Considering adding Guanidinoacetate methyltransferase (GAMT) deficiency to the Washington State Newborn Screening Panel

A narrative of an economic analysis for the Department of Health, State Board of Health, and technical advisory committee

September 2023

Proposed Rule and Brief History

The State Board of Health (Board) is authorized by RCW 70.83.050 to adopt rules and regulations relating to congenital newborn screening (NBS). The Board established rules under Chapter 246-650 WAC regarding which conditions to include on the NBS panel. RCW 70.83.020 grants the Board authority to identify which screening the Department of Health (Department) is required to perform for all infants in the state. RCW 70.83.030 tasks the Board with adopting rules related to the reporting of heritable and metabolic disorders to the Department.

In January 2023, the Secretary of Health and Human approved the recommendation to add GAMT deficiency to the federal Recommended Uniform Screening Panel (RUSP). On February 24, 2023, it was petitioned to the Board to request adding Guanidinoacetate methyltransferase (GAMT) deficiency screening to chapter 246-650 WAC as a condition for newborn screening. The Board directed Department staff to convene a multidisciplinary technical advisory committee (TAC) to consider adding GAMT deficiency to the list of mandated NBS conditions in Washington. The TAC evaluated GAMT deficiency against the Board's criteria for newborn screening.

Overview and Background – Guanidinoacetate methyltransferase 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 (1).

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 (3). 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.

GAMT deficiency can present as a spectrum of disabilities. Patients with severe disabilities often see frequent seizures that are resistant to anti-epileptic drugs (4). As described by several points of literature, those with severe disabilities also have limited intellectual function and likely cannot live alone (3). Those with moderate disabilities often see seizures as well, but with decreased frequency and may be responsive to anti-epileptic drugs (4). Patients have higher intellectual function, described as a grade 3 to 6 level (3). 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 (1), using a pooled population. At present, three states in the U.S screen for GAMT deficiency – Michigan, 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) (4). 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 of Benefit-Cost Analysis

The following summary describes the benefit-cost analysis performed for adding GAMT deficiency to the mandatory NBS panel. The calculations for this analysis were done in a spreadsheet (available upon request) and describes the medical model for comparing the status quo, or a "No Screening Model" (upper section) with a "Screening Model" (lower section). The analysis is from the health sector perspective, in which all costs for providing services are estimated, regardless of who pays the cost.

Point estimates and ranges for input values were derived from published literature, expert clinical opinion, and data from states that screen for GAMT deficiency in their NBS panel. The model predicts a benefit-cost ratio of 1.453, meaning that for every dollar of costs to screen newborns for GAMT deficiency, there will be a $1.45 worth of benefits. The model structure was developed in 2023 by the Washington NBS program and will be presented to the State Board of Health on September 8, 2023.

There is a good newborn screening test for finding newborns with GAMT deficiency. One of the tricky things about GAMT deficiency is that symptoms generally do not appear until 3 months of age. When found early, either through newborn screening or family history, and started on treatment immediately, newborns are found to develop normally.

We constructed an economic model to estimate the costs and benefits of NBS for GAMT deficiency (Newborn Screening Model). The analysis compares these costs to what is happening now (No Screening Model).

The first step is to estimate the number of newborns with GAMT deficiency. We used information from primary literature to estimate the number of babies with GAMT deficiency born in Washington State this year. We chose to use one year of babies for this analysis.

The next step is 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). We use the sensitivity of the screening test to estimate the number of newborns diagnosed early in the Newborn Screening Model. The sensitivity is the ability of the test to correctly identify newborns with GAMT deficiency. Our model predicts that each year there will be 0.0806 (cell H26) newborns identified early each year through screening, compared to identification through family history alone, (estimated 0.0072 newborns identified (cell H4).

Next, we compare the medical outcomes for early versus late identification and the onset of symptoms. The morbidity estimates are the percentages of newborns we 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.

We have constructed what is called a decision tree. The next step is the walk our way through each branch of the decision tree. To do this, we multiply the rates by the number of newborns affected to find out how many newborns have each of the medical outcomes. In the end, we will have estimates for the number of newborns that all into each category. Because GAMT deficiency is rare, the estimates are often less than one baby. Another way of looking at this would be to make the hypothetical population larger. If we multiply our birth population by 1000, 0.0072 newborns with early identified GAMT deficiency would become 7.2 newborns.

Now is the time to compare each of the outcomes. As there is no mortality rate per the literature (1), we do not perform a calculation on death. First, we add each of the severe disability buckets together. We subtract the number of severe disabilities in the Newborn Screening Model from the No Screening Model to find the shift in numbers. We then repeated this process with the moderate disability buckets, giving us two shift values (one for the shift in severe disabilities and one for the shift in moderate disabilities). We also calculate the disability that persists after receiving treatment and include this in our totals. For the No Screening model, 0.0385 (cell T2) babies will have severe disability and 0.0342 (cell T3) babies will have moderate disability. In the Screening Model, 0.00021 (cell T23) babies will have severe disability and 0.00019 (cell T24) babies will have moderate disability. We also calculate the costs of the annual testing for newborns identified early and treatment costs for disabilities in both models and find the shift in costs.

Next, we assign a value to severe and moderate disabilities. Authors Doble et al., 2020 (2), made estimates for the value of health and societal costs of intellectual disability**.** We used a range of $64,000 to $168,000 per year to estimate the value of disabilities averted through NBS, depending on severity. We chose to represent the first 12 years (Years 0-11), as this is the age group presented by Doble et al., 2020. This is reflected later in treatment costs.

We need to estimate how much the NBS program costs. Based on information from the Washington NBS program, we estimated that the costs per baby would be $0.99. Screening tests are not perfect. This means that some babies who do not have GAMT deficiency will have positive NBS results. They need diagnostic testing to rule out GAMT deficiency.

The next step is to add up all the benefits and costs (disability averted, treatment costs, NBS testing costs, and costs of false positive results). We divide the benefits by the costs to get a benefit/cost ratio. Our final result is 1.453. This means that for every dollar spent to screen babies for GAMT deficiency, we receive about $1.45 worth of benefits.

Technical Explanation of Model Parameters

We chose numbers for a base case analysis: if we had several estimates from the published data, we either used an average or middle value. Note: the spreadsheet calculates the percentages and estimates, which in some instances been rounded for simplicity. Subsequent calculations are unaffected by this rounding, so sometimes numbers appear to not match perfectly.

- ***Birthrate.*** This analysis is for a hypothetical birth cohort of **83,000** babies (cells B7 and B27) which is the number of babies expected to be screened per year in Washington State. This number is based on the number of births projected in Washington in 2023.
- ***Prevalence.*** The prevalence used was **9.759 E -07** or **approximately 1 GAMT deficiency case per 1,000,000 births** (cells D8 and D 28), which is the prevalence reported by the Health Resources and Services Administration (HRSA) (1). This predicts **0.081 babies born with GAMT deficiency** in Washington each year (cells E7 and E27).
- ***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** – cell G4) is a calculation from cases reported in literature (4, 5, 6).
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with GAMT deficiency, is estimated at **99.5%** (cell G 26), Although there have been no known missed cases in GAMT deficiency NBS programs (8), 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.
- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have GAMT deficiency, is estimated at **99.998%** (cell G 47), based on the information from the Health Resources and Services Administration (HRSA) (1). The specificity value predicts 1.743 false positives (cell H41): 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 for severe disability from GAMT deficiency (**0%,** cell J3, J25) and moderate disability (**0%**, cell J5, J27) are from primary literature (3, 4, 5). Typically, the benefit for babies identified early is no disability from GAMT deficiency.
- ***Morbidity in cases identified late.*** The morbidity estimates for late identified cases for severe disability from GAMT deficiency (**52.2%**, cell J11, J36) and moderate disability (**47.8%**, cell J13, J38) are from primary literature (3, 4, 5, 6, 7). We then stratified if babies had disability existing after treatment. In severe disability cases **100%** (cell N11, N37) of babies still experienced disability. In moderate disability cases, **97%** (cell N17, N44) of babies still experienced disability.
- ***Treatment costs for cases identified early.*** The cost for Years 1-11 for treatment in babies identified early is estimated at **$12,976.50** (cell S11). This includes medication and monitoring visits.
- ***Treatment costs for cases identified late, severe disability.*** The costs for Years 1-11 in babies identified late exhibiting severe disability is estimated at **$1,779,606.10** (cell S12). This includes medication, intellectual disability associated costs (healthcare and societal) (2) and seizure costs.
- ***Treatment costs for cases identified late, moderate disability.*** The costs for Years 1-11 in babies identified late exhibiting moderate disability is estimated at **$1,571,471.30** (cell S13). This includes medication, intellectual disability associated costs (healthcare and societal) (2) and seizure costs.

The next step is to evaluate the differences between the models to quantify the benefits of screening. This is done by combining the morbidity estimates and assigning a dollar value to disability averted and 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 costs of treatment in each model. (**No Screening = $93.85**, cell T5; **NBS = $1,045.88**, cell T26). The annual treatment cost difference is -$952.03, meaning that there are more costs associated with early identification.
- ***Shift in late treatment (severe) costs.*** The early late treatment costs for each model are calculated and combined to determine the costs of treatment in each model (**No Screening = $68,495.18,** cell T6; **NBS = $376.05,** cell T27). The annual treatment costs saved by screening ($68,119.13, cell T31) meaning that early identification costs less and there are less 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 costs of treatment in each model (**No Screening = $55,443.93** cell T7; **NBS = $304.40,** cell T28). The annual treatment costs

saved by screening ($68,119.13, cell T31) meaning that early identification costs less and there are less costs associated with moderate disability from GAMT deficiency.

- ***Total benefits.*** The total benefits (**$122,306.64**, cell T36) are the sum of the shift in early treatment costs, late treatment (severe) costs and the shift in late treatment (moderate) costs.

Costs are estimated next.

- ***Cost per baby.*** The estimated costs of GAMT deficiency testing are **$0.99 per baby** (cell A35).
- ***Cost of screening.*** The birthrate multiplied by the cost per baby is **$82,008.19** (cell T43).
- ***Cost of diagnostic testing for false positives.*** Only the false positive babies are counted for diagnostic testing costs because babies with GAMT deficiency will have clinical evaluation and diagnostic testing regardless. The cost of false positive screening results is $1,250.00 (cell S56) and includes urine analysis for creatine and GUAC, and molecular genetic testing to confirm GAMT deficiency. This false positive cost is multiplied by the amount of estimated false positive babies, giving a cost of **$2,178.75** (cell T44).
- ***Total costs of Newborn Screening Model.*** The annual costs of NBS for GAMT deficiency are estimated to be **$84,186.94** (cell T46).

Finally, the ratio of benefits to cost 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** (cell T49).

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.

- ***Sensitivity Analysis.*** Table 1 contains 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/cost ratios for each of the scenarios. The model proved to be robust and sensitive to six parameters: birth prevalence, % with GAMT family history, specificity, treatment costs, late ID (severe), treatment costs, late ID (moderate), and cost of NBS test. The lowest the benefit-cost ratio dipped was to 0.422 for the model in which the specificity was a low estimate of 99.8%.

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

Conclusion

Early identification of babies with GAMT deficiency is typically regarded as being beneficial to babies, their families and the medical professionals caring for them. The morbidity rates are greatly reduced with early treatment and medical costs are much lower compared to babies treated after becoming symptomatic.

This analysis used data from primary literature, NBS programs that currently screen for GAMT deficiency, and expert opinion to quantify benefits and costs for babies with GAMT deficiency with early and late treatment. The benefit-cost ratio was 1.453, meaning that for every dollar of costs to provide GAMT deficiency screening, there will be approximately $1.45 worth of benefits. The sensitivity analysis showed that the model is robust because the benefit-cost ratio did not change much when more conservative or liberal estimates for parameters were made in the model.

References:

1. Health Resources and Services Administration. (2022). *Guanidinoacetate Methyltransferase (GAMT) Deficiency Evidence Based Review.* https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/meetings/gamt-deficiency-review-evidence.pdf
2. Doble, B., Schofield, D., Evans, C. A., Groza, T., Mattick, J. S., Field, M., & Rosciloi, T. (2020). Impacts of genomics on the health and social costs of intellectual disability. *J Med Genet., 57*, (479-486). Doi: 10.1136/jmedgenet-2019-106445
3. Khaikin, Y., Sidky, S., Abdenur, J., Anastasi, A., Ballhausen, D., Buoni, S., Chan, A., Cheillan, D., Dorison, N., Goldenberg, A., Goldstein, J., Hofstede, F. C., Jacquemont, M. L., Koeberl, D. D., Lion-Francois, L., Lund, A. M., Mention, K., Mundy, H., O'Rourke, D., Pitelet, G., … Mercimek-Andrews, S. (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.

4. Stockler-Ipsiroglu, S., van Karnebeek, C., Longo, N., Korenke, G. C., Mercimek-Mahmutoglu, S., Marquart, I., Barshop, B., Grolik, C., Schlune, A., Angle, B., Araújo, H. C., Coskun, T., Diogo, L., Geraghty, M., Haliloglu, G., Konstantopoulou, V., Leuzzi, V., Levtova, A., Mackenzie, J., Maranda, B., … Schulze, A. (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
5. 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
6. 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
7. 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
8. Kim Hart, personal email communication, August 11, 2023

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