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Galactosemia: Testing Newborn Infants for Metabolic Disorders

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Abstract: Washington State requires blood spot screening for metabolic disorders in the first days after birth. Galactosemia creates large costs due to hospitalization, difficulty in diagnosis, mortality, and/or brain damage. Some damage can be eliminated through early detection and removal of lactose from the diet. This analysis uses a medical outcome tree to evaluate gains from neonatal screening, shows net benefits of \$14 million for testing, and reviews the results of the first few years of screening. Screening is costly and there is a long term cost because 74% of the infants who would have died will suffer from Classic Galactosemia, which generates a slow reduction in IQ. IQ loss in children with Classic Galactosemia may be reduced by avoiding lactose and galactose but is not eliminated. This analysis values the linked disabilities directly, including them in a cost per QALY estimate of \$22,000. The program has been in effect for nearly 3½ years now. The frequency of detection indicates a higher frequency of the disorder (.0024%) than was expected (.0016%) prior to screening.

Washington's infant blood spot program

One in 3,000 newborn children carries a metabolic disorder that interferes with the growing child's ability to live a normal life. Some of these disorders are detectable and treatable. If screening can detect the disorder early and early treatment makes a difference in the medical outcomes for the children then it is possible that a screening program which covers all infants in the state will have net benefits.¹

Newborn screening blood spots are typically collected on the first and 10th day of life. The screening results are available within 7 days of birth.²

Washington added Galactosemia to screened disorders 4 years ago. Washington added Galactosemia to the testing because:

- Prior to screening about 1/3 of infants with Galactosemia died.
- Galactosemia screening reduces permanent damage by cutting short the duration of exposure to the metabolic disorder.
- For Galactosemia the results of the first blood spot screen become available just as symptoms are developing.
- Galactosemia is rare.
- The enzyme activity assay can identify infants with Galactosemia unless the infant has been transfused.

Background on Galactosemia

Galactosemia is a rare recessive genetic metabolic disorder. Its frequency depends on the genetic mix of the population. Further, in each sub group within a population the genetic trait causing the disorder may vary.³ Washington initially expected one in 60,000 infants (0.0017%)

¹ Washington now tests for PKU, Congenital Hypothyroidism, Hemoglobinopathies, Adrenal Hyperplasia, Biotinidase Deficiency, Galactosemia, MCAD (Medium Chain Acyl Co-A Dehydrogenase Deficiency), Homocystinuria, MSUD (Maple Syrup Urine Disease), Cystic Fibrosis.

² Mike Glass, DOH. Bloodspots are generally sent within 24 hours and received within 2 days. The lab processes them within 24 hours of receiving them and notifies the pediatrician if there is a problem. If the pediatrician is not available, the parents are notified. Generally testing and notification occurs in 4 to 7 days.

³ Even within Europe the genetic origin differs markedly. In the Spanish and Portuguese population p.Q188R is the most prevalent mutation, accounting for 50% and 57.8% of galactosaemic alleles. The gene K285N is the most

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to be born with Galactosemia, or 13.8 infants born with Galactosemia in a ten year period. Thus far in the first 39 months of testing the program detected 6 infants. Two of these were already in the hospital with symptoms and no infants died.

Galactosemia is a serious metabolic disorder caused by the inability of the body to process galactose into glucose.⁴ The initial onset can be severe, causing mortality. Symptoms of untreated Galactosemia include poor weight gain, reduced growth, vomiting, diarrhea, lethargy, hypotonia, jaundice, hepatomegaly, bleeding, anemia, septicemia, IQ deterioration, speech problems, cataracts, and seizures.

In most infants lactose is broken down into galactose and glucose in the intestine. Once galactose is absorbed, it is then converted to glucose primarily by 3 enzymes of the Leloir pathway:⁵ galactokinase (GALK), galactose-1-phosphate uridylyltransferase (GALT), and uridine diphosphate galactose-4'-epimerase (GALE). In galactosemic infants the GALT enzymes are not available in sufficient quantities and galactose-1-P can build up to toxic levels in the body.

Galactosemia Type I or Classic Galactosemia has mutations in the GALT gene and a shortage of the enzyme galactose-1-phosphate uridylyl-transferase. The shortage can be severe resulting in Classic Galactosemia or the shortage can be more moderate resulting in the Duarte variant.

Treatment

Removing lactose from the diet significantly reduces galactose.⁶ Infants who are ill with a variety of symptoms are switched to a soy-based formula to allow the body to recover. The removal generates an improved IQ outcome. However, the long-term success of the diet depends on the genetic basis of the Galactosemia. For some children with Classic al Galactosemia, the IQ may degenerate some over time. Occasionally, a typical child with a severe Galactosemia (Q188R homozygosity) may yield an unexpectedly mild outcome even with noncompliance with a diet, indicating that other genetic factors may moderate a typical result.⁷

Benefits of Galactosemia Screening

Thus far, screening for Galactosemia has provided diagnosis either before or just as the infant first presents with symptoms. Screening allows an immediate shift away from lactose in the diet. Screening and an early diet shift reduces mortality and the immediate impact of high doses of galactose.

common cause of Galactosemia in the Slovenian population and occurs in 0.29% of the population. See Lukac-Bajalo J, Kuzelicki NK, Zitnik IP, Mencej S, Battelino T., *Higher frequency of the galactose-1-phosphate uridylyl transferase gene K285N mutation in the Slovenian population*, *Clin Biochem*. 2006 Dec 5. See Gort L, Boleda MD, Tyfield L, Vilarinho L, Rivera I, Cardoso ML, Santos-Leite M, Giros M, Briones P., *Mutational spectrum of Classic al galactosaemia in Spain and Portugal*, *J Inherit Metab Dis*. 2006 Dec;29(6):739-42.

⁴ Much of the overview information on the function of Galactosemia is drawn from J. B. Holton, J. H. Walter, and L. A. Tyfield, *Galactosemia*, Chaper 72, in *The Metabolic & Molecular Bases of Inherited Disease*, eds.Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill.

⁵ There are other ways that the body transforms galactose such as the pyrophosphorylase pathway or oxidation to galactonate but these are less effective than the Leloir pathway.

⁶ Traces of galactose are found in some fruits and vegetables and the body may generate galactose on its own, however milk and milk products are the primary source.

⁷ Panis B, Bakker JA, Sels JP, Spaapen LJ, van Loon LJ, Rubio-Gozalbo ME., *Untreated Classic al galactosemia patient with mild phenotype*. *Mol Genet Metab*. 2006 Nov;89(3):277-9.

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Benefits of screening in the model include:

- Some infants will not die. Without the program, in a 10 year period, a statistical mortality of 6.5 children would be expected from the onset of infections, poor weight gain, vomiting, diarrhea, lethargy, hypotonia, jaundice, hepatomegaly, bleeding, anemia, septicemia, and seizures. With newborn screening the statistical mortality is reduced to nearly zero.
- Some infants will avoid brain damage from the early high doses of lactose. All infants with earlier diagnosis would have significantly reduced neural damage from the early exposure. Statistically, 3.7 children would shift from having IQ damage to have a normal IQ outcome.
- Screening is expected to reduce the cost of clinical identification. Without the program most galactosemic infants are hospitalized in neonatal intensive care units with an expected reduced cost of stay of \$14,800 per child.⁸
- Finally, screening will identify some infants with Duarte or other forms of mild Galactosemia who may benefit from elimination of lactose from the diet. These infants are not counted in the analysis.

Costs of Galactosemia Screening

The costs of screening include direct costs of screening, indirect medical and lifestyle costs, and negative medical outcomes for children who would otherwise have died. Long-term medical outcome costs dominate the losses associated with the program:

- Screening all newborns: The DOH expects to screen 827,000 newborns at a cost of \$2.80 each over a 10 year period. No cost is added on for the blood spot collection since it is already being done. The expected present value of this cost for the first 10 years of the program is \$2 million.⁹
- Follow-up testing for false positives: Immediate testing of positive screened children will eliminate the false positives.¹⁰ The estimated present value of costs for the first 10 years is \$2,800.¹¹
- Monitoring and tests: Children with Galactosemia have to be monitored. The children who would have died would be expected to have a present value of \$59,000 in testing costs.¹²
- Clinical program: The children who would have died would be expected to need the clinical program which currently trains families how to select food, explains test results, and intervenes with the child when he or she decides to eat inappropriately. This has a lifetime cost of \$400,000.¹³
- Food sorting: This is a time consuming activity, which involves avoidance of foods which contain lactose. Label reading requires knowing the names of the foods and food

⁸ Angus DC, Barnato AE, Linde-Zwirble WT, Weissfeld LA, Watson S, Rickert T, Rubenfeld GD, *Use of Intensive Care at the End of Life in the United States: An epidemiological study*, Critical Care Medicine, 2004 Vol 32(3):638-43.

⁹ Based on a 3% discount rate.

¹⁰ Research has not indicated harm from false positive tests. Brosco JP, Seider MI, Dunn AC. *Universal newborn screening and adverse medical outcomes: a historical note*. Ment Retard Dev Disabil Res Rev. 2006;12(4):262-9.

¹¹ Based on Plus cell enzyme assay cost for all galactosemics and false positive neonates discounted at a 3% discount rate.

¹² Present value based on 2 blood tests per year for life, at a cost of approximately \$300 per year, discounted at a 3% rate.

¹³ Based on current average costs for work with 16 children at the clinical program for Metabolic Disorders at the University of Washington and the estimated share of costs based on the disorder.

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additives which contain lactose. This is expected to require 7 hours per month valued at \$25 per hour for a total cost of \$400,000 over the life span of the children who would have died.¹⁴

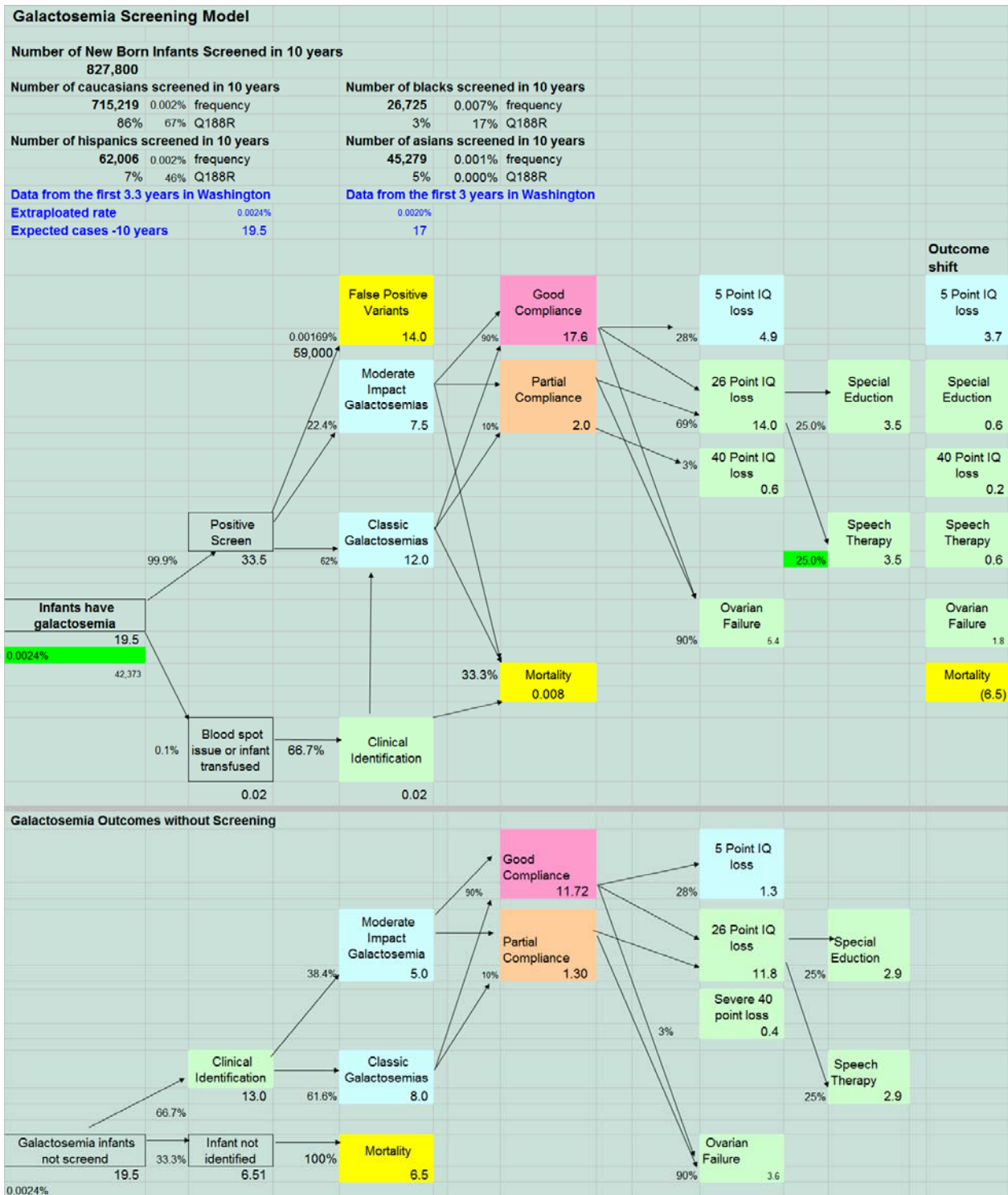
Some infants who have Classic Galactosemia will have negative medical outcomes and reduced capacities.

- IQ loss: Some children who do not die will experience a long-term slow deterioration of IQ and may also have speech difficulty and/or ataxia. This paper uses values that are in the literature which are based on children who were clinically diagnosed and where compliance was not always good. These are valued based on an IQ loss of 5 points, 25 points, and with losses up to 40 points for a few children.¹⁵ Without the program, with average diagnosis periods, 12 children would be expected to experience ataxia, speech problems, and/or a drop in IQ. Based on the literature, with screening, 14 children would be expected to experience ataxia, speech problems, and/or a drop in IQ and half of these will require either speech therapy or special education.¹⁶ However *recent experience with rapidly diagnosed children under the age of 10, who have good compliance, indicates that the model probably overstates the losses.*
- Cost of care: If a child with a severe IQ loss, yielding an IQ of 60, does not die the model uses \$1,022,000 in additional non-medical and indirect costs.
- Ovarian failure: 90% of the surviving girls experience ovarian failure. These young women will require replacement hormones and will be unable to bear children.

¹⁴ Based on Tacoma/Seattle average hourly earnings of \$18.90 per hour and approximately 30% benefits.

¹⁵ The most common gene seems to be responsible for a slow downward drift into the low average IQ range. Antshel KM, Epstein IO, Waisbren SE. *Cognitive strengths and weaknesses in children and adolescents homozygous for the galactosemia Q188R mutation: a descriptive study.* *Neuropsychology*. 2004 Oct;18(4):658-64

¹⁶ This may be a very high figure in that all of the Classic galactosemic children are expected to have a downward IQ drift and only 67% of the moderate form children with good compliance are forecast to experience no IQ damage. Tentative new evidence, through ten years of screening in Georgia, indicates 1 galactosemic child was missed and developed mental retardation, but 47 children would have been expected to have developed retardation due to galactosemia. The results have been left without adjustment due to earlier literature indicating Classic Galactosemia yields IQ reductions over time. Given the time frame, some of the cases may not have had a chance to develop and be diagnosed. *Mental Retardation Following Diagnosis of a Metabolic Disorder in Children Aged 3-10 Years*, *MMWR*, CDC, May 7, 1999, No. 17.



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The Galactosemia Medical Outcomes Model

Medical outcomes were derived based on a tree of outcomes generated by multipliers. Outcome levels are most sensitive to the multipliers at the “front end” or left hand side of the model see Figure 1). These multipliers were chosen based on the literature and medical expertise at the University of Washington.

- **Frequency:** The model applies the current frequency for the disorder in Washington, 0.0024%. This would indicate 19 children are likely to be identified over a 10 year period. This is a slightly higher frequency than the rate found in Texas (0.0021%), possibly due to the larger Caucasian population and substantially higher than the frequency used for the original analysis (0.00167), which supported the adoption of the test.¹⁷
- **False Negatives:** The test itself should report out 100% of the infants. However, if the infant has been transfused the test may generate a false negative. This value has been set at 0.123 based on blood spot issues. If the bloodspot itself is unsuitable and the lab obtains a new one, then there may be a delay. For example in 2005 there were 31 unsuitable bloodspots that were not resolved and 95 invalid screens.

- **True Positives:** This is a function of 1 minus the rate for false negatives.

Washington - Positive Results				(1/1-3/31)
Galactosemia	2004	2005	2006	2007
Classic	2	2	1	1
Partial (referred)	24	6	5	3
False (+)	2	2	1	0

- **False Positives:** 1 in 59,000 is the estimated number of false positives.¹⁸

- **Share of Classic Galactosemics:** Classic Galactosemia generates more severe long-term medical outcomes including IQ and speech deterioration over time. It is caused by several mutations. In North American Caucasians the Q188R mutation, which causes classic symptoms, accounts for 60 to 70% of the mutations. For all of the cases identified by screening, for which we have data, Q188R is identified. Thus, in Washington it is at least half.

Washington Case - and DNA			
Cases	Sick	Treatment	DNA
#1	yes	5 days	
#2	yes	5 days	
#3	no	7 days	
#4	no	8 days	Q188R/?
#5	no (mild jaundice)	6 days	Q188R/?
#6	no	4 days	Q188R/R333W

We extrapolated the rate of 63.5% to the white population in Washington. In Hispanics of Mexican origin it accounts for 50 – 58% of cases. Given the relative rates of Hispanics of Mexican vs. other Hispanic origins, we extrapolated the rate of 46% for Washington Hispanics. In the black population, the rates for Classic Galactosemia range from 12% to 21% of the Galactosemic population. Therefore, we applied the rate of 16.5% to Washington’s black population.¹⁹ Galactosemia is not as common in the Asian

¹⁷ This does not appear to be a small numbers problem because dropping back to the recorded cases of the first 3 years and eliminating a case only reduces this frequency to .0020%

¹⁸ The Magnitude and Challenge of False Positive Newborn Screening Test Results, Charles Kwon, Phillip Farrell, Archives of Pediatric Adolescent Medicine, vol. 154, July 2000

¹⁹ Unless noted, this section relies on: *Galactosemia*, Chaper 72, J. B. Holton, J. H. Walter, and L. A. Tyfield, in The Metabolic & Molecular Bases of Inherited Disease, eds.Scriver, Beaudet, Sly, Valle, Childs, Kinzler, Vogelstein, 8th edition, McGraw Hill, pages 1564 through 1567.

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population. In Japan, only 1 in a million children is expected to be born with Galactosemia. In the Philippines the rate is 1 in 106,006.²⁰ The rate is unknown for other Asian populations. Within these lower levels it is unclear the share that are Classic Galactosemia. Finally, the screening programs are identifying children who might not have been identified clinically. The model retains the early prescreening relative rate of Classic to less severe forms of Galactosemia and may therefore overstate the IQ loss estimated below.

- **Share of moderate impact galactosemics:** Infants with more moderate forms of Galactosemia are the remaining portion of the galactosemic population.
- **Mortality** is estimated at 1/3 for the children who are clinically diagnosed, based on experience at the University of Washington prior to the screening program.²¹ Children who have been screened are diagnosed more rapidly because the results become available just as the child is presenting with symptoms. The estimated mortality for screened infants is zero.
- **Diet compliance:** Parents and children who comply with dietary restrictions have better outcomes. Generally, compliance is excellent because the immediate physical consequences include vomiting, illness and possibly shock and hospitalization. However, 10% partial compliance was assumed in order to provide a conservative analysis.
- **IQ outcomes:** Galactosemia screening is relatively new. The model is conservative basing its results on data from populations for which the IQ loss is high by comparison with the recent Washington experience.

Long term IQ test results were available for 24 Irish children identified through screening.²²

- 5 had IQs in the 64 to 74 range – of these, one was taken off the diet for 8 years.
- 1 had an IQ of 84
- 18 had IQs in 91 to 119 range

British elementary children identified by screening were tested for IQ effects. Not all could be tested.²³

- 34 cases were tested for IQ with a mean score of 79. 10 had scores over 85, 21 had scores of 56 – 85, 3 had scores under 56.
- 1 was homoallelic for Q188R with complete deletion and had an IQ of 60
- 30 were homoallelic for Q188R and 23 had average IQ of 74, of these 18 had scores over 85
- 15 were heteroallelic for Q188R/(K285N or L195P) and 9 had average IQ of 95, of these 6 had scores over 85

Washington's record is better but it is not clear why. The University of Washington program covers Washington and Alaska and on average 3 new Galactosemia patients a year come into the clinic. Children come in semi-annually for testing and education. With good compliance the children do not seem to degenerate as rapidly as recent papers suggest and IQ seems stable. The children are tested for IQ at 6 years of age. It is the

²⁰ Dans LF, Estrada SC, Tamondong MR Jr, Lacey JJ, Bernal RM, Padilla CD, Cost-benefit analysis of newborn screening for galactosemia in the Philippines. *Southeast Asian J Trop Med Public Health*. 2003; 34 Suppl 3:215-20.

²¹ C. Ronald Scott, M.D., Professor, Pediatrics & Medicine, University of Washington School of Medicine

²² Badawi N, Cahalane SF, McDonald M, Mulahir P, Begi B, O'Donohue A, Naughten E, Galactosemia- A Controversial Disorder. Screening Outcome. Ireland 1972 – 1992, *Irish Medical Journal*, Jan/Feb 1996, Vol 89(1):16-7

²³ Shield JP, Wadsworth EJ, MacDonald A, Stephenson A, Tyfield L, Holton JB, Marlow N., *The relationship of genotype to cognitive outcome in galactosaemia*. *Arch Dis Child*. 2000 Sep;83(3):248-50.

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older patients in their 20s and 30s, who suffered significant neurological impacts at onset and who may have had mild noncompliance with the dietary restrictions, who then have significant mental handicaps. While the clinic manages less than 20 of these elementary school age patients who have been IQ tested in the normal range, the odds above indicate that some lower scores should be showing up but they are not. Young teenagers often experiment with lactose by eating something like a cheeseburger with friends. They land in the hospital and their doctor presents them with their choice, which is a relatively normal life without lactose or being violently ill and suffering brain damage. 28% of the children with good compliance are expected to have IQs in the normal range. The remaining children are expected to have some IQ loss.²⁴

- **Special education or speech therapy:** Of those experiencing IQ loss or ataxia, 25% are expected to need special education and 25% are expected to need speech therapy.²⁵
- **Ovarian Failure:** 90% of the girls with Galactosemia will develop ovarian failure and require hormone replacement therapy. They will be unable to have children.

Economic values applied to the medical outcomes

The model generates final values based on the following estimates of the values of the medical outcomes. Several of the values are tested for sensitivity by allowing them to vary for the Monte Carlo procedure, which was run on the model as a whole. The Monte Carlo makes more conservative assumptions than the expected values in the tables.

- The **value of a statistical life** is large and values range from \$458,000 to \$26 million.²⁶ The values are based on cost of illness, wage and risk studies, and reported willingness to pay. The value of a quality adjusted life year (QALY) ranges from \$21,000 to \$1.2 million. In 28 out of 35 articles the value of a QALY is over \$100,000. Thus, this analysis bases the value of life years at \$118,437. This is the median value for revealed preference measures of the value of a quality adjusted life year.
- The **QALY** adjustment for medical outcomes in the form of IQ loss is 0.85. This is extrapolated from a QALY value of .7393 for minor brain damage and .3903 for severe brain damage.²⁷
- **Minor neural damage that reduces IQ** reduces the function of the individual in all areas of life. Without retardation, loss of IQ generates a loss of productivity, which is valued at \$17,100 per IQ point, in 2006 dollars.²⁸ Thus, even when the difference in IQ is as small as a few IQ points, a loss is imposed on the individual. This value has been

²⁴ C. Ronald Scott, M.D., Professor, Pediatrics & Medicine, University of Washington School of Medicine

²⁵ Verbal dyspraxia is reported at rates of 57% for children with 20th percentile cranial size and up. The Washington experience is better than this (25%) but there is a small numbers problem and these numbers should be used with caution. For the Monte Carlo the estimate was attached to a uniform distribution ranging from .25 up to .57.

²⁶ Hirth, Richard A., Michael E Chernew, Edward Miller, A. Mark Fendrick, William G. Weissert, *Willingness to Pay for a Quality Adjusted Life Year: In Search of a Standard*, *Medical Decision Making* 2000: 20 ppg 332-342

²⁷ Bennett JE, Sumner W, Downs SM, Jaffe DM, *Parent's Utilities for Outcomes of Occult Bacteremia*, *Archives of Pediatric Medicine*, 2000, Vol 154:43-8. This paper did not have the same average impact levels as those for Galactosemia. We estimated the parental utility shift for the IQ loss for minor brain damage using an IQ drop of 15 and for the severe brain damage using an IQ drop of 55 based on the descriptors given the parents. This utility loss per IQ point was then extrapolated to a 5 point, a 25 point, and a 40 point IQ loss. The value used is the weighted average of the losses based on the number of children in each medical outcome category.

²⁸ Grosse SD, Matte TD, Schwartz J, Jackson RJ, "Economic gains resulting from the reduction in children's exposure to lead in the United States," *Environmental Health Perspectives*. 2002. 110(6).

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assigned a Weibull distribution with values ranging from \$12,700 to \$17,200 for the Monte Carlo.

- **Ovarian failure** will require hormone replacement therapy at \$360 per year and will mean the girl is unable to bear children. This latter is valued at \$21,000.²⁹

Net Present Value of Galactosemia Screening Benefits

The addition of Galactosemia screening in Washington is expected to generate net benefits of \$14 million over a period of 10 years. The Monte Carlo procedure indicates a range of \$7 million to \$18 million, with a mean of \$12.9 million and a standard deviation of \$1.9 million. The cost per QALY saved is 24700. The Monte Carlo procedure indicates a range of \$20,000 to \$30,000 with a mean of \$25,700.

The fact that screening may save 4 or 5 lives over a 10-year period dominates the other modeled values. The QALYs saved generate a present value of \$18.7 million. The model is sensitive to the assigned value of a QALY and contributes to the high standard deviation of the Monte Carlo. The reduced cost of clinical identification does not have much impact.

Testing of all infants for 10 years generates the largest cost of the program and the UW clinic that serves them adds to a lifetime cost of \$2.4 million. The negative medical outcomes generate over \$1.5 million in costs. Finally, the attendant medical costs of food sorting and following the children medically generate some small costs.

The model is very sensitive to the frequency of the disorder. The model uses the current frequency of detection of the disorder in Washington, since there are no known cases that the program missed. The model is very sensitive to the probabilities attached to reductions in IQ. It is possible that future testing of IQs for the children at the UW clinic will improve our understanding of this population's prognosis.

²⁹ The ability to reproduce is highly valued by some and regarded as a nuisance by others. Couples may spend hundreds of thousands of dollars to conceive a child including enduring significant discomfort. Others may opt for tubal ligations to prevent children. This model assumes that most women would want children and uses expenditures which indicate a minimum willingness to pay from Farquhar CM, Williamson K, Brown PM, Garland J, *An Economic Evaluation of Laparoscopic Ovarian Diathermy versus Gonadotrophin Therapy for Women with Clomiphene Citrate Resistant Polycystic Ovary Syndrome*, Human Reproduction, May 2004, 19(5):1110-5..

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Estimating Net Benefits		
Gain		Expected Value
Mortality avoided and value of QALYs	(6.5040)	\$ 18,753,392
Reduced cost of clinical Identification	19.5	\$ 254,036
Cost		
Foregone income and special Education		
Mild IQ Loss	3.68	\$ (314,509)
Significant IQ Loss	0.55	\$ (156,554)
Significant IQ Loss and Speech Therapy	0.55	\$ (372,475)
Severe IQ Loss	0.61	\$ (623,609)
Ovarian Failure		
	1.80	\$ (32,702)
Cost of effort required for food sorting		
	6.50	\$ (412,036)
Cost of monitoring tests		
	6.50	\$ (59,016)
Follow up test		
		\$ (2,971)
Cost of clinical program (share)		
	6.50	\$ (398,758)
Cost of Newborn Screening		
		\$ (2,036,479)
Measures of gain or loss		
Net		\$ 14,598,318
Net without mortality		\$ (4,155,074)
Cost per QALY		\$ (22,242)

Addendum: Comparison to Other Research

Carroll and Downs³⁰ recently generated a cost per QALY of \$94,000 for Galactosemia and compares it to a \$50,000 cut off point. One point of the article cited³¹ regarding the cut off point of \$50,000 was that this number is not supported and is probably low. We have used \$118,437. Using their \$50,000 cut off, our model still generates net benefits of **\$2.7** million.

We believe the reasons for their high cost per QALY estimate include:

(1) An overestimate of the IQ impact of the disorder

Carroll and Downs extrapolates that 90% of children will experience moderate IQ developmental delay and that 10% will experience severe delay. This paper extrapolates that 28% will experience a 5 point IQ drop, 69% will experience a 26 point IQ drop and 3% will experience a 40 point IQ drop. The average IQ drop reflected by this distribution is 78, which is conservative in that it is lower than the 84 point average reflected in recent work on Q188R by Antshel, Epstein, and Waisbren.³²

(2) Extrapolation of this overestimate to a large utility reduction in the QALYs using a mental retardation basis

Carroll and Downs uses a QALY estimate of .5625 for the children who are moderately delayed and .3909 for children who are severely delayed. The paper³³ these values are taken from only has values of .7393 for mild delays and .3909 for severe delay. The moderate delay figure was extrapolated from these two values. The description of the delay does not match the children who have only a 5 point IQ loss and has behavioral descriptions that take the child out of the normal range. This paper, therefore, assumed the .7393 QALY was for a 15 IQ point loss. Likewise, the description for the severe delay describes a child with a less than 50 IQ. Therefore, we assumed this was for a 55 IQ point loss. We used these assumptions to calculate an IQ point basis for the QALY reduction. We used .913 QALY for the children with a normal IQ or a 5 point loss, a .644 QALY for the children with a 76 point loss, and the .3909 for the children with the 40 point IQ loss. This was used to generate a weighted average of .85 QALY for the Galactosemic population.

(3) Extrapolation of a larger resulting direct and indirect cost for IQ loss

Carroll and Downs uses \$44,192 for mild impairment, \$77,079 for moderate impairment, and \$1,042,110 for mental retardation and sites MMWR (53), where that document only has values for mental retardation. The value for the general category of mental retardation in MMWR(53) includes (1) direct medical costs, (2) direct non-medical, and (3) in-direct care. This paper estimates direct medical costs explicitly for the condition in this paper rather than extrapolating from another disorder. This analysis uses foregone income per IQ point at \$17,100 per

³⁰ Carroll AE, Downs SM., *Comprehensive cost-utility analysis of newborn screening strategies*, *Pediatrics*, 2006 May;117(5 Pt 2):S287-95.

³¹ Hirth, Richard A., Michael E Chernew, Edward Miller, A. Mark Fendrick, William G. Weissert, *Willingness to Pay for a Quality Adjusted Life Year: In Search of a Standard*, *Medical Decision Making* 2000: 20 ppg 332-342

³² Antshel KM, Epstein IO, Waisbren SE. *Cognitive strengths and weaknesses in children and adolescents homozygous for the galactosemia Q188R mutation: a descriptive study*. *Neuropsychology*. 2004 Oct;18(4):658-64

³³ Bennett JE, Sumner W, Downs SM, Jaffe DM, *Parent's Utilities for Outcomes of Occult Bacteremia*, *Archives of Pediatric Medicine*, 2000, Vol 154:43-8.

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point for galactosemics in the 95 point and 75 point category and \$1 million for the non-medical and indirect costs of retardation. Carroll and Downs estimate the cost of ongoing treatment at \$9439 per year, extrapolating from treating Congenital Hyperplasia. Our cost estimate is \$4,400 per year.

(3) An underestimated frequency of the disorder

Carroll and Downs uses a frequency of 1.5 per 100,000 where Washington experience indicates a frequency of 2.4 per 100,000.

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Preliminary – do not cite

Preliminary – do not cite
 Monte Carlo
 Results

Forecasts

Worksheet: [Galactosemia 5 18 07.xls]Values

Forecast: \$/yr of life

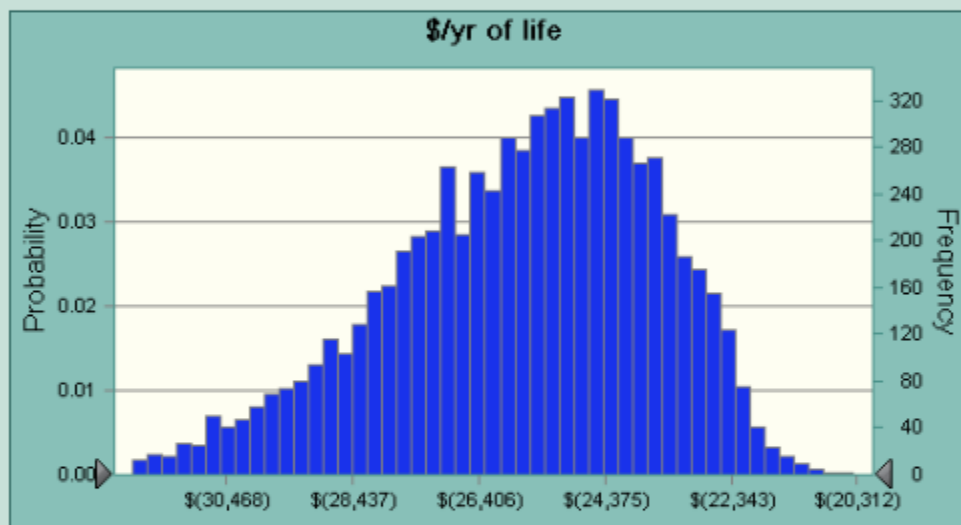
Cell: D46

Summary:

Entire range is from \$(35,066) to \$(20,380)

Base case is \$(24,711)

After 7,227 trials, the std. error of the mean is \$26



Statistics:	Forecast values
Trials	7,227
Mean	\$(25,767)
Median	\$(25,489)
Mode	—
Standard Deviation	\$2,221
Variance	\$4,934,477
Skewness	-0.6299
Kurtosis	3.30
Coeff. of Variability	-0.0862
Minimum	\$(35,066)
Maximum	\$(20,380)
Range Width	\$14,685
Mean Std. Error	\$26

Preliminary – do not cite

Forecast: \$/yr of life (cont'd)

Cell: D46

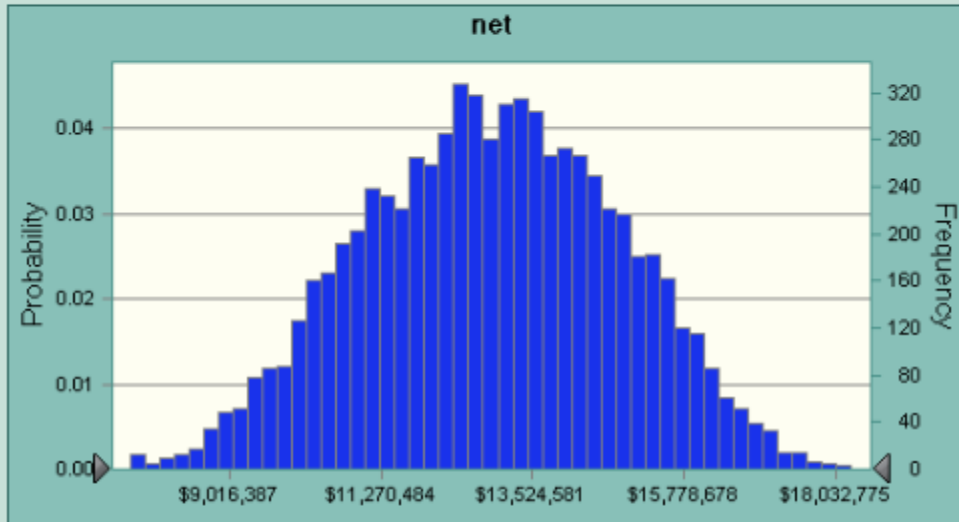
Percentiles:	Forecast values
0%	\$(35,066)
10%	\$(28,814)
20%	\$(27,594)
30%	\$(26,806)
40%	\$(26,087)
50%	\$(25,489)
60%	\$(24,946)
70%	\$(24,391)
80%	\$(23,827)
90%	\$(23,112)
100%	\$(20,380)

Summary:

Entire range is from \$7,092,120 to \$18,809,547

Base case is \$13,181,552

After 7,227 trials, the std. error of the mean is \$22,547



Statistics:	Forecast values
Trials	7,227
Mean	\$12,902,132
Median	\$12,934,473
Mode	—
Standard Deviation	\$1,916,749
Variance	\$3,673,926,823,732
Skewness	-0.0600
Kurtosis	2.58
Coeff. of Variability	0.1486
Minimum	\$7,092,120
Maximum	\$18,809,547
Range Width	\$11,717,427
Mean Std. Error	\$22,547

Preliminary – do not cite

Forecast: net (cont'd)

Cell: D42

Percentiles:	Forecast values
0%	\$7,092,120
10%	\$10,357,557
20%	\$11,170,925
30%	\$11,844,695
40%	\$12,416,070
50%	\$12,934,473
60%	\$13,440,529
70%	\$13,992,406
80%	\$14,604,786
90%	\$15,404,155
100%	\$18,809,547

End of Forecasts