Considering adding Arginase-1 deficiency (ARG1-D) 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.

On March 29, 2023, the Board received a petition request to amend chapter 246-650 WAC to add arginase-1 deficiency (ARG1-D) as a mandatory condition to Washington State's NBS panel. The Board directed Department staff to convene a multidisciplinary technical advisory committee (TAC) to consider adding ARG-1 D to the list of mandated NBS conditions in chapter 246-650 WAC. The TAC evaluated ARG1-D against the Board's criteria for newborn screening.

Overview and Background – Arginase-1 Deficiency

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 (1, 2).

ARG1-D is present in approximately 1 in 1,00,000 babies, when looking at the median value published literature (5). At present, 36 states screen for ARG1-D. There has also been research done on the prevalence outside the United States, for which these studies adjusted rates for consanguinity (7).

Treatment for ARG1-D can consist of several steps. Diet will 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.

Overview of Benefit-Cost Analysis

The following summary describes the benefit-cost analysis performed for adding ARG1-D 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 ARG1-D in their NBS panel. The model predicts a benefit-cost ratio of 2.03., meaning that for every dollar of costs to screen newborns for ARG1-D, there will be a $2.03 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 ARG1-D. One of the tricky things about ARG1-D is that symptoms generally do not appear until 1 to 3 years of age (4). When found early, either through newborn screening or family history, and started on treatment immediately, newborns are generally found to develop normally.

We constructed an economic model to estimate the costs and benefits of NBS for ARG1-D (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 ARG1-D We used information from primary literature to estimate the number of babies with ARG1-D 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 ARG1-D (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 ARG1-D. Our model predicts that each year there will be 0.0826 newborns (cell H39) identified early each year through screening, compared to identification through family history alone, (estimated 0.0132 newborns identified (cell H6)).

Next, we compare the 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 the 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.

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 ARG1-D 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, 0.083 newborns with early identified ARG1-D would become 83 newborns.

Now it is time to compare each of the outcomes. First, we add each of the death estimates together. We subtract the numbers of deaths in the Newborn Screening Model from 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 (cell W45) newborns from dying. We also calculate the costs of annual testing for newborns identified early and treatment costs in both models and find the shift in costs.

Next we assign a value to saving a life. The Federal Government makes estimates for the value of saving a life. We used an estimate of $11,600,000 to estimate the value of a life saved through NBS.

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 ARG1-D will have positive NBS results. They need diagnostic testing to rule out ARG1-D.

The next step is to add up all the benefits and the costs (lives saved, long term disability averted, newborn screening costs, and costs of false positive results). We divide the benefits by the costs to get a benefit/cost ratio. Our final result is 2.03, which means for every dollar spent to screen babies for ARG1-D, we receive about $2.03 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 B8 and B38) 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 **1.000 E-06** or **approximately 1 ARG1-D case per 1,000,000 births** (cells D10 and D 39), which is the prevalence reported by the existing literature (3). This predicts **0.083 babies born with ARG1-D** in Washington each year (cells E8 and E38).
- ***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** – cell H6) is a calculation from cases reported in literature.
- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with ARG1-D is estimated at **99.5%** (cell G 39), Although there have been no known missed cases in ARG1-D NBS programs (11), false negatives are inevitable in screening programs. The sensitivity of the NBS test predicts 0.0826 (cell H39) true positives identified early and 0.00042 (cell H48) 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%** (cell G 47), based on the information primary literature (3) and data from Oregon NBS (8). The specificity value predicts 8.943 false positives (G51): 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%**, cells J3 and J37) is data from existing literature that early identified babies do not have a mortality rate (4).
- ***Mortality of cases identified late.*** The numbers for late identified ARG1-D (**10.6%**, cells J15 and J49) are from articles from Sawad et al., 2022(1) and Schlune et al., 2015 (2). These articles evaluated late identified cases of ARG1-D and reported a mortality rate. Additionally, mortality from liver transplant surgery itself was evaluated, based on existing literature and expert opinion (9, 10) (**3%**, cells N21 and M52).
- ***Monetary value of a life.*** The value of 1 life is estimated at **$11,600,000** (cell W48). This estimate was provided in 2021 by the Department of Transportation (DOT) (6).
- ***Treatment costs for cases identified early.*** The cost for Years 0-10 in babies identified early is estimated at **$1,503,509.80** (cells V11 and U54). This includes medication and monitoring visits.
- ***Treatment costs for cases identified late.*** The costs for Years 0-10 in babies identified late is estimated at **$1.637,128.67**(cells V13 and U56). 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. This is done by combining the mortality and morbidity estimates and assigning a dollar value to death and disability averted, and the difference in treatment costs.

- ***Deaths averted.*** The total number of deaths from each model are compared; there are 0.0075 deaths (cell W2) predicted in the "No Screening Model" and 0.0000456 deaths (cell W34) in the "Newborn Screening Model". The difference between the two models is **0.00749 deaths averted** (cell W45).
- ***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** (cell W49) for saving lives of babies with ARG1-D.
- ***LTD averted.*** The total number of long-term disability cases from each model are compared; there are 0.0637 babies with LTD (cell W3) predicted in the "No Screening Model" and 0.0095 babies with LTD (cell W35) in the "Newborn Screening Model". The difference between the two models is **0.0542 babies with LTD averted** (cell W46).
- ***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. This estimate is provided by expert Scott Grosse. The model estimated yearly benefits of **$81,259.71** (cell W47).
- ***Shift in 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 = $134,117.90**, cell W8; **NBS = $124,846.77**, cell W40). The annual treatment costs saved by screening are **$9,270.54** (cell W50), meaning early identification costs less.
- ***Total benefits.*** The total benefits **$177,511.38**, cell W51are the sums of lives saved, LTD averted and treatment costs saved by screening.

Costs are estimated next.

- ***Cost of screening.*** The estimated costs of ARG1-D testing are **$0.99 per baby** (cell A48).
- ***Costs of diagnostic screening for false positives.*** Only the false positive babies are counted for diagnostic testing costs because babies with ARG1-D will have clinical evaluation and diagnostic testing regardless. The cost of false positive screening results is **$5,255.13** (cell W59) 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** (cell W58).
- ***Total costs of the Newborn Screening Model.*** The annual costs of NBS for ARG1-D are estimated to be **$87,263.32** (cell W60).

Finally, the ratio of benefits to cost 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** (cell W63).

After completing the base case benefit-cost ratio, we performed a sensitivity analysis to evaluate hoe the benefit-cost ratio changed 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 (2.03) 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 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 the benefit-cost ratio dipped was to 0.99 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		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

Conclusion

Early identification of babies with ARG1-D is typically regarded as being beneficial to 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.

This analysis used data from primary literature, NBS programs that currently screen for ARG1-D, and expert opinion to quantify benefits and costs for babies with ARG1-D with early and late treatment. The benefit-cost ratio was 2.03, meaning that for every dollar of costs to provide ARG1-D screening, there will be approximately $2.03 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.

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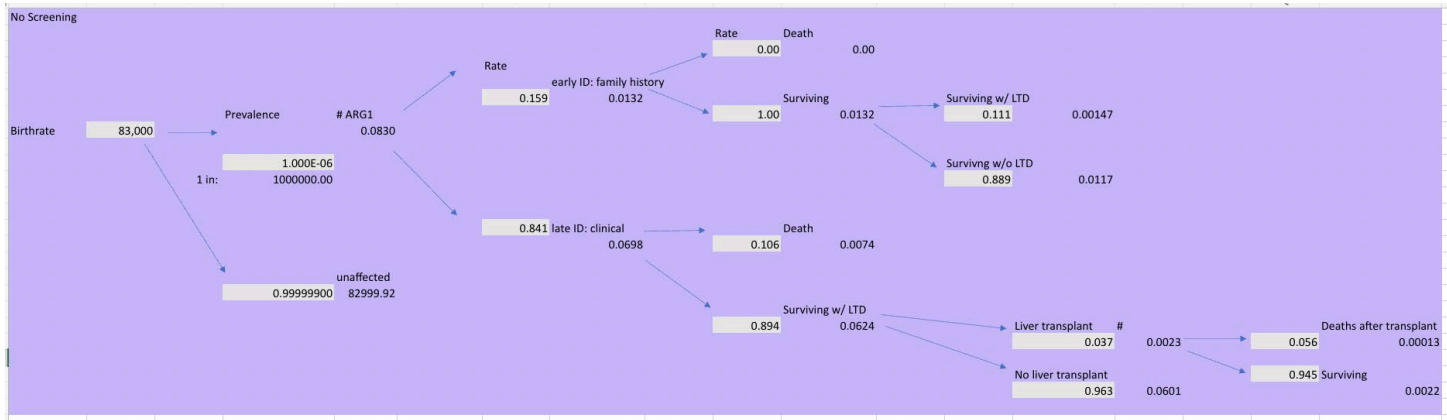
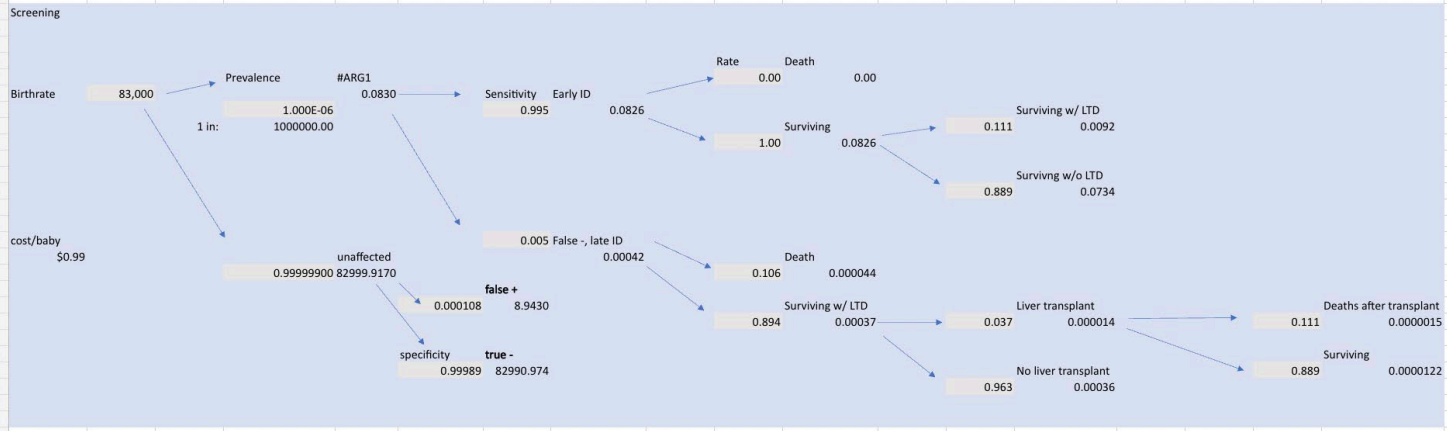
WA State Benefit-Cost Analysis for adding NBS for Arginase-1 deficiency



No Screening	Deaths	0.0075
	Surviving w/LTD	0.0637
	Surviving w/o LTD	0.0117
	Early tx costs	$19,853.16
	Late tx costs	$114,264.14
	Total costs	$134,117.30

Early tx cost per baby (10 Years)	$1,503,509.80
Late tx cost per baby (10 Years)	$1,637,128.67



Screening	Deaths	0.0000456
	Surviving w/LTD	0.0095
	Surviving w/o LTD	0.0734
	Early tx costs	$124,167.36
	Late tx costs	$679.41
	Total costs	$124,846.77

Benefits	Deaths averted	0.007498
	LTD averted	0.0542
	Value of LTD averted	$81,259.71
	Value of a life	$11,600,000.00
	Value of lives saved	$86,981.13
	Less tx costs	$9,270.54
	Total benefits	$177,511.38

Early tx cost per baby (10 Years)	$1,503,509.80
Late tx cost per baby (10 Years)	$1,637,128.67

Costs	costs of screening	$82,008.19
	costs of false +	$5,255.13
	Total costs	$87,263.32

benefit/cost ratio	2.03
Net benefit	$90,248.06

Cost for ARG1 false +
$587.63