Significant Legislative Rule Analysis

Chapter 246-650 WAC
A Rule Concerning Newborn Screening

June 17, 2019

SECTON 1:

Describe the proposed rule, including a brief history of the issue, and explain why the proposed rule is needed.

Proposed Rule and Brief History

RCW 70.83.030 tasks the State Board of Health (Board) with adopting rules related to the reporting of heritable and metabolic disorders to the Department of Health (Department).

Pompe disease and MPS I are genetic lysosomal storage disorders and are severe conditions that can result in death or significant morbidity if not detected and treated early. Pompe disease was added to the U.S. Department of Health and Human Services Recommended Uniform Screening Panel (RUSP) in 2015 and Mucopolysaccharidosis type I (MPS I) was added to the RUSP in 2016.

The Board and the Department convened a Technical Advisory Committee (TAC) twice between April and June of 2017 to assess Pompe disease and MPS I against the Board's criteria for newborn screening conditions and to make recommendations regarding their addition to the mandatory newborn screening panel. The TAC unanimously recommended adding MPS I to the newborn screening panel but the TAC members' recommendations for Pompe disease were mixed. The Board discussed the conditions and the TAC's recommendations at its August 2017 Board meeting and determined that it is in the best interest of the children of Washington and public health to add both conditions to the panel.

The Board is proposing amendments to chapter 246-650 WAC to add a definitions for Pompe and MPS I and to add these two conditions to the list of newborn screening tests performed by the Department. Other changes such as creating a new section outlining critical congenital heart disease screening requirements for hospitals and health care providers attending a birth outside of a hospital to align with RCW 70.83.090, would provide clarity and consistency for stakeholders by aligning the rules with current state and federal statutes and federal regulations.

Overview and Background – Pompe

Pompe disease is an inherited neuromuscular disorder that is caused by the buildup of glycogen in the body. The accumulation of glycogen can impair the ability for certain organs and tissues to function normally. Pompe is caused by mutations in the acid alpha glucosidase gene (GAA) gene, which is responsible for producing an enzyme called acid alpha glucosidase that is involved in metabolism ("Pompe Disease - Genetics Home Reference – NIH", 2016). The severity of Pompe disease and the age of onset of symptoms are related to the degree of acid alpha glucosidase enzyme deficiency ("Pompe Disease", accessed May 2019). Pompe disease is inherited as an autosomal recessive trait, which means that both copies of the gene have mutations. Individuals with one copy of the mutated gene are carriers that typically do not show signs or symptoms of the condition ("Pompe Disease - Genetics Home Reference – NIH", 2016). The three types of Pompe disease are known as classic infantile-onset, non-classic infantile-onset, and late-onset ("Pompe Disease, 2015).

Classic Infantile Pompe Disease:
Patients have very low alpha glucosidase enzyme activity. Clinically, classic infantile Pompe disease is typically suspected following the development of diagnosed muscle weakness, poor muscle tone, an enlarged liver, and specific heart problems ("Pompe Disease - Genetics Home Reference – NIH", 2016). Patients develop cardiac and respiratory failure and without treatment, death most often occurs before the age of 2 years ("Pompe Disease", accessed May 2019).

Non-Classic Infantile Pompe Disease:
Compared to classic infantile Pompe cases, non-classic infantile cases of Pompe disease have slightly greater enzyme activity and typically do not have cardiac problems, but otherwise present with similar symptoms. Presentation of symptoms typically occur by age 1 ("Pompe Disease - Genetics Home Reference – NIH", 2016). Those with untreated non-classic infantile Pompe disease typically live only into early childhood due to illness characterized by weakness and respiratory insufficiency ("Pompe Disease", 2017).

Late-Onset Pompe Disease:
Late-onset Pompe disease most often presents as respiratory symptoms or slight limb muscle weakness in juveniles or adults who are then found to have reduced enzyme activity (Cupler, 2012). Patients experience a progressive loss of respiratory function that may result in acute respiratory failure. The length of survival depends on the rate of disease progression, the extent to which respiratory muscles are involved, and additional comorbidities (Cupler, 2012).

Infantile Pompe disease affects approximately 1 in 89,000 individuals in the United States although the incidence varies among populations and ethnic groups around the world ("Pompe Disease - Genetics Home Reference – NIH", 2016). Studies have shown that there is a higher incidence of the infantile-onset form of Pompe disease among African-Americans and in areas such as China and Taiwan ("Pompe Disease", accessed May 2019). Enzyme replacement therapy (ERT) is an approved treatment that is not curative but has been shown to improve the symptoms for Pompe disease ("Pompe Disease", 2017). In clinical trials with infantile-onset patients, ERT has been shown to, "…decrease heart size, maintain normal heart function, improve muscle function, tone, and strength, and reduce glycogen accumulation" ("Pompe Disease Information Page", 2019). Additional supportive therapies are often required including physical therapy, occupational therapy, and respiratory support ("Pompe Disease, 2017).

Overview and Background – MPS I

MPS I is a multi-system disorder caused by mutations in the alpha-L-iduronidase gene (IDUA) (Clarke, 2016). This gene is responsible for producing IDUA enzyme, a lysosomal enzyme, which when deficient can lead to the accumulation of mucopolysaccharides and other metabolites (Muenzer, 2009). The accumulation of these products increases the size of the lysosomes and can enlarge many tissues and organs ("Mucopolysaccharidosis Type I - Genetics Home Reference – NIH", 2012). Like Pompe disease, MPS I is inherited as an autosomal recessive trait that occurs in about 1 out of every 100,000 newborns ("Mucopolysaccharidosis Type I - Genetics Home Reference – NIH", 2012). MPS I is often separated into three separate diseases based on clinical presentation: Hurler syndrome (severe), Hurler-Scheie syndrome (intermediate), and Scheie syndrome (mild) (Muenzer, 2009). These three MPS I syndromes are

further discussed in two broad groups of severe MPS I, which includes Hurler syndrome, and less severe or attenuated MPS I, which includes Hurler-Scheie and Scheie syndromes (Muenzer, 2009).

Severe MPS I:
Infants with severe MPS I typically appear normal at birth and begin showing signs and symptoms within the first year of life ("Mucopolysaccharidosis Type I - Genetics Home Reference – NIH", 2012). Severe MPS I is characterized by progressive skeletal and joint disease as well as progressive neurodegeneration, with cognitive delay evident by 12-24 months. Other symptoms include: increased intracranial pressure due to accumulation of excess cerebrospinal fluid, severe respiratory insufficiency, cardiac involvement, deafness, profound vision loss, gastrointestinal issues, and hernias ("Mucopolysaccharidosis Type I", 2016). Death, typically due to heart and lung failure and progressive neurologic disease, occurs within the first ten years of life (Clarke, 2016).

Less Severe MPS I (attenuated):
Those with less severe MPS I experience progressive joint disease that leads to a loss of range of motion and they may some or no intellectual impairments ("Mucopolysaccharidosis Type I - Genetics Home Reference – NIH", 2012). Other symptoms include: chronic headaches or mild optic nerve compression due to accumulation of excess cerebrospinal fluid, chronic sinus infections, pulmonary hypertension and congestive heart failure, some hearing loss in adulthood, and gastrointestinal symptoms (Muenzer, 2009). Depending on the severity and the rate of disease progression, death may occur in the second to third decade of life or an individual may have a normal lifespan (Clarke, 2016).

Standard of care for children with severe MPS I is hematopoietic stem cell transplantation (HSCT) (Clarke, 2016). Studies have shown that, "HSCT can increase survival, improve growth, reduce facial coarseness and hepatosplenomegaly, improve hearing, and alter the natural history of cardiac and respiratory symptomatology. … HSCT may slow the course of cognitive decline in children with mild, but not significant, cognitive impairment at the time of transplantation. Due to the morbidity and mortality associated with HSCT, it is currently recommended primarily for children with severe MPS I" (Clarke, 2016). ERT is also recommended for individuals with attenuated disease. This treatment has been shown to improve liver size, growth, mobility, breathing, and sleep apnea (Clarke, 2016). Given the wide range of symptoms associated with MPS I, care from a multidisciplinary team is often required ("Mucopolysaccharidosis Type I", 2016).

SECTION 2:

Is a Significant Analysis required for this rule?

Yes, the Board and the Department evaluated the rule and determined it is a significant legislative rule as defined in RCW 34.05.328 and requires a significant analysis that includes a cost/benefit analysis. However, it has been determined that no significant analysis is required for the following portions of the rule.

Table 1: Non-Significant Rule Identification

WAC Section	Section Title	Reason
WAC 246-650-001	Purpose	Editorial edit.
WAC 246-650-010	Definitions	Changes clarify existing definitions and do not impact existing rule requirements. Adding new definitions for the following terms: Pompe, MPS I, and critical congenital heart disease. The impact of adding the new conditions of Pompe and MPS I are analyzed in Section 5.
WAC 246-650-035	Screening for critical congenital heart disease	Incorporating requirements in RCW 70.83.090 and therefore does not require analysis under RCW 34.05.328(5)(b)(iii).
WAC 246-650-040	Reports to the board and the public	Removes language that indicates that particular subsections are going to expire on January 1, 2020. However, the Department is voluntarily maintaining the majority of the reporting requirements so it is not a significant change from the existing rule. Further discussion in Section 5.
WAC 246-650-050	Privacy and security of newborn screening specimen/information forms	Editorial edits only.
WAC 246-650-990	Screening charge	Editorial edits only.
WAC 246-650-991	Specialty clinic support fee	Aligning more closely with RCW 70.83.023 (Specialty clinics—Defined disorders—Fee for infant screening and sickle cell disease) and does not require analysis under RCW 34.05.328(5)(b)(iii).

SECTION 3:

Clearly state in detail the general goals and specific objectives of the statute that the rule implements.

The general goal of chapter 70.83 RCW is to detect as early as feasible and to prevent, where possible, heritable disorders leading to developmental disabilities or physical defects.

The statute's objectives the rule implements are:

1. Detect Pompe and MPS I through a test performed on the blood spot specimen that is collected from every baby within 48 hours of birth and submitted to the Department's newborn screening program.

2. Report significant screening test results to the infant's attending health care provider or family if an attending health care provider cannot be identified.

In addition, RCW 70.83.090 establishes requirements for critical congenital heart disease (CCHD) screening to ensure that CCHD is detected as early as possible so that timely intervention may occur. The rule implements this objective by incorporating the screening requirements for CCHD in order to create clarity and consistency for the regulated community.

SECTION 4:

Explain how the department determined that the rule is needed to achieve these general goals and specific objectives. Analyze alternatives to rulemaking and the consequences of not adopting the rule.

Population-based newborn screening is the best way to ensure that newborns with Pompe disease and MPS I are identified and can receive treatment before the condition causes irreversible damage or death. In order for universal screening of these conditions to occur in Washington, Chapter 246-650 WAC must be amended to include these conditions.

The Board and Department have assessed and determined that there are no feasible alternatives to rulemaking because infants born with Pompe and MPS I may appear normal and without required screening, the opportunity to begin preventive treatments will be lost. If this rule is not adopted, the result would be babies who are born with Pompe and MPS I will continue to experience long-term health challenges or death associated with the disorder.

The legislation that established the requirements for CCHD screening in RCW 70.83.090 passed in 2015 and took effect later that year. The existing rule specifically outlines requirements for screening conducted through a dried blood spot and Board and Department staff considered not adding the CCHD requirements to the rule given that screening is not conducted in the same way. However, ensuring that all of the requirements for newborn screening are in one rule creates clarity and consistency for the regulated community.

SECTION 5:

Explain how the department determined that the probable benefits of the rule are greater than the probable costs, taking into account both the qualitative and quantitative benefits and costs and the specific directives of the statute being implemented.

Overview of Benefit-Cost Analysis for Pompe Disease (WAC 246-650-020)

The following summary explains the benefit-cost analysis performed for adding Pompe disease to the mandatory newborn screening panel. This was presented to the technical advisory committee and the State Board of Health. The accompanying spreadsheet is the medical model for comparing the status quo, or a "No Screening Model" (upper section) with the Pompe "Newborn 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 costs.

Point estimates and ranges for input variables were derived from published literature, expert opinion, and the Washington Newborn Screening (NBS) program. The model predicts a benefit-cost ratio of -18.02, meaning that for every dollar spent to screen newborns for Pompe, there will be an additional $18 worth of costs. The model structure was developed during 2017 by the Washington NBS program and was presented to the NBS Advisory Committee on June 28, 2017 and later to the State Board of Health on August 9, 2017.

Pompe disease is a neuromuscular disorder that results in the accumulation of glycogen (a type of carbohydrate). It is caused by mutations in the acid alpha glucosidase gene (*GAA*), which result in reduced or absent activity of the acid alpha glucosidase enzyme (a lysosomal protein involved in metabolism). Pompe disease is inherited as an autosomal recessive trait, meaning that an individual needs two mutations to be affected, while individuals with one mutation are carriers and are clinically normal.

While Pompe disease is known to present as a spectrum of phenotypes, historically, people with Pompe have been grouped into three categories based on the age of onset and severity of disease.

Classic Infantile Pompe Disease:
- Patients have very low alpha glucosidase enzyme activity. Clinically, classic infantile Pompe disease is typically suspected following the development of diagnosed muscle weakness or "floppy baby syndrome" along with specific heart problems. Patients develop cardiac and respiratory failure and without treatment, death most often occurs before the age of 2 years.

Non-Classic Infantile Pompe Disease:
- Compared to classic infantile Pompe cases, non-classic infantile cases of Pompe disease have slightly greater enzyme activity and typically do not have cardiac problems, but otherwise present with similar symptoms. Those with untreated non-classic infantile Pompe disease typically do not survive the third year of life due to illness characterized by weakness, respiratory insufficiency.

Late-Onset Pompe Disease:
- Late-onset Pompe disease most often presents as respiratory symptoms or slight limb muscle weakness in juveniles or adults who are then found to have reduced enzyme

activity. Patients experience a progressive loss of respiratory function that may result in acute respiratory failure. Without treatment, most become wheelchair-bound and/or ventilator dependent, with a median length of survival of 27 years following diagnosis.

There is an effective newborn screening test for finding newborns with Pompe although a positive screen cannot predict the onset and severity of Pompe disease with certainty. Some babies also have a pseudodeficiency or are carriers with one mutation, meaning that they have low enzyme activity, but are clinically healthy. Those who meet clinical criteria may receive enzyme replacement therapy (ERT), a synthetic version of the missing enzyme which is administered by IV every two weeks, for life.

We constructed an economic model to estimate the costs and benefits of NBS for Pompe disease (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 Pompe. We used information from IL, MO, and NY's screening programs to estimate the number of babies with Pompe born in Washington State each year. We chose to use one year of babies born for this analysis.

The next step is to find out which newborns will be diagnosed early and benefit from treatment. In the No Screening Model a small percentage of newborns will be diagnosed early because they have a family member with Pompe (positive family history). We use the sensitivity of NBS test to estimate the number of newborns diagnosed early in the Newborn Screening Model. The sensitivity is the ability of the test to correctly find the babies with Pompe. Our model predicts that there will be about one baby with the infantile form of Pompe identified early each year through screening, compared to identification through family history only.

Next we compare the medical outcomes for early versus late identification. We first separate the percentages of newborns we expect will develop the "classic", more severe form of Pompe. We then further divide the "classic" cases into those who are Cross-Reactive Immunologic Material (CRIM)(-) and CRIM(+). The babies who are CRIM(-) produce no enzyme at all and don't respond as well to treatment. The mortality rates are the percentages of newborns we expect will die from Pompe. There is a larger chance for death in late identified Pompe compared to early identified cases. There is also a higher mortality rate for those who are CRIM(-).

We have constructed what is called a decision tree. The next step is to march 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 fall into each category. Because Pompe is rare, the estimates are sometimes less than one newborn. This may feel strange to some readers. Another way of looking at it would be to make the hypothetical population bigger. If we multiplied our birth population by 100, 0.86 newborns with classic Pompe would become 86 newborns.

Now is the 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 0.22 newborns from dying (or about one life saved every four and a half years). We also calculate the costs of treatment for the newborns identified early and late 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 a range of $9 and $13.7 million to estimate the value of a life saved through NBS.

We need to estimate how much the NBS program costs. Based on information from other state screening programs, we estimated that the test would cost $3.12 per baby. Screening tests are not perfect, which means that some babies who do not have Pompe will have positive NBS results. These babies will need diagnostic testing to rule out Pompe disease (their diagnostic test results will be normal).

The next step is to add up all of the benefits and the costs (lives saved, treatment costs, newborn screening testing costs, and costs of false positive results and carrier identification). We divide the benefits by the costs to get a benefit/cost ratio. Our final result is -18.02, which means for every dollar spent to screen babies for Pompe disease, we incur about $18 worth of additional cost.

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 the middle value. Following the base case is a sensitivity analysis that varies the parameters to give what we judge to be very conservative and moderately liberal estimates to see their impact on the benefit-cost ratio. Note: the spreadsheet calculates the percentages and estimates, which have in some instances been rounded for simplicity. Subsequent calculations are unaffected by this rounding, so sometimes the number appear to not match perfectly.

- *Birthrate.* This analysis is for a hypothetical birth cohort of **89,873 babies** (cells A14 and A53) which is the number of babies expected to be screened per year in Washington State. This number is based on the number of births screened in Washington in 2016.
- *Prevalence.* The prevalence used was **1 infantile Pompe case per 88,660 births** (cells C15 and C44) which is the prevalence found among 1,241,243 babies screened for Pompe disease by three newborn screening programs (IL, MO, NY). This predicts **1.01** babies born with infantile Pompe disease in Washington each year (cells D14, D43).
- *Percent of babies with Pompe disease with a positive family history of Pompe disease.* These babies will be treated early in the "No Screening Model" because of a positive family history of Pompe disease. The estimate for this parameter (**33.9%** - cell I3) was reported in the literature (Kishnani, 2006). These babies are assumed to derive the same benefits of early treatment that babies screened at birth would enjoy (better survival rate).
- *Babies with classic presentation.*

Approximately **85%** (cell F6, I37, I47) of babies with infantile Pompe disease will have the "classic" more severe form of the disease that involves heart problems (Kishnani, 2011). The mortality rates were estimated from the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children's Evidence Report for Pompe disease (Kemper, 2013). The mortality rate for early identified babies with classic infantile Pompe disease is **0.1%** (cells L2, K35, K41) at 36 months. For those babies with classic infantile Pompe who are diagnosed late, the mortality rate is **35.1%** (cell L7, K46) at 36 months.

- ***Babies with non-classic presentation.***
  The remaining approximately **15%** (cells F21, I42, I52) of babies with infantile Pompe disease will have the "non-classic" less severe form of the disease (Kishnani, 2011). We assume that in the "No-Screening Model", babies with this form of the disease are not detected early through family history. Instead, we assume **33%** (cell I17) will be detected in the first year of life through clinical symptoms (Kemper, 2013, based on expert opinion and the proportion of cases identified with and without cardiomyopathy from a restropective cohort study). The mortality rate for these late identified babies with non-classic infantile Pompe disease is **8%** (cell L17) at 36 months (Kemper, 2013, based on Kishnani et al.(2009) assuming that efficacy is similar to that observed for individuals with infantile-onset with cardiomyopathy). The remaining non-classic infantile Pompe babies will not be detected until childhood, with a mortality rate of **28.9%** (cell L22) at 36 months (Kemper, 2013, from Winkel el al 2005). In the "Newborn Screening Model", we assume non-classic infantile forms of Pompe disease will be detected very early, with an associated mortality rate of **0.1%** (cell K41) (Kemper, 2013).

- ***CRIM Status.***
  The other parameter affecting babies with classic presentation is their Cross-Reactive Immunologic Material (CRIM) status. Babies with Pompe disease who are CRIM negative (-) are less likely to respond favorably to the treatment for Pompe, Enzyme Replacement Therapy (ERT). We estimate that **25.1%** (cells O3, N36, N47) of classic, infantile babies are CRIM (-) (Bali, 2012). An additional mortality of **14.3%** (cells R2, R7, Q35, Q46) at 20 months is associated with CRIM (-) status (Banugaria, 2013).

- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with Pompe disease, is estimated at **99%** (cell F40). This may be a conservative estimate as there have been no known cases of infantile Pompe disease missed by newborn screening programs (zero false negatives). This sensitivity value predicts **1.004** (cell G40) true positives identified early and **0.01** (cell G48) false negatives (missed cases of infantile Pompe) per year.

- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have Pompe disease, is estimated at **99.95%** (cell F64). The value used is the low estimate from three states currently screening. This specificity value predicts **44.9** (cell G57) false positives per year: these are babies who need diagnostic testing to determine enzyme activity, and sometimes DNA analysis to confirm a pseudodeficiency or other phenotype (they do not have infantile Pompe disease).

- *Monetary value of a life.* The value of one life saved is estimated at **$9 million** (cell AB50). This is the expert opinion of CDC economist Scott Grosse.
- *Difference in treatment costs: early v. late treatment.* In both models, treatment costs include costs for ERT, mechanical ventilation, and Immune Tolerance Induction (ITI) for CRIM (-) babies. To calculate the current value of future costs related to long term ERT and mechanical ventilation, a 3% annual discount was applied to the current market rate for those treatments. Additionally, we applied mortality curves associated with treated Pompe disease adapted from work by Lisa Prosser of the University of Michigan to estimate how many cases would be surviving and on treatment in future years.

  ITI is expected to cost **$4,600** per baby (cells Q18 and Q58). The lifetime, discounted ERT cost is expected to be **$13 million** for cases identified early (cells Q23 and Q62), and **$930,000** (cells V18, V62) for cases identified late. The ERT cost for non-classic cases missed until childhood is **$630,000** (cell V22). The lifetime, discounted mechanical ventilation costs for an early identified baby are estimated to be **$2,000,000** (cells Q27, Q66) and **$270,000** for late identified cases (cells V27, V66).

  In the "No Screening Model", the early treatment costs are **$3.6** million (cell AB4, the sum of R18, R23 and R27), and late treatment costs are **$470,000** (cell AB5, the sum of W18, W22, and W27). The total treatment costs in the "no screening" model are **$4.1 million** (cell AB6, the sum of AB4 and AB5).

  In the "Newborn Screening Model", the early treatment costs are **$12.5 million** (cell AB39, the sum of R58, R62, and R66), and late treatment costs are **$7,000** (AB40, the sum of W66 and W62). The total treatment costs in the "Newborn Screening Model" are **$12.5 million** (cell AB41, the sum of AB39 and AB40).

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

- *Deaths averted.* The total number of deaths for each model are compared; there are 0.26 deaths (cell AB2) predicted in the "No Screening Model" and 0.035 deaths (cell AB37) in the "Newborn Screening Model." The difference between the two models is **0.22 deaths averted** (cell AB49). This means that approximately one baby every 4.5 years will not die because of early treatment afforded by newborn screening.
- *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 estimates yearly benefits of **$2 million** (cell AB51) for saving lives of babies with Pompe disease.
- *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 = $4.1 million**, cell AB6; **NBS = $12.5 million** cell AB41). The annual treatment costs saved by screening (**$-8.4 million**, cell AB52) is the difference between these totals. The treatment costs in the "Newborn Screening Model" are greater because more babies survive to receive lifelong treatment.

- ***Total benefits.*** The total benefits (**$-6.4 million**, cell AB53) are the sum of the value of lives saved and the treatment costs incurred by screening.

Costs are estimated next.

- ***Cost of screening.*** The estimated costs of GAA enzyme activity analysis is **$3.12 per baby** (cell A57).
- ***Costs of diagnostic testing for false positives.*** Only the false positive babies are counted for diagnostic testing costs because the babies with infantile Pompe disease will have diagnostic enzyme and DNA testing regardless of newborn screening. Note: infants with late-onset Pompe disease will likely be represented within the false positive group. Although they may benefit from early detection, that benefit is not quantified in the model.
- ***Total costs for Pompe newborn screening.*** The birthrate multiplied by cost per baby is **$280,200** (cell AB58).
- ***Total costs for diagnostic testing of false positives.*** The total cost per year for the false positive cases outlined above is **$75,300** (cell AB59)
- ***Total costs of Newborn Screening Model.*** The annual costs of NBS for Pompe disease are estimated to be **$355,500** (cell AB60).

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

- ***Benefit/Cost Ratio.*** $-6.4 million of benefits divided by $355,500 of costs yields a benefit/cost ratio of -**18.02** (cell AB64).

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 2 contains three estimates for each parameter, the best guess estimate used in the base case 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 very robust. The highest the benefit-cost ratio reached was -6.13 for the model in which the cost for a dose of Myozyme was halved.

Table 2: Pompe Sensitivity Analysis

Parameter	Base Case	Conservative Estimate	Liberal Estimate	B/C Ratio Swing
Prevalence	1:88,660	1:171,184	1:38,500	-11.95 to -34.43
% early ID – family history of Pompe	0.339	0.1	0.4	-23.06 to -16.74
Sensitivity	0.99	0.98	1	-18.22 to -17.82
Specificity	0.9995	0.9992	0.9998	-15.99 to -20.64

Mortality – classic, early ID	0.001	0	0.029	-18.03 to -17.86
Mortality – classic, late ID	0.351	0.267	0.439	-19.04 to -16.96
Monetary value of a life	$9,000,000	$4,200,000	$13,700,000	-21.02 to -15.08
CRIM (-) %	0.251	0.2	0.3	-18.12 to -17.92
Cost of Myozyme (per dose)	$975	$487.50	$1,950	-6.13 to -41.81
Cost of ventilation (annual)	$84,600	$42,300	$258,840	-18.09 to -17.74
Cost of NBS test	$3.12	$5.00	$1.00	-38.78 to -12.21
Cost of false (+)	$1,675.38	$837.69	$1,775.10	-20.15 to -17.80

ID=identification

Conclusion

Early identification of babies with infantile Pompe disease is critical to their health. The mortality rate is greatly reduced with early identification and treatment, but treatment costs are also dramatically higher compared to babies treated after becoming symptomatic because they live much longer lives. This analysis used data from the primary literature, states currently screening for Pompe disease, and expert opinion to quantify the costs and benefits for babies with early and late treatment. The benefit-cost ratio was -18.02, meaning that for every dollar of costs to provide Pompe disease screening, there will be $18 worth of additional costs. 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.

Overview of Benefit-Cost Analysis for MPS-I (WAC 246-650-020)

The following summary explains the benefit-cost analysis performed for adding MPS-I to the mandatory newborn screening panel. This was presented to the technical advisory committee and the State Board of Health. The accompanying spreadsheet is the medical model for comparing the status quo, or a "No Screening Model" (upper section) with the MPS-I "Newborn 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 costs.

Point estimates and ranges for input variables were derived from published literature, expert opinion, and the Washington NBS program. The model predicts a benefit-cost ratio of 0.88, meaning that for every dollar of costs to screen newborns for MPS-I, there will be $0.88 worth of benefit. The model structure was developed during 2017 by the Washington NBS program and was presented to the NBS Advisory Committee on June 28, 2017 and later to the State Board of Health on August 9, 2017.

MPS-I is a multi-system disorder in which a lysosomal enzyme is deficient, leading to the accumulation of mucopolysaccharides (a type of carbohydrate), and other metabolites. It is caused by mutations in the alpha-L-iduronidase, gene (IDUA). MPS-I is inherited as an autosomal recessive trait, meaning that an individual needs two mutations to be affected, while individuals with one mutation are carriers.

While MPS-I is known to present as a spectrum of phenotypes, historically, people with MPS-I have been grouped into "severe" or "less severe" categories.

Severe MPS-I:
- Severe MPS-I is characterized by progressive skeletal and joint disease that produces deformities such as a characteristic "humpback" in patients by 6-14 months of age. Patients also exhibit progressive neurodegeneration, with cognitive delay evident by 12-24 months. Other symptoms include: increased intracranial pressure due to accumulation of excess cerebrospinal fluid, severe respiratory insufficiency, cardiac involvement, deafness, profound vision loss, gastrointestinal issues, and hernias. The median age of death for those with severe, untreated MPS-I is 6.8 years due to heart and lung failure and progressive neurologic disease. HSCT is typically recommended for those with severe MPS-I, before 6-12 months of age.

Less Severe MPS-I:
- Those with less severe MPS-I experience progressive joint disease that leads to a loss of range of motion with normal to slightly impaired cognition. Other symptoms include: chronic headaches or mild optic nerve compression due to accumulation of excess cerebrospinal fluid, chronic sinus infections, pulmonary hypertension and congestive heart failure, some hearing loss in adulthood, and gastrointestinal symptoms. If untreated, this form of MPS-I usually results in death in adolescence to early adulthood due to a variety of causes, consistent with the variety of clinical presentations.

There is a good newborn screening test for finding newborns with MPS-I. One of the tricky things about MPS-I is that a positive screen cannot predict the onset and severity of disease with certainty. Also, some babies have a pseudodeficiency or have one mutation and are carriers, meaning that they have low enzyme activity, but are clinically healthy. Those who meet clinical criteria may receive enzyme replacement therapy (ERT), a synthetic version of the missing enzyme which is administered by IV every week, for life. In addition, those with a severe form of MPS-I undergo a Hematopoietic Stem Cell Transplant, which is shown to prolong survival and preserve brain function and IQ.

We constructed an economic model to estimate the costs and benefits of NBS for MPS-I (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 MPS-I. We used information from IL, MO, and NY's screening programs to estimate the number of babies with MPS-I born in Washington State each year. We chose to use one year of babies born for this analysis.

The next step is to find out which newborns will be diagnosed early and benefit from treatment. In the No Screening Model a small percentage of newborns will be diagnosed early because they have a family member with MPS-I (positive family history). We use the sensitivity of NBS test to estimate the number of newborns diagnosed early in the Newborn Screening Model. The sensitivity is the ability of the test to correctly find the babies with MPS-I. Our model predicts that there will be about one baby with the severe form of MPS-I identified early each year through screening, compared to identification through family history only.

Next we compare the medical outcomes for early versus late identification.

We have constructed what is called a decision tree. The next step is to march 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 fall into each category. Because MPS-1 is rare, the estimates are sometimes less than one newborn. This may feel strange to some readers. Another way of looking at it would be to make the hypothetical population bigger. If we multiplied our birth population by 100, 0.4 newborns with severe MPS-I would become 40 newborns.

Now is the time to compare each of the outcomes. First we add the estimates of patients surviving, IQ points saved and babies with severe disability avoided together. We subtract the numbers of IQ points saved and severe disability avoided 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 2.59 IQ points and 0.078 babies from severe disability. We also calculate the costs of treating severe disability in both models and find the shift in costs.

Next we assign a value to saving an IQ point and avoiding severe disability. The value of one IQ point is estimated at $15,000. This is per unpublished, expert opinion by CDC economist, Scott Grosse. The lifetime costs of severe disability to age 40 is $3,500,000 per the expert opinion of Scott Grosse.

We need to estimate how much the NBS program costs. Based on information from other state screening programs, we estimated that the test would cost $3.12 per baby. Screening tests are not perfect. This means that some babies who do not have MPS-I will have positive NBS results. They need diagnostic testing to rule out MPS-I (their diagnostic test results will be normal).

The next step is to add up all of the benefits and the costs (IQ points saved, severe disability costs, newborn screening 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 0.88 which means for every dollar spent to screen babies for MPS-I, we receive about $0.88 worth of benefit.

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 the middle value. Following the base case is a sensitivity analysis

that varies the parameters to give what we judge to be very conservative and moderately liberal estimates to see their impact on the benefit-cost ratio. Note: the spreadsheet calculates the percentages and estimates, which have in some instances been rounded for simplicity. Subsequent calculations are unaffected by this rounding, so sometimes the number appear to not match perfectly.

Birthrate. This analysis is for a hypothetical birth cohort of **89,873 babies** (cells B10 and B41) which is the number of babies expected to be screened per year in Washington State. This number is based on the number of births screened in Washington in 2016.

- ***Prevalence.*** The prevalence used was **1 severe MPS-I case per 226,485 births** (cells D11 and D33) which is the prevalence found among 679,454 babies tested for MPS-I by three newborn screening programs (IL, MO, NY). This predicts 0.4 babies born with severe MPS-I in Washington each year.

- ***Percent of babies with MPS-I with a positive family history.*** These babies will be treated early in the "No Screening Model" because of a positive family history of MPS-I. The estimate for this parameter (**19%** - cell G5) was derived from data presented by Pastores, 2007. These babies are assumed to receive the same benefits of early treatment that babies screened at birth would enjoy (more IQ points).

- ***Sensitivity.*** The sensitivity, or the ability of the screen to correctly identify babies with MPS-I, is estimated at **99%** (cell G29). This may be a conservative estimate as there have been no known cases of MPS-I missed by newborn screening programs (zero false negatives). This sensitivity value predicts 0.39 true positives identified early and 0.01 false negatives (missed cases of severe MPS-I) per year.

- ***Specificity.*** The specificity, or the ability of the screen to correctly identify babies who do not have MPS-I, is estimated at **99.95%** (cell G53). The value used is the low estimate from three states currently screening. This specificity value predicts 44.9 false positives per year: these are babies who need diagnostic testing to determine enzyme activity, and sometimes DNA analysis to confirm a pseudodeficiency or other phenotype (they do not have severe MPS-I).

- ***Transplant-associated Mortality.*** In both the "no screening" and "newborn screening" models, babies receive a hematopoietic stem cell transplant (HSCT) as soon as possible following a diagnosis of severe MPS-I. In both models, the mortality associated with the HSCT is **13%** (cells J5, J14, J28, J36). This percentage comes from the expert opinion of Dr. Kanwaldeep Mallhi and is between the percentages found in the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) evidence report of 11% mortality at 36 months and 14% at 60 months for babies treated before 8 months of age (Kemper, 2015). The percent of babies who need a second HSCT due to graft failure (**8%,** cells L9, L19, L33, and L41) is also per the expert opinion of Dr. Mallhi. These babies experience the same transplant associated mortality rate of **13%** (cells O9, O19, O34, O41) for a second time.

- ***Difference in IQ: early vs. late treatment***. For babies identified and treated with a HSCT early, the benefit is an increased IQ. Data indicates that for each month of delayed treatment for severe MPS-I, babies lose 0.78 IQ points (Shapiro, 2015). Given that the single case of severe MPS-I detected so far by the Illinois newborn screening program received a HSCT at 3 months, and that the median age of transplant from a study of those clinically diagnosed was 15.6 months (Beck, 2014), the treatment delay in the "non-screening" model versus the

"newborn screening" model is 12.6 months. Multiplying these 12.6 months by the 0.78 IQ points lost per month, means that early treatment saves **9.79** IQ points (cells R7, R31) per patient. For those babies who require a second transplant, the treatment is essentially delayed by six months, per expert opinion of Dr. Elsa Shapiro, and therefore fewer IQ points (**5.13**, cells R11, R36) are saved.

- **Treatment costs.** The cost associated with the enzyme replacement therapy (ERT) and HSCT is **$842,500** according to the Wholesale Acquisition Cost of laronidase and expert opinion of Dr. Scott Baker (cells R17 and R44).There is no difference in treatment costs between early and late identified babies with severe MPS-I. Regardless of when or how the cases are detected, they are treated with the same procedure and the same associated cost. Similarly and using the same sources, the graft failure costs (additional HSCT and ERT) of **$798,100** (cells R20 and R48) are the same in both models.

The next step is to evaluate the differences between the models to quantify the benefits of screening. This is done by combining the IQ and associated severe disability estimates and assigning a dollar value to IQ points saved and the difference in severe disability support costs.

- **IQ Points saved.** The total number of IQ points for each model are compared; there are **0.61** IQ points (cell X3) in the "No Screening Model" and **3.2** IQ points (cell X26) in the "Newborn Screening Model." The "Newborn Screening Model" has five times the IQ points saved as the "No Screening Model." The difference between the two models is **2.59 IQ points saved** (cell X34).
- **Value of IQ points saved.** The value of one IQ point is estimated at **$15,000** (cell V35). This is per unpublished, expert opinion by CDC economist, Scott Grosse. The value of IQ points saved by newborn screening is the number of IQ points saved multiplied by the monetary value of an IQ point. The model estimates yearly benefits of **$39,000** (cell X36) for saving IQ points of babies with MPS-I.
- **Difference in Severe Disability: early vs. late treatment**. By retaining IQ points in babies with severe MPS-I through early treatment, about **28%** (cell V37) will be spared from the severe disability associated with an IQ less than 70. This statistic is derived from Shapiro, 2014.
- **Severe Disability Avoided.** In the "No Screening Model", **0.07** (cell X2) early identified patients were surviving. In the "Newborn Screening Model", **0.34** (cell X25) early identified patients were surviving. Therefore, an additional **0.28** (cell X33) babies will be early identified annually through screening and **0.078** (cell X38) of them will be spared from severe disability.
- **Value of Severe Disability Avoided.** The lifetime costs of severe disability to age 40 is **$3,500,000** (cell V39) per the expert opinion of Scott Grosse. The model estimates yearly benefits of **$271,000** (cell X40) for saving babies with MPS-I from severe disability.
- **Total benefits.** The total benefits (**$309,700**, cell X43) are the sum of the value of IQ points saved and the severe disability cost saved by screening.

Costs are estimated next.

- **Cost of screening.** The estimated costs of IDUA enzyme activity analysis is **$3.12 per baby** (cell B46).

- *Costs of diagnostic testing for false positives.* Only the false positive babies are counted for diagnostic testing costs because the babies with MPS-I will have diagnostic enzyme and DNA testing regardless. Note: infants with less severe MPS-I will likely be represented within the false positive group. Although they may benefit from early detection, that benefit is not quantified in the model. The cost for diagnostic testing is **$1,600** per baby (J45) per Rhona Jack of Seattle Children's laboratory.
- *Total costs for MPS-I newborn screening.* The birthrate multiplied by cost per baby is **$280,200** (X46).
- *Total costs for diagnostic testing of false positives.* The total cost per year for the false positive cases outlined above is **$73,300** (cell X47)
- *Total costs of Newborn Screening Model.* The annual costs of NBS for MPS-I are estimated to be **$ 353,500** (cell X48).

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

- *Benefit/Cost Ratio.* $309,700 of benefits divided by $353,500 of costs yields a benefit/cost ratio of 0.88 (cell X49).

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 3 contains three estimates for each parameter, the best guess estimate used in the base case 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 sensitive to reasonable changes in several parameters. That is, several alternative estimates in key parameters generated a benefit/cost ratio greater than one, which indicates that benefits outweigh the costs.

Table 3: MPS-I Sensitivity Analysis

Parameter	Base Case	Conservative Estimate	Liberal Estimate	B/C Ratio Swing
birth prevalence - 1 in:	226,485	352970	100000	0.56 to 1.98
% with MPS-I family hx	0.19	0.1	0.28	0.97 to 0.78
sensitivity	0.99	0.98	1	0.87 to 0.89
specificity	0.9995	0.9992	0.9998	0.78 to 1
median age at tx (months)	3	1.5	6	0.89 to 0.85
rate of graft failure	0.08	0.04	0.16	0.88 to 0.87
transplant-related mortality	0.13	0.07	0.26	0.94 to 0.74
rate of IQ loss (per month tx delay	0.78	0.39	1.55	0.82 to 0.99
value of an IQ pt	$15,000.00	$10,000.00	$20,000.00	0.84 to 0.91
% saved from severe disability	0.28	0.22	0.35	0.7 to 1.05
cost of treating disability (40y)	$3,471,584.73	$2,944,435.13	$3,863,833.53	0.76 to 0.96
cost of NBS test	$3.12	$1.00	$5.00	1.9 to 0.59
cost of false (+)	$1,631.30	$815.65	$16,313.00	0.98 to 0.31

hx = history, tx = treatment, pt = point

Conclusion (WAC 246-650-020)

Early identification of babies with severe MPS-I is critical to their brain development. The rate of cognitive decline is greatly reduced with early treatment and medical costs associated with lifetime severe disability are lower compared to babies treated after becoming symptomatic. This analysis used data from the primary literature, states currently screening for MPS-I, and expert opinion to quantify the costs and benefits for babies with early and late treatment. Using our best estimates for parameters, the benefit-cost ratio was 0.88, meaning that for every dollar of costs to provide MPS-I screening, there will be $0.88 worth of benefits. The sensitivity analysis showed that the model is sensitive to several key parameters. Under a number of reasonable estimates in the sensitivity analysis, the cost-benefit ratio became greater than one.

<u>Reports to the Board and the Public (WAC 246-650-040)</u>

WAC 246-650-040 outlines requirements for the Department to compile an annual report for the Board and a separate annual report for the public. The annual reports to the public are required by RCW 73.83.080, which has an expiration date of January 1, 2020. The Department would like to voluntarily maintain this reporting requirement beyond the expiration date so the proposed rule leaves the requirement but eliminates the expiration date in subsection 5. The report currently includes 3 components related to compliance rates and performance rates of hospitals in meeting required deadlines for newborn screening. The third component in the report is, "the time taken by health care providers to notify parents and guardians after being notified by the department about infant screening tests that indicate a suspicion of abnormality that requires further diagnostic evaluation. Notification times will be summarized and reported in increments of days." The proposed rule eliminates this requirement from the reports to the public. The Department has indicated that this data is often not complete and is currently not being used in anyway. Eliminating this data component will not have a monetary cost and may actual reduce staff time associated with collecting the information.

SECTION 6:

Identify alternative versions of the rule that were considered, and explain how the department determined that the rule being adopted is the least burdensome alternative for those required to comply with it that will achieve the general goals and specific objectives state previously.

Alternative 1:

The Board considered not adding Pompe and MPS I to the required screening panel. Population-based newborn screening is the least burdensome alternative because it is the best way to ensure that newborns with these conditions are identified and can receive treatment before the condition advances to the point where it is untreatable.

Alternative 2:

The second alternative considered was to establish a system to screen only newborns who are at high risk because of a positive family history. This strategy presents challenge because at a maximum, only a minority of babies at risk for Pompe (33.9%) and MPS-I (19%) would benefit from early identification and there is no current avenue for educating prospective parents about such a program.

SECTION 7:

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

SECTION 8:

Determine 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 rule does not impose more stringent performance requirements on private entities than on public entities.

SECTION 9:

Determine 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 rule does not differ from any applicable federal regulation or statute.

SECTION 10:

Demonstrate 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.

There are no other applicable laws.

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