EVIDENCE REPORT:
NEWBORN SCREENING FOR POMPE DISEASE

by

The Condition Review Workgroup:

Alex R. Kemper, MD, MPH, MS
Chair
Condition Review Workgroup
(Duke University)

Anne Marie Comeau, PhD
(University of Massachusetts)

Nancy S. Green, MD
(Columbia University)

Aaron Goldenberg, PhD
(Case Western University)

Jelili Ojodu, MPH
Public Health System Impact Task Leader
(American Public Health Laboratories)

Lisa A. Prosser, PhD,
Decision Analysis Task Leader
(University of Michigan)

Susan Tanksley, PhD
(Texas State Public Health –
Newborn Screening Program)

Stephanie Weinreich, PhD
(VU University Medical Center,
Amsterdam, The Netherlands)

K.K. Lam, PhD
Project Leader
Condition Review Workgroup
(Duke University)

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This report was prepared to inform the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children about the benefits and harms of newborn screening for Pompe disease and about the capability of state newborn screening programs to add Pompe disease to the conditions included in their screening panels.

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Executive Summary

Overview

This report describes the evidence regarding benefits and harms of newborn screening for Pompe disease and the capability of state newborn screening programs to offer comprehensive testing and follow-up for the condition. Pompe disease is an autosomal recessive disorder that leads to a deficiency of the enzyme acid α-glucosidase (GAA), resulting in the accumulation of lysosomal glycogen. The condition has a broad phenotype, ranging from an *infantile form* associated with significant morbidity and death in early childhood to a *late-onset form*, associated with progressive weakness and respiratory failure, with highly variable onset and progression. Screening for Pompe disease can be done through dried-blood spots using several different technologies, including fluorometric assay, immunocapture, tandem mass spectroscopy, and digital microfluidics. Pompe disease can be confirmed based on low GAA activity, the finding of specific condition-associated mutations, and clinical correlation. Some individuals have low measured GAA but do not develop Pompe disease. This is referred to as "pseudodeficiency." The infantile-onset form can be diagnosed after a positive screen based on supportive clinical signs (e.g., cardiomyopathy) and by genotype. For the purposes of screening, detection of pseudodeficiency is considered to be a false-positive result. Treatment of Pompe disease involves enzyme replacement therapy (ERT), which requires infusions every two weeks. ERT is not curative. Some individuals may develop antibodies to the ERT, which can reduce the effectiveness of the therapy. At greatest risk for developing antibodies are individuals who produce no endogenous enzyme. This is referred to as being Cross-Reactive Immunologic Material (CRIM) Negative.

This executive summary highlights key findings from the complete report developed for the United States Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children regarding newborn screening for Pompe disease. This summary is not intended to replace the complete report, which describes the methods for evidence identification and synthesis and a full discussion of findings. This summary instead provides a high-level review of findings from the complete report.

Pompe Disease: Epidemiology and Clinical Course

Based on one large-scale analysis of anonymous dried blood-spots in the United States, the prevalence of Pompe disease is approximately 1 in 28,000. The prevalence of pseudodeficiency is less than 1%. Based on a pooling of clinical studies, 28% of Pompe disease cases are infantile-onset, of which about 85% are classic infantile-onset. About 75% of cases of classic infantile-onset Pompe disease are CRIM+, although there is geographic diversity in the distribution of CRIM status. The majority of those with Pompe disease have late-onset disease. There is significant variability in the age of onset of symptoms among those with late-onset Pompe disease, that can only partially be predicted by genotype.

Without treatment, classic infantile-onset disease is associated with significant morbidity and mortality within the first year of life. Nonclassic infantile-onset disease may also be associated with death in early childhood to a lesser extent. There is great variability in the age of onset (mild symptoms may appear in childhood but most serious symptoms usually appear in adulthood) and the degree of impairment of those affected with late-onset Pompe disease (the majority experience muscle weakness and mobility and functional limitations).

Potential Benefits of Newborn Screening

Infantile-onset Pompe Disease. Studies suggest that early identification and treatment can lead to decreased morbidity and mortality for those with classic infantile-onset Pompe disease compared to clinical detection. Although those who are CRIM- can develop neutralizing antibodies and have poor outcome, immunomodulation can decrease this risk. Some who are CRIM+ also develop antibodies to ERT. Recent case studies suggest that immunotherapy can decrease the antibody titer in both CRIM- and CRIM+ patients and improve health outcomes.

Late-onset Pompe Disease. Little is known about the degree to which detection of late-onset Pompe disease in infancy leads to improved health outcomes. Imaging and histologic studies suggest that there is muscle damage by the time that cases of late-onset Pompe disease are clinically detected. The argument in favor of screening is that treatment does not reverse muscle damage but that treatment begun before the onset of muscle damage may prevent it from occuring. However, the benefit of presymptomatic treatment in the prevention of progressive muscle damage has not yet been clearly established.

Current Newborn Screening Outcomes for Pompe Disease

Taiwan has developed a fluorometric assay associated with a low rate of false positives and positive predictive value similar to other newborn screening tests. Little is known about the false-negative rate. Missouri is screening newborns with digital microfluidics. As of May 1, 2013, 27,724 samples had been tested, with identification of one case each of classic and nonclassic infantile-onset Pompe disease and one case of late-onset Pompe disease. In addition, there were three false-positive results (carrier status unknown), one case of pseudodeficiency, two carriers that were identified, and two positive screens pending status confirmation.

Anticipated Harms of Screening and Treatment

The expected harms associated with screening include short-term psychosocial harms from false positives, which include the identification of pseudodeficiency and the identification of carriers. The degree to which identification of late-onset disease is beneficial or harmful is unclear. The economic cost of lifelong treatment, as well as health risks associated with placement of a central line for infusion, could lead to long-term harm given the variability in prognosis and the lack of data regarding the benefit of early identification. Newborn screening programs and clinical specialists will need to develop standardized protocols for the long-term follow-up and treatment of children identified with late-onset Pompe disease. Collecting prospective data about outcomes from these protocols could help decrease uncertainty about clinical management. Current screening methods do not allow detection of only infantile-onset Pompe disease.

Impact on Public Health Systems

The Association of Public Health Laboratories surveyed and conducted indepth interviews with representatives of twelve state newborn screening programs, including four that have legislative mandates to screen for Pompe disease. Most respondents expressed concern about the need for assistance in adopting a screening test for Pompe disease (e.g., more information about the different tests available, a quality-control process, education, personnel, funding). Most newborn screening programs also expressed concern about the challenge of considering adding Pompe disease to their newborn screening panel while also adding newborn screening for severe combined immunodeficiency disease and critical congential heart disease. Most states reported that they would

be able to arrange short- and long-term follow-up for Pompe disease. However, some expressed concern about a shortage of specialists.

Costs of Screening for and Follow-up of Pompe Disease

Although cost is an important consideration, the review found few data about the cost implications of newborn screening for Pompe disease. In addition to the upfront costs for implementing the screening test (e.g., equipment purchase, space allocation, staff education and training, development of reporting and tracking systems), there are ongoing costs associated with screening (e.g., dried-blood spot evaluation), short- and long-term follow-up. Although Pompe disease is rare, the costs of long-term management, including ERT infusions and other supportive care over the life of individuals with Pompe disease are not well described in the published literature. The per-patient cost of ERT is high. For infantile-onset disease, it is not clear whether newborn screening would raise or lower treatment costs because infants are placed on treatment in any case once identified based on symptoms. Newborn screening would lead to earlier identification of infantile-onset Pompe disease compared to clinical detection, which would decrease the need for some aspects of complex medical care (e.g., mechanical ventilation) and associated costs. The cost implication of early detection and lifelong treatment of late-onset Pompe disease is serious for both families and health care payers. More information is needed regarding the benefits, harms, and costs of early treatment.

LIST OF ABBREVIATIONS

Abbreviation	**Definition**
Advisory Committee	Secretary's Advisory Committee on Heritable Disorders in Newborns and Children
CI	Confidence Interval
CK	Creatine kinase
CRIM	Cross-Reactive Immunologic Material
CRW	Condition Review Workgroup
GAA	Acid alpha-glucosidase
GLC_4	Glucose tetrasaccharide
GSD II	Glycogen Storage Disorder-Type II
ERT	Enzyme Replacement Therapy
FDA	United States Food and Drug Administration
LSD	Lysosomal Storage Disorder
MS/MS	Tandem mass spectroscopy
NBS	Newborn Screening
RhGAA	Recombinant human GAA
RUSP	Recommended Uniform Screening Panel

1 INTRODUCTION

Pompe Disease - Overview

Pompe Disease Definition and Etiology
Pompe disease (OMIM 232300) is an autosomal recessive disorder that leads to a deficiency of the enzyme acid α-glucosidase (GAA), resulting in the accumulation of lysosomal glycogen. It is one of at least 40 different types of Lysosomal Storage Disorders (LSDs), which are characterized by enzyme dysfunction that leads to the accumulation of material in lysosomes and ultimately tissue damage. Although all individuals with Pompe disease share the underlying GAA enzyme deficiency, variability in enzyme activity leads to a broad spectrum of illness.[1]

The American College of Medical Genetics[2] classifies Pompe disease into two broad categories, infantile and late-onset disease, with the following characteristics:

Infantile-onset Pompe Disease: This is the most severe form of the disease. It can be further divided into the classic form, with profound and progressive hypotonia and cardiomyopathy, and death in the first year of life. The nonclassic infantile form is not associated with cardiomyopathy and survival may be longer.

Late-onset Pompe Disease: Individuals with late-onset disease may not develop clinically significant weakness until later in childhood or as adults. This form of Pompe disease is associated with progressive weakness. Premature death can occur in middle age or older ages due to respiratory failure. Hypertrophic cardiomyopathy is not typically associated with late-onset Pompe disease.

This dichotomous classification was used whenver possible in this report. However, this classification scheme has limitations. Late-onset Pompe disease is heterogeneous in age of onset and degree of morbidity. Late-onset Pompe disease can also be associated with cardiac involvement (e.g., Wolff-Parkinson-White syndrome, left ventricular hypertrophy and dilatation of the ascending aorta). Furthermore, at the time of diagnosis and through the first year of life, it may be difficult to classify cases, which can make the description of ongoing prospective case-finding activities challenging to describe.

In addition to low-enzyme activity levels leading to Pompe disease, some individuals have low levels of enzyme activity but do not develop disease. This is referred to as pseudodeficiency.

Genetics of Pompe Disease
The GAA enzyme gene is located on chromosome 17 (17q25.3). More than 300 mutations of the gene have been described.[3] Classic infantile-onset Pompe disease develops when neither of the two alleles produce functioning enzyme. Late-onset forms of Pompe disease develop when there is partial deficiency in GAA production. The phenotype can be variable if some functioning enzyme is produced. Many of the mutations in the GAA enzyme gene have been associated with specific phenotypes. For mutations that have not been previously described, the phenotype can sometimes be predicted from the type of mutation. For example, a mutation leading to a premature stop codon can be predicted to lead to early-onset disease. However, for mutations that could lead to the production of some enzyme, it can be difficult to predict phenotype.

The pseudodeficiency mutations (c.[1726A;2065A]) cause low measured GAA enzyme activity in the assay system but not Pompe disease. Although pseudodeficiency is not associated with disease, some have hypothesized that the presence of pseudodeficiency mutation could modify the effect of another mutation in the trans allele.[4]

Epidemiology of Pompe Disease

Data regarding the epidemiology of Pompe disease has been derived from gene frequency studies, evaluation of anonymous dried-blood spots, and population-based screening programs. Reports from the studies of anonymous dried-blood spots and population-based screening programs are included in the systematic evidence review. In 1999, a report from the Netherlands[5] evaluated 3,043 dried-blood spots for three common mutations and used these findings to predict the birth incidence of Pompe disease. The overall prevalence of all forms was estimated to be 1/40,000 (95% confidence interval, 1/17,622-1/100,073), of which 29% were estimated to be infantile.[5] This finding is based on a relatively small number of samples and represents a hypothetical calculation based on frequencies of known alleles and assuming Hardy-Weinberg equilibrium. It has been superceded by later estimates based on frequencies of observed cases of Pompe disease in population-based samples. Data from the University of Washington provide a more robust estimate of about 1/28,000.[6] This is described in the systematic evidence review.

Natural History of Pompe Disease

The Pompe Disease Registry is a key source to further understand the natural clinical symptomology and treatment outcomes for Pompe disease. This Registry is an international data repository designed to allow treating physicians to enter and share data longitudinally on the clinical course of Pompe disease patients.[7] The Pompe Registry was started in 2004 by Genzyme Corporation, which owns and maintains the database. A Registry Board of Advisors, comprised of researchers and other clinical experts in Pompe disease, has been established to determine data reporting elements and analyses most relevant to advance clinical and scientific knowledge about Pompe disease.

In the first five years (2004 to 2009), the Registry included data from 742 patients across 28 countries. Of these cases, most (70%) had late-onset of symptoms (>12 months of age), while 23% had symptom onset as infants (<12 months of age). Data were not available regarding the remaining 7%.[7] As with all registries, ascertainment bias may limit generalizability to the general population. By pooling estimates from studies of large population-based samples of dried-blood spots from the University of Washington and Austria with findings from newborn screening activities in Taiwan, we estimate that 28% of all cases of Pompe disease will be infantile onset.

Infantile-Onset Pompe Disease

Among those with symptoms in the first year of life, 14.7% did not have cardiomyopathy, suggesting nonclassic infantile-onset Pompe disease.[7,8] Median symptom onset was 3.0 months, and median age of diagnosis was 4.6 months. Infants presenting with cardiomyopathy have been found to experience disease progression earlier than those without cardiomyopathy: median age of symptom onset: 2.88 vs. 4.4 months, respectively; median age of diagnoses: 6.0 vs. 15.6 months, respectively.[8]

In 2006, a large international retrospective study was conducted to describe the natural history of infantile-onset Pompe disease. These historical data are often used as the comparison to evaluate the effectiveness of ERT, the only approved therapy for infantile-onset Pompe disease.[9] Cases were identified through a questionnaire sent to treatment centers in Israel, Taiwan, North America, and

Europe. Subjects were included if they had symptoms by 12 months of age and if low levels of GAA enzyme activity or GAA gene mutations were described in their medical record. No subject could have received ERT. Overall, 168 subjects were included; 33.9% (n=57) had a known family history of Pompe disease. This study included both classic and nonclassic infantile-onset Pompe disease. At presentation, most (91.7%, n=154) had cardiomegaly while 87.5% (n=147) had cardiomyopathy. Because of the sampling method, it is unclear if these proportions reflect the underlying distribution of classic versus nonclassic infantile-onset Pompe disease. More severe cases may be identified earlier, leading to spectrum bias.

In this records review of infantile-onset Pompe disease cases, the median age of symptom development was 2.0 months (range: 0-12 months) and the median age of diagnosis was 4.7 months (range: prenatal to 84.2 months). Almost one-third, or 29.2% (n=49) required mechanical ventilation; of those requiring ventilation assistance, the median age of initiation was 5.9 months (range 0.1-39.5 months). Deaths were reported in 85.7% cases (n=144). The median age of death was 8.7 months (0.3-73.4 months). The Kaplan-Meier survival rates at 12, 18, and 24 months are listed in Table 2. After accounting for major variables, results of a multivariate regression analysis found that earlier ages of symptom onset and diagnosis significantly increased the likelihood of death; symptom onset and diagnosis by 6 months of age increased risk of death by 2.83 and 2.11, respectively.[9] Data regarding formal assessments of gross motor or neurodevelopment were not sufficiently available in the subjects' medical record to assess these outcomes. Table 1.1a. summarizes the natural course and survival of infantile-onset Pompe disease patients who did not receive ERT.

Table 1.1a. Natural Course and Survival among Infantile-onset Pompe Disease Patients

	Symptom Onset *Median Age*	Diagnosis *Median Age*	Mechanical Ventilation Assistance *Median Age, %*		Death *Median Age*	% Survival [% Ventilator-Free]		
	Mos (range)	Mos (range)	Mos (range)	%	Mos (range)	12 mos	18 mos	24 mos
Infantile-onset	2.0 (0- 12)	4.7 (<0–84.2)	5.9 (0.1–39.5)	29	8.7 (0.3–73.4)	25.7 [16.9]	14.3 [8.5]	9.0 [4.9]
WITH cardiomyopathy	2.9	6.0	--		--	--	--	--
WITHOUT cardiomyopathy	4.4	15.6	--		--	--	--	--

Table 1.1b. Natural Course and Survival among Late-onset Pompe Disease Patients

	Symptom Onset (med consult) *Median Age*	Diagnosis *Median Age*	Death *Median Age*	Estimated Survival Post-Diagnosis (%)			
				+5 yrs	+10 yrs	+20 yrs	+30 yrs
Late-onset	28 years	38 years	+27 years post-dx	95	83	65	40

Late-Onset Pompe Disease

In a 2010 report of 424 late-onset Pompe patients enrolled in The Pompe Registry,[10] median age of symptom onset and diagnosis was estimated at 28 and 36 years, respectively; median age of last recorded follow up was 43.5 years. Symptoms most commonly experienced by these patients were proximal muscle weakness of the lower (88%) and upper (75%) extremities. Respiratory involvement was noted for at least 76% of the patients. Although median age of symptom onset is typically reported after age 18, careful medical history has identified disease-related manifestations an average three to 10 years earlier, attributed to the non-specific and slow progression of symptoms.[11] Late-onset Pompe disease can be associated with a significant decrease in quality of life and affected individuals may need substantial nursing care or informal caregiver support.[12] Most late-onset patients eventually become wheelchair-bound, ventilator-dependent, or both.[13,14] Late-onset Pompe disease is a multi-system disorder, with reports of bowel and bladder incontinence, basilar artery and ascending aorta dilatation, ptosis, and swallowing dysfunction.

As part of an ongoing, prospective database of patient-reported outcome measures, a 2011 report calculated survival and prognosis factors from a sample of 268 late-onset Pompe patients who had not begun ERT.[15] Participants represented countries across North America, Australia, and Europe, and reported a median age of diagnosis of 38 years (range 1–68 years). The median (50%) estimated length of survival after diagnosis was 27 years. In the present sample, 17% had died ten years after diagnosis. The estimated Kaplan-Meier 5-year survival rate after diagnosis was 95%; at 10, 20 and 30 years the estimated survival rate was 83, 65 and 40%, respectively. Table 1.1b summarizes the natural course and survival of late-onset Pompe disease patients who did not receive ERT.

Factors that Affect the Detection and Course of Pompe Disease

Carriers

As an autosomal recessive trait, individuals may inherit only one GAA mutation for Pompe disease, and thus be a carrier but not have the disease. Because the GAA levels of Pompe carriers may be lower than normal, screening procedures measuring GAA activity level may identify some Pompe disease carriers. Mutation analysis through genotyping can accurately distinguish Pompe carriers from those likely to be affected by the disease.

Pseudodeficiency

There are many genetic mutations associated with Pompe disease. The pseudodeficiency allele, as mentioned earlier, can cause low GAA enzyme activity levels in otherwise healthy individuals. For those who are homozygous for pseudodeficiency, GAA activity levels have been found to be as low as those affected by Pompe disease or may overlap those who are heterozygote for Pompe disease.[4] The pseudodeficiency mutation has relatively higher frequency in those of Asian origin, with up to 3.9% of Taiwan-Chinese and Japanese populations reported to be homozygous.[4,16,17] Because of the high prevalence of pseudodeficiency mutations, the initial newborn screening algorithm in Taiwan

yielded a high rate of false-positve results.[18] However, adjustments to the screening algorithm were developed that effectively separate the pseudodeficiency cases from Pompe disease, lowering the false-positive rate.[19-21] These newborn screening activities are described in the systematic evidence review. In addition, measurement of urinary GLC_4, which has been used to monitor ERT effects, may also be used to rule out pseudodeficiency and help establish the diagnosis.[22] However, genotyping is definitive.

Cross-Reactive Immunologic Material (CRIM)

Among those with infantile-onset Pompe disease, the most significant risk factor for poor outcome is the lack of production of any GAA enzyme. Newborns who produce no enzyme can develop high titers of antibodies to the main treatment, enzyme replacement therapy (ERT), which can neutralize the treatment. Cross-reacting immunologic material (CRIM) negative implies the presence of no GAA enzyme, regardless of function. The established method for determining CRIM status is by presence or absence of GAA protein by Western blot. However, investigators were recently able to predict CRIM status based on mutation analysis of infantile-onset Pompe patients (n=140) with 90% accuracy.[23] This finding is significant because the current Western blot method, though valid and reliable, typically requires several weeks before results are available. Prediction of CRIM status through mutation analysis can be conducted as part of diagnostic genotyping for newborns with a positive screen. Therefore, genotyping can be used not only to rule out pseudodeficiency mutations, and confirm Pompe disease and severity of course, but also identify CRIM status. A blood-based assay for CRIM status is also in development.

Screening and Diagnostic Strategies

Screening

Screening for Pompe disease is based on assessment of GAA activity, measured in whole- or dried-blood spots (DBSs). Currently available methods include fluorometric assay, immunocapture, and tandem mass spectroscopy (MS/MS). Recently, a digital microfluidics system has been developed that is based on a fluorometric assay. Measurement of Pompe's GAA activity after an enzyme assay can be multiplexed with measures of other lysosomal storage enzyme assays using tandem mass spectrometry. Researchers at the University of Washington have conducted large-scale evaluations of anonymous dried-blood spots using MS/MS. According to an expert interview with Dr. Dietrich Matern (see Appendix B), he and other researchers at the Mayo Clinic are conducting a comparative trial of these three different multiplex assays to screen for 13 LSDs, Friedrich's ataxia, Wilson's disease, and X-linked adrenoleukodystrophy. This study is analyzing prospectively 100,000 anonymous dried-blood spots provided by the California newborn screening program. The researchers intend to complete analyses in 2013, with the aim to identify an effective and efficient testing approach. The study will include a comprehensive comparative cost analysis of resources needed for each approach (e.g., equipment, space, consumables, hardware, software, personnel effort, repeat rate). In addition, the researchers plan to develop a web site resource for data, analytical protocols, reference and disease ranges, and interpretive guides.

Validity of Screening

The systematic evidence review describes the prospective studies of screening. These studies provide information about the expected clinical utility of newborn screening for Pompe disease. However, these studies do not necessarily address analytic validity. The other non-prospective study designs can provide important insight into screening methods and analytic validity.

We identified eight studies which evaluated MS/MS to identify GAA enzyme activity in dried-blood spots from subjects with Pompe disease, heterozygotes, and normal controls[24-29] or by comparing enzyme activity in dried-blood spots to leukocytes.[30] In each study, accuracy was high, with the ability to distinguish cases from controls in dried-blood spots and high concordance between enzyme activity in dried-blood spots and leukocytes. Similarly, five studies of fluorometric assays found high accuracy.[20,31-35] No study was found that evaluated the validity of digital microfluidics, which can be considered a type of fluorometric test.

The Centers for Disease Control and Prevention's Newborn Screening Quality Assurance Program recently reported the results of quarterly proficiency testing of GAA screening assays, based on analyses of five, blind-coded dried-blood spot specimens which were sent to seven different US laboratories for analysis.[36] Results from six labs were reported, of which five used MS/MS (four with flow injection analysis MS/MS and one with liquid chromatography MS/MS) and the sixth lab used digital microfluidic technology. Among the samples, four had normal GAA enzyme activity and one had low GAA activity. No false-negative or false-positive results were reported from these laboratories.

Current Screening Programs

Population-based newborn screening for Pompe disease has been implemented in part of Taiwan. Several other countries, including Austria, Japan, and Italy, and the United States have evaluated anonymous dried-blood spots for Pompe disease. In the United States, to date, four states, Illinois, Missouri, New Jersey, and New Mexico, have passed legislation mandating newborn screening for Pompe disease. New Jersey currently has funding proposed for the next budget year (starting July 1, 2013) that would support the mandate passed in January 2012 to require newborn screening for Pompe disease and five other LSDs.

Illinois is preparing to begin screening using MS/MS and has conducted preliminary pilot work to establish these methods for high-throughput screening. The program anticipates initiating population-based screening activities in 2014. Missouri began a statewide implementation phase to screen for Pompe disease in January 2013. This includes full population testing followed by patient evaluation and confirmation on all positive cases through Missouri's contracted referral centers. Though they are actively testing all newborns and clinically following all positive cases, the screening results are not provided on the standard newborn screening reports sent out by the State Laboratory at this time. Once more permanent thresholds for out-of-range values can be established through this initial testing phase, laboratory reports will be standardized to include GAA level test results for Pompe disease and the other LSD screening results.

Diagnosis

The mainstay of diagnosis is establishing low functional GAA enzyme levels. Although this is commonly done in whole blood or dried-blood spots, enzyme activity can also be measured in fibroblasts or muscle biopsy. Muscle biopsy carries risk of serious adverse events in those with infantile-onset Pompe disease. GAA enzyme activity <1% of normal controls is associated with the infantile-onset Pompe disease. Late-onset Pompe disease can have wide variation in GAA enzyme activity level. Diagnosis can be confirmed by genotyping if a known mutation is identified. As of June 2012, at least 456 GAA mutations were documented in the Pompe Disease Mutation Database (http://www.pompecenter.nl), of which at least 315 were known to be pathogenic for Pompe disease. The database also includes severity ratings of the Pompe mutations (i.e., very severe, less severe, potentially less severe, potentially mild) to estimate the likely severity of disease to facilitlate

diagnosis and counseling for patients and families.[37] In addition, genotyping can help predict the majority of those with infantile-onset Pompe disease who will be CRIM-negative.[23,37] There is a high degree of genotype-phenotype correlation for infantile-onset Pompe disease. However, there is variable genotype-phenotype correlation for late-onset Pompe disease.

Treatment Strategies

In 2006, the U.S. Food and Drug Administration (FDA) approved Myozyme (alglucosidase alfa; Genzyme Corp., Cambridge, MA) for therapy. This recombinant human GAA (rhGAA) enzyme replacement therapy (ERT) is produced from Chinese hamster ovary cells. The ERT is provided intravenously, typically every two weeks with infusion times lasting about four hours. Higher doses can be used based on clinical need.

Early trials found that ERT could reduce mortality and the need for invasive ventilator management in young children with infantile-onset Pompe disease. ERT is not curative; infusions are needed throughout life. Some patients, especially those who do not produce any endogenous GAA (referred to as being cross-reacting immunologic material [CRIM] negative) develop antibodies that may reduce the effectiveness of therapy.[38] Allergic reactions, including anaphylaxis, have been reported with the ERT. Due to its limited availability, Myozyme in the United States has been reserved to treat infantile-onset Pompe disease. In 2010, the FDA approved Lumizyme (alglucosidase alfa) for patients ages 8 years and older with late-onset Pompe disease without cardiac hypertrophy. Both products are made from the same master cell bank.

Because ERT is required throughout life, most patients have a central line placed. During initial management and until patients are stable, infusions are provided at a medical center. However, once stable, infusions can be provided at a local clinic or at home with home health care assistance. A typical dose is 20mg/kg. As of March 2013, the wholesale acquisition cost of each 50 mg vial for Myozyme is $975 and for Lumizyme is $725.[39] The wholesale acquisition cost is the list price to wholesalers or other direct purchasers in the United States; however, other discounts or rebates could be available. These prices are per unit, and do not include actual body weight dosages, frequency or duration of treatment, labor or supplies for infusion, or any other costs.

The most common biomarker of progression of Pompe disease is creatine kinase (CK). CK is an indicator of muscle inflammation and destruction. Findings related to ERT effects on CK are described in the systematic review. Another biomarker is glucose tetrasaccharide (GLC_4), which is excreted in the urine of individuals with Pompe disease. Measurement of GLC_4 has been used to monitor individuals receiving ERT.[22]

In January 2013, the Agency for Healthcare Research and Quality released a Technical Brief entitled, *Enzyme-Replacement Therapies for Lysosomal Storage Diseases*.[40] For Pompe disease, the study reviewed eight clinical studies of treatment, of which five included at least some patients with the infantile form. The report does not provide the level of detailed information regarding the benefits or harms of treatment necessary to inform decision making for newborn screening.

Scope of the Review

This report was developed to support the Secretary of Health and Human Services' (HHS) Advisory Committee on Heritable Disorders in Newborns and Children ("Advisory Committee") in making

recommendations to the Secretary, HHS, about whether newborn screening for Pompe disease should be added to the Recommended Uniform Screening Panel (RUSP).

Rationale for Review
Pompe disease was initially nominated to the Advisory Committee for inclusion in the RUSP in May 2006. At that time, the Committee requested a systematic review of the potential benefits and harms of screening for Pompe disease. Based on this systematic review of evidence,[41] in 2006, the Advisory Committee concluded that there was insufficient evidence upon which to make a recommendation to add Pompe disease to the RUSP. The Advisory Committee identified four important issues:

- The need to improve screening test specificity;
- The need for a standardized method of diagnosis after a positive newborn screen;
- The lack of data regarding potential benefits and harms of diagnosing late-onset Pompe disease in infancy; and
- The lack of cost or cost-effectiveness data regarding screening for Pompe disease.

In 2008, the External Evidence Review Workgroup[1] updated the 2007 report to expand the key questions and address the issues of particular relevance to the Advisory Committee. In October 2008 the Advisory Committee concluded that the evidence was insufficient to recommend adding Pompe disease to the RUSP at that time. The Committee identified additional evidence gaps and recommended that additional studies be conducted to address those gaps. Based on the updated evidence review, primary gaps identified by the Advisory Committee included the following:

- A need for a population-based study of newborn screening for Pompe disease in the United States;
- An evaluation of the impact of screening on public health;
- Additional evidence regarding the public health impact (i.e., harms and benefits) of newborn screening on late-onset Pompe disease; and
- An evaluation of the role of high-titer antibody formation and CRIM status in affecting outcomes of Pompe treatment with ERT.

In light of newly published data and current advances in screening and treatment for Pompe disease since the 2008 review, in May 2012 the Advisory Committee accepted a nomination to re-review Pompe disease, and requested that the Condition Review Workgroup develop a report about the key considerations regarding adding Pompe disease to the RUSP.

Key Questions

The key questions for the systematic evidence review were developed from the general analytic framework used by the Condition Review Workgroup and the specific needs of the Advisory Committee. The technical expert panel on Pompe disease was convened to refine the key questions (see Appendix B).

[1] The "External Evidence Review Workgroup" has since been renamed the "Condition Review Workgroup" to reflect more comprehensive considerations of systematically reviewed empirical evidence, expert opinion, and public health impact in its review procedures.

Key Question 1: What is the natural history and epidemiology of Pompe disease? What factors predict morbidity or mortality?

As is common for rare disorders, studies of natural history are rarely conducted. Epidemiology is difficult to determine because case ascertainment often relies on population identification through screening activities. Therefore, findings related to Key Question 1 are embedded in the review of the other key questions. However, key findings related to Key Question 1 are highlighted in the results and conclusions of this report.

Key Question 2: What is the direct evidence that newborn screening for Pompe disease leads to improved health outcomes compared to usual clinical care?

- Population: Newborns not known to have or be at increased risk for Pompe disease who were identified around the time of birth through screening
- Interventions: Any care received subsequent to the screening test
- Comparators: Contemporaneous or historical controls with Pompe disease
- Outcomes: Survival; any measure of morbidity
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 3:

3A. What is the analytic validity or clinical validity of the screening approaches used to detect (a) infantile-onset Pompe disease? (b) late-onset Pompe disease?

3B. What diagnostic testing methods are available to confirm or identify (a) infantile-onset Pompe disease? (b) late-onset Pompe disease? (c) age of onset or disease severity?

There are two standard measures of analytic validity, sensitivity and specificity. To estimate these requires validated proficiency testing samples. Few such data exist. Consequently, one must use screening studies, which represent the combination of analytic and clinical validity.

- Population: Newborns without known diagnosis of, or risk factor for Pompe disease; de-identified dried-blood spots
- Interventions: Any screening methods for Pompe disease conducted in the first month of life. For analytic validity, studies must report proficiency
- Comparators: Diagnosis by genotype and follow-up evaluation or genotype alone
- Outcomes: Sensitivity, specificity, positive predictive value, negative predictive value, reliability, and yield (i.e., prevalence)
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 4:

4A. Does initiation of enzyme replacement therapy (ERT) modify the intermediate health outcomes when Pompe disease is detected through newborn screening or through other methods in early infancy compared with usual clinical care? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presence of pseudodeficiency allele)?

4B. Do follow-up protocols exist for the management of Pompe disease that do not require immediate initiation of enzyme replacement therapy? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes?

- Population: Newborns and others diagnosed with Pompe disease through newborn screening or other methods in the first month of life
- Interventions: ERT using the currently available FDA-approved therapies (i.e. alglucosidase alfa derived from a Chinese hamster ovary cell line)
- Comparators: Contemporaneous or historical controls with Pompe disease or no comparator
- Outcomes: Changes in intermediate outcomes, such as improvements in biomarkers (e.g. CK) of inflammation or muscle destruction. Because GLC_4 is not a measure of inflammation or destruction, this biomarker was not included in the analysis. GLC_4 can be used to assess overall glycogen burden.
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 5: Does early initiation of enzyme replacement therapy improve health outcomes when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presence of pseudodeficiency allele)?

- Population: Newborns and others diagnosed with Pompe disease through newborn screening or other methods in the first month of life
- Interventions: ERT using the currently available FDA-approved therapies (i.e. alglucosidase alfa derived from a Chinese hamster ovary cell line)
- Comparators: Contemporaneous or historical controls with Pompe disease or no comparator
- Outcomes: Survival or any measure of morbidity, including need for mechanical ventilation or neurodevelopment
- Timing: Any duration of follow-up
- Settings: All settings

In assessing the impact of early intervention, it is important to distinguish whether cases were identified through newborn screening or risk (e.g., family history of Pompe disease) versus early identification of symptoms (i.e., clinical detection). Those infants detected clinically based on symptomology significantly earlier than is typical may have more severe disease, and thus could have worse outcomes. Therefore, evaluating cases detected clinically early in infancy as a proxy for evaluation of newborn screening could introduce bias against the benefit of newborn screening.

Key Question 6: How strong is the association between changes in intermediate outcomes of Pompe disease (e.g., biomarkers) of Pompe disease and changes in health outcomes?

- Population: Newborns and others diagnosed with Pompe disease through newborn screening or other methods in the first month of life
- Interventions: ERT using the currently available FDA-approved therapies (i.e. alglucosidase alfa derived from a Chinese hamster ovary cell line)
- Comparators: Contemporaneous or historical controls with Pompe disease or no comparator
- Outcomes: Survival or any measure of morbidity and intermediate health outcome
- Timing: Any duration of follow-up

- Settings: All settings

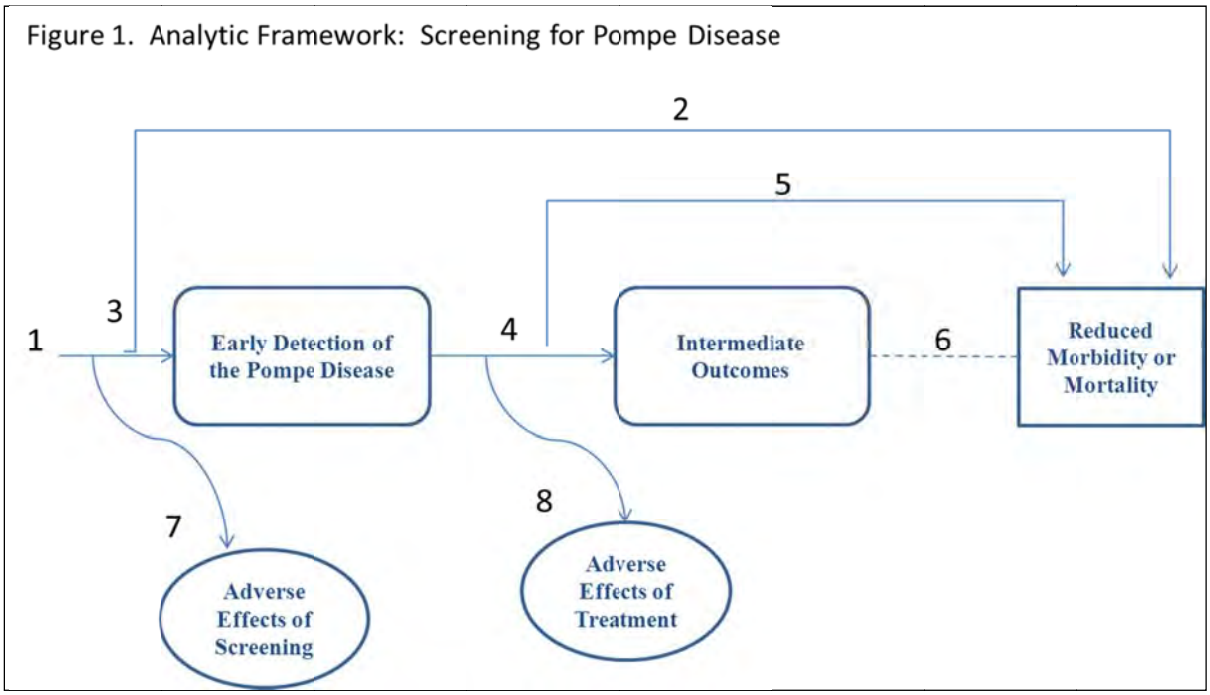
Key Question 7: What are the harms associated with newborn screening for Pompe disease to the individual or the family?

- Population: Newborns screened for Pompe disease and their families
- Interventions: Any newborn screening for Pompe disease
- Comparators: Any population or none
- Outcomes: Systematic assessment of harms, including harm related to false-positive screening results, false-negative screening results, early identification of late-onset disease, or perceived harms or acceptability of screening for Pompe disease.
- Timing: Any duration of follow-up
- Settings: All settings

Key Question 8: What are the harms associated with ERT for Pompe disease in early childhood? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presence of pseudodeficiency allele)?

- Population: Any child < 3 years begun on ERT using the currently available FDA-approved therapies (i.e. alglucosidase alfa derived from a Chinese hamster ovary cell line) for Pompe disease
- Interventions: Any systematic assessment of harm
- Comparators: Any population or none
- Outcomes: Any description of harm
- Timing: Any duration of follow-up
- Settings: All settings

Figure 1. Analytic Framework: Screening for Pompe Disease



Note: The numbers correspond to the Key Questions.
Assumption: An approved treatment is received, with equal access for all patients.

2 METHODS

The methods guiding this systematic evidence review followed approaches outlined in the Condition Review Workgroup – Manual of Procedures (April, 2012). These procedures are based on the AHRQ SER Methods Guide,[42,43] the United States Preventive Services Task Force (USPSTF) Procedures Manual,[44] and other established evidence review standards, with adaptations to address the nature of research on rare disorders (e.g., few large RCTs) and the established review and comment timeline of the SACHDNC. This chapter describes specific procedures that guided this Condition Review of newborn screening for Pompe Disease.

Developing the Case Definition
In published reports, there is variation in how Pompe disease is classified. To be consistent in evaluating the evidence, a Technical Expert Panel was convened (see Appendix B for TEP members and meetings). The following definitions were used in the review process. Specific notation is made in the evidence review in cases for which these terms could not be applied.

Infantile-onset Pompe disease: Affected subjects have GAA enzyme activity <5% confirmed in leukocytes, fibroblasts, or muscle and have at least one pathologic mutation (i.e., not mutations associated with pseudodeficiency) on each allele. We chose to accept enzyme activity < 5% although the true enzyme activity level for those with the infantile-onset Pompe disease is typically much lower (i.e., <1%). However, some assays may not be able to detect enzyme activity that low, and therefore are only able to report <5%. In addition to low GAA enzyme activity, affected infants must have hypertrophic cardiomyopathy or muscle weakness before 1 year of age. Those with hypertrophic cardiomyopathy or significant cardiomegaly were classified as having classic infantile-onset Pompe disease. Otherwise, subjects were classified as having nonclassic infantile-onset Pompe disease. Identification of mutations known to be associated with Pompe disease can be supportive of the diagnosis.

Because GAA enzyme activity is not consistently reported, individuals were also considered to have infantile-onset Pompe disease if the GAA was reported to be low during the newborn period with associated cardiomyopathy or weakness and had mutations associated with infantile-onset Pompe disease.

Late-onset Pompe disease: Affected subjects have GAA enzyme activity lower than normal subjects, with confirmation in leukocytes, fibroblasts, or muscle biopsy. Identification of mutations known to be associated with Pompe disease can be supportive of the diagnosis. Affected patients typically have no clinical symptoms during the first year of life, although they may have elevated creatine kinase (CK) levels. Patients with late-onset disease develop weakness or reduced pulmonary function after 1 year of age.

We considered CRIM status as follows:

CRIM -: Affected subjects produce no GAA enzyme.
CRIM +: Affected subjects produce GAA enzyme, which may be active or inactive.

Literature Search Strategy

Literature Search
We identified published literature from MEDLINE and EMBASE from 1966 (the start of MEDLINE). The previous evidence reviews have included literature through July 2008. However, because the present search strategy reflects updated Medical Subject Heading (MeSH) terms and includes late-onset Pompe disease publications relevant to early detection and treatment, the present search re-reviewed literature from 1966 to ensure comprehensiveness.

This review used the following MeSH terms and their associated key words:

- Glycogen storage disease type II
- Pompe Disease
- Pompe's Disease

This search strategy also identified reports related to other synonyms for the disease, including acid maltase deficiency and glycogenosis type II.

An experienced medical librarian conducted the initial literature search which included publications through July, 18 2012; the search was updated for literature published through April 30, 2013. An initial screening of titles and abstracts was conducted by two independent reviewers for exclusion and inclusion; disagreements were reconciled through discussion or by a third independent reviewer as needed. Reviewers screened the initially included articles with full-text screening using pre-developed data abstraction forms.

Literature Screening: Inclusion and Exclusion Criteria

Inclusion criteria
Articles that reported on studies with human subjects and published in English were included. All study designs were considered, including case reports, case series, observational, studies, uncontrolled, and controlled intervention trials.

Additional eligibility criteria regarding included Populations, Interventions, Comparators Outcomes, Timing, and Settings for each key question are outlined above. Further details of the article screening procedures and flow diagram can be found in Appendix A.

Exclusion criteria
Non-human studies, studies with no English language abstracts, and articles with no new data were excluded.

Technical Expert Panel

A panel of Technical Experts was identified to advise this review throughout its development. We first met with technical experts to review our scope of review and methods, identify current issues in research and practice, and to describe the typical care standards for newborn screening and treatment procedures to ensure relevance and applicability of the review. Technical Expert Panel members also met to provide input and feedback throughout development of the decision analysis model to estimate the impact of newborn screening on the population. During the review, additional experts were identified and interviewed to further inform unpublished newborn screening implementation and laboratory

practices. Appendix B lists the expert panel members, meetings, and interviews conducted to inform this review.

3 RESULTS

This chapter reports on the results of the literature review and synthesis. First, we outline the results of our literature search and selection process. We then present the evidence available to address target outcomes for each key question section. A list of abbreviations is provided at the beginning of this report.

Several appendices are included to provide supporting information to the results and findings presented in this section. Appendix A presents the PRISMA diagram of the search results, and a summary of reasons for article exclusions. Appendix B lists the Technical Expert Panel members and participation in scheduled panel meetings and interviews. Appendix E presents the summary table of reviewed articles for which evidence was reported.

Results of Literature Search

The search strategy identified 2,180 citations from PubMed and EMBASE, after removing duplications. Screening based on title and abstracts identified 368 potentially relevant articles which were obtained for further review. Based on inclusion criteria, an additional title and abstract screening excluded 98 citations, leaving 270 articles for full-text review. Using detailed selection criteria for each key question, 73 articles were retained for data abstraction. Many of the articles that did not meet criteria for inclusion in the systematic review provided important background information.

Evidence Review Results and Key Findings

Key Question 1.

1. What is the natural history and epidemiology of Pompe disease? What factors predict morbidity or mortality?

As a rare condition, generalizable findings about the life course and epidemiology of Pompe disease come from screening and treatment studies. Therefore, findings from this Key Question are described within the other Key Questions.

Summary of Key Findings:

- Based on the evaluation of population-based anonymous dried-blood spots from Washington State,[6] the prevalence of Pompe disease among newborn infants in the United States is approximately 1/28,000. This estimate is more reliable than that from the Netherlands (1/40,000), which was based on a small sample and several assumptions. In contrast, the first four months of population-based screening (n=27,724) in Missouri suggest a higher prevalence of 1/8,657. However, since Missouri has only recently begun to screen, further data are needed to reliably estimate the prevalence of Pompe disease in that state.
- Findings from Washington State and Missouri suggest that the prevalence of pseudodeficiency in the United States is less than 1%.
- About 28% of cases of Pompe disease would be expected to present before 12 months of life and about 85% of cases that present in infancy have cardiomyopathy, implying that they represent

classic infantile-onset Pompe disease. These data come from findings from the Pompe Disease Registry and findings from the assessment of dried-blood spots.

- About 25% of cases of classic infantile-onset Pompe disease are CRIM-. CRIM- is associated with worse outcomes, which can be improved with immunotherapy to prevent the development of antibodies to ERT.
- Differences in region-specific mutations could affect estimates of prevalence, ratio of infantile-onset versus late-onset disease, and prevalence of pseudodeficiency.

Key Question 2.

2. What is the direct evidence that newborn screening for Pompe disease leads to improved health outcomes compared to usual clinical care?

No randomized trials of screening were identified. Three reports were identified which provide empirical data regarding health outcomes of newborn screening compared to usual clinical care. Each of these reports present data from the Taiwan newborn screening program between October 2005 and December 2007.

A 2008 report of newborn screening for Pompe disease in Taiwan described the identification of 3 cases of classic infantile-onset Pompe disease after screening 132,538 newborns.[18] This activity included about 45% of newborns in Taiwan. During this time, another 3 cases of classic infantile-onset Pompe disease were identified clinically from a group of newborns not included in screening. Cases identified clinically were diagnosed at an older age (median 3.6 months) compared to those detected through newborn screening (median 22 days).

A subsequent 2009 report described five cases of classic infantile-onset Pompe disease identified through screening of 206,088 newborns between October 2005 and December 2007.[45] Outcomes of these cases were compared to ten other cases that were identified clinically, including five historical controls from before the initiation of the screening program and five cases identified who were born after the start of the screening program but who were not included in screening because they were born in other parts of Taiwan.

Another report from 2009 describes all cases identified in Taiwan between 1983 and 2008, including the five cases of classic infantile-onset Pompe disease identified through screening compared to historical cases and those cases identified in regions of Taiwan in which screening was not offered.[46] Because outcomes of cases identified through newborn screening are compared to both historical and contemporaneous, clinically-identified casesreceiving treatment, results are summarized in the section for Key Questions 4A, 5 and 6. However, one of the key findings is survival and ventilator-free survival among cases of classic infantile-onset Pompe disease among those detected through screening and those detected clinically (Table 3.1).

Table 3.1. Survival outcomes when detected through screening and by clinical detection.

	Detected Through Screening (%) (n=5)		**Clinically Detected (%)** (n=9)	
Age	Survival	Ventilator- free Survival	Survival	Ventilator-Free Survival
12 months	100	100	100	100
24 months	100	100	89	67

Summary of Key Findings:

- There are no randomized trials of screening for Pompe disease. However, compared to historical and contemporaneous controls, early detection of classic infantile-onset Pompe disease reduces mortality and significant morbidity.

Key Question 3.

3. A. What is the analytic validity or clinical validity of the screening approaches used to detect (a) infantile-onset Pompe disease? (b) late-onset Pompe disease?
3. B. What diagnostic testing methods are available to confirm or identify (a) infantile-onset Pompe disease? (b) late-onset Pompe disease? (c) age of onset or disease severity?

Newborn Screening forPompe Disease

We present published data from screening studies in the United States, Austria, Taiwan, and Italy. We also summarize reports gathered through technical expert interviews with representatives from the Illinois and Missouri state newborn screening programs and investigators in Washington State. Of these studies, only data from Taiwan are based on a prospective, active NBS program that includes follow-up information on infants with a confirmed diagnosis of Pompe disease detected through newborn screening. We do not present studies in which screening was not focused on prospective, population-based newborn screening using dried-blood spots with unknown Pompe disease status.[17,24,25,27,32,33,47-54]

United States

University of Washington Study

One research study[6] evaluated anonymous dried-blood spots in Washington State using MS/MS for a multiplex screen for Fabry disease, Pompe disease, and MPS-I. For Pompe disease, a cutoff of GAA activity ≤ 2.60 µmol/h/l, corresponding to 15% of the mean, was used. Of the 111,544 samples, 17 screened positive for low GAA activity at the first tier.

Follow-up genotyping through mutation analysis of these DBS samples revealed the following:

- 4 samples "consistent with possibly developing Pompe disease";
- 4 samples from carriers;
- 3 samples from carriers who also had one pseudodeficiency allele; and
- 6 samples from heterozygotes for pseudodeficiency.

Based on these findings, the epidemiology and screening test characteristics were as follows:

- Overall birth prevalence of infants who "may eventually develop clinical symptoms of Pompe disease": 1/27,800 (95% CI: 1/90,900-1/10,200).
- The overall positive rate (calculated from the report): 1/6,561(95% CI: 4,098-11,261).
- The positive predictive value: 24% (95% CI: 8%-50%)
- False positive rate: 1/8,600 (95% CI: 1/5,000-1/14,800)

According to Dr. Scott, incubation time in preparation for MS/MS for Pompe disease typically takes one to two hours. However, for logistical purposes, the incubation was set to run overnight. He noted that

the mass spectrometers currently used by state newborn screening programs are adequate for Pompe disease screening. Dr. Scott reports that MS/MS screening costs less than $2 per sample for reagents, excluding instrument and labor costs.

Illinois

Illinois mandated screening for Pompe disease and three other LSDs in 2008. In an initial start-up screening trial in 2011, the newborn screening program used digital microfluidics to analyze 8,012 dried-blood spots. Of these, none were positive for Pompe disease. The screening program has decided to switch to MS/MS for screening six LSDs. The decision to switch was based on concerns about whether digital microfluidics was sufficiently efficient to meet the demands of the newborn screening program and concerns about fluctuations in reported GAA activity from the evaluation of screening. According to the Illinois key informants, the digital microfluidics process has been improved to address these concerns. However, evaluation is now underway for MS/MS Pompe disease screening with full screening anticipated to begin in 2014.

Missouri

In response to legislation signed in August 2009, the Missouri Newborn Screening Program began statewide implementation of screening on January 15, 2013 using a digital microfluidics platform. A positive dried-blood spot leads directly to referral for diagnostic confirmation. As of May 15, 2013, 27,724 dried-blood spots have been screened for Pompe disease with the following confirmed results:

- Two carriers of Pompe disease;
- Three false positives (GAA enzyme activity level in the normal range, carrier status unknown);
- One case of pseudodeficiency;
- One case with likely classic infantile-onset Pompe disease;
- One case of non-classic infantile-onset Pompe disease; and
- One case of late-onset Pompe disease.

These findings suggest an overall prevalence of Pompe disease of 1/8,657 and a false-positive rate (including carriers and pseudodeficiency) of about 0.02%. However, these data are preliminary given the early stages of population-based screening.

Austria

One study evaluated 34,736 anonymous dried-blood spots in Austria for Fabry's disease, Gaucher's disease, Neimann-Pick desease types A and B, and Pompe disease using a multiplex MS/MS platform from January 2010 to July 2010.[55] Samples which screened positive were retested in the laboratory with mutation analysis of the same dried-blood sample to confirm cases affected by Pompe disease.

For first tier screening for Pompe disease, a cutoff of GAA activity <2.80 µmol/h/l was considered abnormal. Of the 34,736 samples, 25 screened positive. Those that screened positive were retested, with 5 samples still positive. Genotyping revealed the following:

- One subject with no mutations;
- Two individuals homozygous for missense mutations associated with potentially less severe phenotype;
- One individual homozygous for a splicing mutation associated with potentially less severe phenotype; and

- One individual with a different splicing mutation on each allele, one associated with potentially mild phenotype and one associated with very severe phenotype.

This study did not describe any sample with pseudodeficiency.

Based on these findings, the epidemiology and screening test characteristics were as follows:

- The overall prevalence of Pompe disease: 1/8,684 (calculated 95% CI: 1/342,000 – 1/1,559);
- The overall positive rate for Pompe disease, calculated from the report: 1/6,947 (95% CI: 1/21,413-1/29,777)
- The positive predictive value: 80% (95% CI: 28%-99%); and
- The false positive rate: 1/33,333 (95% CI: 1/1,000,000 – 1/6,250).

Italy

One report[56] described a population-based screening study in Italy conducted between January 2010 and June 2012. Using a fluorometric assay, 3,403 newborns were screened for Fabry disease, Gaucher disease, Pompe disease, and MPS-I. Enzyme levels <25% of the average control activities occurred in 12 samples. A second dried-blood spot was obtained, and found to still be low in 3 of the 12. Follow-up whole-blood samples revealed normal enzyme activity.

Based on these findings, the epidemiology and screening test characteristics were as follows:

- No cases of Pompe disease were identified;
- The overall positive rate based on the requirement for a second dried-blood spot (calculated from the report): 1/284 (95% CI: 1/549-1/163);
- The positive predictive value based on the second dried-blood spot (calculated from the report): 0 (confidence interval not calculated); and
- False positive rate after the second dried-blood spot: 100% (confidence interval not calculated).

Taiwan

The screening experience in Taiwan has been presented in multiple reports.[18,19,45,57] The cumulative number screened has increased over time from 132,358 during October 2005 to March 2007,[18] 206,088 from a report published in 2009,[45] and, 473,738 through December 2011.[19] For the present report, we focus on the most recent results.[19]

In the reports from Taiwan, newborns are classified as having either "infantile," which corresponds to classic infantile-onset or "later-onset" Pompe disease. Later-onset includes those with nonclassic infantile-onset Pompe disease and late-onset Pompe disease. The term "later-onset" is used because at the time of case identification of newborns, it is often not possible for the screening program to distinguish non-classic infantile-onset Pompe disease from late-onset Pompe disease.

A fluorescence assay is used to screen for GAA activitiy in Taiwan. Over time, the screening program has adjusted the algorithm to use two thresholds for a positive screen to minimize false-positive results. The most recent report[19] describes the following screening algorithm:

- From the dried-blood spot, the NAG/GAA ratio is measured. GAA is measured with the presence of acarbose. NAG is measured without acarbose. Acarbose improves the sensitivity of GAA assays by inhibiting maltase-glucoamylase activity. Evaluating the ratio of NAG/GAA helps adjust for the

number of leukocytes in the dried-blood spot. Earlier collected dried-blood spots can have higher GAA activity because of an increased number of leukocytes.

- *Critical threshold*: A critical cut-off NAG ratio (≥100) leads directly to confirmatory testing (i.e., positive screen)
- *Inconclusive threshold*: An intermediate range (≥30 to <100) is considered inconclusive and leads to measurement of the NAG/GAA ratio and total GAA on another dried-blood spot (referred to as the "second or recall dried-blood spot"). The total GAA enzyme activity is measured to determine the percentage inhibited by acarbose. If results of this second tier screen fall within the critical or intermediate range (i.e., positive screen), the newborn is referred for confirmatory testing.

In a follow-up interview regarding screening in Taiwan, Dr. Chien reported that 32,444 newborns were screened between October 2012 and March 2013 using the revised algorithm, above. These results are not reported in the published reports. Among these newborn screening tests, four samples required second-tier screening (i.e., NAG/GAA ratio and total GAA on a second-tier test) and then subsequent diagnostic confirmation. However, none of these four newborns had Pompe disease.

On the whole, as reported in the published study,[19] screening outcomes of the Taiwan newborn screening program for Pompe disease, since inception, which includes testing for 473,738 newborns are as follows:

- 9 cases of infantile-onset Pompe disease and 19 cases of later-onset Pompe disease were identified. This represents 1 case per 16,919 screened (calculated 95% CI: 1/25,445-1/11,709).
- The percentage of inconclusive screens was 0.47% (calculated 95% CI: 0.45%-0.49%) and the percentage of positive screens was 0.007% (calculated 95% CI: 0.004%-0.009%).
- Among the inconclusive results, 9.9% (calculated 95% CI: 8.7%-11.2%) had a positive second tier test.
- The total percentage that required confirmatory testing, either from the first or second-tier test among all newborns screened was 0.053% (calculated 95% CI: 0.046%-0.059%).
- The positive predictive value among inconclusive screens was 0.9% (calculated 95% CI: 0.11%-3.3%). This led to identification of two children with later-onset disease.
- The positive predictive value of the complete algorithm among initial positive screens, as reported by the investigators, was 84% (calculated 95% CI: 66%-95%).[2] This led to the identification of 9 cases of infantile-onset Pompe disease and 17 cases of later-onset Pompe disease. The program was not able to distinguish for this report whether these cases were nonclassic infantile-onset Pompe disease or late-onset Pompe disease.

Based on these data, the report also describes the impact of changing the critical NAG/GAA ratio to 60 from 100 and using the percentage of acarbose inhibition as the second tier test (≥88% is positive) to improve the specificity of screening. If these modifications were in place:

- Two cases of later-onset Pompe disease would be missed. The other 26 cases would be identified. However, one of the nine cases of infantile-onset Pompe disease would be detected after testing of the recall dried-blood spot because the original result was in the intermediate range.

[2]If the cases identified in the inconclusive screening group are counted as positives, the positive predictive value would be 16%.

- The percentage of inconclusive screens would decrease about 100 fold to 0.005% (calculated 95% CI: 0.003%-0.007%).
- The positive predictive value of an inconclusive screen would be 90% (calculated 95% CI: 55%-99%) and for an initial positive screen would be 94% (calculated 95% CI: 73%-99%).

Dr. Chien reports that now second-tier testing for intermediate results is done on a second punch of the original dried-blood spots. Newborns are not recalled for a second dried-blood spot if the result is intermediate. If the second-tier test is positive, newborns are referred directly for diagnostic evaluation.

The following table summarizes the different estimates of inconclusive, abnormal, and false-positive results that could be expected to occur with the various cut-offs described in the Taiwan algorithm.

Table 3.2. Taiwan screening algorithm estimates[19] of abnormal, intermediate, and false-positive results.

	Rate Per 100,000			
Screen result	**Most Likely**	**Min**	**Max**	**Sources**
Inconclusive first DBS screen (NAG/GAA ≥60)	4.86 (0.0049%)	4.79 (0.00479%)	4.91 (0.00491%)	Chiang, 2012
Abnormal second tier screen (% inhibition ≥88)	2.1 (43.5% of inconclusive first screen)	1.1 (23.2%)	3.1 (63.7%)	Chiang, 2012
(1) FP rate on first DBS screen (i.e., FP rate of Inconclusive [NAG/GAA ≥60] or Abnormal [NAG/GAA ≥100] first DBS screen)	3.17 (0.0032%)	3.12 (0.00312%)	3.22 (0.00322%)	Chiang, 2012
(2) FP rate using combined first DBS screen & second tier screens (i.e., FP rate of Abnormal screens [NAG/GAA ≥100] on first DBS screen OR on second tier screen [% inhibition ≥88])	0.422 (0.0004%)	0.416 (0.00416%)	0.428 (0.00428%)	Chiang, 2012

Comparative Effectiveness of Screening Methods

No published study has directly compared screening methods. However, an ongoing study at the Mayo Clinic is addressing this issue. The goal of this study is to evaluate 100,000 de-identified dried-blood spots from California for 13 lysosomal storage disorders, Friedreich Ataxia, Wilson disease, and X-linked adrenoleukodystrophy. Three methods are being used to screen each of the dried-blood spots for Pompe disease as first-tier assays: MS/MS, digital microfluidics, and a Luminex immunoassay. Each of these first-tier assays are being run in parallel. Positive screens identified by any of the three screening methods undergo a second-tier biochemical assay. Case samples that have abnormal results from the second-tier assay undergo confirmatory molecular genetic analysis. Planned screening activities are expected to be completed after October 2013.

Summary of Key Findings:

- Studies not included in the systematic review suggest that measuring GAA enzyme activity has good laboratory validity. However, the laboratory validity using digital microfluidics has not been reported.
- Sensitivity and specificity cannot be directly calculated from the anonymous dried-blood spot studies because not all dried-blood spots had genetic analysis for Pompe disease-associated mutations.
- Sensitivity and specificity cannot be directly calculated from the screening activity in Missouri because it is too early for missed cases to be identified.
- The sensitivity and specificity of the modified Taiwan screening algorithm can be estimated. Overall, the specificity is >99.9%. If the goal of screening is to only detect infantile-onset Pompe disease, the sensitivity is 100%. However, if the goal is to detect all cases of Pompe disease, the sensitivity is 93%.

The following table summarizes the estimated screening algorithm characteristics based on the available evidence. This is derived from the Taiwan experience, in which the only false-negative were cases of late-onset Pompe disease.[19] These estimates have not been adjusted for differences in the prevalence of pseudodeficiency between Taiwan and the United States.

Table 3.3. Screening Algorithm Characteristics

Screen Result[19]	Most Likely	Lower Estimate	Upper Estimate
Pompe (All Forms)			
Sensitivity	0.9286	0.9278	0.9293
Specificity[†]	0.99997	0.99990	1
Infantile-Onset			
Sensitivity	1	1	1
Specificity[1]	0.99993	0.99990	1
Late Onset			
Sensitivity	0.8947	0.8939	0.8956
Specificity[1]	0.99995	0.99990	1

[†]False positives were defined as an abnormal initial screen (NAG/GAA ≥100) that did not result in a positive confirmation; or an inconclusive initial screen (NAG/GAA ≥60) that came back negative upon secondary screening or during confirmation.

Key Question 4A.

Does initiation of enzyme replacement therapy (ERT) modify the intermediate health outcomes when Pompe disease is detected through newborn screening or through other methods in early infancy compared with usual clinical care? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presence of pseudodeficiency allele)?

Key Question 5.

Does early initiation of enzyme replacement therapy improve health outcomes when the condition is caught early or through newborn screening compared with usual clinical care? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presense of pseudodeficiency allele)?

Key Question 6.

How strong is the association between changes in intermediate outcomes of Pompe disease and changes in health outcomes?

The highest quality data regarding the benefit of treatment of infantile-onset Pompe disease come from the international trials of ERT and the subsequent follow-up reports from those detected through screening in Taiwan.

Survival and Major Morbidity

Trials of ERT

In 2001, the first phase I/II open-label trial of ERT for classic infantile-onset Pompe disease was reported.[58] This high-quality case series enrolled 3 subjects from 2.5 months through 4 months of age and followed to 16-22 months of age. All of the patients survived. Two of the subjects had marked cardiomegaly, which was reduced in size after treatment by 60-70% of the baseline size.

A subsequent 52-week open-label study with optional extension enrolled 8 subjects with classic infantile-onset Pompe disease.[59-61] The age of initiation of therapy ranged from 2.7 months to 14.6 months of life. All had significant hypotonia at presentation. Two subjects were CRIM -. At one year, 6 of the 8 subjects (75%) were alive and vent-free. Two subjects had died, one who was CRIM- and the other who did not begin ERT until 14.6 months of life. During the extension phase of continued ERT up to 153 weeks, one subject, who was CRIM- , became ventilator dependent. Muscle biopsies demonstrated an association between glycogen clearance and outcome.[60]

A multicenter, 52-week open-label clinical trial comparing 20 mg vs. 40 mg doses of ERT with younger Pompe patients enrolled 18 subjects with infantile-onset Pompe disease who began ERT before the age of 6 months.[59,62] As part of this trial, patients were randomized to ERT dose. After 52 weeks, all subjects survived and 15 of 18 subjects were ventilator free. According to a Kaplan-Meier survival analysis, ERT reduced the risk of death by 95% and the risk of death or invasive ventilation by 87% compared with untreated historical controls.[62] With treatment, overall survival and ventilator-free survival at 36 months of life were 72% and 49%, respectively. CRIM- status was associated with worse outcomes.

A longer open-label trial enrolled 21 infants from 3 to 43 months of age (median 13 months) with classic infantile-onset Pompe disease who started ERT after 6 months of age.[63] The median age of ERT initiation was 13 months and the median duration of follow-up was 120 weeks. In this study, outcomes were compared to historical controls. At the start of therapy, 5 required invasive ventilation and 2 required non-invasive ventilation. Two patients were CRIM -. At 104 weeks, overall survival was 71% (15/21). Compared to historical controls, the risk of death was reduced by 79% and the risk of invasive ventilation was reduced by 58%.

A secondary analysis[38] of a series of cases previously reported from 1999-2006 to evaluate the impact of CRIM status on morbidity. This included 21 subjects who were CRIM+ and 11 subjects who were CRIM-. After one year of therapy, 54.5% of CRIM- subjects had either died or required mechanical ventilation, compared to 4.8% of those who were CRIM+. By 27.1 months of age, all CRIM- subjects were dead (n=5) or required mechanical ventilation (n=6) versus 1 death and 3 requiring mechanical ventilation of the 21 subjects who were CRIM+.

Outcomes of Identification through Screening in Taiwan

One case series evaluated the effect of ERT by age of initiation among the 40 subjects identified with classic infantile-onset Pompe disease from 1983-2008.[46] These cases were divided into those identified before the availability of ERT (n=26), subjects who were identified by symptom development and who began ERT after 5 months of age (n=5), subjects who were identified by symptom development and who began ERT before 5 months of age (n=4), and those identified through newborn screening (n=5). The amount of follow-up time was variable.

However, by 20 months of life, the proportion surviving varied by group:

- 20% among those born before ERT;
- 80% among those who were begun on ERT after 5 months of age;
- 100% among those who began ERT before 5 months of age; and
- 100% among those detected through newborn screening.

By 70 months of life, the survival among those who began ERT after 5 months of age was 60%. Similar differences were found by evaluating the proportion who were alive and did not require long-term mechanical ventilation at 20 months of life:

- 20% among those born before ERT;
- 40% among those who were begun on ERT after 5 months of age;
- 100% among those who began ERT before 5 months of age; and
- 100% among those who were detected through newborn screening.

These data support the benefit of early compared to later initiation of ERT, but do not directly provide evidence regarding the benefit of detection through screening versus clinical detection. Table 2, described under Key Question 2, describes the overall differences in survival and ventilator-free survival among those who were detected through screening and those who were detected clinically.

CRIM status was not presented. However, the most common mutation in Taiwan is associated with being CRIM+, and based on the reported genotype, allwould be predicted to be CRIM+. A subsequent report[64] included some of the same subjects and provided more detail about the left ventricular remodeling associated with ERT.

A separate report[45] describes outcomes for five cases of classic infantile-onset Pompe disease and one case of non-classic infantile-onset Pompe disease detected by newborn screening in Taiwan. All subjects were CRIM+. After follow-up of between 14 and 33 months, all subjects have survived and none have required mechanical ventilation. The subject with nonclassic infantile-onset Pompe disease began treatment at 14 months of age because of weakness.

Findings from the Pompe Disease Registry

We requested that Genzyme query the Pompe disease registry to compare survival and ventilator-free survival comparing those who began ERT before 3 months of age to those who began ERT at three months of age and older for those with classic infantile-onset Pompe disease. The results of this request as directly reported appear in the box below. Genzyme provided two analyses. The first includes all subjects in the database, and the second excludes those managed in Taiwan, many of whom would have been detected by newborn screening and have higher rates of ventilator-free survival. The second table in this analyis describes the expected outcomes for clinically detected cases.

Survival Outcomes for Infantile-Onset Pompe Disease by Age at First ERT: Findings from the Pompe Disease Registry

Summary

Patients from the Pompe Registry with symptom onset ≤12 months of age with evidence of cardiomyopathy who received their first treatment with ERT prior to 3 months of age report better survival and invasive ventilator-free survival at 12 months, 24 months, and 36 months of age than patients who received their first treatment with ERT at 3 months of age or older.

Results

Table 3.4. All Patients with Symptom Onset ≤12 months of age with Evidence of Cardiomyopathy

	Age of First Treatment	
	ERT <3 months	ERT ≥3 months
Survival	(Percent Surviving (95% CI))	
	n=36	n=104
12 months	94.1% (78.5, 98.5)	91.3% (84.0, 95.4)
24 months	84.6% (66.8, 93.3)	73.3% (63.3, 81.0)
36 months	80.9% (62.2, 91.0)	63.5% (52.7, 72.5)
Mechanical Ventilation-Free Survival		
	n=24	n=69
12 months	91.3% (69.5, 97.8)	89.8% (79.8, 95.0)
24 months	81.7% (58.2, 92.7)	66.4% (53.1, 76.8)
36 months	76.2% (51.7, 89.4)	56.5% (42.6, 68.2)

Table 3.5. Patients with Symptom Onset ≤12 months of age with Evidence of Cardiomyopathy, Excluding Patients from Taiwan

	Age of First Treatment	
	ERT <3 months	ERT ≥3 months
Survival	(Percent Surviving (95% CI))	
	n=30	n=96
12 months	92.9% (74.3, 98.2)	90.6% (82.7, 95.0)
24 months	81.0% (60.2, 91.7)	72.1% (61.5, 80.3)
36 months	76.5% (54.8, 88.8)	61.3% (49.9, 70.9)
Mechanical Ventilation-Free Survival		
	n=20	n=65
12 months	89.5% (64.1, 97.3)	89.2% (78.6, 94.6)
24 months	77.5% (50.5, 91.0)	65.9% (52.1, 76.7)
36 months	71.1% (43.6, 86.9)	55.3% (40.9, 67.5)

Discussion

The analysis is descriptive in nature; no adjustments have been made for severity of disease or any potential confounding factors that may influence the time of diagnosis, the time of treatment, length of survival or ventilator-free survival, or variables that may influence censoring (i.e. loss to follow-up in the Registry).

The Pompe Registry does not collect information on newborn screening. Because patients from Taiwan may have been identified by newborn screening (and not clinically diagnosed), all patients from Taiwan were excluded from the analysis presented in Table 4.2.

Data are not presented for patients with symptom onset ≤12 months without evidence of cardiomyopathy. No deaths from this population meeting the study criteria were reported to the Registry.

Methods

All treated patients in the Pompe Registry with symptom onset ≤12 months with a record of treatment with ERT were eligible for analyses. Patients were stratified into those with and without evidence of cardiomyopathy; and data for patients with cardiomyopathy were included.

Kaplan-Meier curves were fitted, stratified by those patients with a record of first infusion <3 months of age or ≥3 months of age, for the population with symptom onset ≤12 months and evidence of cardiomyopathy. Events were defined as (1) death, and (2) use of invasive ventilation therapy or death. The time to the event was derived as time from birth. Only patients at risk for the event were included in the Kaplan-Meier analyses.

The 95% confidence intervals (CIs) of event-free survival are reported from the Kaplan-Meier estimation. The CIs are calculated using a transformation of the log (-logS(t)) function; the limits are then transformed back to the survival function.

Patients with a reporting physician from Taiwan were excluded from the second analysis.

Other Case Series

One good quality case series described two cases of classic infantile-onset Pompe disease in China. The first case was identified after the subject was found to have cardiomyopathy.[65] ERT was begun at 6 months of life, at which point she was ventilator dependent. Left ventricular function did not improve with treatment. The subject developed antibodies to ERT and had episodes of hypotension with therapy. At 20 months, ERT was stopped. The subject died of heart failure at 33 months of age. The second case was also identified after the development of cardiomyopathy. ERT was begun at 2 months of age, with improvement in cardiomyopathy and normalization of left ventricular function. Within three months of treatment, low levels of ERT antibodies developed. Developmental evaluation at 23 months of age showed good fine motor skills, but gross motor skills lagged by about 10 months. This subject was still living, at age 2 years, at the time of this report.

One case series describe the outcomes for 11 subjects with classic infantile-onset Pompe disease who survived to five years of age or older.[66] Ten subjects developed low-titer antibodies to ERT; information was not available regarding the other subject. Six of these subjects were previously reported as part of the initial dosing studies. All subjects were CRIM+ and began ERT between 0.2 and 6 months of age. The age at the time of final analysis ranged from 5.4 to 12.0 years. At this age, seven were ambulatory and four required walkers, either full or part time. Four required at least partial gastrostomy tube feeds. Seven patients required hearing aids.

One case series described 20 cases of classic infantile-onset Pompe disease who received ERT between 2000 and 2009.[67] Data were based on survey responses from treatment centers. It is unclear if these cases have been reported elsewhere as well. Overall survival was 65% and 30% were ventilator dependent. CRIM status was known for five subjects. Of these, the two CRIM- subjects had died. Although the report describes that those who were diagnosed before 6 months of age had a poorer outcome (44% mortality), no data are presented regarding whether this was because those with worse baseline cardiomyopathy would be more likely to be identified earlier and also have worse outcome.

One fair quality case series described 3 cases of classic infantile-onset Pompe disease identified through prenatal ultrasounds for fetal cardiomyopathy in the United Arab Emirates.[68] ERT was begun at or before 2 weeks of life for all three cases. One patient died at 19 months of age and the others were alive at 4 and 30 months of age.

Case Reports

One fair-quality case report[69] describes a 4 month old diagnosed with classic infantile-onset Pompe disease in Turkey. This subject died at 9.5 months of age with cardiac failure and respiratory infection. Therapy had “slightly reduced” cardiomegaly during the initial 2 months of ERT.

One fair-quality case report[70] describes a 2 day old diagnosed after identification of cardiomyopathy presenting as persistant bradycardia. ERT was begun at 20 days of life. The cardiomyopathy resolved by 3 months. She had normal growth and motor development. No antibodies developed. At 18 months of life, a muscle biopsy showed involvement in about 10% of muscle fibers. No formal assessment of cognitive or motor development was presented in this report.

One fair-quality case report describes a newborn that was suspected prenatally due to family history of Pompe disease and confirmed shortly after birth in the United Arab Emirates.[71] ERT began at 18 hours of age. By 11 weeks, the cardiac hypertrophy resolved, but the patient had left ventricular dilation and systolic dysfunction. At 10 months of life, the patient had normal neurodevelopment and growth. This subject also was included in the case series report, described above.[68]

One fair-quality case report describes a 1-month old who developed heart failure and was subsequently diagnosed with classic infantile-onset Pompe disease.[72] He was begun on ERT at 1.5 month of age. He had cardiac arrest one week after ERT was begun, but survived. The cardiomyopathy resolved by about 5 months of life.

One fair-quality case report described a subject with classic infantile-onset Pompe disease who began ERT at 9 months of age.[73] This subject already had significant hypotonia, cardiomyopathy, and required mechanical ventilation. After ten months of therapy, her cardiomyopathy improved and she was switched to noninvasive continuous positive airway pressure for ventilation. No information was provided on CRIM status.

One well-described case report describes a subject with CRIM- classic infantile-onset Pompe disease who began ERT in the first month of life.[74] Although the subject developed antibodies, the titer was considered moderate in comparison to other CRIM- subjects. However, by 2.5 years of life, the subject required mechanical ventilation and subsequently died by 3 years 9 months.

Cognitive, Language, Motor and Social Development

One fair-quality case series[75] was conducted primarily to evaluate brain MRI changes in 5 subjects with classic infantile-onset Pompe disease who began ERT at a median age of 6 months. CRIM status was not described; however, none developed antibodies to ERT. Discussion of the MRI findings appears in the section on development. After 12 months of treatment, 3 subjects did not have head control or the ability to sit and one could not perform antigravity arm movement. At baseline and at after 6 months of treatment, there was delay in myelination, which improved by 18 months in 4 of the 5 subjects.

One case series[76] described cognitive development among 17 children with who were participating in the previously described treatment study.[77] All subjects had classic infantile-onset Pompe disease, diagnosed < 6 months of age, and none required invasive mechanical ventilation. One subject from the treatment study was excluded because of "discrepancies in the cognitive test results." The main outcomes, cognitive development (Mental Scale of the Bayley Scales of Infant Development, Second Edition) and gross motor development (Alberta Infant Motor Scales), were measured prior to the start of ERT and at weeks 12, 26, 38, and 52 weeks of life. The key findings were as follows:

- At baseline, the mean mental development was one standard deviation below the mean for age, and considered borderline range of cognitive functioning. Over time, the mean mental development remained one standard deviation below the mean for age.
- The mean motor development was consistent with severe neuromotor impairment at baseline, but increased over time (on average, 7.7 at baseline to 37.2 at study end, $p<0.0001$).
- There was a strong correlation ($r=0.80$) between mental and motor development.
- Four subjects were considered to be limited responders, with "negligible" motor gains after 1 year of ERT. Among these subjects, one was CRIM negative. However, there were two CRIM negative subjects who were considered "high responders" to ERT during the 52-week preiod. In a follow-up report, all four CRIM- patients did poorly.[60]

Another case series[78] evaluated 8 children with classic infantile-onset Pompe disease started on ERT within 6 months of age and 2 children with nonclassic infantile-onset Pompe disease started on ERT between 1 and 2 years of age. Two of the subjects with classic infantile-onset Pompe disease were in the previously described case series.[76] Multiple different assessments of cognitive and adaptive

functioning were given over time. At a median age of 7 years, the median IQ of the children with classic infantile-onset Pompe disease was 85 (low normal) and 125 (above average) for those with nonclassic infantile-onset Pompe disease. The adaptive functioning score was borderline between average and significantly impaired for 5 of the 7 children with classic infantile-onset Pompe disease.

Another case series[79] described cognitive outcomes in ten subjects with classic infantile-onset Pompe disease. Subjects were followed for varying amounts of time, beginning from 2 months of age through 4 years with most receiving multiple psychological assessments. Five subjects were followed past 4 years of age, with the eldest followed to 12 years. Although the subjects had variable gross motor function, cognitive development overall was normal to mildly delayed.

One case series evaluated the speech and language of 12 subjects with classic infantile-onset Pompe disease between 13 and 98 months of life.[80] Half of the subjects had the evaluation twice. Hearing was normal for 11 subjects; one (8.5%) had bilateral mild-moderate high frequency loss. Overall, receptive language was within in the mild disorder to the normal range. However, three subjects initially had moderate language delay. Not all subjects had speech, articulation, or phonation evaluated. In marked contrast, another report which evaluated 11 subjects with classic infantile-onset Pompe disease reported sensorineural hearing loss in 9 (82%) subjects. This hearing loss persisted despite ERT.[81] The discrepancy in rates of hearing loss between these two studies requires explanation.

One case series[82] evaluated 11 subjects with classic infantile-onset Pompe disease. The range in age at the start of ERT was 0.1 months to 8.3 months. The age at the study end ranged from 0.8 years to 12 years. Three subjects died, one at 0.8 years and two at 4 years. Four subjects required invasive ventilation before the end of the study period, including two of those who died. The subjects were followed for 24 months after the start of ERT with photographs to evaluate for facial muscle weakness. The subset who became 24 months or had more than 10 words (n=4) had their speech evaluated at two points, separated by one year. Another subset (n=6) who did not feed by percutaneous gastrostomy tube had swallowing evaluated at two points, separated by one year. The key findings were:

- All patients developed facial-muscle weakness at a median age of 6.6 months which for 9 of the 11 subjects was considered mild, even when ERT was started early. By 24 months of follow-up, facial muscle weakness was considered severe in 7 of the 11 subjects.
- Among the four subjects who had speech evaluated at a median age of 4.1 years, articulation was disordered because of the facial weakness. Among the three patients who had follow-up one year later, these speech disorders persisted.
- Endoscopy revealed dysphagia among five of the six subjects, with significant swallowing problems and poor protective reflexes. Follow-up in one of four subjects demonstrated worsening swallowing difficulties.

In the previously described open-label study with historical controls,[63] 13 of 21 subjects had improvement in gross and fine motor skills. These subjects also had better motor scores at baseline. Of the 10 subjects younger than 12 months at the initiation of ERT, 10 showed acquisition of functional skills based on a standardized instrument (the Pompe Pediatric Evaluation of Disability Inventory).

In the previously described report from the Taiwan screening program of 6 subjects detected through newborn screening,[45] all had normal motor development as measured by the Alberta Infant Motor Scales at 1 year of age. Before ERT, early motor delay (e.g., head control) was described in 4 of the 5 subjects with classic infantile-onset Pompe disease. However, these subjects were begun on ERT within about the first month of life.

Other Specific Comorbidities

One case series found that among 38 with classic infantile-onset Pompe disease treated in the open-label trials, 7 had a tachyarrhythmia at some point.[83] Assessing predictors of the arrhythmia is difficult because of variation in underlying disease state and variation in follow-up.

The previously described report that stratified subjects by age of initiation of therapy[46] found that six patients had arrhythmias after ERT (60% who began after 5 months of age after symptom development, 50% who began before 5 months of age after symptom development, and 20% who were identified through newborn screening). The clinical significance of these findings were variable.

One case series of 19 subjects with classic infantile-onset Pompe disease[84] who began ERT between 2 and 12 months of age and followed for a median of 6 months of age found EKG changes associated with improvement in cardiomyopathy. These changes included decreases in left ventricular voltage. Six subjects died (range 11.8-51.8 months). CRIM status was not reported. No relationship was described between EKG changes and mortality. Another case series of 12 subjects,[85] at least some of whom were included in the previous study,[84] also found improvement in EKG changes associated with cardiomyopathy. One subject had frequent premature ventricular contractions that peaked during the 11th week of ERT and which required medical treatment. One subject was also found to have Wolff-Parkinson-White syndrome.

One fair-quality case report described a subject with CRIM- classic infantile-onset Pompe disease who developed nephrotic syndrome on ERT at 27 months of life while receiving high dose (50 mg/kg/week) ERT.[86] After temporarily stopping ERT and resuming at a lower dose, the nephrotic syndrome resolved for four months of reported follow-up. However, the subject did require immune tolerance therapy and increased doses of ERT for the development of antibodies and clinical decline prior to the development of the nephrotic syndrome.

One case series evaluated the impact of developing antibodies to ERT among both CRIM+ and CRIM- subjects with classic infantile-onset Pompe disease.[87] This study included 11 CRIM- subjects and 23 CRIM+ subjects. Among those who were CRIM+, 14 as having low titer ERT antibodies. Survival and ventilator-free survival of the high titer CRIM+ subjects was similar to the CRIM- subjects. Before 150 weeks of age, all high-titer CRIM+ subjects and CRIM- subjects were either dead or required mechanical ventilation. In contrast, no low titer CRIM- subject had died and only three required mechanical ventilation.

Immunotherapy or Desensitization for Subjects with Pompe Disease who are CRIM(-)

One well-described case report[88] described the antibody development in a subject with classic infantile-onset Pompe disease who was started on ERT at 4 months of age. Antibodies developed after 1 month of therapy, which was associated with worsening symptoms, including the need for tracheostomy, gastrostomy tube, and worsening cardiac function by 19 weeks. Initial immunotherapy included cyclophosphamide, IVIG, and plasmapheresis, which was given a total of three times. In addition, high dose ERT (10 mg/kg/day for 5 days/week) was tried. Rituximab was added in weeks 99 through 102. This therapy reduced the CD19 circulating B-cell count to 0. However, no clinical improvement occurred. The subject died at 4 years of age after withdrawal of ventilator support.

One good-quality case report described a 44 month old subject with CRIM - classic infantile-onset Pompe disease who began ERT at 4 weeks of life who developed significant allergies to infusion that could not be managed with dose reduction and premedication antihistamines and corticosteroids.[89] After

adding ormulizamab, the other premedications were able to be stopped and slowly the ERT dose could be increased, up to 14 mg/kg every 10 days. ERT IgG levels remained <1:8000.

One good-quality case series describes a tolerance-induction regimen involving 2 subjects with CRIM - classic infantile-onset Pompe disease who were treated with rituximab, methotrexate, and IVIG after developing rhGAA antibodies and another 2 CRIM - subjects who were treated prophylactically, before developing antibodies.[90] For the therapeutically treated subjects, antibodies were eliminated after 3 months and after 19 months of therapy; the length of sustained immune tolerance has been 4.5 years and 3 years, respectively. At the time of report, these subjects were 53 and 35 months of age. One subject has been ventilator free; the other was ventilator dependent after 11 months, but showed sufficient improvement to reduce ventilation dependency to nighttime only. The two subjects treated prophylactically received the tolerance-induction therapy at 15-16 weeks of age; each has since tolerated ERT without significant antibody response. At the time of report, these subjects were 33 months and 22 months of age. One subject has achieved developmental skills of independent walking and running. The second subject has achieved more limited ability of sitting up only briefly without hand support.

Another good-quality case series described two cases of infantile-onset Pompe disease, one CRIM+ and one CRIM-, and one case of late-onset Pompe disease all of whom developed increasing anti-rhGAA IgG titers with decline in clinical function.[91] Each subject was initially treated with rituximab and methotrexate, but symptoms worsened. Botezomib was added to the immunosuppressive therapy, leading to reduced antibody titers and clinical improvement.

A good-quality care series compared five infants with classic infantile-onset Pompe disease who received immunotherapy before beginning ERT to one infant with classic infantie Pompe disease who did not receive immunotherapy before beginning ERT.[92] In the group that received immunotherapy before initiation of ERT, four of the five were CRIM-. The comparator infant was CRIM+. The immunotherapy included methylprednisolone and rituximab followed by sirolimus or mycophenolate. The goal of this approach was for B-cell depletion and T-cell immunomodulation. The subjects also received monthly IVIG to provide passive immunity. After ten months, one CRIM- subject developed high antibodies to ERT and died. Another CRIM- subject, who has been on ERT for 31 months, required chronic ventilator support at 17 months. Two of the other CRIM- subjects have not required chronic ventilator support, and have been on treatment for 34 and 36 months. The CRIM+ subject has been on ERT for 16 months. The refererent has been on ERT for 107 months.

Dr. Kishnani reported during an interview on February 21, 2013, that a short course of immunomodulation therapy when first providing ERT for CRIM- subjects in early infancy may provide long-term protection against the development of anti-rhGAA antibodies. Dr. Kishnani is now reporting an additional seven cases for which treatment has been sustained for 18 months without the development of a significant titer of antibodies. According to Dr. Kishanani, there are at least six more patients who have begun this regimen with no development of antibodies to ERT and no significant safety events.

Key Question 4B.

4. B. Do follow-up protocols exist for the management of Pompe disease that does not require immediate initiation of enzyme replacement therapy? What is known about the effectiveness of follow-up protocols in modifying intermediate health outcomes?

Guidelines based on expert opinion have been developed regarding the frequency of follow-up for individuals identifed with late-onset Pompe disease,[93,94] with frequent follow-up (e.g., every 3 months) in early infancy to less frequently (e.g., every six to twelve months) in older children. However, the systematic evidence review did not identify any evaluation of such protocols.

We identified case reports and case series of individuals with late-onset Pompe disease that received ERT early in their disease course. [95-99] However, there was significant heterogeneity in how these cases were detected and the criteria for beginning ERT. Therefore, these provide little evidence regarding the benefits and harms associated with detection of late-onset Pompe disease through newborn screening.

We also identified two reports of a randomized trial of ERT for late-onset Pompe disease.[100,101] In this study, 90 subjects (≥8 years of age) were randomized to placebo or ERT. The inclusion criteria included the following:

- Able to walk 40 m on the 6-minute walk test, with assistive devices if needed;
- Forced vital capacity within 30% to 80% when upright with a drop of 10% or more when supine;
- Evidence of lower extremity weakness; and
- No need for invasive ventilation or noninvasive ventilation while awake.

After 78 weeks, those treated with ERT had an increase of 28.1 meters on the 6-minute walk test ($p=0.03$) and an absolute increase of 3.4% in forced vital capacity ($p=0.006$).[101] In a secondary data analysis, no change was found in cardiovascular status.[100]

The Taiwan newborn screening program did not classify individuals as having late-onset disease. Instead, the term "later-onset" disease was used, which included overlap between nonclassic infantile-onset disease and late-onset disease. Individuals with later-onset disease were followed up every 3 to 6 months for signs of weakness. In addition, the Peabody Developmental Motor Scale, Second Edition (PDMS-II) was administered every 12 months. ERT was begun for significant elevation of CK or onset of significant motor delay. Thirteen patients were identified with late-onset Pompe disease. Four of the 13 subjects began treatment, at ages 1.5 months, 14 months, 34 months and 36 months.[57] In the classification used in this report, the subject that required treatment at 1.5 months would be considered to have nonclassic infantile-onset Pompe disease. It is also possible that the subject that began treatment at 14 months would be considered to have nonclassic infantile onset-disease.

In a subsequent report of 15 newborns, which included overlap with the 13 cases previously described, five had a delay in motor development or elevation of CK and were started on ERT.[102] The additional case that was treated was begun at 7 years, and was identified with weakness after the subject's sibling had been diagnosed through newborn screening. Muscle biopsy before ERT initiation showed abnormalities associated with glycogen storage that by 6 months after treatment was "largely absent." No formal strength testing was reported. The current status of these patients is presented in Table 3.6.

Table 3.6. Age of ERT initiation and status of Infantile (nonclassic) and Late-onset patients identified through the Taiwan Newborn Screening program.

Age at Initiation	Report Classification	Current Age	Status
1.5 months	Nonclassic Infantile-onset	37 months	Normal
2 months	Nonclassic Infantile-onset*	10 months	Sit well
14 months	Nonclassic Infantile-onset	67 months	Normal, slight lordosis
34 months	Late-onset	43 months	Frequent falling
36 months	Late-onset	51 months	Less endurance
7 years	Late-onset	9.1 years	Less endurance, lordosis

*According to one of the investigators, this subject developed cardiomyopathy at 3 months of age and therefore would now be classified as having classic infantile-onset disease.

Dr. Kishnani reported in an interview that she has conducted an evaluation of whole-body MRI findings of patients with late-onset Pompe disease prior to beginning ERT. According to Dr. Kishnani, even with mild functional impairment, significant skeletal muscle damage is found on MRI. Because ERT cannot reverse muscle damage, this finding suggests that individuals with late-onset Pompe disease may benefit from therapy before the development of weakness or significant biomarkers of muscle damage (e.g., elevated CK). This hypothesis is also supported by autophagic inclusion bodies that can be found in muscle biopsies of those with late-onset Pompe disease, which persist even after treatment with ERT and reduction of glycogen in muscle cells.[103] Studies are now being planned to evaluate this hypothesis.

Summary of Key Findings

- Compared to no treatment, ERT dramatically improves the morbidity and mortality associated with infantile-onset Pompe disease. Presymptomatic treatment appears to improve benefit.
- Cognitive development can be difficult to assess if there is motor weakness. Furthermore, some affected individuals have hearing impairment. Studies suggest that those who respond to ERT maintain their level of cognitive development.
- Patients who are CRIM- without immunotherapy have poor outcomes. Immunotherapy may allow tolerance of ERT. However, further research is needed to identify the best strategy to induce tolerance and to assess how long tolerance lasts.
- Although there are no data evaluating presymptomatic treatment of late-onset Pompe disease, there is a theoretical benefit.

Key Question 7.

What are the harms associated with newborn screening for Pompe disease to the individual or the family?

Newborn screening for Pompe disease could lead to harms associated with false-postive screening results, identification of infants with late-onset disease, or other related psychosocial implications of screening. Although identification of late-onset Pompe disease could be of benefit to parents and children, this information could also lead to harms such as medicalization, anxiety and stigmatization. These potential harms have been explored in studies regarding the addition of other conditions to newborn screening panels; however, little is known about the potential harms associated with Pompe disease.

One recent survey in the Netherlands[104] addressed the public's balancing of benefits and harms of potentially introducing newborn screening for Pompe disease, comparing a neutral consumer panel and a sample of parents of individuals with Pompe disease. The study found a high level of support for the introduction of newborn screening in both groups. In addition, both groups saw benefit for children even in cases of a false positive or the identification of probable late-onset Pompe disease. The neutral consumer respondents expressed more concern that parents and children may experience some level of harm due to both false positives or identification of late-onset disease.

The systematic evidence review did not identify any reports of harms measured after a false positive or related to the early identification of late-onset Pompe disease.

In a follow-up interview with Dr. Chien regarding screening in Taiwan, the families of three of 22 patients with late-onset Pompe disease refused follow-up care. No further information is available regarding why follow-up was refused.

Summary of Key Findings

- Screening would identify more infants with late-onset disease than infantile-onset disease. Although infants identified with late-onset disease will eventually develop symptoms, the age at which muscle damage occurs or symptoms develop cannot be predicted. At least some families in Taiwan choose not to have follow-up after diagnosis with late-onset Pompe disease. The appropriate medical services and related public health response upon detection of presymptomatic late-onset Pompe disease is not well understood.

Key Question 8.

What are the harms associated with ERT for Pompe disease in early childhood? How does this vary by phenotype (e.g., infantile-onset vs. late-onset, CRIM status, presence of pseudodeficiency allele)?

The only significant direct harm related to ERT identified in the reports is the development of anti-rhGAA antibodies. An examination of CRIM status among a sample (n=243) of patients with infantile-onset Pompe disease found 25.1% (n=61) to be CRIM-.[23] This estimate was consistent with the experience of members of the Technical Expert Panel (see Appendix B). New approaches to immunotherapy appears to decrease the poor outcomes associated with the development of antibodies in patients who are CRIM-. High titers of neutralizing antibodies can also develop in those who are CRIM+. Clinical experts estimate that approximately 20% of CRIM+ patients develop this reaction to ERT.

Summary of Key Findings

- Some patients with Pompe disease who are CRIM+ will develop ERT-related antibodies. The impact of these antibodies is variable.
- Immuomodulation therapy appears to decrease the risk of poor outcome among those who are CRIM-.

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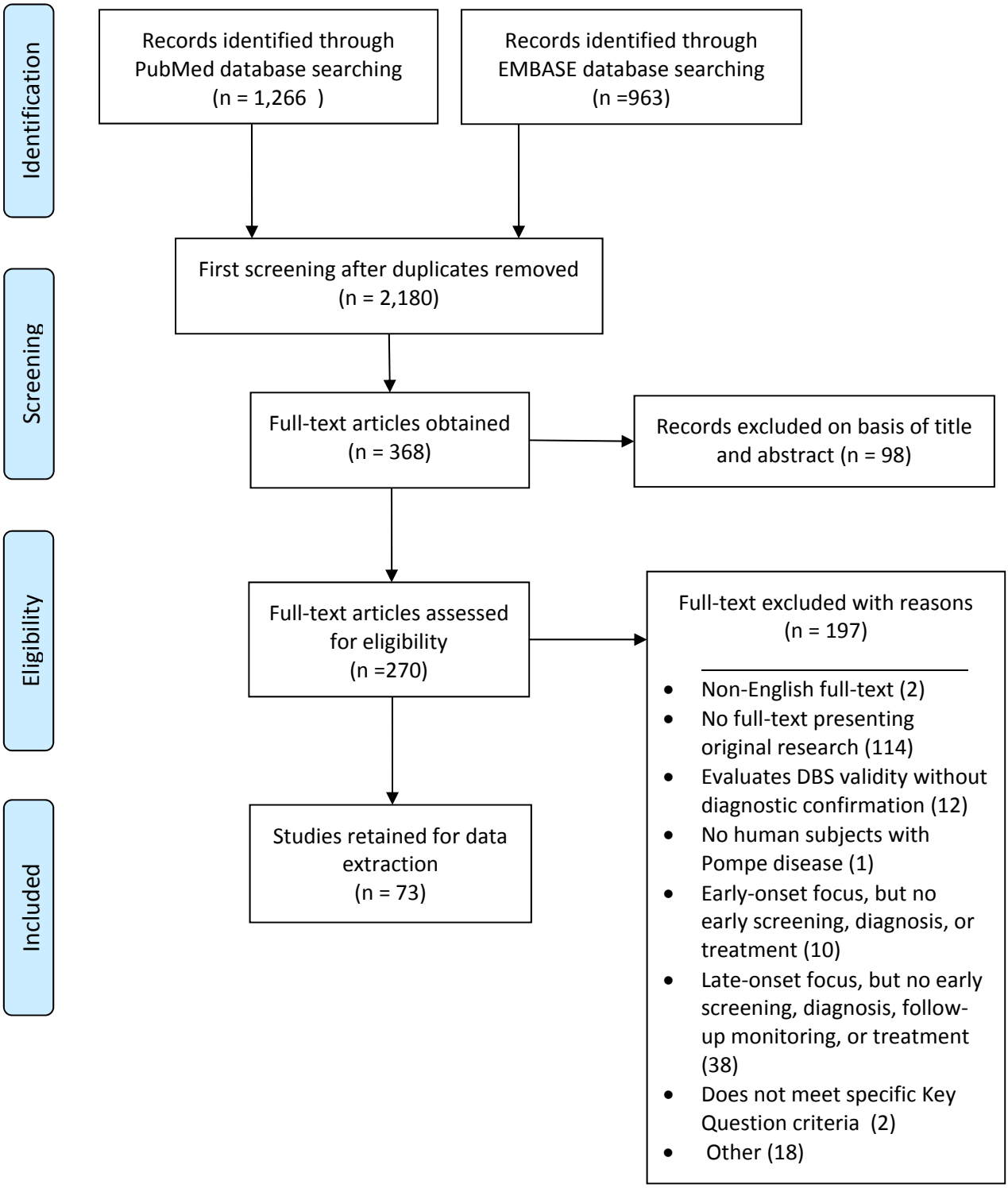
APPENDICES

Appendix A: PRISMA Flow Diagram of Literature Screen

Figure A.1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of published literature identified through database and title screening, article review, and data extraction for evidence review for newborn screening for Pompe disease.



Appendix B. Technical Expert Panel (TEP)

Table B.1. Expert Panel Teleconferences

TEP MEMBERS	TEP 1 (SER) 10 Jul 2012	TEP 2 (SER) 25 Jul 2012	TEP 3 (Dec Anal) 6 Dec 2012	TEP 4 (Dec Anal) 8 Jan 2013	TEP 5 (Dec Anal) 25 Apr 2013
Olaf Bodamer, MD, PhD[†]	√			√	√
Barry Byrne, MD, PhD		√	√		
Sharon Kardia, PhD	√		√		
Priya Kishnani, MD, MBBS[†,*]	√	√		√	√
C. Ronald Scott, MD	√			√	√
Muhammad Ali Pervaiz, MD		√			
Deborah Marsden, MBBS[†]			√		√

Table B.2. Expert Panel: Individual Interviews

Pompe NBS - Individual Expert Interviews	Date
Robert F. Vogt, Jr., PhD/Hui Zhou, PhD (CDC/ONDIEH/NCEH – NBS Branch)	Jan 17, 2013
Vamula Pamsee (Advanced Liquid Logic)	Feb 13, 2013
Priya Kishnani, MD, MBBS†, - (Duke)	Feb 21, 2013
Joan Keutzer, PhD (Genzyme)	Mar 5, 2013
Yin-Hsiu Chien, MD, PhD (Taiwan NBS)	Mar 6, 2013
C. Ronald Scott, MD (WA state NBS/research)	Mar 20, 2013
S. Rogers, MD/P. Hopkins/L. Smith, MD (MO NBS)	Mar 21, 2013
Khaja Basheeruddin, PhD (IL NBS)	Mar 27, 2013
Dietrich Matern, MD, PhD (Mayo/screening CER)	(Apr 18, 2013)[**]

[†]Served on TEP for previous 2008 review of newborn screening for Pompe disease.
[*]Nominator of Pompe disease for consideration to be added to the RUSP.
[**]Provided written responses to questions.

Appendix C: Applying Decision Analysis to Assess Population-Level Benefits

OVERVIEW OF PROCESS

Evidence Evaluation and Methods Workgroup

In May 2012, an Evidence Evaluation and Methods Workgroup was convened to consider methods and approaches utilized by the External Condition Review Workgroup (CRW) for the SACHDNC. Participants included current CRW members and invited participants with expertise in evidence review and decision analytic modeling. One of the recommendations from this Workgroup was to incorporate the application of decision analysis into the evidence review process. This process was previously used in the evaluation of hyperbilirubinemia. Pompe disease is the second condition to incorporate decision analytic modeling into the evidence review and synthesis process.

Objectives of Decision Analysis

Decision analysis is a systematic approach to decision making under conditions of uncertainty that has been applied to clinical and public health problems.[1] Decision analytic models can be used to simulate randomized clinical trials for new health interventions, to project beyond the clinical trial time frame, or to compare treatment protocols not directly compared in head-to-head trials. The decision analytic approach allows the decision maker to identify which alternative is expected to yield the most health benefit. It can also allow researchers to characterize the uncertainty associated with projections of clinical and economic outcomes over the long-term[2], which is important given the lack of long-term outcomes data for most conditions considered for newborn screening. A decision analytic model (or decision tree) defines the set of alternatives and short-and long-term outcomes associated with each alternative. In the application to screening for Pompe disease, this approach was anticipated to aid in the estimation of the range of health outcomes that could be expected for universal newborn screening of Pompe disease compared with clinical identification.

Applying Decision Analysis to Screening for Pompe Disease

Pompe disease was originally considered for addition to the RUSP in 2006 and 2008, but was not added to the panel at that time due to a lack of evidence. Published literature for rare phenomena is usually very limited with respect to data for prevalence, natural history, or response to treatment. New data have become available for screening and treatment outcomes relevant to Pompe disease. By utilizing modeling for this review, the Advisory Committee anticipated that a model would supplement the evidence base by providing projections of key health outcomes at the population level and highlight evidence gaps, thereby enhancing the overall decision making process.

Expert Panel Meeting Process

Clinical and scientific experts in the screening and treatment of Pompe disease were identified and invited to serve on an Expert Panel (see Appendix B for list of expert panelists). Expert panel members were asked to provide input on the structure of the decision analysis model, including the identification of key health outcomes to be included in the analysis. A series of three expert panel meetings (12/6/12;

1/8/13; 4/25/13) were conducted to identify sources and derive probabilities for each outcome in the model; to provide feedback on the structure of the initial and revised decision analytic model, including the relevant timeframe for key health outcomes; and to develop assumptions where little or no data were available. All meetings were conducted via webinar. Expert panel participants received a discussion guide prior to the meeting that included background information, proposed data inputs, and proposed modeling inputs for discussion by the group. The identification of data sources and the development of a decision analytic model is typically an iterative process.

Table C.1. Timeline - Application of Decision Analytic Model for Pompe Disease Screening

	Decision Analysis Milestones
2012	Pompe disease nominated for addition to uniform newborn screening panel; referred to external condition review group
Fall 2012	Initial development of decision analytic model to evaluate newborn screening for Pompe Disease
Dec 2012	Technical Expert Panel 3 – Review Model Structure
Jan 2013	Technical Expert Panel 4 – Review Revised Model Structure & Assumptions
April 2013	Technical Expert Panel 5 – Review Model Inputs
May 2013	Final Pompe evidence review report and decision analysis findings presented to Advisory Committee

METHODS

An initial decision analysis model was developed based on information from the evidence review. This initial model was reviewed with the expert panel in December 2012 and January 2013. Based on feedback from the experts, a revised model was developed. A simplified schematic of the Pompe disease model is shown in Figure C.2.

The **key features** of the decision analytic model are as follows:

- Target population: Annual newborn cohort for the US (n=4 million), excluding newborns at higher risk for Pompe disease
- Interventions: A strategy of universal newborn screening (NBS/Treated Immediately) is compared with diagnosis through clinical identification (Clinical Identification/Treated). The analysis assumes that identified cases of infantile onset Pompe disease will be treated with ERT whether they are diagnosed through newborn screening or through clinical identification. In other words, the difference between the two modeled cohorts indicates the benefits of earlier diagnosis and treatment – infants identified through clinical identification will initiate treatment, on average, between 4-5 months of age.
- Timeframe: 36 months
- Key health endpoints: Mortality and ventilator-free survival for infantile-onset cases (both with and without cardiomyopathy)

A second expert panel meeting met in April 2013 reviewed the proposed set of parameter inputs for the decision model which were based on published and unpublished data. These parameter estimates were revised following the expert panel based on new data sources identified during the expert panel (published and unpublished) and supplemented by expert opinion in cases where no data were available. The final set of parameter inputs and associated ranges for the analysis are shown in Tables C.2 and C.3 below. New data were obtained from the Pompe registry following the third expert panel in May 2013 and were also incorporated into the parameter ranges reported below.

Key assumptions:

- All identified infantile onset cases are expected to receive ERT whether identified through newborn screening or clinical identification. Table C.3. also reports mortality and ventilator-free survival for clinically-identified cases that are not treated with ERT. These estimates are included in order to account for some cases on infantile-onset Pompe without cardiomyopathy that would likely be missed with clinical identification until later in childhood.
- All cases of infantile onset with cardiomyopathy would be detected under newborn screening or clinical identification within the first 12 months of life, but at a later age of identification for CI. The difference is in timing of identification, diagnosis, and treatment. Cases identified through clinical identification are assumed to be identified and receive treatment several months later than those identified through newborn screening. The modeling results represent the difference for earlier diagnosis and treatment for newborn screening compared with clinical identification.

- Some cases of infantile onset without cardiomyopathy would be missed within the first 12 months of life under clinical identification. The modeling results also reflect the health benefits of identifying and treating this group of infantile onset cases without cardiomyopathy that would be identified at or close to birth under a newborn screening recommendation.
- Mortality and morbidity are less severe for cases of infantile onset without cardiomyopathy compared to infantile cases with cardiomyopathy (Table C.3).
- The decision analysis does not include any specific assumptions regarding CRIM status and adjustment of treatment based on CRIM status in the model. Treatment effectiveness reflects the observed effects from 2 studies that were both conducted prior to the identification of CRIM status, its effect on ERT, and the use of immunomodulatory treatment to ameliorate these effects.
- Timing and onset of late-onset cases for newborn screening compared with clinical identification is unknown. At this time, late-onset cases are not included in health outcomes predicted by the decision analytic model.

Table C.2. Key probability inputs, Pompe disease prevalence and subtypes[1]

	Universal newborn screening (NBS)				Clinical Identification (CI)			
Pompe	**Most Likely**	**Min**	**Max**	**Sources**	**Most Likely**	**Min**	**Max**	**Sources**
Pompe disease (all subtypes)	1/27,800	0.3/27,800	2.7/27,800	Scott et al, 2013	1/27,800[2]	0.3/27,800	2.7/27,800	Scott et al, 2013
Infantile (<12 mos)	0.278	0.132	0.424	Chiang et al, 2012 Mechtler et al, 2012 Scott et al, 2013	0.250	0.109	0.391	Chiang et al, 2012 Mechtler et al, 2012 Scott et al, 2013 Expert opinion[3]
Infantile with cardio-myopathy (classic)	0.236 (0.85)	0.195 (0.70)	0.250 (0.90)	Expert opinion	0.235 (0.94)	0.2 (0.80)	0.250 (1.00)	Expert opinion, Kishnani, 2006
Infantile without cardio-myopathy (non-classic)	0.042 (0.15)	0.028 (0.10)	0.083 (0.30)	Expert opinion	0.015 (0.06)	0 (0.0)	0.05 (0.20)	Expert opinion, Kishnani, 2006
Late-onset (≥12 mos)	0.722	0.576	0.868	Chiang et al, 2012 Mechtler et al, 2012 Scott et al, 2013	0.750[2]	0.609	0.891	Chiang et al, 2012 Mechtler et al, 2012 Scott et al, 2013 Expert opinion

[1] 95% confidence interval derived using a binomial distribution

[2]This number does not represent "clinical prevalence". It is assumed that under clinical detection that some proportion of the late-onset cases identified under newborn screening would never be detected. There is very scant data on this parameter. The assumption is that clinical prevalence may fall somewhere between 1/40,000 and 1/100,000 which would imply that as many as 40-70% of cases would be missed.

[3]Adjusted to assume that only 2 out of 6 cases of infantile onset without cardiomyopathy would be detected under clinical identification compared with newborn screening based on expert opinion and the proportion of cases identified with and without cardiomyopathy from a retrospective cohort study.

Table C.3. Key health outcomes for 3 populations, infantile-onset cases only (<12 mos): screened & treated, clinically-diagnosed & treated, clinically-diagnosed & untreated.[1]

a. **Mortality**

	Mortality, 24 mos.		Mortality, 36 mos.	
	Infantile with cardiomyopathy	**Infantile without cardiomyopathy**	**Infantile with cardiomyopathy**	**Infantile without cardiomyopathy**
Screened/Treated Immediately				
Most Likely	<0.001	<0.001	<0.001	<0.001
(Min, Max)	(0, 0.029)	(0, 0.029)	(0, 0.029)	(0, 0.029)
Sources	Chen et al, 2009[2]	Assumption[3]	Chen et al, 2009[2] Personal communication[4]	Assumption[3]
Clinically Diagnosed/Treated[5]				
Most Likely	0.258	0.012	0.351	0.080
(Min, Max)	(0.182, 0.334)	(0.001, 0.111)	(0.267, 0.439)	(0.020, 0.208)
Sources	Primary data[6]	Derived[7]	Primary data[6]	Derived[7]
Clinically Diagnosed/Untreated				
Most Likely	0.928	0.203	0.979	0.289
(Min, Max)	(0.882, 0.960)	(0.093, 0.364)	(0.959, 0.999)	(0.161, 0.468)
Sources	Chen et al, 2009[2] Kishnani et al, 2006	Winkel et al, 2005	Chen et al, 2009[2] Kishnani et al, 2006	Winkel et al, 2005

b. Ventilator-free survival

	Ventilator-free survival, 24 mos.		Ventilator-free survival, 36 mos.	
	Infantile with cardiomyopathy (<12 mos)	**Infantile without cardiomyopathy (<12 mos)**	**Infantile with cardiomyopathy (<12 mos)**	**Infantile without cardiomyopathy (<12 mos)**
Screened/Treated Immediately				
Most Likely	>0.999	>0.999	>0.999	>0.999
(Min, Max)	(0.971, 1)	(0.971, 1)	(0.971, 1)	(0.971, 1)
Sources	Chen et al, 2009	Assumption[3]	Chen et al, 2009	Assumption[3]
Clinically Diagnosed/Treated[5]				
Most Likely	0.686	0.875	0.590	0.843
(Min, Max)	(0.476, 0.694)	(0.710, 0.965)	(0.476, 0.694)	(0.672, 0.947)
Sources	Primary data[6]	Derived[7]	Primary data[6]	Derived[7]
Clinically Diagnosed/Untreated				
Most Likely	0.046	0.667	0.010	0.524
(Min, Max)	(0, 0.159)	(0.499, 0.814)	(0, 0.024)	(0.347, 0.681)
Sources	Chen et al, 2009[2] Kishnani et al, 2006	Derived[8]	Chen et al, 2009[2] Kishnani et al, 2006	Derived[8]

[1]Minimum and maximum values derived from 95% CIs assuming a binomial distribution

[2] The article describing treatment effectiveness does not specify whether cases of infantile-onset include cardiomyopathy; however, a separate study (10) published contemporaneously delineates which infants had confirmed hypertrophic cardiomyopathy. These are the infants whose results are reported as the NBS subgroup from which we derive effects of treatment in the Screened/Treated arm. Of the clinically identified patients, it is unclear which had cardiomyopathy. Our assumption is that all or most of these patients had cardiomyopathy.

[3]Assumes similar effects of treatment for infantile-onset cases with cardiomyopathy as derived from Chen et al. (2009).

[4] Data on 36 month outcomes for patients reported in the Chen et al. (2012) study were communicated to the condition review working group via telephone interview with researchers from Taiwan.

[5]Clinically-diagnosed cases are identified and treated several months after birth (on average between 4 and 5 months of age).

[6]Effectiveness of treatment in the clinically diagnosed/treated population was derived from the Genzyme Pompe Registry and provided to the CRW via personal communication from Joan Keutzer (4/30/13). This panel excludes patients from Taiwan, some of whom would have been detected by newborn screening and would have higher rates of survival and ventilation-free survival.

[7]Effectiveness of treatment for the subgroup of infantile-onset without cardiomyopathy is based on results from Kishnani et al.(2009) and assuming that efficacy is similar to that observed for individuals with infantile-onset with cardiomyopathy.

[8]Assumes same proportion between alive & vent-free conditional on being alive for infants with and without cardiomyopathy.

Results

Using a decision analytic model, universal newborn screening for Pompe disease is projected to provide health benefits as measured by averted deaths and averted cases of ventilator-dependence when compared with clinical identification followed by treatment.

Projected cases of infantile onset Pompe disease:
We projected the annual number of infantile-onset cases that would be identified with newborn screening compared with clinical identification (Table C.4):

- Projected annual cases of Pompe disease identified through newborn screening would be 144 cases on average (based on a prevalence of 1/27,800). This includes both infantile and late onset cases.
- Of these identified cases, approximately 28% (range: 13-42%) or 40 (range: 19-61) cases would be infantile onset.
- Of the infantile onset cases identified under newborn screening, 34 (28-36) would be infantile-onset cases with cardiomyopathy and 6 (4-12) would be infantile onset without cardiomyopathy.
- Compared with clinical identification, it is anticipated that all cases of infantile-onset with cardiomyopathy would be identified but at a later age of identification than with newborn screening.
- It is anticipated that approximately 2/3 of cases of infantile-onset without cardiomyopathy would not be identified within the first year of life with clinical identification compared with newborn screening.

Table C.4. Projected cases for newborn screening for Pompe disease compared with clinical identification for a cohort of 4 million children[1,2] (US population), infantile-onset only

	Newborn Screening	Clinical Detection
Infantile onset (<12 mos.), no. of cases	40 (19-61)	36 (16-56)
With cardiomyopathy	34 (28-36)	34 (28-36)
Without cardiomyopathy	6 (4-12)	2 (0-8)

[1]Not at higher risk for Pompe disease
[2]Ranges represent one-way sensitivity analysis on each parameter

Averted deaths and cases of ventilator-dependence for infantile-onset cases:
The key health outcomes estimated by the model were deaths and ventilator-dependence associated with infantile-onset cases. Using 36-month outcomes, we project that identifying infantile onset cases of Pompe disease using newborn screening would avert 13 deaths per year (range: 9 –19) and 26 cases of ventilator-dependence (range: 20-28). (Some of these averted ventilator-dependent cases are also included in deaths averted. It is assumed that patients will require ventilator assistance prior to death.)

- The projected number of deaths at 36 months is 13 (9-19) for clinical detection compared with 0-1 deaths for infantile-onset cases identified under newborn screening. This assumes that all cases of infantile-onset Pompe disease receive enzyme replacement treatment following

diagnosis either through clinical detection or newborn screening. The difference in outcomes relates to the difference in the timing of the initiation of treatment which will be closer to birth for newborn screening cases (at approximately 22 days of life) and typically at 4-5 months of life for those identified through clinical detection. It also includes a small proportion of deaths associated with infantile-onset without cardiomyopathy that would not be detected within the first 12 months of life by clinical detection.

- The projected number of ventilator-free cases at 36 months for infantile-onset cases under newborn screening are 39-40 for newborn screened cases compared with 12-19 cases with clinical detection.

Most deaths averted are associated with cases of infantile-onset Pompe disease with cardiomyopathy, but there are additional morbidity and mortality benefits for cases of infantile-onset without cardiomyopathy that would be identified and treated under a newborn screening program.

Table C.5. Projected health outcomes for newborn screening for Pompe disease compared with clinical identification for a cohort of 4 million children (US population), infantile-onset cases only[1]

	Newborn Screening	Clinical Detection	Cases Averted
Projected deaths, 36 mos	0 (0-1)	13[2] (9-19)	13 (8-19)
Projected ventilator-free cases, 36 mos	40 (39-40)	14 (12-19)	26 (20-28)

[1]Infantile cases both with and without cardiomyopathy
[2]Includes 12 deaths associated with infantile-onset with cardiomyopathy and one death associated with infantile-onset without cardiomyopathy.

Screening algorithm results using ranges for sensitivity and specificity from the Taiwan experience are shown in Table C.6.

Table C.6. Projected screening algorithm outcomes for newborn screening for Pompe disease compared with clinical identification for a cohort of 4 million children (US population)

	Newborn Screening (n)[1]	Range[2]
Total positive screens	262	134-2,934
True positives[3]	134	--[4]
False positive[5]	128	0-2,800
Total negative screens	3,999,738	3,997,066 - 3,999,866
True negatives	3,999,728	3,997,056 - 3,999,856
False negatives	10	--[4]
Repeat screens[6]	147	75-1,646[7]

[1]Base case test characteristic values for sensitivity (0.9322) and specificity (0.99997) were derived from Chiang et al, 2012, and applied to the US population prevalence of Pompe disease.
[2]Ranges for sensitivity (0.9315-0.9329) and specificity (0.9993-1.0000) were derived from Chiang et al, 2012.
[3]Includes all subtypes.
[4]Varying test characteristics resulted in very small changes for true positives and false negative cases but not reported here due to rounding.
[5]False positive rates were calculated based on definition (1) of Table 3 in the Results section of this report (i.e., FP rate of Inconclusive (NAG/GAA ≥ 60) or Abnormal (NAG/GAA ≥ 100) first DBS screen).
[6]Repeat screens are defined as an inconclusive first DBS screen (NAG/GAA ≥ 60), as described in Table 3 of this report.
[7]This range assumes the same proportion of Inconclusive to Abnormal initial screens as the base case value.

Limitations

This analysis uses a simplified model to evaluate projected outcomes for identified cases of infantile-onset Pompe disease under a universal screening recommendation. The model includes health outcomes of death and invasive ventilator use but does not quantify any additional health benefits that could be associated with earlier identification and treatment of cases of infantile-onset Pompe disease not does it include potential harms (e.g., adverse events associated with treatment). The analysis did not evaluate economic outcomes such as costs or cost-effectiveness of alternative screening modalities. The analysis did not consider short- or long-term effects on identified cases of late-onset Pompe disease but focused on health benefits for infantile-onset cases which can be identified following screening.

Summary

- Assuming an annual US newborn cohort of 4 million that is not at increased risk for Pompe disease, newborn screening is projected to identify 134 cases, including both infantile and late-onset Pompe disease, and 10 false negative results (which are assumed to be late-onset cases only)
- Of these 134 identified cases,
  - 40 cases are expected to be infantile-onset
  - 94 cases are expected to be late-onset (40-70% of which may be undetected with clinical identification)
- Earlier identification and treatment is expected to avert approximately 12 deaths for infantile-onset with cardiomyopathy and approximately one death for infantile-onset without cardiomyopathy.
- Earlier identification and treatment will also result in reduced morbidity including a reduction in the number of individuals that require invasive ventilation.

Appendix C. References

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Figure C.2. a. Simplified Schematic for Pompe Disease Model, Part 1

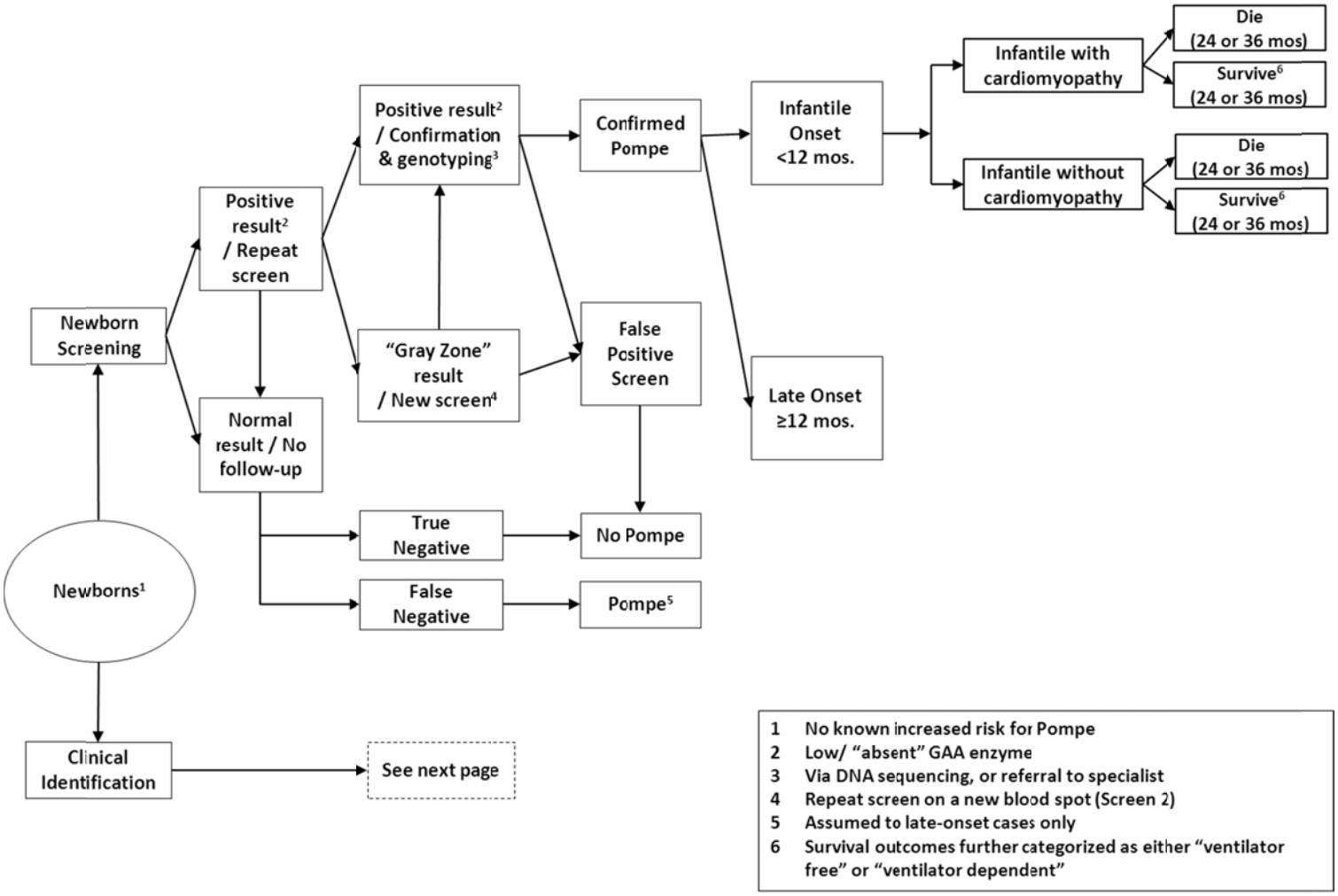
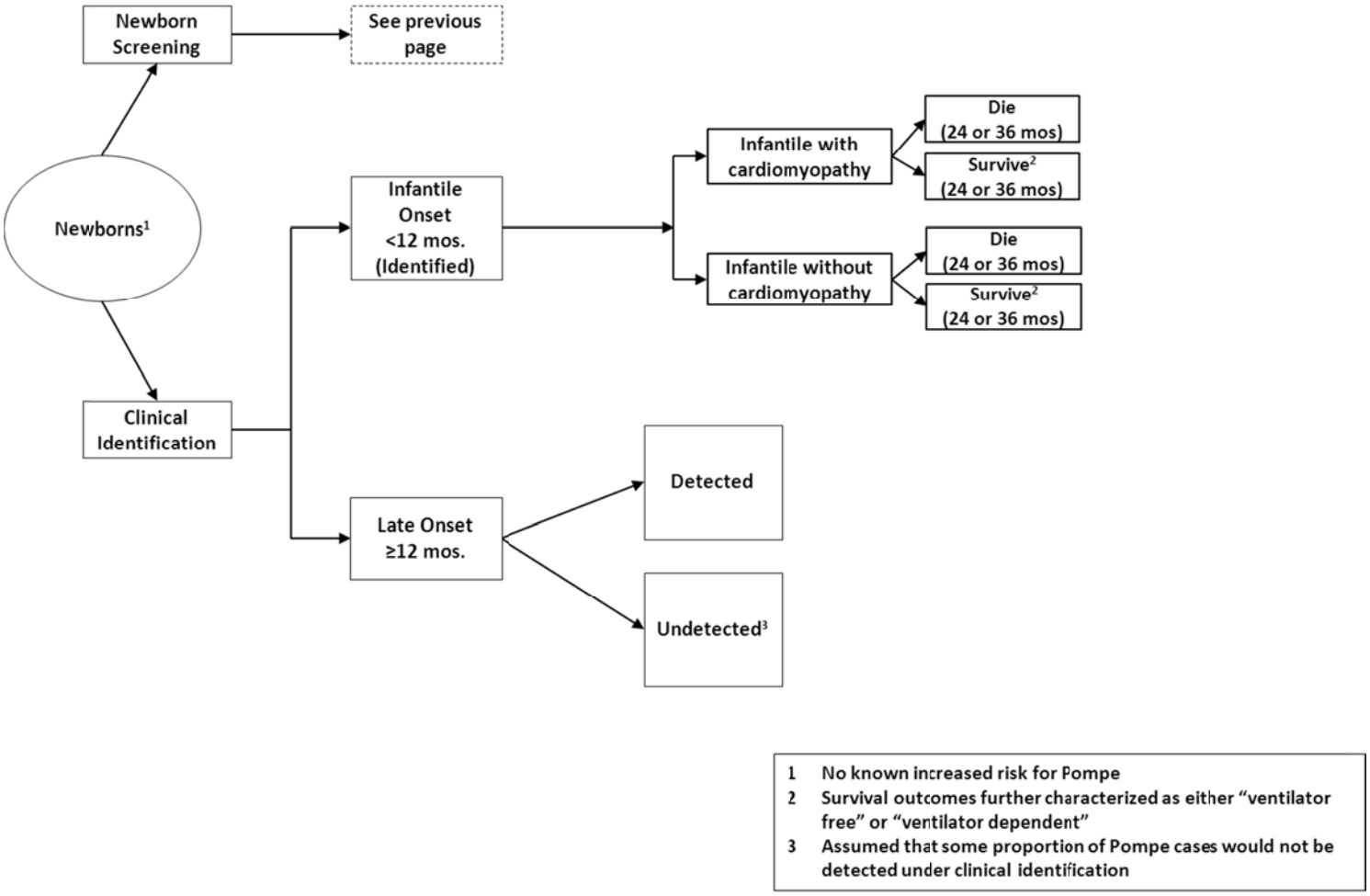


Figure C.2.b. Simplified Schematic for Pompe Disease Model, Part 2



Appendix D: Public Health System Impact Assessment

Public Health Impact Assessment:
Feasibility and Readiness of State Public Health Programs

Prepared by:

Jelili Ojodu, MPH
Director
Phone: 240.485.2772
e-mail: jelili.ojodu@aphl.org

Elizabeth Jones, MPH
Senior Specialist
Phone: 240.485.2717
e-mail: elizabeth.jones@aphl.org

Newborn Screening and Genetics
Association of Public Health Laboratories (APHL)
8515 Georgia Avenue, Suite 700
Silver Spring, MD 20910 USA

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- New Mexico Department of Health
- New Jersey Division of Public Health & Environmental Laboratories
- Oregon State Public Health Laboratory
- State Hygienic Laboratory at the University of Iowa
- Texas Department of State Health Services
- Washington Public Health Laboratories

Disclaimer

The contents of this report reflect current views of the newborn screening programs included in this report. These programs were not asked to represent the views of other newborn screening programs in the nation and made no pretense of doing so. The results also do not necessarily represent the official views of APHL.

Methods

APHL conducted a public health impact assessment for Pompe Disease in two phases. Phase I consisted of creating and distributing a survey (Exhibit D.1) to the newborn screening program directors in thirteen state newborn screening programs. Phase II consisted of in-depth interviews of the same directors following the survey.

A variety of criteria were used to select participants (e.g., region of the country, number of births, programs that outsource versus those that do not, mandate to screen for Pompe disease). States chosen for the survey included Delaware, Iowa, Illinois, Massachusetts, Minnesota, Missouri, Nebraska, New Jersey, New Mexico, Oregon, South Carolina, Texas, and Washington.

Survey questions were designed to probe for newborn screening program feasibility and readiness and were written and compiled by a group of five newborn screening experts. For the purpose of this report, feasibility was defined by whether respondents believed that there was:

- *An established screening test*: The screening test should be valid and reliable and have adequate throughput to meet the demands of a newborn screening program. Systems should be in place to help with the adoption of the screening test, including adequate training and the availability of quality-control samples and a quality-control program.
- *A clear approach to diagnostic confirmation:* Depending on the condition, the method of diagnostic confirmation can range from a simple laboratory test to comprehensive clinical follow-up. The method of diagnostic confirmation must be well-established and newborn screening programs must have access to the process. AND
- *A clear approach to long-term follow-up:* Among the components of long-term follow-up, treatment must be well-defined, and newborn screening programs should have access to coordinating treatment for individuals identified through newborn screening.

While readiness was defined by whether respondents believed that they had the following:

- *The availability of resources for screening, diagnostic confirmation, and long-term follow-up:* This includes financial resources, availability of the laboratory expertise, laboratory equipment, laboratory space, and access to specialists for diagnosis and treatment.
  AND
- *Authorization for screening*: Newborn screening programs vary in the type of authorization needed to implement a new screening test. Some conditions may raise important concerns.

Survey questions focused on identification of processes for adding conditions to the state panel, barriers to implementation, and the timeline for implementation. The questions were then entered into a Qualtics survey platform and the survey links were sent to newborn screening program directors. Most surveys for Phase I were completed between February 2013 and April, 2013. Summary statistics were collected in aggregate and common themes were identified and reported here.

Phase II consisted of follow-up phone interviews with the newborn screening program directors surveyed in Phase I (and in some cases, their laboratory and follow-up colleagues). The follow-up interviews were conducted by APHL newborn screening staff from April 8, 2013 to April 19, 2013 and were customized based on the written survey responses. Questions differed slightly depending on whether or not the individual newborn screening program had received a mandate to screen for Pompe Disease. An example of interview questions used for a newborn screening program mandated to screen for Pompe Disease is included in Exhibit D.2, while an example of interview questions for a newborn screening program that was not screening for Pompe Disease is included in Exhibit D.3.

Results

Thirteen state newborn screening programs were sent the survey and 12 (92%) responded within the time frame. Each of the 12 newborn screening programs that participated in the survey also took part in the one-hour follow-up phone interview. Currently, 4 states have legislative mandates to screen for Pompe Disease and all of them were included in the assessment. Of these, three have the mandate written in law Pompe disease screening does not need to begin until it is feasible (e.g., they have funding and have procured equipment). Among these three states, two have not yet conducted pilot or feasibility studies. Currently, only one of the states with a legislative mandate is screening all newborns for Pompe Disease. Another state in the assessment that does not have a legislative mandate to screen for Pompe Disease has conducted

pilot studies using an IRB protocol. None of the states in the public health assessment have completed method validation for Pompe Disease screening as of April 26, 2013.

Many of the survey questions were based off of the premise that "if Pompe Disease screening was implemented today" and since one state is currently screening statewide for Pompe Disease, this state did not complete these questions.

Table D.1. summarizes the status of Pompe screening in the states included in this study.

State	Legislative Mandate	Statewide Pilot	Other Pilot	No Screen
Missouri	X	X		
Illinois	X		X	
New Jersey	X			
New Mexico	X			
Washington			X	
Minnesota				X
Massachusetts				X
Delaware				X
Nebraska				X
Oregon				X
Texas				X
Iowa				X

A. Feasibility

An established screening test: The primary methods for Pompe Disease screening is measurement of acid α-glucosidase (GAA) enzyme activity by tandem mass spectrometry (MS/MS) or fluorometry. Advanced Liquid Logic uses digital microfluidics platform to multiplex several lysosomal storage disorders (LSDs) and relies on fluorescence to determine enzyme activity. Several of the programs in this survey are experimenting with digital microfluidics and MS/MS.

Furthermore, clinical validity of these methods when applied to population-based screening currently remains unclear, largely due to a lack of an established validation method in an environment outside of pilot studies. It is also uncertain whether these methods can handle the high throughput necessary in a newborn screening laboratory. It is important to note that validation of a screening method is not a single step process, but rather a complex procedure that must take into account several factors involved in the test method. Performance characteristics of a validated screening method must evaluate the accuracy and

precision of the screening method to detect the disorder and to be able to duplicate results. Analytical specificity as well as sensitivity must be taken into account when results of the screen are interpreted to minimize the number of false positive screens reported. It may take several months or more to establish suitable reference ranges for reportable results. Missouri is in a pilot implementation phase and has spent several months working on validation. They have been able to get enough positive controls for screening and have adjusted their cutoffs to avoid picking up too many Pompe Disease carriers from its screen.

During the follow-up interviews, the following challenges were reported by newborn screening program directors (n=6) who had investigated digital microfluidics for Pompe Disease screening:

- "Increased plate failures, decreasing the reliability of the test"
- "A lot of variability and run-to-run differences"
- "Not designed for high throughput"
- "Cannot automate liquid handling"
- "Completely new method that will require training and more difficult to validate"

During the follow-up interviews, the following challenges were reported by newborn screening program directors who had investigated MS/MS for Pompe Disease screening (n=6):

- "May substantially increase turnaround time, causing delays in getting and reporting results"
- "Cannot multiplex with MS/MS conditions on the existing panel so it will require the purchase/lease of several additional MS/MS machines"

There are negative and positive aspects of each of these methods and testing situations vary greatly among programs. For example, one state newborn screening program director using digital microfluidics has been "pleased with their program's ability to multiplex four other LSDs with Pompe Disease in their pilot implementation." Likewise, several other state newborn screening programs have shown in pilots that the assay for Pompe Disease can be multiplexed with assays for other LSDs when enzyme activity is measured by MS/MS. During the follow-up interviews, program directors emphasized the technical importance of multiplexing Pompe Disease with other disorders so that the testing is streamlined and results can be reported the same day.

During the follow-up interviews, the following benefits were reported by newborn screening program directors who had investigated digital microfluidics for Pompe Disease screening:

- "Good sensitivity and specificity"
- "Only need small volumes"
- "Fast results"
- "Machines are small and do not take up a lot of space"

During the follow-up interviews, the following benefits were reported by newborn screening program directors who had investigated MS/MS for Pompe Disease screening:

- "Technique we are familiar with so it would not require a lot of training and may be easy to validate"
- "Can get results back the same day"
- "Can handle high throughput"
- "Can multiplex with other lysosomal storage disorders (LSDs)"

When assays for more than one newborn screening condition can be multiplexed, or run at the same time, the efficiencies in terms of cost, instrumentation and labor are great. Currently assays for GAA cannot be multiplexed with other conditions that have met criteria for the Recommended Uniform Screening Panel (RUSP). Although work is underway to multiplex screening for Pompe Disease with other LSDs that are also based on enzyme assays using MS/MS and fluorometry and the majority of the newborn screening laboratory directors interviewed believed this was possible, none of the LSDs have even been nominated for the RUSP. The surveyed newborn screening programs that are conducting pilot testing for Pompe Disease are using dedicated equipment to assay for GAA, and this often means purchasing additional instrumentation and dedicating staff to these instruments.

Most public health newborn screening programs were confident that should the need for Pompe Disease quality assurance and quality control and proficiency testing materials arise, they would be able to obtain them from CDC or may be able to produce some themselves initially.

The general consensus among the newborn screening community included in this study is that there has not been adequate training with regards to understanding methodology for screening of Pompe Disease and there is a need for more guidance as to which method should be used. "Uncertainty affects validation of the method as well as the decision to add these conditions to the panel in the first place. Uncertainty and

questions delay the implementation process every step of the way. A clear understanding of the method is necessary for screening," stated one newborn screening program director.

A clear approach to diagnostic confirmation

Fifty-five percent (n=6), of newborn screening programs surveyed were fairly comfortable with the newborn screening system's ability to provide diagnostic confirmation, while 45% (n=5), of them were uncertain. Like the screening test, the diagnostic test for Pompe Disease entails measuring activity of the enzyme GAA. The laboratory test is usually followed with mutation analysis which assists with the diagnosis. Currently, the mutation analysis for Pompe Disease has the ability to identify carriers and the interpretation of variants can be difficult. Additionally, the clinical spectrum for Pompe Disease varies greatly in terms of age of onset (classic infantile-onset, non-classic infantile-onset, and late-onset), severity, and organ involvement. There is uncertainty about the diagnostic test predicting disease severity. One newborn screening program director stated "unintended consequences that come as a result of the screening may put an additional strain on laboratory and clinical interpretation as well as follow-up. These consequences will not be fully realized until screening for Pompe Disease begins."

A clear approach to long-term follow-up:

Newborn screening programs have historically been primarily concerned with short-term follow-up only, thus long-term follow-up could not be evaluated by this study. Most state newborn screening programs surveyed were fairly comfortable with their program's ability to provide/facilitate treatment (73%, n=8) and follow-up services (64%, n=7) if Pompe Disease screening were implemented today. Eighty-two percent (n=9) of programs claimed their short-term follow-up system was equipped to handle the addition of Pompe Disease; 9% (n=1) did not know; and 9% (n=1) did not think its program was equipped. If the approach to follow-up for Pompe Disease is similar to other conditions then it may be feasible; otherwise, it will require "extensive training and education for newborn screening program staff, clinicians, and specialists," stated one of the newborn screening program directors during an interview. Short-term follow-up programs would need to develop additional protocols and educate hospitals and providers on what to do with out-of-range results.

B. Readiness

The availability of resources for screening, diagnostic confirmation, and long-term follow-up:

Staffing was listed most frequently as the greatest barrier to implementing Pompe Disease for program directors surveyed. Seventy-three percent (n=8) of program directors surveyed believed that if Pompe Disease were implemented today, they would not have adequate staff. Generally, programs would need to hire between one and three additional individuals in the laboratory for Pompe Disease screening. In addition to not having enough staff, many program directors reported difficulties recruiting adequate staff with the necessary expertise (55%, n=6), and the same number anticipated new challenges. One program director stated that, "the bidding process is complicated and it is often hard to hire staff with the right experience." Also, the additional training and education required to implement Pompe Disease screening was a large concern, particularly if it meant relying on a method that had not yet been used in the laboratory.

The ability to add conditions to a newborn screening panel is often based on the ability to obtain funding. Funding was listed as the second greatest barrier to implementing Pompe Disease screening statewide. Seventy-three percent (n=8) of newborn screening program directors surveyed stated that they did not have adequate funding if screening for Pompe Disease were implemented today. A program director explained that there "could be long (2-3 year) delays in implementing conditions if funding was not available." Others thought it could take even longer. Many of the newborn screening programs indicated that their states would have to fund Pompe Disease screening by increasing newborn screening fees or charging fee for service. Additionally, programs would "have to collect more from Medicaid for patients enrolled in Medicaid and state general revenue for those unable to pay who are not enrolled in Medicaid (charity care)". One program director also indicated that his program would have to rely on "developmental funds to pay for validation of the assay and pilot tests before state wide screening could even take place." Some state newborn screening program directors indicated that they needed legislative approval for fee increases. Although, newborn screening program directors stated that the timeline to identify and obtain funding approval for Pompe Disease had many variables, the majority of them (45%, n=5) estimated that it would take more than one year but less than three years for funding approval. Historically, programs have been able to implement disorders, including SCID, much faster if funds are available.

An additional consideration to implementation of Pompe Disease screening is that several states have been unable to get funding to conduct appropriate testing for SCID and CCHD, the most recent additions to the RUSP. It was noted by these individuals that their program's priority would be in conducting screening for SCID, which is already on the RUSP before considering the addition of other conditions.

As stated in the feasibility section, the methods used to analyze GAA in newborn screening blood spots consist of flourometry (including digital microfluidics) and MS/MS. Tandem mass spectrometry requires the addition of instrumentation to perform the testing as well as additional staff, staff time, and laboratory space. A dedicated MS/MS is needed for Pompe Disease and other LSD testing. The equipment used for the digital microfluidics method has a smaller footprint than the instrumentation needed for MS/MS, but it may require the purchase of multiple digital microfluidics instruments to reach the capacity of one MS/MS unit. Seventy-three percent (n=8) of newborn screening program directors surveyed stated that they did not have adequate equipment and instrumentation if screening for Pompe Disease were implemented today, while 18% (n=2) said they did and 9% (n=1) said they did not know.

Thirty-six percent (n=4) of program directors surveyed stated that they did not have adequate laboratory space if screening for Pompe Disease were implemented today, while 36% (n=4) said they did and 27% (n=3) said they did not know. During the interviews some of the laboratory directors stated that laboratory space may be an issue if they were required to purchase extra instrumentation. Thirty-six percent (n=4) of laboratorians surveyed thought their laboratory would have to be retrofitted in order to screen for Pompe Disease, while 45% (n=5) did not know and 18% (n=2) believed this was not needed.

The majority of the newborn screening program directors (82%, n=9) surveyed felt that they had access to trained professionals for treatment and ongoing care of individuals diagnosed with Pompe Disease in their state; however during the interview 73% (n=8) of the program directors noted that there was a shortage of metabolic specialists/those trained to handle cases of Pompe Disease. Thirty-six percent (n=4) of laboratory programs believed that equitable treatment and follow-up for Pompe Disease will have more challenges than other conditions relative to geographic distribution of patients and treatment centers. The shortage of specialists and difficulty accessing specialists for certain segments of the population may be especially concerning for those being treated for Pompe Disease, since it requires frequent enzyme replacement infusions. In addition to these issues, program directors were concerned that the specialists may have limited knowledge of how to handle cases of Pompe Disease due to the lack of knowledge about the disorder and clinical manifestations.

One hundred percent (n=11) of state newborn screening programs surveyed indicated that they would need to make changes to their laboratory information management systems if Pompe Disease screening were to be added to their panel. This would take anywhere between one month to a year (six months average).

Authorization for screening: The process for adding a condition to a state panel is often complicated and may entail input from multiple parties. Most of the state programs surveyed rely upon their newborn screening advisory committees (83%, n=10) and state health officials (83%, n=10) to assist with this process. During the interview process, it was noted by several program directors that their state advisory committee typically conducts its own evidence review and votes on the possible addition of new conditions to a panel. Other decision makers and decision making entities involved in the process to determine if a condition should be added to a state panel include legislators/governors, public health directors, public health commissioners, and State Boards of Health. According to the survey, 58% (n=7) of states require a change in state rules, and 42% (n=5) require legislative action when they add conditions to the panel. States vary greatly with regard to their legislative process for adding a condition and often there are multiple mechanisms for adding conditions. Below are examples of the process from two states.

> *Possible additions to the newborn screening panel are presented to the Newborn Screening Expansion Subcommittee of the Genetic and Metabolic Diseases Advisory Committee. Decisions of the Subcommittee and supporting scientific evidence are then presented to the full Advisory Committee for consideration. Positive recommendations are then passed through the Director of the Department of Public Health to the Governor's office, which would then work with the state General Assembly to draft appropriate legislation mandating testing for the condition. Administrative rules are then written to codify the legislation.*

> *A formal proposal is submitted by an "interested party" to the Department of Public Health's Center for Congenital and Inherited Disorders Advisory Committee (CIDAC) for review. The Advisory Committee then makes a recommendation to the Director of Public Health to either approve or reject the proposal (or they can request further information before making a decision). Once the Advisory Committee makes a recommendation for approval, the Director of Public Health considers the recommendation and, if the recommendation is supported, a formal request is made to the State Board of Health to add the disorder to the state panel of newborn screening disorders. The State Board of*

Health is the authorized body to then add a condition to the state's panel of newborn screening disorders.

Four states in this assessment had been mandated by legislation to screen for Pompe Disease. According to one newborn screening program director "mandates can be at odds with evidence-based decision making." Another program director, stated that "newborn screening programs implement disorders really well. It is important that legislators do not get in the way." Advocacy groups have played a major role in creating legislative mandates before a good test is available to screen for condition, treatment is available, and programs are able to appropriately pilot implementation for a new disorder. According to the survey, 42% (n=5) of laboratory directors stated that it typically takes between six months to one year to decide to add a condition; 17% (n=2) stated it took more than a year but less than three years; 8% (n=1) stated it took less than 6 months; and 33% (n=4) stated other. Many pointed out that this timeframe is variable and "truly depends on the identification of additional funds." Approximately half of state program directors interviewed depend on the RUSP when making decisions to add conditions to their panel, but even those who did not, stated that there was "pressure to add a condition once it was on the RUSP."

IV. Summary

There are many steps involved with adding conditions to state newborn screening panels and the process often takes several months to years. Once a decision is made to add a condition, a state newborn screening program attempts to obtain funds, purchase equipment, validate a method, hire and/or train new staff, and provide educational materials to providers. Additionally, if funds are not provided, then the newborn screening program must figure out how to increase newborn screening fees or cover the cost of the test. There is still a great deal of uncertainty on behalf of the newborn screening programs regarding testing methodologies, clinical diagnosis and follow-up for Pompe Disease. Once these knowledge gaps are filled and programs have more guidance in terms of laboratory method, diagnostic confirmation and follow-up, programs can make more informed decisions about adding Pompe Disease to their state panels and the screening process will become more robust.At the moment, state newborn screening programs are in the in the process of validating different testing platforms for population-based screening for Pompe Disease and there is an uncertainty related diagnostic follow up for treatment. Newborn screening for Pompe disease also represents a paradigm shift, where most infants identified will have the late-onset form - since NBS cannot be performed for infantile-onset only.

Appendix D.1. Public Health Impact Assessment: Readiness and Feasibility Survey

Condition Neutral

Process for Obtaining Approval

1. In your state, how is the decision to add a particular condition to your newborn screening panel made?

2. Who is involved in making this decision? *Please check all that apply.*

- o NEWBORN SCREENING Advisory Committee
- o State health official
- o Legislators
- o Other-please specify:

3. Does adding a new condition to the panel require… *Please check all that apply*.

- o Legislative action
- o Change in state rules
- o Other-please specify:

4. Typically, once your state undertakes the decision about the addition of a new condition, how long does the process take to reach a decision?

- o Less than 6 months
- o Between 6 months and 1 year
- o More than 1 year but less than 3 years
- o At least 3 years
- o Other-please specify:

Condition Specific

5. Does your state currently screen infants for Pompe Disease (screening in this context indicates linkage of sample to infant and reporting of results)?

- o Yes, we are screening all babies in a routine manner statewide *(please go to question 5 a)*
- o Yes, we are offering screening statewide, but as a research study *(please go to question 5b)*
- o Yes, we are screening a subpopulation by hospital or some other way *(please go to question 5b*)
- o No *(please go to question 5b)*
- o Other- please specify : *(please go to question 5b)*

5a. What were the **top five** challenges your NEWBORN SCREENING program faced in implementing screening for Pompe Disease in a routine manner statewide? Please rank with 1 being the most challenging and 5 the least. *(End of survey)*

- o Gaining authority to screen
- o Training/education
- o Staffing (follow-up and lab)
- o Equipment/instrumentation
- o Laboratory space
- o Test/method availability
- o QC materials availability
- o Funding to implement
- o Diagnostic testing availability
- o Clinical subspecialty availability
- o Treatment and follow-up costs
- o Other-please specify:

5b. Is your state investigating routine screening for Pompe Disease?

- o Yes, we are currently testing with anonymous samples
- o Yes, we are investigating the theory but are not yet testing any samples
- o No

Process for Implementing

6. Once authority is in place, please rank the **top five** challenges your NEWBORN SCREENING program would face in implementing screening for Pompe Disease in a routine manner statewide (with 1 being the most challenging and 5 the least).

- o Training/education
- o Staffing (follow-up and lab)
- o Equipment/instrumentation
- o Laboratory space
- o Test/method availability
- o QC materials availability
- o Funding to implement
- o Diagnostic testing availability
- o Clinical subspecialty availability
- o Treatment and follow-up costs
- o Other-please specify:

7. If Pompe Disease screening was implemented today, does your NEWBORN SCREENING program have…

	Yes	No	I don't know
Adequate equipment/instrumentation			
Adequate laboratory space			
Adequate funding			
Legislative support			
Authority to implement			
Adequate training/education			
Adequate staff			
Available test/method			
Necessary throughput			
Available QC materials			
A platform in existence that can be used			
A method for multiplexing the assay with an existing test			
Available diagnostic test			
Available treatment			
Available follow-up services			
Mechanism for covering treatment and follow-up			

Funding Considerations

8. How would your state fund the implementation and ongoing testing of Pompe Disease?

9. What is the timeline to identify and obtain funding approval for Pompe Disease?

- o Less than 6 months
- o Between 6 months and 1 year
- o More than 1 year but less than 3 years
- o At least 3 years
- o Other-please specify:

Technical and Resource Considerations

10. Does your state require use of an FDA approved kit IF Pompe Disease is implemented?

- o Yes
- o No
- o I don’t know

11. Historically have you experienced difficulties recruiting adequate staff with the necessary expertise?

- o Yes
- o No
- o I don't know

12. Do you anticipate new challenges recruiting adequate staff with the necessary expertise?

- o Yes
- o No
- o I don't know

13. Would your laboratory space need to be retrofitted in order to add Pompe Disease?

- o Yes
- o No
- o I don't know

14. Would changes need to be made to your newborn screening information system IF Pompe Disease is implemented?

- o Yes
- o No
- o I don't know

15. Do you report any results electronically (e.g. via HL7 messaging)?

- o Yes *(please go to question 16)*
- o No *(please go to question 17)*

16. How much time would be needed to revise the electronic message and test it with partners IF Pompe Disease is implemented? *Please enter time in months.*

17. What other technical or resource considerations could impact the timeline for addition of Pompe Disease to the panel?

Follow-up, Medical Management, and Ethics Considerations

18. Is your short-term follow-up system equipped to handle the addition of Pompe Disease?

- o Yes
- o No
- o I don't know

19. Are there trained professionals available for treatment and ongoing care of individuals diagnosed with Pompe Disease?

- o Yes
- o No
- o I don't know

20. Given your experience with other conditions, do you think that equitable treatment and follow-up for Pompe Disease will have more challenges than other conditions relative to geographic distribution of patients and treatment centers?

- o Yes- please explain:
- o No- please explain:
- o I don't know

Other

21. Once all hurdles are cleared (e.g. the decision is made to add the condition to the state panel and funding is obtained), how long do you estimate it would take to implement addition of Pompe Disease test?

- o Less than 6 months
- o Between 6 months and 1 year
- o More than 1 year but less than 3 years
- o At least 3 years
- o Other-please specify:

22. If Pompe Disease was added to the RUSP, would this make the implementation process move faster?

- o Yes
- o No

23. Please provide any additional comments. If none, please type NA.

Thank you for completing the survey!

Appendix D.2. Interview Questions for Programs with Mandate to Screen for Pompe Disease

Process to Add

Please describe your process to add Pompe to your panel and the parties involved with that decision.

Feasibility/Readiness

- Please describe your experience conducting pilot screening for Pompe (LSDs) under a mandate. What has come as a surprise? Key findings?
- What screening method are you using to screen for Pompe in your laboratory? Describe your experience with this method and reason for choosing it.
- Please explain your validation process including length of time it took.
- Please discuss issues related to treatment and follow-up for Pompe that you have experienced.
- Please elaborate on your top three barriers your program faced when implementing screening and provide us with examples where appropriate.
    1) Test/Method Availability– (timeframe)
    2) Funding to Implement- (timeframe)
    3) Staffing (follow-up and lab) – (timeframe)

Timeline

- Considering your current situation in implementing statewide Pompe Disease screening, how do you feel if would have differed if you had been able to address all issues of feasibility and readiness prior to having this mandate? (i.e. if the time had been unlimited for implementing this screening).

Appendix D.3. Interview Questions for Programs Without Mandate for Pompe Disease

Process to Add

- Please elaborate on your process and parties involved in adding conditions to your state panel. What is entailed with changing administrative rules?

Feasibility/Readiness

- Please elaborate on your top three barriers to implementation and provide us with examples where appropriate – feel free to elaborate on any other barriers you can think of.

    1) Staffing
    2) Training/Education
    3) Laboratory Space

- What would validation of this test involve for your lab?

- Would you be willing or able to outsource Pompe Disease screening?

Timeline

- If Pompe Disease were added to the RUSP tomorrow, when do you think you would be able to begin population-based screening?
- If you received pressure/mandate to implement screening for Pompe Disease what would your newborn screening program look like?

Appendix E. Summary of Evidence

The following table is an extraction of articles abstracted and included in the evidence for the systematic review. This table is complex because of the varying study designs, population, and outcomes.

				SAMPLE										
Year 1st 2 Authors	Title	Journal	STATED OBJ	(N)	US (N)	AGES_DX -> N>10 (Age Mean/Med and Range)	AGE_TX -> N>10 (Age Mean/Med and Range)	IOPD-C	IOPD-NC	IOPD NOS	Major Outcomes	OTHER FINDINGS	8. OTHER STUDY DESIGNS/FINDINGS Indicate any important study findings, outcomes, conclusions not covered by prior sections.	9. RELATED/LINKED ARTICLES
2012 Van Gelder, Van Capelle	Facial-muscle weakness, speech disorders and dysphagia are common in patients with classic infantile Pompe disease treated with enzyme therapy	Journal of Inherited Metabolic Disease	Using standardized articulation tests and fibreoptic endoscopic evaluation of swallowing, we investigated speech and swallowing function in a subset of patients.	11		0.7 mo median (range 2 -3.6 months)	2.4 mos median (range 0.1-8.3)	11		0	SPEECH/SWALLOWING median 6.6 months (range 1-15 months) in all patients. Developed facial weakness. At first, mild for 9/11. By the end of treatment, facial muscle weakness severe 7/11. Maximum major milestone - 1 with minimal movements, 2 tetraplegic, 2 sitting, 6 walking	Speech assessed for 4 patients at a median age of 4.1 years. Impaired by reduced movement and/or weekness of the lip and/or tongue. At median age of 5.5 years (range 5.1-11.1 years), no major changes in speech. Swallowing was assessed in 6 patients at median age of 8.0 years (range 8-9.9 years). Feeding difficulties in 5/6. Reassessed in 4 patients at median age of 5.3 years (range 2-11.1 years). Deteriorated in 1/4 stable in 3/4.		
2012 Spiridigliozzi, Heller	Early cognitive development in children with infantile Pompe disease	Molecular Genetics and Metabolism	This report describes the cognitive development of 17 children with infantile Pompe disease who participated in a 52-week clinical trial of the enzyme replacement therapy (ERT)	17		5.07 mos mean (range 0.43 -7.17 mos)		17		0	MOTOR/COGNITIVE DEVELOPMENT The mean adjusted MDI of 79.9 obtained at baseline was more than one standard deviation below the mean for age and considered to be in the borderline range (i.e., 70–84) of cognitive functioning. At 4 weeks, 12, 26, 38, and 52, mean adjusted MDI scores were 88.9, 88.5, 90.3 and 82.8, respectively. These scores were approximately one standard deviation below the standardized mean for age of 100 and clustered within the lower end of the average range of cognitive functioning	Mean AIMS scores increased dramatically throughout the first year of ERT (Fig. 1), from 7.7 (sd=5.8) at baseline to 37.2 (sd=22.9) at week 52. The mean AIMS score of 7.7 at baseline is indicative of a severe neuromotor impairment with a functional level of an average 6-weekold infant. The increase in AIMS scores from baseline to week 12 was significant (paired t=−5.95, p<0.0001), as well as the increase in AIMS scores at all other visits.	*four subjects (limited responder group) maintained extremely low AIMS scores (mean AIMS score=2.8 at week 52) with negligible motor gains despite 12 months of ERT, suggesting a limited response to **There were three subjects with CRIM-negativestatus. One of the three was included in the limited responder group with a week 52 AIMS score of 0 and an MDI of 89.	2007 Kishnani et al., *Neurology* .
2012 Spiridigliozzi, Heller	Cognitive and adaptive functioning of children with infantile Pompe disease treated with enzyme replacement therapy: Long-term follow-up	American Journal of Medical Genetics, Part C: Seminars in Medical Genetics	This report documents the long-term cognitive and adaptive outcome of children with infantile Pompe disease	9	9		4.9 mos median (range 0.2-20.8 mos)	7	2		COGNITIVE DEVELOPMENT/ADAPTIVE BEHAVIOR The median age was 57 years 1 month. The median Full Scale IQ of the children with classic infantile Pompe disease was 1 (median Full Scale IQ of the two children (age 5 yr 4 mo and 5 yr 11 mo) with atypical infantile Pompe disease was 124.5 (122 and 127). The VABS-II was completed for five of seven children with classic infantile Pompe disease (ie yr 11 mo, 5 yr 6 mo, 6 yr 7 mo, 8 yr 0 mo, 8 yr 11 mo) at the time of their IQ testing (Table IV). The median ABC score for these patients was 79 (range 72–105). The ABC score for the one child (age 5 yr 11 mo) with atypical Pompe was 93.		All trim+	
2010 Hamdan, El-Zoabi	Antenatal diagnosis of pompe disease by fetal echocardiography: impact on outcome after early initiation of enzyme replacement therapy	Journal of Inherited Metabolic Disease	To describe outcomes for infants identified with Pompe disease after fetal echocardiography.	3			18 hrs median (rg: 2 hrs-14 days)	5			MORTALITY/PULMONARY/COGNITIVE DEVELOPMENT Patient 2 died at 150 months of age. Patient 1 and 3 were alive at 30 months and 33 months of age, respectively. None required respiratory support. Patient 1 had "normal" scores in the Griffiths Mental Development scale at 25 months. Patient 2 - severe global delay which was most profound in gross motor at 15 months.		Between Jan 2006 and December 2009, 1,137 preg women underwent fetal echocardiography. Detected 5/1268 with HCM, of which 3 were confirmed to have IOPD	2008 Hamdan et al., *Inherit Metab Dis* . (Patient 1 reported)
2009 Poon, Kwok	Variable response to enzyme replacement therapy in two Chinese children with infantile-onset Pompe disease in Hong Kong	Hong Kong Journal of Paediatrics	We report our experience of the use of recombinant human acid alpha-glucosidase in the treatment of two Chinese patients with infantile-onset Pompe disease in Hong Kong.	2		3.5 mos (median (<2-5 mos)	4.5 mos (mean (rg: 2-7 mo)	2			MORTALITY Patient 1 was CRIM positive but developed anti-rhGAA antibodies. Because of clinical deteriation, ERT was discontinued after 13 months of treatment. Pt. died at 33 months of age, 13 months after stopping ERT. Patient 2 - developed low level antibody against rhGAA. Maintained nomral cardiac function. One episdode of SVT after ERT, treated with propranolol for 1 year. Still alive after 2 years.			
2009 Muller, Jones	Language and speech function in children with infantile Pompe disease	Journal of Pediatric Neurology	A retrospective study of the language and speech skills of 12 children enrolled in clinical trials for treatment with ERT at a tertiary care center was completed.	12	9		6.5 mos (median (rg: 0.5 - 37.8 mos)	10	2		Assessment 1 (mean 18.5 months (range 13-31 months) *8/12 had age-appropriate receptive language skills *7/12 had age-appropriate expressive language skills Assessment 2 (mean age 37 months (range 29-47 months) *5 but of 6 had normal receptive langague *5 but of 6 had normal expressive language After 24 months of life		*dropouts at different points *subjects enrolled as part of a larger trial	
2012 Ebbink, Aarsen	Cognitive outcome of patients with classic infantile Pompe disease receiving enzyme therapy	Neurology	Although enzyme-replacement therapy (ERT) significantly increases survival, its potential limitation is that the drug cannot cross the blood-brain barrier. We therefore investigated long-term cognitive development in patients treated with ERT.	10		0.7 mos (median (rg: 0.1m - 8.3m)	2.33 mos median (rg: 0.1m - 8.3m)	10			PULMONARY/COGNITIVE AND MOTOR DEVELOPMENT *2 subjects ventilator dependent by age 1 and tetraplegic at ages 11 and 12 years (subjects 2 and 4) *Subject 3 died at 14 years *5/10 were ventilator dependent *The subjects were grouped based on the age of initiation of therapy: 1999-2003 and after 2003. Those born after 2003 (5 subjects) had earlier start of ERT. Relative to group 1, the 5 months after the start of therapy (z = 2.61, p = 0.01) and 2 years after the start of therapy (z = 2.25, p = 0.04), group 2 scored better. Those who were ventilator dependent (4/5 in group 1) had lower scores on	*follow-up to 12 years only available in half of the subjects.	* 9/10 with hearing aids *7/10 with impaired vision	
2012 Prater, Banugaria	The emerging phenotype of long-term survivors with infantile Pompe disease treated with enzyme replacement therapy	Genet Med	We describe an emerging phenotype in a retrospective review of long-term survivors.	11		age 1 to 8x hard because adjusted for prematurity	4.9 mos median (rg: 0.2-6 mo)	11			CARDIOVASCULAR/PULMONARY/COGNITIVE DEVELOPMENT *0/11 required ventilatory support *2/11 had mild obstructive sleep apnea *Cardiomegaly resolved by about 5 mo after the start of ERT *5/11 had SVT *7/11 were ambulatory without assistive devices *4/11 required walkers *10/11 - residual weakness	*10/11 had normal physical growth	Inclusion criteria: onset of symptoms <=6 months, ERT <=6 months, survival 3 to 5 years *For 10/10 - not data on one patient, developed anti-rhGAA IgG antibodies, from 0.9 to 15 months.	2007 Kishnani et al., *Neurology* *2009 Kishnani et al., *Pediatr Res* *2001 Amalfitano et al., *Genet Med* *2006 Kishnani et al., *J Pediatr* *2009 Young et al., *Genet Med*
2010 Barker, Pasqual	Use of cardiac magnetic resonance imaging to evaluate cardiac structure, function and fibrosis in children with infantile Pompe disease on enzyme replacement therapy	Mol Genet Metab	We report the first use of CMR in a feasible protocol to quantify left ventricular (LV) mass, function, and the presence of fibrosis in the Pompe population.	10	US		4 mos (median (rg: 1-10 mos)	10			CARDIOVASCULAR Overall, there decreased in CMR measured LVMI over time. LVMI as assessed by echo was unchanged from baseline to follow-up study. There was also no significant change in EF over time as assessed by either echo or CMR.	*Four subjects had a peak antirhGAA titer of 25,600, but in only 2 subjects was this elevation sustained on 2 or more measurements separated by 4 week intervals. Both subjects with sustained high anti-rhGAA titers were CRIM-negative. One of these subjects (subject 1) demonstrated the increase in LVMI despite ERT, while the second (subject 10) was the single subject to demonstrate delayed enhancement in the region of the basal to mid anterior and anterolateral walls on CMR	Unclear how subjects were identified	Part of a larger study - not referenced
2010 Chakrapani, Vellodi	Treatment of infantile Pompe disease with alglucosidase alpha: the UK experience	J Inherit Metab Dis	United Kingdom since the availability of the enzyme, using a questionnaire-based survey circulated to all treating centres.	20		5.75 mos median (range 0.25-31 months)	6.5 mos (median (rg: 0.5-32 mos)	X	X	20	MORTALITY/PULMONARY/FEEDING/SWALLOW *7 died *7 alive and on ventilator free *6 alive but on ventilator dependent *Feeding via nasogastric tube or gastrostomy was required in 13/20 cases (65%); none of the patients who commenced assisted feeding were able to come off this after long-term ERT. *Patients who were diagnosed before 6 months of age had a poorer outcome than the overall cohort. Of 14 such cases, 6 (44%) had died, 4 (28%) were alive and on ventilator-free and 4 (28%) were on long-term ventilation. *Median duration of treatment in this group was 20.5 months (range 1.5–102 months); 3 of the 8 living patients had been treated for 3 11 year.	*CRIM status was known in only 5 cases (25%); 3 were CRIM-positive and all these patients were alive and on long-term invasive ventilation, while both their CRIM-negative cases had died. Antibody status was known in only 2 cases: both patients were positive for antibodies, alive and on long-term invasive ventilation.		
2009 Kishnani, Corzo	Early treatment with alglucosidase alpha prolongs long-term survival of infants with Pompe disease	Pediatr Res	To describe extension study of treatment from 52 weeks up to 3 years	18				18			MORTALITY/CARDIOVASCULAR/PULMONARY/MOTOR FUNCTION Of the 18 patients, 8 (death rate 19.8 mo, 30.1 mo, 31.9 mo, 34.3 mo, 40.7 mo. 13/18 3 survived through the extension study. *9/18 required invasive ventilation, 5/9 no ventilation *Ventilation-free survival rate 66.7% at 24 mo and 39.4% at 36 mo. *Final AIMS assessment 7 walking, 4 sitting, 7 minimal gains *At the end of the extension study, mean LVMI Z-scores remained stable at slightly above the upper limit of the normal (range 2.0)		length or partial GAA protein product, designated as cross-reacting immunologic material (CRIM). Serum samples from three of the four CRIM-negative patients exhibited in vitro inhibitory antibody activity, as determined by analysis of enzyme activity or rhGAA uptake assays. Overall, patients in the 20 mg/kg dose group tended to have higher anti-rhGAA IgG titers. However, because of the small number of CRIM-negative patients in this study and the fact that three of the four CRIM-negative patients (C, L, and P) were randomized to the 20 mg/kg dose group, statistical analyses regarding the relationship among dose, immune response, and IARs were not feasible. *Outcomes also reported in comparison to historical controls.	2007 Kishnani et al., *Neurology*
2009 Young, Zhang	Long-term monitoring of patients with infantile-onset Pompe disease and enzyme replacement therapy using a urinary glucose tetrasaccharide as a biomarker	Genet Med	urinary glucose tetrasaccharide, Glc1-4Glc1-4Glc1-4Glc, (Glc4) with skeletal muscle glycogen content and the long-term clinical response to enzyme replacement therapy with recombinant human acid alpha glucosidase in infantile Pompe disease.	18				18			MOTOR FUNCTION/OTHER *Subjects were broken into 3 groups; group 1 = 7/18 with best motor gains at 52 weeks, group 2 = 6/18 had measurable motor gains by 52 weeks but not further gains or clinical decline in the extension; group 3 = 5/18 - failed to gain motor milestones. *Higher Glc4 levels associated with worse outcomes	Urinary Glc4 levels were positively correlated with the glycogen content in 11, 12, and 52 weeks (r 0.43, 0.47, and 0.51, respectively, P 0.01)		2007 Kishnani et al., *Neurology*
2009 Chen, Chen	Reversal of cardiac dysfunction after enzyme replacement in patients with infantile-onset Pompe disease	J Pediatr	The purpose of this study was to explore the association between clinical status in ERT initiation and the effects of ERT on cardiac performance in patients with infantile-onset Pompe disease.	14			See Comments	14			MORTALITY/CARDIOVASCULAR/PULMONARY Figure 3A - survival curve Figure 3B - Death or long-term ventilator dependence curve Figure 4 A and B - LVEF and LVMI No deaths in Clin-E or NBS, but 2 in Clin-L	Compared 30 groups: *Clin-L = detected and treated after 53 months of age; n=5; median age of ERT 5.87 mo *Clin-E = detected and treated before 5 months of age; n=4; median age of ERT 3.18 mo *NBS= asymptomatic newborns identified through newborn screening; n=5; median age of treatment 0.87 mo		
2009 Nicolino, Byrne	Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease	Genet Med	We sought to evaluate whether treatment was safe and effective in patients with Pompe disease when alglucosidase alfa therapy was initiated after 6 months of age.	21	US	6.8 mos (median (rg: 1.5-22.6 mos)	13.0 mos median (rg: 3.7-43.1 mos)	21			*Fifteen of 21 patients (71%) treated with alglucosidase alfa for a median of 120 weeks (range, 0.6–168 weeks) were alive at the end of the study period. causes of death were cardiac and/or respiratory failure in all cases. *Before treatment, of these 21 patients 16 were free of invasive ventilation (two of those 16 patients were noninvasively ventilated, via a mask) and five required 24-hour invasive ventilation (via a tracheostomy). *At the end of the study period, seven of these 16 patients remained alive and free of invasive ventilation, four had become invasive ventilation-dependent, and five had died. *Among the five patients who were invasively ventilated at baseline, three continued to require invasive ventilation 24 hours a day, one decreased the number of hours of ventilation from 24 hours to 12 hours, and one died. *ERT with alglucosidase alfa reduced the risk of death by 79% (P 0.0009) and the risk of death or invasive ventilation by 58% (P 0.0207). *Over the course of the study, mean LVMI improved steadily, resulting in a 42% reduction by Week 52 and a 63% reduction by Week 104. *Thirteen of 21 patients (62%) had measurable motor development gains. *Eighteen of 19 patients with follow-up data showed improvements in age-equivalent BSID-II	*age equivalent weight values were at or above the third percentile in 81% (17/21) of patients. *Eleven (52%) patients experienced 122 IARs.		
1190 McDowell, Li	Arrhythmias in patients receiving enzyme replacement therapy for infantile Pompe disease	Genet Med	to determine the prevalence and types of arrhythmias.	38			7 mos (median (rg: 6-13 mos) or arrythmia group; 8 mos median (rg: 1-43 mos) no arrythmia	38			CARDIOVASCULAR 7 (18%) with arrhythmia No significant differences in LV mass			Two open-label, multicenter, international, clinical trials (NCT00059280; NCT00053573)
2007 Kishnani, Corzo	Recombinant human acid [alpha]-glucosidase: Major clinical benefits in infantile-onset Pompe disease	Neurology	The safety and efficacy of recombinant human (rh) GAA were evaluated in 18 patients with rapidly progressing infantile-onset Pompe disease	18	US	4.3 mo (rg: 0.2-6.8 mo)	5.3 mos (rg: 1.2-6.1 mos)	18			CARDIOVASCULAR/PULMONARY *The baseline indexed LV mass ranged from 157 to 565 gm/m2 and fell to a range of 54 to 124 gm/m2 at study end (p\) 0.001). *Six patients had normal indices of systolic function at study entry, whereas two had mildly depressed systolic function. With the start of therapy, five patients experienced a decline in indices of systolic function. *The patient with the largest change experienced a cardiac arrest before the 6 week measurement. It is likely that this acute event contributed to the transiently poor function in this patient. *All the patients had normal indices of systolic function by 36 weeks into the study period (p 0.84). *11 died of respiratory complications at 4.7 months of age. Another patient, who began treatment at 14.6 months of age died 16 weeks into treatment (pneumonia/cardiac arrest) *4 patients died during the extension phase (33.8 months and 24.8 months - pneumonia)	*15/18 were above 3rd percentile *11/18 had IARs - none severe *16/18 developed IgG antibodies to rhGAA		
2006 Cook, Kishnani	Ambulatory electrocardiogram analysis in infants treated with recombinant human acid alpha-glucosidase: enzyme replacement therapy for Pompe disease	Genet Med	We evaluated 24-hour ambulatory electrocardiograms (ECGs) at baseline and during ERT in patients with infantile Pompe disease	12			7.4 mos (median (rg: 2.9-37.8 mos)	12			CARDIOVASCULAR *The left ventricular mass at baseline ranged from 179 to 404 g/m2 (median 269 g/m2). After 10 to 12 weeks of ERT the left ventricular mass decreased to a range of 115 to 305 g/m2 (median 242 g/m2). There was a significant reduction in left ventricular mass during ERT (Fig. 1) with a range of 40 to 286 g/m2 (median 180 g/m2; p 0.001). *The ejection fraction at baseline ranged from 16% to 89% (median 58%) and tended to decrease for the first several weeks after ERT. It then tended to normalize after several more weeks of ERT (10–15 weeks)			
2006 Ansong, Li	Electrocardiographic response to enzyme replacement therapy for Pompe disease	Genet Med	We evaluated the effect of recombinant human GAA (rhGAA) enzyme replacement therapy (ERT) on these ECG parameters in patients with infantile-onset Pompe disease.	19		19		19			MORTALITY/CARDIOVASCULAR *The median follow-up period was 6 months (range 2–30 months). Decrease in LVH voltage noted on ECG correlated with a concomitant decrease in LV mass on two-dimensional echo. *Twelve of the patients are currently alive with a mean age of 34.9 months (8.1–69.7 months) and continued to receive ERT. Six patients died at a mean age of 30.6 months (11.8–51.8 months).			2001 Amalfitano et al., *Genet Med* 2003 Kishnani et al., *Pediatr Res*
2001 Amalfitano, Bengur	Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: Results of a phase I/II clinical trial	Genet Med	The purpose of this study was to investigate the safety and efficacy of recombinant human GAA (rhGAA) enzyme therapy	3	US		3 mos (median (rg: 2.5-4 mos)	3			MORTALITY Still alive (survival 22 mo, 38 mo, 166 mo)	increased LV mass, concentric thickening of the ventricular wall, and a decrease in size of the ventricular cavity, all classical findings noted in infantile GSD-II patients. With treatment, a steady decreases of LV masses were seen; both patients after 1 year of therapy had LV masses reduced to 60–70% of the baseline pretreatment levels *Patient 3 had cardiomyopathy at two standard deviations above the norm (LV mass of 64 g/m2, normal 48.868), but and otherwise normal baseline cardiac evaluation, and has continued to have normal cardiac assessments 14 months after the therapy.	*three episodes of skin rash, accompanied by a mild fever and increased irritability, occurred	
2008 Hamdan, Almaliki	Early administration of enzyme replacement therapy for Pompe disease: Short-term follow-up results	Journal of Inherited Metabolic Disease	this is the youngest patient reported to receive ERT for Pompe disease, and the first report of prenatal diagnosis of Pompe disease by fetal echocardiography.	1			18 hrs	1			CARDIOVASCULAR *Subsequent echocardiograms showed gradual improvement in LV hypertrophy but progressive dilation and systolic dysfunction which peaked at 11 weeks of age. *The patient had no cardiac symptoms, and appropriate weight gain. Normal development			
2012 Ishigaki, Yoshikawa	High-density CT of muscle and liver may allow early diagnosis of childhood-onset Pompe disease	Brain and Development	case study	1					1	1	CARDIOVASCULAR *After 1 month, efficacy on hepatomegaly was immediately apparent. The liver decreased in size within 1 month and was hardly palpable. Abdominal CT revealed a marked decrease in its density, from 106 to 73 HU 3 months after ERT initiation. *ALT and LDH levels decreased to normal ranges. AST improved to around 50–60 U/L, but then remained at this level.	After 1 year, had not developed any skeletal muscle symptoms; serum CK level was almost normal.		
2010 Deli Rizzo, Fanin	Long-term follow-up results in enzyme replacement therapy for Pompe disease: a case report	Journal of Inherited Metabolic Disease	case report	1				1			CARDIOVASCULAR *Subsequent cardiac ultrasounds showed gradual improvement in left ventricular hypertrophy. *At baseline, Left Ventricular Mass Index (LVMI) was 171 g/m2 (Z-score = 4.3), while ejection fraction (EF) was still in range of normal values. *At 24-month follow-up, a cardiac ultrasound revealed normal pattern and function of the myocardium, with LVMI decreased to 85 g/m2 (Z-score = -2.1), while the ECG showed normal PR interval and slightly high voltages in V2–V5 leads. *Rapid improvement of both parameters since the 3-month follow-up. No cardiac dysfunction was detected during the remodelling period.	The patient had normal growth parameters, normal psychomotor development and had no cardiac symptoms. No antibodies to ERT. -At the 24-month follow-up, EMG showed a stable mild myopathic pattern. -18-month follow-up, muscle biopsy - 10% of muscle fibres exhibited intracytoplasmic vacuoles.		
2009 Tanzer, Buyukkayhan	Enzyme replacement therapy in an infant with Pompe's disease with severe cardiomyopathy	J Pediatr Endocrinol Metab	Describes a case	1				1			CARDIOVASCULAR *Within the first 2 months of therapy, ventricular septum and left posterior wall thickness was slightly reduced. *After five infusions, the patient could raise her head. She was able to lift her arms up slightly. MORTALITY *Died at 9.5 mo of age			
2009 But, Lee	Enzyme replacement therapy for infantile Pompe disease during the critical period and identification of a novel mutation	Hong Kong Med J	Case description	1				1			CARDIOVASCULAR *One week after the first dose of ERT, oxygen saturation dropped suddenly and he developed sinus bradycardia of 50 beats/minute, followed by cardiac arrest. *At 5.5 months, after eight doses of ERT, his LVMI had decreased to 75 g/m2, which was within normal limits (47-75 g/m2) and this left ventricular cavity size had increased. MOTOR *Total Score on Alberta Infant Motor Scales improved to 14 (5th centile) at 5 months of age compared to a total score of 8 (<5th centile) at 2 months of age.			
2008 Pereira, Berditchevisky	Report of the first Brazilian infantile Pompe disease patient to be treated with recombinant human acid alpha-glucosidase	J Pediatr (Rio J)	Describes first case treated in Brazil	1				1			CARDIOVASCULAR *After the 12th infusion, bi-nCPAP and could move arms *After 10 months treatment, LVM mass improved.			