory Committees (TACs) and the Board. This SA first outlines these initial cost assumptions and concludes with the actual costs of screening.

It’s important to note that early cost-benefit analyses may differ from acutal implementation costs due to the evolving nature of data, and inflation during the gap of time required from analysis to securing legislative approval. There is typically a gap of several years between the department’s initial analysis, TAC review, and the actual implementation of the program. For further details, see the “Actual Costs of Screening” in Section 5.

Overview and Background – OTCD

Ornithine transcarbamylase deficiency (OTCD) is an inherited metabolic disorder that impairs the body’s ability to remove ammonia, a toxic byproduct of protein metabolism.[1] [2] OTCD is an X-linked condition, meaning it affects males more severely than females.[3]

Ornithine transcarbamylase (OTC) is an enzyme in the urea cycle, the body’s metabolic pathway for eliminating nitrogen by converting it into urea for excretion. When the OTC enzyme is deficient or not functioning properly, the body cannot fully break down protein, leading to elevated levels of ammonia in the blood (hyperammonemia). Excess ammonia is toxic to the nervous system and can cause significant health complications.[4]

The signs and symptoms of OTCD vary widely and may appear anytime from infancy through adulthood. In infants, symptoms may include poor feeding, vomiting, lethargy, floppy muscle tone, difficulty breathing, and seizures. In both children and adults, OTCD can cause recurrent vomiting, neurological and behavioral changes, developmental delays, intellectual disability, coma, or even death.[2]

OTCD can be detected through newborn screening using tandem mass spectrometry. Confirmatory diagnostic testing includes blood tests for ammonia and amino acid levels, as well as urine testing for organic acids such as orotic acid. Genetic testing can be used to confirm the diagnosis.

OTCD is present in approximately 1 in 157,833 babies, based on personal communication with the California Newborn Screening Program.[5] At present, at least nine states in the U.S screen for OTCD – California, Connecticut, Florida, Kentucky, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, as well as several other countries.

Treatment for OTCD focuses on preventing hyperammonemia and may include a low-protein diet, specialized formulas, amino acid supplementation, nitrogen-scavenging medications, and dialysis to reduce ammonia levels in emergencies. In severe cases, liver

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[1] Donovan K, Vagar S, Guzman, N. Ornithine transcarbamylase deficiency- NIH Bookshelf. In: StatPearls. StatPearls Publishing; 2024. Accessed July 17, 2024. https://www.ncbi.nlm.nih.gov/books/NBK537257/

[2] Health Resources and Services Administration. Ornithine transcarbamylase deficiency | Newborn Screening. Updated July 2024. Accessed July 17, 2024 https://newbornscreening.hrsa.gov/conditions/ornithine- transcarbamylase-deficiency

[3] Brassier, A., et al. Long-term outcomes in Ornithine Transcarbamylase deficiency: a series of 90 patients. (2015) *Orphanet journal of rare diseases*, *10*, 58. https://doi.org/10.1186/s13023-015-0266-1

[4] Merritt, J. L., et al. Newborn screening for proximal urea cycle disorders: Current evidence supporting recommendations for newborn screening. (2018) *Molecular genetics and metabolism*, *124*(2), 109–113. https://doi.org/10.1016/j.ymgme.2018.04.006

[5] Tang H, personal email communication, 2021.

transplantation can provide a permanent cure but carries surgical risks and requires lifelong immunosuppression.[3]

Overview and Background – GAMT deficiency

Guanidinoacetate methyltransferase (GAMT) deficiency is an autosomal recessive disorder of the GAMT gene that impairs the production of creatine in the body, while also increasing levels of guanidinoacetate (GUAC in this report, but also referred to GAA in other literature). Without proper levels of creatine, the body cannot use energy or grow appropriately, which can then lead to the development of intellectual disability. High levels of GUAC can lead to the rise of seizures.[6]

GAMT deficiency signs usually do not present until at least 3 months of age and newborns are asymptomatic. Literature shows that individuals diagnosed later in life have increased disability.[7] Early identification of GAMT deficiency can allow babies to begin treatment to increase levels of creatine and decrease GUAC concentration, leading to normal development as they grow.[8]

GAMT deficiency can present as a spectrum of disabilities. Patients with severe disabilities often see frequent seizures that are resistant to anti-epileptic drugs.[9] As described by several points of literature, those with severe disabilities also have limited intellectual function and likely cannot live alone.[7] Those with moderate disabilities often see seizures as well, but with decreased frequency and may be responsive to anti-epileptic drugs.[8] Patients have higher intellectual function, described as a grade 3 to 6 level.[7] Early identified babies represented in literature show to have normal development and no disabilities when compliant with treatment.

GAMT deficiency is present in approximately 1 in 1,000,000 babies, using a pooled population.[5] At present, three states in the U.S screen for GAMT deficiency – Michigan,

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[6] Health Resources and Services Administration. Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence-Based Review. (2022). Accessed August 2023. https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/gamt-deficiency-final-report.pdf

[7] Doble, B. et al. Impacts of genomics on the health and social costs of intellectual disability. J Med Genet., 57, (479-486). (2020). Doi: 10.1136/jmedgenet-2019-106445

[8] Khaikin, Y., et. al. Treatment outcome of twenty-two patients with guanidinoacetate methyltransferase deficiency: An international retrospective cohort study. (2018) European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society, 22(3), 369–379. https://doi.org/10.1016/j.ejpn.

[9] Stockler-Ipsiroglu, S. et al. Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring (2014). Molecular genetics and metabolism, 111(1), 16–25. https://doi.org/10.1016/j.ymgme.2013.10.01

New York, and Utah. Outside of the U.S, British Columbia, Ontario, and Victoria, Australia also currently screen for GAMT deficiency.

Treatment for GAMT deficiency depends on the diagnosis and can include creatine in the form of oral creatine monohydrate to increase creatine levels (typically 400 mg/kg of body weight/day), L-ornithine supplements to reduce levels of GUAC (100-800 mg/kg/day), and sodium benzoate to reduce glycine levels (100 mg/kg/day).[8] In addition to these dietary supplements, a protein restricted diet reduces arginine in the body. A combination of these treatments depends on severity and works to increase creatine levels and prevent guanidinoacetate in the nervous system. The treatment regimen is necessary every day.

Overview and Background – ARG1-D

Arginase-1 deficiency (ARG1-D) is a rare, inherited disorder. The enzyme arginase is involved in the urea cycle and the removal of nitrogen as it is catalyzed into ornithine. In the cases of ARG1-D, this enzyme is no longer functional, either partially or fully, leading to increased levels of plasma arginine. Toxic ammonia is also allowed to build up, as it is not removed properly.

ARG1-D signs usually do not present until 1 to 3 years of age. Newborns do not show symptoms. Literature shows that individuals diagnosed later in life have increased disability and mortality, as well as the increased risk for hyperammonemia, which can result in liver transplantation. Early identification of ARG1-D can allow babies to begin treatment early and begin nitrogen-scavenging drugs to normalize levels of arginine, leading to normal development.

ARG1D can present several disabilities – intellectual and developmental delay, spasticity in the lower extremities, and seizures. Extreme cases of elevated ammonia can lead to hyperammonemia. Those with extremely severe disabilities have a mortality rate of about 10.6%. These deaths have only been associated with late identified cases.[10] [11]

ARG1-D is present in approximately 1 in 1,00,000 babies, when looking at the median value published literature.[12] At present, 36 states screen for ARG1-D. There has also been

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[10] Sawad, A., B. et al. Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. (2022). JIMD Reports, 63(4): 330-340. doi:10.1002/jmd2.12283

[11] Schlune, A., et al. Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. (2015). Amino Acids, 47: 1751-1762. DOI 10.1007/s00726-015-2032-z

[12] Sawad, A., B., et al. Epidemiology, methods of diagnosis, and clinical management of patients with arginase 1 deficiency (ARG1-D): A systematic review. (2022). Molecular Genetics and Metabolism, 137(1-2): 153-163. https://doi.org/10.1016/j.ymgme.2022.08.005

research done on the prevalence outside the United States, for which these studies adjusted rates for consanguinity.[13]

Treatment for ARG1-D can consist of several steps. Diet can be changed in order to reduce arginine and protein intake. This often supported with the inclusion of essential amino acids. Nitrogen scavengers, such as sodium benzoate or sodium phenylbutyrate, are used to reduce the levels of plasma ammonia. If seizures arise, medications such as carbamazepine can be prescribed. Finally, in extreme cases of very high levels of ammonia, liver transplantation can take place.

[13] Catsburg, C., et al. Arginase 1 Deficiency: using genetic databases as a tool to establish global prevalence. (2022). Orphanet Journal of Rare Diseases, 17(1). https://doi.org/10.1186/s13023-022-02226-8

SECTION 2

Significant Analysis Requirement

Under RCW 34.05.328, this rule requires significant analysis to ensure that the benefits of adding these three new conditions to the Washington State newborn screening panel outweigh the costs.

The following SA Table 1 identifies rule sections or portions of rule sections that have been determined exempt from significant analysis based on the exemptions provided in RCW 34.05.328(5) (b) and (c).

SA Table 1. Summary of Sections not requiring Significant Analysis

WAC Section and Title	Description of Proposed Changes	Rationale for Exemption Determination
WAC 246-650-010 – Definitions	Adding definitions for OTCD, GAMT deficiency, and ARG1-D; amending the definition of amino acid disorders; and adding a definition for urea cycle disorders.	Exempt from SA under RCW 34.05.328 (5)(b)(iv) because the proposed changes clarify the meaning of terms used in the rules by add new definitions for OTCD, GAMT, and ARG1-D. Defining these conditions is not setting screening standards. Tests for screening (required newborn screening tests) are listed under WAC 246-650-020. The impacts of adding the new conditions are analyzed in Section 5.

SECTION 3

Goals and objectives of the statute that the rule implements.

Chapter 70.83 RCW establishes a newborn screening program, implemented by the department, to identify and prevent heritable disorders that may lead to developmental disabilities or physical defects. The goal of this program is to detect these conditions as early as possible, allowing for timely treatment and improved health outcomes. The proposed rule supports these objectives by adding screening for OTCD, GAMT, and ARG1-D to the panel of conditions tested using the blood spot specimen collected from every newborn within forty-eight hours of birth. The department will report significant screening results to the newborn's healthcare provider or directly to the family if no provider is identified.

SECTION 4

Explanation of why the rule is needed to achieve the goals and objectives of the statute, including alternatives to rulemaking and consequences of not adopting the proposed rule.

Population-based newborn screening is the most effective way to identify OTCD, GAMT, and ARG1-D early, enabling timely diagnosis and treatment. Without early detection, affected infants are at high risk of serious, irreversible health problems and potentially death. To protect public health, the board and department propose amending chapter 246-650 WAC to add these three conditions to the newborn screening panel.

After careful review and assessment, the department and board found that early screening is essential. Alternatives to rulemaking and implementing these screening tests, such as waiting for symptoms to appear or limiting testing to infants with a known family history, are not sufficient. These approaches miss most cases, delay diagnosis, and reduce the effectiveness of available treatments. By contrast, universal screening allows interventions to begin before symptoms emerge, improving outcomes and preventing severe disability or death.

Failure to adopt the proposed rule would mean continued delayed diagnoses for babies born with OTCD, GAMT, and ARG1-D, preventable health complications, and missed opportunities to save lives and reduce long-term health impacts.

SECTION 5

Analysis of the probable costs and benefits (both qualitative and quantitative) of the proposed rule being implemented, including the determination that the probable benefits are greater than the probable costs.

WAC 246-650-020 – Performance of Screening Tests

Description: This section of the rule establishes the list of heritable conditions that all babies in Washington must be screened for within 48 hours after birth. It also sets the responsibilities of hospitals and birth care providers in conducting newborn screening, including parental notification, specimen collection, and timely submission. In addition, the rule details the department's newborn screening program duties upon receipt of specimens, including the specific heritable conditions to be tested.

The board is proposing to amend WAC 246-650-020(2)(b) to add three new candidate conditions, OTCD, GAMT, and ARG1-D to the list of conditions on the Washington State mandatory newborn screening panel. GAMT deficiency is listed as its own screening test, while OTCD and ARG1-D will be listed under "urea cycle disorders," in alignment with the definition proposed in WAC 246-650-010.

Additionally, the board is proposing to repeal subsection (3) as the requirement for the attending health care provider to notify the department of the date which the test results were disclosed to the parent or guardian which expired January 1, 2020.

Cost-Benefit Overview:

The below analysis outlines the department's original cost-benefit assumptions from 2021 (OTCD) and 2023 (GAMT and ARG1-D), which were used to evaluate these conditions for inclusion in the screening panel. In the initial analysis, the department estimated that the cost of screening would range from $8 to $12 per screen. These cost estimates influenced decisions made by both the Technical Advisory Committees (TACs) and the Board. This SA outlines these initial cost assumptions followed by the actual costs of screening, which is $4.02 per screen.

<u>**Cost-Benefit Analysis for OTCD**</u>

The following summary presents the benefit-cost analysis for adding OTCD to the mandatory newborn screening panel. Calculations were performed using a spreadsheet model (available upon request), comparing a "No Screening" scenario (the status quo) with a "Screening" scenario. The analysis adopts a health sector perspective, estimating all costs associated with providing services, regardless of the payer.An economic model

(model) was used to estimate the costs and benefits of NBS for OTCD (Screening). The analysis compares these costs to what is happening now (No Screening).

Point estimates and ranges for input variables were drawn from primary literature, data from a newborn screening program that includes OTCD, and consultations with expert scientists and clinicians. The model predicts a benefit-cost ratio of 0.69, indicating that for every dollar spent on screening for OTCD, there will be $0.69 in benefits. Data were imputed into the model structure in 2021 by the NBS program and presented to the board on October 13, 2021.

The first step in the model was to estimate the number of newborns with OTCD. Information was used from primary literature to estimate the number of babies born in Washington State with OTCD in 2021. The model uses a one year birth cohort (2021) for this analysis.

The model accounts for newborns who will be diagnosed early and benefit from intervention. In the No Screening Model, a small percentage of newborns will be diagnosed early because they have a family member with OTCD (positive family history). The department used the sensitivity of the screening test to estimate the number of newborns diagnosed early in the Screening Model. The sensitivity is the ability of the test to identify newborns with OTCD correctly. The model predicts that each year, 0.3403 newborns will be identified early through screening, or approximately 1 baby identified every 3 years, compared to identification through family history alone, estimated at 0.1042 newborns, or about 1 baby identified every 10 years.

The model compares the medical outcomes for early versus late identification and the onset of symptoms. The morbidity estimates are the percentages of newborns expected to develop the specific severity of OTCD listed.

The model constructs a decision tree. First, disorder rates are multiplied by the number of newborns affected to determine how many newborns experience each of the medical outcomes. Ultimately, the department has estimates for the number of newborns that fall into each category.

The next step compares each of the outcomes. Estimates for premature death are added together, then the number of deaths in the Screening Model were subtracted from the number of deaths in the No Screening Model to find the shift in numbers. For this model, each year, NBS will save 0.1727 newborns from premature death. The department also calculated the costs of annual testing for newborns identified early and treatment costs in both models, and identified the shift in the expenses.

The model input assigned to the value to saving a life was estimated at $11,600,000.[14]

Based on information from the Washington NBS program, the model input for the cost to the NBS program was estimated at $8.03 per baby. Screening tests are not perfect, meaning that some babies who do not have OTCD will have positive NBS results and will need diagnostic test to rule out OTCD.

The model then adds up all the benefits and the costs (lives saved, long-term disability averted, newborn screening costs, and costs of false positive results) and divided the benefits by the costs to calculate the benefit-to-cost ratio. Resulting in 0.69, meaning for every dollar spent to screen babies for OTCD, the health sector receives $0.69 worth of benefits.

Technical Explanation of Model Parameters

The department selected numbers for a base case analysis: if there were multiple estimates from the published data, the department either used the average or the median value.[15]

- ***Birthrate.*** This analysis is based on a hypothetical birth cohort of 74,000 babies, representing the number of babies expected to be screened annually in Washington State based on the projected number of births in Washington for 2021.
- ***Prevalence***. The prevalence used was 6.3 E-06 or approximately 1 OTCD case per 157,833 births, which is the prevalence reported by the California Newborn Screening Program[16] and the existing literature.[17] This predicts 0.468 babies born with OTCD in Washington each year.
- ***Percent of babies with OTCD with a positive family history of OTCD.*** We assumed that these babies will be treated early in the "No Screening Model" because of a positive family history of OTCD (typically an older affected sibling in the family). The estimate for this parameter (0.1042) is a calculation from cases reported in the literature.[16]
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with OTCD is estimated at 93.3%. False negatives are inevitable in screening programs; the state of California's Newborn Screening Program reported 4 missed

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[14] Departmental Guidance on Valuation of a Statistical Life in Economic Analysis | US Department of Transportation. Estimate of VSL from 2020.

[15] Note: the model calculates the percentages and estimates, which in some instances have been rounded. Subsequent calculations were unaffected by this rounding, so sometimes numbers do not appear to match perfectly.

[16] Tang H, personal email communication, 2021.

[17] Brassier, A., Gobin, S., Arnoux, J. B., Valayannopoulos, V., Habarou, F., Kossorotoff, M., Servais, A., Barbier, V., Dubois, S., Touati, G., Barouki, R., Lesage, F., Dupic, L., Bonnefont, J. P., Ottolenghi, C., & De Lonlay, P. (2015). Long-term outcomes in Ornithine Transcarbamylase deficiency: a series of 90 patients. *Orphanet journal of rare diseases*, *10*, 58. https://doi.org/10.1186/s13023-015-0266-1

cases of OTCD.[18] The sensitivity of the NBS test predicts 0.0916 true positives identified early and 0.024 false negatives (missed cases of OTCD) per year.

- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have OTCD, is estimated at 99.94%, based on information from the CA NBS program. The specificity value predicts 44.3997 false positives: these are babies who will need diagnostic testing and sometimes clinical follow-up.
- ***Mortality of cases identified early.*** The mortality rates used for the early identified OTCD cases (0%) are based on data from existing literature,[19] indicating that early identified babies do not have a higher mortality rate.
- ***Mortality of cases identified late.*** The numbers for late-identified OTCD (47%) are from a literature review[18] that evaluated late-identified cases of OTCD and reported a corresponding mortality rate. Additionally, mortality from liver transplant surgery was assessed, based on existing literature and expert opinion[20] (11%).
- ***Monetary value of a life.*** The value of 1 life is estimated at $11,600,000 (cell W48)..[21]
- ***Treatment costs for cases identified early.*** The estimated price for years 0 through 10 in babies identified early from the model is $1,741,284.00. This includes medication and monitoring visits.
- ***Treatment costs for cases identified late***. The treatment remains the same for cases identified late, so the costs for years 0 through10 in babies identified late are still estimated at $1,741,284.00.

The next step is to evaluate the differences between the models (Screening and No Screening) to quantify the benefits of screening by combining the mortality and morbidity estimates, assigning a dollar value to the averted deaths and disabilities, and accounting for the difference in treatment costs.

- ***Deaths averted.*** The total number of deaths from each model is compared; there are 0.02056 deaths predicted in the "No Screening Model" and 0.01671 deaths in

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[18] Tang H, personal email communication, 2021

[19] Brassier, A., Gobin, S., Arnoux, J. B., Valayannopoulos, V., Habarou, F., Kossorotoff, M., Servais, A., Barbier, V., Dubois, S., Touati, G., Barouki, R., Lesage, F., Dupic, L., Bonnefont, J. P., Ottolenghi, C., & De Lonlay, P. (2015). Long-term outcomes in Ornithine Transcarbamylase deficiency: a series of 90 patients. *Orphanet journal of rare diseases*, *10*, 58. https://doi.org/10.1186/s13023-015-0266-1

[20] Morioka, D., Kasahara, M., Takada, Y., Shirouzu, Y., Taira, K., Sakamoto, S., Uryuhara, K., Egawa, H., Shimada, H., & Tanaka, K. (2005). Current role of liver transplantation for the treatment of urea cycle disorders: a review of the worldwide English literature and 13 cases at Kyoto University. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*, *11*(11), 1332–1342. https://doi.org/10.1002/lt.20587

[21] Departmental Guidance on Valuation of a Statistical Life in Economic Analysis | US Department of Transportation. VSL estimate from 2020.

the "Screening Model". The difference between the two models is 0.039 deaths averted.

- ***Value of lives saved.*** The value of lives saved by newborn screening is the number of deaths averted multiplied by the monetary value of a life. The model estimated yearly benefits of $447,552.89 for saving the lives of babies with OTCD.
- ***LTD averted.*** The total number of long-term disability cases from each model is compared; there are 0.1706 babies with LTD predicted in the "No Screening Model" and 0.1277 babies with LTD in the "Screening Model". The difference between the two models is 0.043 babies with LTD averted.
- ***Value of LTD averted.*** The value of LTD averted by newborn screening is the number of LTD averted multiplied by the monetary value of severe disabilities. The model estimated yearly benefits of $64,303.
- ***Shift in treatment costs.*** The early and late treatment costs for each model are calculated and combined to determine the total treatment costs for each model: No Screening = $515,620.58 and Screening = $591,200.87. The annual treatment costs saved by screening are -$75,580.28, indicating that early identification is more expensive.
- ***Total benefits.*** The total benefits are $436,276.18; the sum of lives saved, LTD averted, and treatment costs saved by screening.

<u>Estimated costs</u>

- ***Cost of screening.*** The estimated costs of OTCD testing are $6 to $10 per baby.
- ***Costs of diagnostic screening for false positives.*** Only the false-positive babies are counted for diagnostic testing costs, because babies with OTCD will undergo clinical evaluation and diagnostic testing regardless. The cost of false positive screening results is $38,938.55 and includes plasma testing for amino acids, blood ammonia levels, and urine organic acids.
- ***Total costs of OTCD newborn screening.*** The birthrate multiplied by the price per baby is $594,241.00.
- ***Total costs of the Newborn Screening Model.*** The annual expenses of NBS for OTCD are estimated to be $633,179.55.

Finally, the ratio of benefits to costs is calculated. Any ratio greater than 1 signifies that the benefits outweigh the costs.

- ***Benefit/Cost Ratio.*** $436,276.18 of benefits divided by $633,179.55 of costs yields a benefit/cost ratio of 0.69.

<u>Sensitivity Analysis</u>

After completing the base case benefit-cost ratio, the department performed a sensitivity analysis to evaluate how the benefit-cost ratio changed when estimates for the parameters were varied. The goal of a sensitivity analysis is to better understand each input to the model and how varied each input would need to be to effect the base case finding.OTCD Analysis Table 1 presents three estimates for each parameter: the estimate used in the base case (0.69), followed by conservative and liberal estimates. Only one parameter was changed at a time to generate unique benefit-to-cost ratios for each scenario.

OTCD Analysis Table 1: Sensitivity Analysis

			B/C ratio			
	B/C ratio swing		0.69		B/C ratio swing	sensitive?
		low	base	high		
birthrate	0.66	63,000	74,000	85,000	0.71	No
birth prevalence - 1 in:	0.55	197,292	157,833	17,000	6.4	Yes
% with OTCD family hx	0.72	0.19	0.22	0.25	0.66	No
sensitivity	0.64	86.67%	93.33%	100.00%	0.74	No
specificity	0.66	99.90%	99.94%	100.00%	0.73	No
Pre-Sx Callout Mortality	0.69	0.00	0.00	0.02	0.66	No
Post-Sx Callout Mortality	0.58	0.37	0.47	0.57	0.79	No
Treatment Cost	0.75	$870,642.00	$1,741,284.00	$6,965,136.02	0.33	No
Value of a life	0.57	$9,600,000.00	$11,600,000.00	$13,600,000.00	0.81	No
cost of NBS test	0.9	$ 6.00	~ $6 - $10	$ 10.00	0.56	Yes
cost of false (+)	0.71	$ 438.50	$ 877.00	$ 8,770.00	0.44	No
% call out postsymptoms (NBS)	1.3	46.15%	73.08%	86.54%	0.34	Yes

- ***Break-Even Points.*** OTCD Analysis Table 2 contains the break-even point for each parameter. This is what the estimate would need to be, holding all other parameters constant, to increase the unfavorable benefit/cost ratio to 1(a ratio equal to 1 means the benefits equal the costs while a ratio greater than one means the costs outweigh the benefits).

OTCD Analysis Table 2: Break-Even Points

	B/C ratio	
	0.69	break even
	base	B/C=1
birthrate	74,000	impossible
birth prevalence - 1 in:	157,833	109,000
% with OTCD family hx	0.22	impossible
sensitivity	93.33%	impossible
specificity	99.94%	impossible
Pre-Sx Callout Mortality	0.00	impossible
Post-Sx Callout Mortality	0.47	0.77
Treatment Cost	$1,741,284.00	impossible
Value of a life	$11,600,000.00	$16,700,000.00
cost of NBS test	~ $6 - $10	$5.35
cost of false (+)	$ 877.00	impossible
% call out postsymptoms (NBS)	73.08%	61.00%

Benefits of early identification of babies with OTCD is critical to reduce damage to the nervous system. The risk of severe disability is significantly reduced with early treatment, and the medical costs associated with lifetime severe disability are lower compared to babies treated after becoming symptomatic. Benefits include lives saved, prevention of irreversible neurological damage, and reduced diagnostic odyssey on families, which align with the goals of RCW 70.83 to prevent heritable disorders whenever feasible.

Finding

Using best estimates for the parameters, the benefit-cost model ratio was 0.69, meaning that for every dollar of costs to provide OTCD screening, the health sector receives $0.69 worth of benefits.

Cost-Benefit Analysis for GAMT Deficiency

The following presents the benefit-cost analysis for adding GAMT deficiency to the mandatory newborn screening panel. Calculations were performed using a spreadsheet model (available upon request), comparing a “No Screening” scenario (the status quo) with a “Screening” scenario. The analysis adopts a health sector perspective, estimating all costs associated with providing services, regardless of the payer.An economic model was used to estimate the costs and benefits of NBS for GAMT deficiency (Screening). The analysis compares these costs to what is happening now (No Screening).

Point estimates and ranges for input values were drawn from published literature, expert clinical opinion, and data from states that currently screen for GAMT deficiency. The model predicts a benefit-cost ratio of 1.453, indicating that for every dollar of costs associated with screening newborns for GAMT deficiency, there will be $1.45 worth of benefits. Data were imputed into the model structure in 2023 by the NBS program and was presented to the board on October 9, 2023.

GAMT deficiency can be reliably detected through newborn screening. Because symptoms typically do not appear until around three months of age, diagnosis without screening is often delayed. When identified early—through newborn screening or family history—and treatment begins promptly, affected newborns can develop normally.

The first step in the model was to estimate the number of newborns with GAMT deficiency. Information was used from primary literature to estimate the number of babies born in Washington State with GAMT deficiency in 2023. The model uses a one year birth cohort (2021 birth data but modeled for a birth cohort in 2023).

The next step was to find out which newborns will be diagnosed early and benefit from intervention. In the No Screening Model, a small percentage of newborns will be diagnosed early because they have a family member with GAMT deficiency (positive family history). The sensitivity of the screening test was used to estimate the number of newborns diagnosed early in the Screening Model. The sensitivity of the test refers to its ability to identify newborns with GAMT deficiency accurately. The model predicts that each year there will be 0.0806 newborns identified early each year through screening, compared to identification through family history alone which estimated 0.0072 newborns identified.

Next, the medical outcomes for early versus late identification were compared and the onset of symptoms. The morbidity estimates are the percentages of newborns are expect to develop the specific severity of GAMT deficiency listed. There is a larger chance for both moderate and severe disability in late-identified GAMT deficiency compared to early identified cases.

The model constructs a decision tree The rates were multiplied by the number of newborns affected to determine how many newborns experience each of the medical outcomes. Estimates were used for the number of newborns that fall into each category.

There is no mortality rate per the literature reviewed, therefore there is no calculation on premature death. To compare outcomes the severe disability outcomes were added together. The number of severe disabilities in the Screening Model was subtracted from the No Screening Model to find the shift in numbers. This process was then repeated with the moderate disability outcomes, giving two shift values (one for the change in severe disabilities and one for the shift in moderate disabilities). The disability that persists after receiving treatment was also calculated and included in the totals. For the No Screening model, 0.0385 babies are estimated to have severe disability, and 0.0342 babies are estimated to have moderate disability. In the Screening Model, 0.00021 babies are estimated to have severe disability, and 0.00019 babies are estimated to have moderate disability. The costs of annual testing for newborns identified early and treatment costs for disabilities were also calculated in both models and determine the shift in expenses.

Next, a value was assigned to severe and moderate disabilities Estimates from literature were used for the value of health and societal costs associated with intellectual disability.[22] A range of $64,000 to $168,000 per year to estimate the value of disabilities averted through NBS, depending on severity was used. The first 12 years (Years 0-11), the age group presented in literature was used and reflected later in treatment costs. [21]

Based on information from the Washington NBS program, the model input for the cost to the NBS program were estimated at $0.99 per baby. Screening tests are not perfect, meaning that some babies who do not have GAMT deficiency will have positive NBS results. They need diagnostic testing to rule out GAMT deficiency.

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[22] Doble B, Schofield D, Evans CA, Groza T, Mattick JS, Field M, Roscioli T. Impacts of genomics on the health and social costs of intellectual disability. J Med Genet. 2020 Jul;57(7):479-486. doi: 10.1136/jmedgenet-2019-106445. Epub 2020 Jan 24. PMID: 31980565.

The model then adds up all the benefits and costs (disability averted, treatment costs, NBS testing costs, and costs of false positive results) and divides the benefits by the costs to calculate the benefit-to-cost ratio. Resulting in 1.453, meaning for every dollar spent to screen babies for GAMT deficiency, the health sector receives $1.45 worth of benefits.

Technical Explanation of Model Parameters

We selected numbers for a base case analysis: if we had multiple estimates from the published data, we either used the average or the median value.[23]

- ***Birthrate***. This analysis is based on a hypothetical birth cohort of 83,000 babies, representing the number of babies expected to be screened annually in Washington State. This number is based on the projected number of births in Washington for 2023.
- ***Prevalence.*** The prevalence used was 9.759 E -07 or approximately 1 GAMT deficiency case per 1,000,000 births, which is the prevalence reported by the Health Resources and Services Administration (HRSA).[24] This predicts 0.081 babies born with GAMT deficiency in Washington each year.
- ***Percent of babies with GAMT deficiency with a positive family history of GAMT deficiency.*** We assume that these babies will be treated early in the "No Screening Model" because of a positive family history of GAMT deficiency (mostly an older affected sibling in the family). The estimate for this parameter (0.0893) is based on calculations from cases reported in the literature.[25, 26,27]
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with GAMT deficiency, is estimated at 99.5%. Although there have been no known missed cases in GAMT deficiency NBS programs, false negatives are inevitable in screening programs. The sensitivity of the NBS test predicts 0.086 true positives identified early and 0.0004 false negatives (missed cases of GAMT deficiency) per year.

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[23] Note: the model calculates the percentages and estimates, which in some instances have been rounded. Subsequent calculations were unaffected by this rounding, so sometimes numbers do not appear to match perfectly.

[24] Health Resources and Services Administration. Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence Based Review. June 2, 2022. Accessed August 2025. https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/gamt-deficiency-final-report.pdf#:~:text=This%20report%20summarizes%20the%20evidence%20regarding%20the%20benefits,comprehensive%20testing%20and%20follow%20up%20for%20the%20condition.

[25] Stockler-Ipsiroglu, S. et al. (2014). Guanidinoacetate methyltransferase (GAMT) deficiency: outcomes in 48 individuals and recommendations for diagnosis, treatment and monitoring. Molecular genetics and metabolism, 111(1), 16–25. https://doi.org/10.1016/j.ymgme.2013.10.018

[26] Viau., K., S., Ernst, S., L., Pasquali, M., Botto, L., D., Hedlund, G., & Longo, N. (2013). Evidence-Based Treatment of Guanidinoacetate Methyltransferase (GAMT) Deficiency. Molecular Genetics and Metabolism, 110, 255-262. http://dx.doi.org/10.1016/j.ymgme.2013.08.020

[27] El-Gharbawy, A. H., Goldstein, J. L., Millington, D. S., Vaisnins, A. E., Schlune, A., Barshop, B. A., Schulze, A., Koeberl, D. D., & Young, S. P. (2013). Elevation of guanidinoacetate in newborn dried blood spots and impact of early treatment in GAMT deficiency. Molecular genetics and metabolism, 109(2), 215–217. https://doi.org/10.1016/j.ymgme.2013.03.003

- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have GAMT deficiency, is estimated at 99.998%, based on the information from the Health Resources and Services Administration's (HRSA) evidence-based review. The specificity value predicts 1.743 false positives: these are babies who will need diagnostic testing and sometimes clinical follow-up.
- ***Morbidity in cases identified early.*** The morbidity estimates for early identified cases of severe disability from GAMT deficiency (0%) and moderate disability (0%) are based on primary literature.[25, 26, 28] Typically, the benefit for babies identified early is that they have no disability from GAMT deficiency.
- ***Morbidity in cases identified late.*** The morbidity estimates for late-identified cases of severe disability from GAMT deficiency (52.2%) and moderate disability (47.8%) are based on primary literature. We then stratified the babies by whether a disability existed after treatment. In severe disability cases 100% of babies still experienced disability. In moderate disability cases, 97% of babies still experienced disability. [25,26,27,28,29]
- ***Treatment costs for cases identified early.*** The price for years 1 through11 for treatment in babies identified early is estimated at $12,976.50. This includes medication and monitoring visits.
- ***Treatment costs for cases identified late, severe disability.*** The costs for years 1 through11 in babies identified late exhibiting severe disability are estimated at $1,779,606.10. This includes medication, intellectual disability associated costs (healthcare and societal), and seizure costs.
- ***Treatment costs for cases identified late, moderate disability.*** The costs for years 1 through11 in babies identified late exhibiting moderate disability are estimated at $1,571,471.30. This includes medication, intellectual disability associated costs (healthcare and societal), and seizure costs.

The next step is to evaluate the differences between the models to quantify the benefits of screening, by combining the morbidity estimates and assigning a dollar value to the disability averted, as well as the difference in treatment costs.

- ***Shift in early treatment costs.*** The early and late treatment costs for each model are calculated and combined to determine the total treatment costs for each model. (No Screening = $93.85; Screening = $1,045.88). The annual treatment cost

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[28] Khaikin, Y., Sidky, et al. (2018). Treatment outcome of twenty-two patients with guanidinoacetate methyltransferase deficiency: An international retrospective cohort study. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society, 22(3), 369–379. https://doi.org/10.1016/j.ejpn.

[29] Narayan, V., Mahay, S. B., Verma, I. C., & Puri, R. D. (2020). Case Series of Creatine Deficiency Syndrome due to Guanidinoacetate Methyltransferase Deficiency. Annals of Indian Academy of Neurology, 23(3), 347–351. https://doi.org/10.4103/aian.AIAN_367_18

difference is -$952.03, meaning that there are more costs associated with early identification than with screening.

- ***Shift in late treatment (severe) costs.*** The early and late treatment costs for each model are calculated and combined to determine the total treatment costs for each model (No Screening = $68,495.18; Screening = $376.05). The annual treatment costs saved by screening ($68,119.13) indicate that early identification is more cost-effective, resulting in fewer costs associated with severe disability from GAMT deficiency.
- ***Shift in late treatment (moderate) costs***. The early and late treatment costs for each model are calculated and combined to determine the total treatment costs for each model: No Screening = $55,443.93 and Screening = $304.40. The annual treatment costs saved by screening ($68,119.13) indicate that early identification is more cost-effective, resulting in fewer costs associated with moderate disability from GAMT deficiency.
- ***Total benefits.*** The total benefits ($122,306.64) are the sum of the shift in early treatment costs, late treatment (severe) costs, and the change in late treatment (moderate) costs.

Estimated costs

- ***Cost of screening.*** The estimated costs of GAMT deficiency testing are $0.99 per baby.
- ***Cost of screening.*** The birthrate multiplied by the cost per baby is $82,008.19.
- **Cost of diagnostic testing for false positives.** Only the false-positive babies are counted for diagnostic testing costs, because babies with GAMT deficiency will undergo clinical evaluation and diagnostic testing regardless. The cost of false-positive screening results is $1,250.00 and includes urine analysis for creatine and GUAC, as well as molecular genetic testing to confirm GAMT deficiency. This false positive cost is multiplied by the number of estimated false positive babies, equaling $2,178.75.
- **Total costs of Newborn Screening Model.** The annual expenses of NBS for GAMT deficiency are estimated to be $84,186.94.

Finally, the ratio of benefits to costs is calculated. Any ratio greater than 1 signifies that the benefits outweigh the costs.

- ***Benefit/Cost Ratio:*** $122,306.64 of benefits divided by $84,186.94 of costs yields a benefit/cost ratio of 1.453.

Sensitivity Analysis

After completing the base case benefit-cost ratio, we performed a sensitivity analysis to evaluate how the benefit-cost ratio changes when estimates for the parameters are varied. The goal of a sensitivity analysis is to better understand each input into the model and how varied each input would need to be to effect the base case finding.

GAMT Analysis Table 1 presents three estimates for each parameter: the best-guess estimate used in the base case (1.453), followed by conservative and liberal estimates. Only one parameter was changed at a time to generate unique benefit-to-cost ratios for each scenario. The model proved to be robust and sensitive to six parameters: birth prevalence, % with a GAMT family history, specificity, treatment costs, late ID (severe), treatment costs, late ID (moderate), and the cost of the NBS test. The lowest benefit-cost ratio was 0.422 for the model with a low specificity estimate of 99.8%.

GAMT Analysis Table 1. Sensitivity Analysis

			B/C ratio		
	B/C ratio swing		1.453		B/C ratio swing
Parameter		low/conservative estimate	base	high/liberal estimate	
birthrate	1.453	62,250	83,000	103,750	1.453
birth prevalence - 1 in:	1.063	1,400,000	1,024,654.67	273,902	5.435
% w/ GAMT family hx	1.496	0.0625	0.0893	0.333	1.061
sensitivity	1.421	97.50%	99.50%	100%	1.461
specificity	0.422	99.80%	100.00%	100.00%	1.462
tx cost, early ID	1.458	$6,488.25	$12,976.50	$25,953.00	1.441
tx cost, late ID, severe	1.048	$889,803.05	$1,779,606.10	$3,559,212.20	2.262
tx cost, late ID, moderate	1.125	$785,735.65	$1,571,471.30	$3,142,942.60	2.108
cost of NBS test	2.827	$0.50	$0.99	$1.48	0.978
cost of false +	1.472	$625.00	$1,250.00	$5,000.00	1.348

ID = identification, hx = history, tx = treatment

Benefits of early identification of babies with GAMT deficiency benefits both the infants and their families, as well as the medical professionals caring for them. Morbidity is significantly reduced with early treatment, and medical costs are substantially lower compared to those incurred when treatment is initiated after symptoms appear.

Finding

The benefit-cost ratio was 1.453, meaning that for every dollar of costs to provide GAMT deficiency screening, the health sector will receive $1.45 worth of benefits. The sensitivity analysis showed the model is robust, as the benefit-cost ratio remained stable under both conservative and liberal parameter estimates.

Cost-Benefit Analysis for ARG1-D

The following presents the benefit-cost analysis for adding ARG1-D to the mandatory newborn screening panel. Calculations were performed using a spreadsheet model (available upon request), comparing a “No Screening” scenario (the status quo) with a “Screening” scenario. The analysis adopts a health sector perspective, estimating all costs associated with providing services, regardless of the payer.

Point estimates and ranges for input values were drawn from published literature, expert clinical opinion, and data from states that currently screen for ARG1-D. The model predicts a benefit-cost ratio of 2.03, indicating that for every dollar of costs associated with screening newborns for ARG1-D, there will be $2.03 worth of benefits. Data were imputed into the model structure in 2023 by the NBS program and was presented to the board on October 9, 2023.

There is a reliable newborn screening test for identifying infants with ARG1-D. A key challenge is that symptoms usually do not appear until 1 to 3 years of age. When detected early—through newborn screening or family history—and treatment is started immediately, affected infants generally develop typically.

The first step in the model is to estimate the number of newborns with ARG1-D. The department used information from primary literature to estimate the number of babies with ARG1-D born in 2023. The model uses a one year birth cohort (2021 birth data but modeled for a birth cohort in 2023).

The model accounts for newborns diagnosed early and benefit from intervention. In the No Screening Model, a small percentage of newborns will be diagnosed early because they have a family member with ARG1-D (positive family history). The department used the sensitivity of the screening test to estimate the number of newborns diagnosed early in the Screening Model. The sensitivity is the ability of the test to identify newborns with ARG1-D correctly. The model predicts that each year there will be 0.0826 newborns identified early each year through screening, compared to identification through family history alone (estimated 0.0132 newborns identified.

The model compares medical outcomes for early versus late identification and the onset of symptoms. The mortality estimates are the percentages of newborns we expect to die from ARG1-D. The morbidity estimates are the percentages of newborns we expect to develop long-term disability. There is a larger chance for both death and long-term disability in late identified ARG1-D compared to early identified cases.

The model constructs a decision tree. The next step was to walk through each branch of the decision tree. To do this, the department multiplied the rates by the number of newborns affected to determine how many newborns experience each of the medical outcomes. Ultimately, the department created estimates for the number of newborns that fall into each category.

The next step compares each of the outcomes. Estimates are added together then the number of deaths estimates and subtracted the number of premature deaths in the Screening Model from the number of premature deaths in the No Screening Model to find the shift in numbers. This is the difference made by NBS. For this model, each year, NBS will save 0.00749 newborns from premature death. The department also calculated the costs of annual testing for newborns identified early and treatment costs in both models, and found the shift in the expenses.

The model input assigned to the value of saving a life was estimated at $11,600,000.[30].

Based on information from the Washington NBS program was estimated at $0.99 per baby. Screening tests are not perfect, meaning that some babies who do not have ARG1-D will have positive NBS results. They need diagnostic testing to rule out ARG1-D.

The model added up all the benefits and the costs (lives saved, long-term disability averted, newborn screening costs, and costs of false positive results)and divided the benefits by the costs to calculate the benefit-to-cost ratio. The result is $ 2.03, which means that for every dollar spent to screen babies for ARG1-D, the health sector receives $2.03 worth of benefits.

Technical Explanation of Model Parameters

The department selected numbers for a base case analysis: if the department had multiple estimates from the published data, they either used the average or the median value.[31].

- ***Birthrate.*** This analysis is based on a hypothetical birth cohort of 83,000 babies, representing the number of babies expected to be screened annually in Washington State, based on the projected number of births in Washington for 2023.

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[30] Departmental Guidance on Valuation of a Statistical Life in Economic Analysis | US Department of Transportation. VSL estimate from 2020.

[31] Note: the model calculates the percentages and estimates, which in some instances have been rounded. Subsequent calculations were unaffected by this rounding, so sometimes numbers do not appear to match perfectly

- ***Prevalence.*** The prevalence used was 1.000 × 10^ (-6) or approximately 1 ARG1-D case per 1,000,000 births, which is consistent with the prevalence reported in the existing literature.[32] This predicts 0.083 babies born with ARG1-D in Washington each year.
- ***Percent of babies with ARG1-D with a positive family history of ARG1-D.*** We assume that these babies will be treated early in the "No Screening Model" because of a positive family history of arginase-1 deficiency (typically an older affected sibling in the family). The estimate for this parameter (0.00132) is a calculation from cases reported in the literature.
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with ARG1-D, is estimated at 99.5%.[33] Although there have been no known missed cases in ARG1-D NBS programs, false negatives are inevitable in screening programs. The sensitivity of the NBS test predicts 0.0826 true positives identified early and 0.00042 false negatives (missed cases of ARG1-D) per year.
- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have ARG1-D, is estimated at 99.989%, based on information from the primary literature and data from the Oregon NBS program.[32,34] The specificity value predicts 8.943 false positives: these are babies who will need diagnostic testing and sometimes clinical follow-up.
- ***Mortality of cases identified early.*** The numbers used for mortality for the early identified ARG1-D cases (0%) are based on data from existing literature, which indicates that early identified babies do not have a mortality rate.[35]
- ***Mortality of cases identified late.*** The numbers for late-identified ARG1-D (10.6%) are from articles by Sawad et al. (2022)[36] and Schlune et al. (2015).[37] These articles evaluated late identified cases of ARG1-D and reported a mortality rate.

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[32] Therrell, B. L., Currier, R., Lapidus, D., Grimm, M., & Cederbaum, S. D. (2017). Newborn screening for hyperargininemia due to arginase 1 deficiency. Molecular genetics and metabolism, 121(4), 308–313. https://doi.org/10.1016/j.ymgme.2017.06.003
[33] Bonn, G, personal email communication, August, 21, 2023.
[34] Held.P. K. personal email communication, August,28, 2023.
[35] Sun, A., Crombez, E. A., & Wong, D. (2020, May 28). Arginase deficiency. GeneReviews® - NCBI Bookshelf. https://www.ncbi.nlm.nih.gov/books/NBK1159/
[36] Sawad., A., B., Pothukuchy, A., Badeaux, M., Hodson, V., Bubb, G., Lindsley, K., Uyei, J., & Diaz., G. A. (2022). Natural history of arginase 1 deficiency and the unmet needs of patients: A systematic review of case reports. JIMD Reports, 63(4): 330-340. doi:10.1002/jmd2.12283
[37] Schlune, A., Dahl., S. V., Haussinger, D., Ensenauer, R., & Mayatepek, E. (2015). Hyperargininemia due to arginase I deficiency: the original patients and their natural history, and a review of the literature. Amino Acids, 47: 1751-1762. DOI 10.1007/s00726-015-2032-z

Additionally, mortality from liver transplant surgery itself was evaluated, based on existing literature and expert opinion (3%).[38] [39]

- ***Monetary value of a life.*** The value of 1 life is estimated at $11,600,000.[40]
- ***Treatment costs for cases identified early.*** The estimated cost for years 0 through10 for babies identified early is $1,503,509.80. This includes medication and monitoring visits.
- ***Treatment costs for cases identified late.*** The costs for years 0 through10 for babies identified late are estimated at $ 1,637,128.67. This includes medications, the cost of seizures, and the cost of liver transplantation in those who require it.

The next step is to evaluate the differences between the models to quantify the benefits of screening,by combining the mortality and morbidity estimates, assigning a dollar value to the averted deaths and disabilities, and accounting for the difference in treatment costs.

- ***Deaths averted.*** The total number of deaths from each model is compared; there are 0.0075 deaths predicted in the "No Screening Model" and 0.0000456 deaths in the "Screening Model". The difference between the two models is **0.00749 deaths averted**.
- ***Value of lives saved.*** The value of lives saved by newborn screening is the number of deaths averted multiplied by the monetary value of a life. The model estimated yearly benefits of $86,981.13 for saving the lives of babies with ARG1-D.
- ***LTD averted.*** The total number of long-term disability cases from each model is compared; there are 0.0637 babies with LTD predicted in the "No Screening Model" and 0.0095 babies with LTD in the "Screening Model". The difference between the two models is 0.0542 babies with LTD averted.
- ***Value of LTD averted.*** The value of LTD averted by newborn screening is the number of LTD averted multiplied by the monetary value of severe disabilities. The model estimated yearly benefits of $81,259.71.
- ***Shift in treatment costs.*** The early and late treatment costs for each model are calculated and combined to determine the total treatment costs for each model: No Screening = $134,117.90 and Screening = $124,846.77. The annual treatment costs saved by screening are $9,270.54, indicating that early identification results in lower costs.

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[38] Held.P. K. personal email communication, August,28, 2023.
[39] Shelkowitz, E, personal email communication, August, 30, 2023.
[40] Putnam, J., & Coes, C. (2021). Guidance on the Treatment of the Economic Value of a Statistical Life (VSL) in U.S. Department of Transportation Analyses – 2021 Update. https://www.transportation.gov/sites/dot.gov/files/2021-03/VSL%20Update%202021%20-%20Transmittal%20Memo.pdf

- ***Total benefits.*** The total benefits, $177,511.38, are the sum of lives saved, LTD averted, and treatment costs saved by screening.

Estimated costs

- ***Cost of screening.*** The estimated costs of ARG1-D testing are $0.99 per baby.
- ***Costs of diagnostic screening for false positives.*** Only the false-positive babies are counted for diagnostic testing costs, because babies with ARG1-D will undergo clinical evaluation and diagnostic testing regardless. The cost of false positive screening results is $5,255.13 and includes plasma testing for arginine levels and sequencing for the ARG1 gene.
- ***Total costs of ARG1-D newborn screening.*** The birthrate multiplied by the cost per baby is $82,008.19.
- ***Total costs of the Newborn Screening Model.*** The annual expenses of NBS for ARG1-D are estimated to be $87,263.32.

Finally, the ratio of benefits to costs is calculated. Any ratio greater than 1 signifies that the benefits outweigh the costs.

- ***Benefit/Cost Ratio.*** $177,511.38 of benefits divided by $87,263.32 of costs yields a benefit/cost ratio of 2.03.

Sensitivity Analysis

After completing the base case benefit-cost ratio, the department performed a sensitivity analysis to evaluate how the benefit-cost ratio changed when estimates for the parameters were varied. The goal of a sensitivity analysis is to better understand each input to the model and how varied each input would need to be to effect the base case finding.

ARG1-D Analysis Table 1 contains three estimates for each parameter: the best guess estimate used in the base case (2.03), followed by conservative and liberal estimates. Only one parameter was changed at a time to generate unique benefit-to-cost ratios for each scenario. The model proved to be robust and somewhat sensitive to six parameters: birth prevalence, % with ARG1-D family history, specificity, treatment costs, cost of NBS test, and cost of false positives. The lowest benefit-cost ratio was 0.99 for the model with a low specificity estimate of 99.8%.

ARG1-D Analysis Table 1: Sensitivity Analysis

			B/C ratio			
	B/C ratio swing		2.03		B/C ratio swing	sensitive?
Parameter		low/conservative estimate	base	high/liberal estimate		
Birthrate	2.03	62250	83,000	103750	2.03	no
birth prevalence - 1 in:	1.87	1088000	1000000	54065.67	37.62	yes
% w/ ARG1-D family hx	2.42	0	0.159090909	0.33	1.62	yes
sensitivity	1.99	97.50%	99.50%	100%	2.05	no
specificity	0.99	99.80%	99.99%	100%	2.16	yes
treatment cost, late ID	1.38	$818,564.33	$1,637,129	$3,274,257.33	3.34	yes
value of a life	1.86	$9,600,000.00	$11,600,000.00	$13,600,000.00	2.21	no
cost of NBS	3.83	$0.50	$0.99	$1.48	1.39	yes
cost of false +	2.1	$293.81	$587.63	$5,876.25	1.32	yes

ID = identification, hx = history

<u>Benefit</u>

Early identification of babies with ARG1-D is generally regarded as beneficial to the babies, their families, and the medical professionals caring for them. The morbidity and mortality rates are reduced with early treatment, and medical costs are lower compared to babies being treated after becoming symptomatic.

The benefit-cost ratio was 2.03, meaning that for every dollar to provide ARG1-D screening, the health sector will receive $2.03 worth of benefits. The sensitivity analysis revealed that the model is robust, as the benefit-cost ratio remained stable under both conservative and liberal parameter estimates.

SA Table 2. Summary of Section 5 probable cost(s) and benefit(s)

WAC Section and Title	Probable Cost(s)	Probable Benefit(s)
WAC 246-650-020 – Performance of Screening Tests, Addition of OTCD	The cost of screening would be approximately $594,241.00 per year, or $8.03 per baby. Total expenses, including the costs of screening, courier service, and false positive diagnostic testing, would be $633,179.55.	For every dollar spent on providing OTCD screening, there would be approximately $0.69 worth of benefits. The total benefits would be: $436,276.18. The net benefit would be approximately $-196,903.37. Early identification of babies with OTCD is critical to reduce damage to the nervous system. The risk of severe disability is significantly

		reduced with early treatment, and the medical costs associated with lifetime severe disability are lower compared to babies treated after becoming symptomatic
WAC 246-650-020 – Performance of Screening Tests, Addition of GAMT Deficiency	The cost of screening would be approximately $82,008.19 per year, or $0.99 per baby. Total expenses, including the costs of screening and those associated with false positives, would be $84,186.94 per year.	For every dollar spent on providing GAMT Deficiency screening, there would be approximately $1.45 worth of benefits. The total benefits would be $122,306.64. The net benefit would be approximately $38,119.70 per year. GAMT deficiency can be reliably detected through newborn screening. Because symptoms typically do not appear until around three months of age, diagnosis without screening is often delayed. When identified early—through newborn screening or family history—and treatment begins promptly, affected newborns can develop normally.
WAC 246-650-020 – Performance of Screening Tests, Addition of ARG1-D	The cost of screening would be approximately $82,008.19 per year, or $0.99 per baby. This includes startup lab costs, laboratory staffing, and supplies. Total expenses, including the costs of screening and those associated with false positives, would be $87,263.32 per year.	For every dollar spent on providing ARG1-D screening, there would be approximately $2.03 worth of benefits. The total benefits would be $177,511.38 per year. The net benefit would be approximately $90,248.06 per year. There is a reliable newborn screening test for identifying infants with ARG1-D. A key challenge is that symptoms usually do not appear until 1 to 3 years of age. When detected early—through newborn screening or family history—and treatment is

		started immediately, affected infants generally develop typically.

Summary of Estimated Costs and Benefits

OTCD

- **Screening Cost per baby:** ~$6–$10
- **Total screening costs:** $594,241.00 annually
- **Total expenses (including false positives):** $633,179.55
- **Benefit-cost ratio:** 0.69
- **Net benefit:** $196,903.37
- **Total benefits:** $436,276.18 annually

Although the benefit-cost ratio for OTCD is less than 1, early detection still produces large net and total benefits due to significant long-term cost savings from preventing serious medical complications in symptomatic infants.

GAMT Deficiency

- **Screening Cost per baby:** $0.99
- **Total screening costs:** $82,008.19 annually
- **Total expenses (including false positives):** $84,186.94
- **Benefit-cost ratio:** 1.45
- **Net benefit:** $38,119.70
- **Total benefits:** $122,306.64 annually

Screening for GAMT deficiency provides substantial benefits, with early treatment improving developmental outcomes and lowering medical costs compared with care initiated after symptoms appear.

ARG1-D

- **Screening Cost per baby:** $0.99
- **Total screening costs:** $82,008.19 annually
    - **Total expenses (including false positives):** $87,263.32
- **Benefit-cost ratio:** 2.03
- **Net benefit:** $90,248.06
- **Total benefits:** $177,511.38 annually

Screening for ARG1-D is expected to yield substantial benefits. Early detection allows newborns to receive timely treatment, improving health outcomes and reducing downstream medical costs.

Actual Costs of Screening Implementation

Description: Adding OTCD, GAMT deficiency, and ARG1 deficiency to the newborn screening panel requires a fee increase. The department charges a one-time screening fee that covers all necessary newborn screens, including repeat tests when needed. This fee funds laboratory screening, follow-up services, and coordination with specialty care.

To increase the fee, the department must secure additional spending authority from the Legislature. Funding to support this fee increase was approved during the 2025 Legislative session as part of the department's decision package to the Governor's Office and Legislature.

Cost: In the request, the department estimated the combined cost for adding OTCD, ARG1, and GAMT deficiencies to be $1.75 per baby.

Additionally, the department requested $2.75 per baby to implement DNA sequencing for Pompe Disease and MPS-I. The Legislature approved $220,000 for the addition of OTC, ARG1, and GAMT deficiencies, equating to about $2.75 per baby. However, the request for funding to implement DNA sequencing was partially approved, and the total fee increase request for 2025 was $4.02 per baby. As such, starting January 1, 2026, the newborn screening fee will increase by $4.02.

The current fee for screening is $135.10 per baby, and this fee was last modified in July 2023. This fee increase included funding to support an overnight newborn screening courier delivery service and expanded DNA testing sequencing for cystic fibrosis. The fee cost before the increase in 2023 was $119.30.

Initial and Actual Cost Estimates

Initial cost estimates in the benefit-cost analysis may differ from actual implementation costs due to evolving data, and inflation during the gap of time required from analysis to securing legislative approval for fee increases. There is typically a gap of several years between the department's initial analysis, TAC review, and actual implementation, as the department must request legislative approval to adjust the newborn screening fee.

The discrepancy between initial and actual costs arises primarily from the availability of more precise data during implementation. For instance, the department's initial estimate for OTCD screening and the associated courier service was between $6-$10 per baby, based on preliminary data from other states and lacking formal quotes. This was noted in the 2021 TAC presentation, where the department acknowledged the absence of an official quote and emphasized that the estimate was based on available data.

In the 2022 fee increase request, the department revised the OTCD cost estimate to $1.20 per baby, though this request did not result in funding for OTCD screening. The Legislature approved funding only for courier delivery and CF DNA testing expansion, both of which have since been implemented. The Legislature did not provide a rationale for not funding OTCD screening.

The original cost estimate was higher due to the inclusion of overnight courier delivery for time-sensitive OTCD testing. However, further analysis revealed that courier costs were lower than initially projected.

For ARG1 and GAMT deficiencies, the estimated cost was $0.99 per baby in 2023, as these tests rely on the existing MS/MS amino acid/acylcarnitine analysis, with the primary cost driver being staff time rather than new infrastructure or delivery services.

When combining OTC, ARG1, and GAMT deficiencies, the incremental cost increase is minimal. The 2025 fee increase request for these conditions is estimated at $1.75 per baby. Additionally, the department requested $2.75 per baby to implement DNA sequencing for Pompe Disease and MPS-I. The Legislature approved $220,000 for the addition of OTC/ARG1/GAMT deficiencies, which amounts to about $2.75 per baby. However, funding for DNA sequencing was only partially approved, bringing the total fee increase request to $4.02 per baby.

Total cost of the rule: $4.02 fee increase per baby × 83,000 estimated births annually in Washington = $333,660. These costs will be covered by either private insurance, Medicaid, or patients will pay out of pocket.

Approximately 50% of births in Washington are covered by Medicaid; the remaining 50% are assumed to be covered by private insurance. Based on this, the cost impact is estimated as follows:

- Medicaid: $166,830
- Private Insurance: $166,830

To estimate potential cost impacts for providers serving uninsured populations (i.e., not covered by Medicaid or private insurance), we assume an 8% uninsured rate, based on 2024 U.S. Census and CDC data. Accordingly, the estimated cost impact on health providers collecting newborn screening specimens for uninsured patients is: $333,660 × 0.08 = $26,692

Determination

Probable Benefits greater than Probable Costs

The cost-benefit analyses show that screening for GAMT deficiency and ARG1-D provides net positive benefits, with benefit-cost ratios of 1.45 and 2.03, respectively. Screening for OTCD yields a benefit-cost ratio of 0.69, indicating that quantified benefits do not exceed costs under base-case assumptions. However it is of note that, qualitative benefits—such as lives saved, prevention of irreversible neurological damage, and reduced diagnostic odyssey on families which align with the goals of RCW 70.83 to prevent heritable disorders whenever feasible.

SECTION 6

List of alternative versions of the rule that were considered including the reason why the proposed rule is the least burdensome alternative for those that are required to comply and that will achieve the goals and objectives of the proposed rule.

<u>Alternative 1:</u>

The board considered not adding OTCD, GAMT deficiency, and ARG1-D to the required newborn screening panel. However, population-based newborn screening is the least burdensome alternative because it ensures that newborns with these rare conditions are identified early and can receive treatment before the conditions progress to an untreatable stage.

<u>Alternative 2:</u>

The Board considered conducting screening only when there is a family history suggesting a likelihood of OTCD, GAMT deficiency, or ARG1-D. This approach is less effective because it would miss cases in newborns with no known family history or in families where parents have not undergone genetic testing for relevant mutations.

SECTION 7

Determination that the rule does not require those to whom it applies to take an action that violates requirements of another federal or state law.

The proposed rule does not require any affected party to take actions that would violate federal or state law.

SECTION 8

Determination that the rule does not impose more stringent performance requirements on private entities than on public entities unless required to do so by federal or state law.

The proposed rule does not impose stricter performance requirements on private entities than on public entities.

SECTION 9

Determination if the rule differs from any federal regulation or statute applicable to the same activity or subject matter and, if so, determine that the difference is justified by an explicit state statute or by substantial evidence that the difference is necessary.

The Recommended Uniform Screening Panel (RUSP) is a national guideline for U.S. newborn screening programs. It lists heritable conditions that the U.S. Secretary of Health and Human Services (HHS) recommends screening for shortly after birth, based on evidence of the benefits of screening, feasibility, and the availability of effective treatments.

The RUSP categorizes conditions as core or secondary. Core conditions are recommended for inclusion in every newborn screening program. Secondary conditions may be identified during screening for a primary condition.

Most states screen for the majority of RUSP conditions, though some may exclude newly added conditions or include additional conditions not on the RUSP. States determine which conditions to include in their programs. Still, the RUSP provides a standardized list supported by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and recommended by the Secretary of HHS.

In Washington, new conditions are evaluated through a structured process. Members of the public, department staff, or board members can request a review. The board may convene an advisory committee to assess candidate conditions using three guiding principles and evidence-based criteria.

Currently, GAMT deficiency is a core RUSP condition, and ARG1-D is a secondary condition. Although OTCD is not on the RUSP, a Technical Advisory Committee (TAC) recommended its addition to Washington’s universal newborn screening program following an evidence-based review.

SECTION 10

Demonstration that the rule has been coordinated, to the maximum extent practicable, with other federal, state, and local laws applicable to the same activity or subject matter.

The rule has been coordinated, to the maximum extent practicable, with other federal, state, and local laws applicable to the same activity or subject matter. No other applicable laws were identified.