

EVIDENCE REVIEW: POMPE DISEASE

**Prepared for: THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN
NEWBORNS AND CHILDREN**

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Authors: Alex R. Kemper, MD, MPH, MS and Marsha Browning, MD, MPH

Evidence Review Group: Chairperson, James M. Perrin, MD
(MGH Center for Child and Adolescent Health Policy)

Committee Members:

Marsha Browning, MD, MPH, MMSc.
(Massachusetts General Hospital)

Anne Comeau, PhD
(University of Massachusetts)

Nancy Green, MD
(Columbia University)

Alex R. Kemper, MD, MPH, MS
(Duke University)

Alixandra Knapp, MS
(MGH Center for Child and Adolescent Health Policy)

Ellen Lipstein, MD
(MGH Center for Child and Adolescent Health Policy)

Lisa Prosser, PhD
(University of Michigan)

Denise Queally, JD
(Consumer Representative)

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I. OVERVIEW:

Pompe disease (OMIM #232300) is a lysosomal storage disease caused by mutations in the glucosidase alpha acid (GAA) gene located on the long arm of chromosome 17q25.2-q25.3 and inherited in a classic autosomal recessive manner. This genetic mutation causes deficient *acid alpha-glucosidase* enzyme activity (Engel et al. 1973, Hirschhorn 1995, Raben, Plotz & Byrne 2002) which is required for the degradation of some cellular glycogen. As a result, glycogen cannot effectively be removed from various organ systems such as muscle, heart, and lungs. Accumulation of glycogen in these tissues results in progressive damage and often life-threatening symptoms. Pompe disease is also referred to as acid maltase deficiency (AMD) and glycogen storage disease type II (GSD-II).

Pompe and Putschar first described Pompe disease in infants in 1932; Engel and Dale subsequently described later-onset disease. At present, the spectrum of this disorder is generally divided into infantile-onset and late-onset (Slonim et al. 2000, Kishnani et al. 2006, Muller-Felber et al. 2007). Infantile-onset can be further subdivided into classic infantile-onset and non-classic infantile-onset disease. Although non-classic disease is associated with slightly longer survival than classic disease, those with untreated infantile Pompe disease die by the third year of life after an illness characterized by severe weakness, respiratory insufficiency often requiring ventilatory support, and cardiomyopathy.

There are over 200 known mutations of the GAA gene, some of which are associated with specific phenotypes of Pompe disease. For example, a specific splicing mutation (Huie et al. 1994) is associated with late-onset disease and several different mutations (e.g., nonsense, insertion/deletion, splice mutations) are associated with infantile-onset disease.(Kroos et al. 2008).

Case Definition

It is necessary to have a clear and explicit case definition in order to evaluate any condition. We have developed the following case definition for infantile-onset Pompe disease in children < 1 month of age. For this report we did not develop a case definition for late-onset Pompe disease

This case definition requires both laboratory and clinical confirmation.

A. Laboratory Confirmation:

Either confirmed low enzyme activity or genotypic confirmation, as described below:

1. Confirmed Low Enzyme Activity.

Low *GAA* from newborn screening must be noted in a repeat specimen testing. The following tissue testing may be used for diagnosis:

- a. Cultured skin fibroblast enzyme assay.

Complete deficiency (activity <1% of normal controls) of GAA enzyme activity is associated with classic infantile-onset Pompe disease. Non-classic infantile cases have levels of <2% of normal controls (Kishnani et al. 2006). Adult (late-onset) cases are variable but generally < 8% activity. (Reuser et al. 1978, Beratis, Wilbur & Sklower 1983, McVie-Wylie et al. 2008)

b. Muscle enzyme activity.

Muscle biopsy is not usually part of diagnosis because of the risk of the procedure to infants. Secondly, muscle biopsies can be falsely normal in 20-30% of patient biopsy specimens (Laforet et al. 2000, Winkel et al. 2005).

c. Peripheral blood lymphocytes or mononuclear cell enzyme activity.

Leukocytes have been used to measure GAA enzyme activity but alternate isoenzymes such as maltase-glucoamylase may interfere with the assay (Jack et al. 2006) Infantile-onset disease will be <8 nmole/mg/protein or <10% of the upper limit of normal.

d. Whole blood enzyme assay.

GAA levels in Pompe disease can range from 0.59 - 3.88 pmol/punch/hour in dried blood spots.(Chamoles et al. 2004, Zhang et al. 2006).

2. Genotypic Confirmation.

In order for a patient to have confirmation of Pompe disease by molecular genetic diagnostics, two deleterious, disease causing mutations (not a polymorphic variant) must be present in *trans*; meaning one mutation on each allele.(Pittis et al. 2008). There is a fair amount of genotype-phenotype variation.

There are other laboratory results that are suggestive, but not diagnostic, of Pompe disease, including creatine kinase concentration,(Laforet et al. 2000, Kishnani et al. 2006) and urine Hex4/oligosaccharides. (An et al. 2005, Kallwass et al. 2007).

B. Clinical Confirmation:

1. Cardiac Disease

Cardiac involvement is a hallmark of classic infantile-onset Pompe disease, but may not be present in non-classic infantile-onset disease. Cardiomegaly may be demonstrable *in utero* or later.

Cardiac disease includes:

- Cardiomegaly or cardiomyopathy
- Left ventricular hypertrophy or EKG changes (Kishnani et al. 2006)
- Elevated Plasma BNP (B-type natriuretic peptide) (Soker, Kervancioglu 2005)

2. Hypotonia

Hypotonia is variable and difficult to assess in the first month of life.

II. RATIONALE FOR REVIEW

The Advisory Committee (AC) directed the Evidence Review Workgroup (ERW) to produce this report for the nominated condition of Pompe Disease. Pompe disease has been nominated because of the following reasons:

- A. Newborn screening to identify Pompe disease is possible by measuring GAA enzyme activity in dried blood spots by a variety of methods, including immunofluorescence (Kallwass et al. 2007, Chien et al. 2008) and tandem mass spectrometry (MS/MS).(Gelb et al. 2006, Meikle et al. 2006, Dajniki et al. 2008b)
- B. A large population-based pilot study of newborn screening has recently been completed in Taiwan (Chien et al. 2008).
- C. Studies have been published regarding the effectiveness of enzyme replacement therapy treatment for infantile-onset Pompe disease with alglucosidase alfa (rhGAA) (Kishnani et al. 2006, Kishnani et al. 2007).

III. OBJECTIVES OF REVIEW

This report updates a previously conducted systematic review commissioned by the Health Resources and Services Administration for use by the Advisory Committee regarding the potential benefits and harms of screening for Pompe disease (Kemper et al. 2007). The objectives of the current review are to add more recent evidence to complement the earlier review, with a focus on questions of particular relevance to the AC. The earlier review had several limitations:

- The impact of detecting late-onset Pompe Disease in newborns was not considered.
- No peer-reviewed pilot screening data were available.
- No cost-effectiveness analyses were identified.
- Unpublished data were not systematically sought for inclusion.

Thus, this review summarizes the earlier review, provides greater in-depth information about more recent published evidence, and provides information from unpublished data.

IV. MAIN QUESTIONS

We sought to answer four over-arching and critical questions arising from the AC and nominating subcommittee to inform recommendations concerning newborn screening for Pompe disease:

- Do current screening tests effectively and efficiently identify cases of Pompe disease that may benefit from early identification?
- Does intervention in newborns identified by screening compared to those identified clinically lead to improved health outcomes?
- What is the cost-effectiveness of newborn screening for Pompe disease?

- What critical information is missing that is needed to inform screening recommendations for Pompe disease?

In the context of addressing these over-arching questions, we also considered the following specific questions:

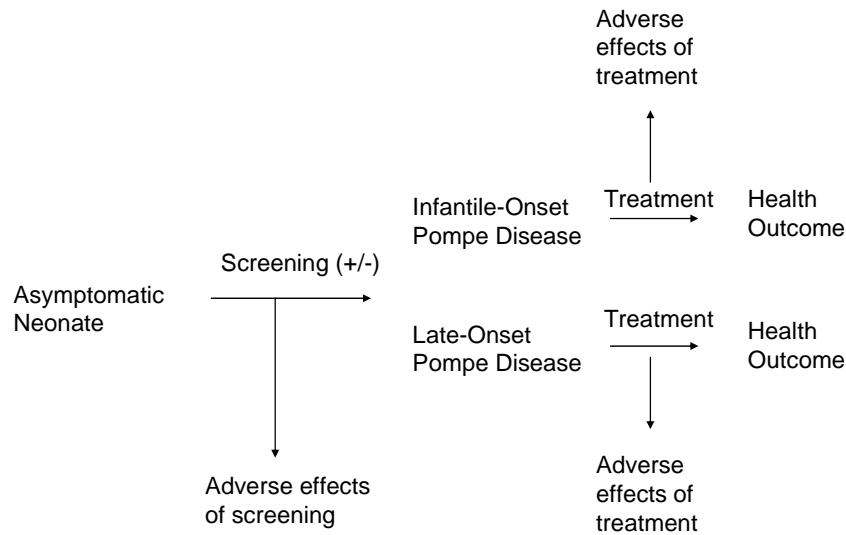
- A. What is the natural history of Pompe disease?
- B. What is the prevalence of Pompe disease?
- C. What are the methods of screening and diagnosis?
- D. How accurate are the screening tests?
- E. What are the benefits of treatment?
- F. What is the relationship between treatment outcomes and the timing of treatment intervention?
- G. What are the potential harms of screening, diagnosis, and treatment?

V. DECISION MODEL AND DEVELOPMENT OF EVIDENCE QUESTION/OUTCOME TABLE

In preparing this review, we separated infantile-onset Pompe disease from late-onset Pompe disease wherever possible. We only considered screening test accuracy in newborns and the effectiveness of treatment begun in early childhood (i.e., by 2 years of age). As described below, evidence was gathered from a variety of sources. However, the evidence table only summarizes peer-reviewed published studies.

Figure 1. Conceptual Framework.

The conceptual framework illustrates the salient factors in considering newborn screening for Pompe disease addressed by this review. Newborns can either be screened or not screened. Those who are screened may suffer adverse events, including false positive or false negative screens. Regardless of screening, individuals may develop infantile- or late-onset Pompe disease. Treatment, which impacts health outcomes, may begin earlier for those who are identified through screening. Those who receive treatment may have associated adverse effects.



VI. METHODS

For this report, we conducted a systematic evidence review which updated the original systematic review prepared for the use of the AC. As in the original review, we searched Medline for all studies published in English from 1966 (the start of MEDLINE) through July 2008 (updating the original review by two years). Medline searches were conducted using the National Library of Medicine Medical Subject Headings term “glycogen storage disease type II” and the keywords “Pompe disease” and “Pompe’s disease.” To ensure completeness of the literature search, we reviewed reference lists and the nomination form submitted to the AC. We excluded research that did not include human subjects, but did consider all other study designs including case reports, case series, and uncontrolled intervention trials.

One author (ARK) abstracted the data from articles to address the key questions regarding the natural history and burden of suffering related to Pompe disease, methods for screening and diagnosis, effectiveness of treatment, and accuracy of screening. Due to the variations in study design and the small sample size of most studies, no quality score was assigned to the articles. However, details regarding the study design, study population, and sample size were abstracted, and we report limitations regarding specific studies in this review. Articles that were included in the original review were re-evaluated as part of this update, and we report here the findings from both the original review and the update.

In addition to the systematic reviews of published literature, one author (MFB) interviewed subject matter experts to identify unpublished data related to screening methods, including MS/MS-based assays and fluorescence-based assays, and the effectiveness of treatment.

Subject matter expert were identified by review of the scientific literature, recommendation of the AC, and knowledge of the ERW. Experts were asked to provide primary data regarding in order for independent evaluation (conducted by MFB). In order to participate in this process, each investigator submitted a standardized conflict of interest form. The experts who contributed to this review include:

1. Deeksha Bali, PhD; Laboratory Director, Duke University Glycogen Storage Disease Lab, Durham NC.
2. Olaf Bodamer, MD FACMG; Newborn Screening Program, Division of Biochemical Genetics, University Children's Hospital, Vienna, Austria.
3. Paul Wuh-Liang Hwu, MD; Taiwan Newborn Screening Program, Department of Pediatrics and Medical Genetics, National Taiwan University Hospital.
4. Joan Keutzer, PhD; Vice-President of Scientific Affairs; Genzyme Corporation, Cambridge, MA.
5. Priya Kishnani, MD; Division Chief, Medical Genetics, Duke University, Durham, NC.
6. Deborah Marsden, MBBS; Metabolism Laboratory Director; Children's Hospital Boston; Director, Global Medical Affairs –Myozyme, Genzyme Corporation, Cambridge MA.
7. Alfred E. Slonim MD, Clinical Professor of Pediatrics. Division of Molecular Biology. Columbia University Medical College, New York.

We include findings arising from data to which we were given complete access. To help identify such data we began by asking the experts the following questions:

Table 1. INITIAL EXPERT SURVEY:

I. Screening.

1. Have you developed a screening protocol? If so, please describe your screening protocol, including:
 - a. What is your first tier test (e.g., fluorometry, mass spectrometry)?
 - b. What, if anything, is your second tier test (i.e., testing on the same screening sample if the first tier test is abnormal)?

- c. What subsequent testing do you perform on a new sample from an individual with an abnormal first tier/second tier test (i.e., third tier testing)?
 - d. What are the advantages and disadvantages of your screening protocol?
2. If your screening protocol has been implemented, please describe your experience, including:
 - a. When screening began
 - b. The number of children who have been screened
 - c. The total number of children that had a positive screening test that required a diagnostic evaluation
 - d. The number of cases identified. If possible, please characterize the phenotype of these cases (e.g., classic infantile, late-onset).
 - e. The cost of screening. Because costs can be determined in many different ways, please outline what is included in your calculation.

II. Diagnosis

1. Do you have any data regarding the distribution of the different phenotypes of Pompe disease?
2. At the time of initial diagnosis, how do you predict the phenotype, especially if the child was identified through screening?

III. Treatment

1. What is your treatment protocol for presymptomatic late-onset Pompe disease either diagnosed clinically or through newborn screening?
2. What are the major challenges to the treating infantile Pompe disease?
3. What unique outcomes data for the treatment of Pompe disease, regardless of phenotype, can you provide?

IV. Other Information

1. Is there anything else about Pompe disease that you would like to share with us?
2. Do you have any recommendations about changing this form to make it easier for others to use?

These surveys were reviewed by one member of the ERW (MFB). Follow up telephone interviews were conducted for additional information.

VII. RESULTS:

Within this section we present results from the systematic literature review followed by information arising from data obtained from the key experts. Tables are provided within selected sections highlighting important studies or evidence obtained from the experts.

Overall, our literature search identified 717 articles. All abstracts were reviewed, from which 26 were selected for inclusion for this review (see Evidence Table) because they met all inclusion criteria and directly addressed one or more of the key questions. Among these articles, four (Meikle et al. 2006, Chien et al. 2008, Dajnoki et al. 2008b, Kroos et al. 2008) were published after the original systematic review and four (Ausems et al. 1999a, Winkel et al. 2004, Hagemans et al. 2005, Winkel et al. 2005) were not included in the initial review because they addressed only late-onset Pompe disease.

A. Natural History, including Phenotype Variations

Pompe disease is divided into infantile (classic or nonclassic) and late-onset disease. The differences between these conditions are described below.

1. Infantile-onset Pompe Disease

Systematic Review Findings

Symptoms typically develop around two months of age and diagnosis is made by five months of age. Patients with infantile-onset Pompe disease generally exhibit poor feeding and failure to thrive, gross motor delay with muscle weakness, early respiratory insufficiency, and significant cardiac issues with the most severe concern being cardiomyopathy. (van den Hout et al. 2003, Kishnani et al. 2006). Without treatment, the median age of death is nine months due to cardiac dysfunction. (Kishnani et al. 2006) Fewer than 10% survive past 24 months of age. (Kishnani et al. 2006) Some with infantile-onset Pompe disease may have longer survival. (Slonim et al. 2000) Those individuals who develop symptoms in infancy, but who survive longer, are considered to have non-classic infantile-onset Pompe disease. Newborn screening methods distinguish classical from non-classic infantile onset disease.

Table 2. Characterization of Disease.

Study	Design	Subjects	Comments
Kishnani, 2006	Case Series	168 patients from Israel, Taiwan, North America, or Europe with Pompe disease who were diagnosed by 12 months of age and who did not receive enzyme replacement therapy. 45% were born before 1995.	Possible selection bias – cohort was assembled based on questionnaires sent to physicians. This is the largest natural history study.
Slonim, 2000	Case Series	7 infants referred to one US center and 15 infants for whom their pediatricians consulted the center, all with non-classic infantile-onset Pompe disease (later age of onset: 4.8 ± 2.9 months, no cardiomegaly before 12 months of age, traces of residual GAA activity (<0.5%)). None were treated with enzyme replacement therapy. 3/12 died (11	This study has a small sample size and is subject to selection bias. The authors compared results to classic infantile-onset cases. The methods of case ascertainment do not allow determination of the proportion of classic vs. non-classic infantile-onset Pompe disease.

		months, 13 months, and 32 months), with the remainder surviving past 2-years with gastrostomy and tracheostomy.	
Van den Hout, 2003	Case Series	20 infantile-onset cases diagnosed in Dutch centers and 133 infantile-onset cases from the literature. The 20 cases were identified from 1980-1998.	Methods of assembly of the cases from the literature are unclear. According to the authors, much of the data on the 20 infantile cases were incomplete.

2. Late-onset Pompe Disease

Systematic Review Findings

Unlike with infantile-onset Pompe disease, cardiomegaly is not typically present. Late-onset Pompe disease is characterized by muscle weakness and respiratory insufficiency. A review of published case reports found a wide range of death (median 25 years, range 0.9-66 years), primarily due to respiratory failure. (Winkel et al. 2005) We could not directly determine the duration of symptoms prior to diagnosis or death from this review. However, the authors state that "The deceased patients had experienced their first symptoms significantly earlier (at the age of 7, range 0-60 years vs. 24 years...) and were significantly younger at the time of diagnosis (24 years, range 0.7-65 vs. 33 years...) than the patients who were still alive at the time of description". (Winkel et al. 2005) A study of a convenience sample of individuals with late-onset Pompe disease from a registry found that the mean age of symptom development was quite variable (28 ± 14 years) with an average age of diagnosis of 37 ± 13 years. (Hagemans et al. 2005) A separate study of a convenience sample of individuals with late-onset Pompe disease identified through a registry reported that the odds for wheelchair use increased by 13% for each year that an individual has the disease. Similarly, the odds of requiring respiratory support increased 8% for each year. (Hagemans et al. 2005)

Late-onset Pompe disease is highly variable in both presentation and progression. Natural history studies based on convenience samples may be biased towards more significant disease. For example, individuals with slowly progressive or mild disease may not be appropriately diagnosed; therefore, such subjects would not be included in studies. No studies were found that describe the natural history of people with late-onset disease detected through newborn screening or prior to the development of symptoms, and such individuals could have lower severity disease than those identified by symptoms at a later age.

B. Prevalence of Pompe Disease

There are different ways to calculate prevalence:

1. Classical prevalence reporting: This is the number of cases of the condition within the population at a particular time or within a particular time period divided by the population size. Classical prevalence across an entire population may underestimate the burden of infantile-onset Pompe disease vs. late-onset Pompe disease because those with infantile-onset Pompe disease may not survive past infancy
2. Birth prevalence reporting: The birth prevalence is a special case of classical prevalence reporting. It is the number of cases compared to the total number of births over a defined period of time. Birth prevalence may better represent the burden of infantile-onset Pompe disease assuming that case ascertainment is effective.
3. Estimated gene frequency with extrapolation to the population burden of the condition: The expected frequency of individuals affected with an autosomal recessive condition such as Pompe disease can be estimated from the population prevalence of heterozygotes. Since heterozygotes are asymptomatic, such analyses are usually based on carrier mutation analysis from a large sample of unaffected individuals.

Systematic Review Findings

There are 289 reported mutations associated with Pompe disease.(Kroos et al. 2008) Particular mutations have been associated with certain clinical outcomes. For example, a database of mutations collected in the Netherlands including samples collected from North America, Europe, and Asia, has linked specific mutations to the severity of disease based on the amount of GAA enzyme produced, ranging from severe (i.e., minimal GAA enzyme production) to non-pathologic. (Kroos et al. 2008) Although it is expected that severe mutations would be associated with infantile-onset Pompe disease, no prospective studies have directly linked mutation to clinical outcome. Similarly, the relationship between less severe mutations and the development of late-onset Pompe disease is unclear. More specifically, no mutations specifically and consistently distinguish early vs late onset disease.

Carrier mutation analysis for seven mutations associated with infantile and late-onset Pompe disease conducted on 928 randomly selected normal individuals in New York suggested a total prevalence of Pompe disease, regardless of type, to be about 1 case per 40,000. (Martiniuk et al. 1998) No data were provided regarding estimates of the relative distribution of infantile vs. late-onset disease. A carrier mutation analysis in the Netherlands conducted on 3,043 anonymous newborn screening blood spots identified 31 mutations and concluded that the prevalence of infantile Pompe disorder to be about 1 case per 138,000 and of late-onset Pompe disease to be about 1 case per 57,000. (Ausems et al. 1999b) These estimates are associated with very wide confidence intervals because of the rarity of the conditions. Because Pompe disease is rare, small mathematical errors in estimates of the relative distribution of gene frequencies could lead to significant over- or under-estimates of prevalence. For

example, one of these studies (Martiniuk et al. 1998) estimated that the seven mutations assessed in their study accounted for 29% of Pompe disease.

A recent report of a pilot population screening program in Taiwan (Chien et al. 2008) identified four cases of Pompe disease out of 132,528 screened newborns, for a prevalence of about 1 in 33,000. Three of the newborns had cardiac involvement at the time of diagnosis (i.e., classical infantile-onset Pompe disease). The other newborn did not have cardiac involvement and did not develop muscle weakness until 9 months of age (i.e., nonclassical infantile-onset Pompe disease). No cases of late-onset Pompe disease were reported. The lack of identification of late-onset cases could be because the tiered screening method eliminated those with late-onset disease (e.g., those with marginal levels of GAA tested negative at some point along the screening cascade), that late-onset disease is less common than suspected, or the diagnostic methods employed in the study do not identify those with late-onset Pompe disease. Further details of the screening process are described in our evaluation of screening test characteristics (Section J).

Table 3. Prevalence Estimates.

Study	Design	Subjects	Estimated Prevalence	Comments
Ausems, 1999	Cross-sectional	3,043 anonymous dried blood spots in the Netherlands screened for 3 mutations	Infantile: 1/138,000 (95% CI: 43,169-1/536,482) Late-onset: 1/57,000 (95% CI: 1/27,734-1/28,255) Combined: 1/40,000 (95% CI: 17,622-1/100,073)	No clinical correlation. Only three mutations were included. Very wide confidence interval. This study suggests that late-onset Pompe disease is 2 to 3 times more common than infantile-onset disease.
Ausems, 1999 – community Genetics	Retrospective Cohort in the Netherlands.	Incidence of Pompe disease between	Birth prevalence of infantile Pompe disease: 1/101,000 (excluding prenatal diagnoses); juvenile (onset	These estimates are dependent on case-finding.

		1972 and 1996	after 1-year but before 18-years): 1/53,000; adult: 1/53,000	The prevalence is similar to that predicted based on gene frequency.
Martiniuk, 1998	Cross-sectional	928 randomly selected adults in New York screened for 7 mutations	Combined prevalence (infantile and late-onset): 1/40,000 (no confidence interval provided)	Published as a research letter-to-the-editor.
Chien, 2008	Prospective	132,538 newborns screened in Taiwan	Infantile Pompe (classical and nonclassical): 1/33,135 Late-onset: No cases detected	Only population-based prospective study of screening

Additional Findings from the Expert Interviews:

Dr. Hwu reports that from the time of the original publication above, the Taiwan screening program has completed the fluorometric-based screening on a total of 206,008 infants. Of this number screened, 0.3% have been recalled for a second blood spot test, and 0.04% of the total were required to undergo confirmatory testing (a total of 21.4% of the recalled tests). He reports that of the 206,008 screened, 6 have infantile-onset Pompe disease and 5 have late-onset Pompe disease.

C. Methods of Diagnosis

Systematic Review Findings

Diagnosis of Pompe disease can be made by enzyme assay or the identification of two mutations in the GAA gene associated with severe reduction in the production of GAA enzyme. (Kroos et al. 2008)

Muscle biopsy is not routinely done because of lack of sensitivity in general and the risk of anesthesia in patients with Pompe disease. (Ing et al. 2004, Winkel et al. 2005) Skin fibroblast GAA enzyme activity can be used to diagnose Pompe disease, but is not practical for screening because of expense, complexity, and time intensity (i.e., up to 2 months before results are available).

D. Methods of Screening

Systematic Review Findings

Measurement of GAA enzyme activity in whole blood dried on filter paper is possible. Methods include fluorometric tests (Umapathysivam et al. 2000, Chamoles et al. 2004, Jack et al. 2006) and tandem mass spectroscopy (MS/MS). (Gelb et al. 2006, Dajnoki et al. 2008a)

In a study of MS/MS newborn screening in Austria, 10,279 anonymous dried blood spots were collected to define a pediatric reference range. (Dajnoki et al. 2008a) An adult reference range was developed based on 229 samples submitted to the laboratory for GAA enzyme analysis. The sensitivity of the test was evaluated against samples of 14 infantile-onset and 15 late-onset patients. The assay appropriately identified all cases of Pompe disease, but could not differentiate infantile from late-onset disease. Four of the anonymous dried blood spots (0.04%) tested positive. No subsequent testing or clinical correlation is available.

A multiplexed immune-quantification assay to detect eleven lysosomal storage disorders, including Pompe disease has been developed. (Meikle et al. 2006) In a study evaluating 30 dried blood spots from individuals with Pompe disease, of whom three had infantile-onset, 173 unaffected adults and 426 unaffected newborns, the sensitivity was 90% and the specificity >99%. This study also reported test accuracy for other lysosomal storage disorders (e.g., Fabry disease and Gaucher disease). The sensitivity for the lysosomal storage disorders other than Pompe disease and Gaucher disease were 100%. The sensitivity for Gaucher disease was only 50%, based on 12 patients.

A recent pilot test in Taiwan (Chien et al. 2008) used a multi-tier test designed to maximize sensitivity. Dried blood spots were initially tested for GAA enzyme using a fluorometric test. If the activity was less than 55% of the mean, a second test was conducted on the same dried blood spot. If the GAA activity was <25% and the ratio of total neutral glucosidase activity (NAG) to GAA, which controls for the quality of the sample, was >25 and ≤ 100 , children were recalled for a second blood spot. However, if the ratio of NAG to GAA was >100, children were recalled for diagnostic testing. Among those children who had a second blood spot, those who had GAA activity <8%, percent total GAA inhibition > 80% and NAG to GAA ratio > 60, were recalled for diagnostic testing.

Among the 132,538 newborns tested, 8 were referred for diagnostic testing after the first blood spot (0.006%); 1,093 required a second blood spot (0.82%), of whom 113 (10.3%) were referred for diagnostic testing. Among those who were referred for diagnostic testing (including GAA assay, physical examination, creatine kinase and creatine kinase myocardial band assays), four were found to have infantile Pompe disease (3.5%). The authors are unaware of any false-negative screening tests during this time. No cases of late-onset Pompe disease were detected.

Based on the GAA activity among the 117 false positive cases referred for diagnostic testing, the authors suggest that the cutoff for the NAG/GAA ratio for recalling for a second blood spot can be increased from 25 to 30 to decrease the recall rate for a second blood spot to 0.37% with no loss of sensitivity. Based on these data, we generated the following table illustrating the expected rates of recall and diagnosis, assuming a population of 100,000 newborns:

Table 4. Expected rates of Recall per 100,000:

	Referred for Diagnostic Confirmation after the First Blood Spot	Recalled for Second Blood Spot	Referred for Diagnostic Confirmation after the Second Blood Spot	Cases Diagnosed
Original Criteria	6	820	85	3
Increased NAG/GAA Ratio	6	370	38	3

*Assuming similar proportion to the original criteria for referral rates for diagnostic confirmation after the second blood spot.

E. Feasibility and Acceptability of Screening

Systematic Review Findings

The Taiwan pilot study suggested that large-scale screening is feasible. However, no data were presented regarding the costs of screening or other challenges related to implementing screening more broadly. No data from the Taiwan pilot study were reported regarding the acceptability of screening to families or the harms associated with false positive screens.

F. Benefits of Treatment in Screen Positive Individuals

Systematic Review Findings

Alglucosidase alfa, the FDA-approved form of recombinant human GAA (rhGAA) can be life saving for cases of infantile Pompe disease. One study evaluated the impact of treatment among a cohort of 18 children with infantile Pompe disease diagnosed before 27 weeks of age who were not ventilator dependent. Among these children, who had a median age of five months, all survived the 52-week study period. Six required ventilatory assistance, including three who required endotracheal tube or tracheostomy. Compared to historical controls, treatment reduced the risk of death by 99% and reduced

the risk of death or the need for invasive ventilation by 92%.(Kishnani et al. 2007) Historical controls were used because of ethical concerns about not treating individuals. rhGAA treatment also appears to be beneficial for individuals with symptomatic late-onset Pompe disease.(Winkel et al. 2004) We are unaware of any studies that have evaluated the impact of presymptomatic therapy in individuals with late-onset Pompe disease.

Patients who do not produce any active or inactive endogenous GAA (referred to as cross-reacting immunologic material [CRIM] negative) may produce higher and more persistent titers of antibodies to rhGAA, and thus have worse clinical outcomes.(Kishnani et al. 2006) Among the cohort of 18 children, 16 developed IgG antibodies to rhGAA. However, only 3 of the 18 (17%) were CRIM negative. One of these patients made no motor gains while on therapy.

Additional Evidence from Expert Review:

Active research is ongoing regarding the prevalence of CRIM negative status in infantile-onset patients at Duke University (Drs. Kishnani/Bali). Within the Duke repository of 86 patients with infantile Pompe disease collected over the past ten years, 19% were CRIM negative.

The Taiwan group has follow up data on the five infants identified by newborn screening, who had cardiomegaly on initial evaluation and who were begun on enzyme replacement treatment within the first month or two of life. All of these children have survived with essentially normal growth and minimal motor impairment. In comparison with 10 children in a group treated later (not identified by newborn screening but by clinical presentation), there was no statistically significant difference in mortality, but the early treated group has had significantly earlier walking than the late treated group. Among the 10 in the later treated group, two have died, although the analysis of Kaplan-Meier survival curves did not indicate a statistically significant difference in mortality between the two populations.

A separate prospective cohort study of rhGAA treatment enrolled 21 children with Pompe disease between the ages of 6 and 36 months who developed symptoms by 12 months of age (corrected for prematurity). Compared to historical controls, after 104 weeks of treatment the risk of death was reduced by 79% and the risk of death or invasive ventilation by 58%. About 60% of patients had improvement in motor development and about 80% had improvement in functional independence. The authors conclude that rhGAA can “reduce the mortality...even when treatment is started at a more advanced stage of disease.” (Nicolino et al. In Press). This study underscores the benefit of rhGAA treatment, but does not provide direct evidence about the benefit of beginning therapy before the development of symptoms.

G. Harms of Screening

Systematic Review Findings

We did not identify any studies of the harms of screening, including the potential harms associated with false positive or false negative screens, or the potential harms associated with identification of presymptomatic late-onset Pompe disease.

H. Harms of Diagnosis

Systematic Review Findings

We did not identify any studies of the harms of diagnosis.

I. Harms of Treatment

Systematic Review Findings

Patients who are CRIM negative may develop antibodies that limit the effectiveness of treatment, as described above.

J. Cost-Effectiveness of Screening or Treatment

Systematic Review Findings

We were not able to identify any study of the cost-effectiveness of screening or treatment for Pompe disease.

VIII. SUMMARY

Key findings:

Pompe disease affects about 1 in 30,000 to 1 in 50,000 individuals but may be influenced by the underestimation of the true prevalence of the infantile form of Pompe, due to increased mortality in the first 15 months and/or the lack of capture of accurate diagnosis prior to death. The ratio of infantile to late-onset Pompe disease in newborns is unknown. No cases of late-onset Pompe disease were identified in the published reports from the Taiwan screening program. The pilot program in Taiwan showed that screening is possible, but will have many false positives.

Infantile Pompe disease is fatal, often within the first fifteen months of life, and treatment with enzyme replacement therapy can be life saving. Indirect evidence suggests that earlier treatment for infantile Pompe disease improves health outcomes. Further data are needed regarding the long-term effectiveness of treatment.

Late-onset Pompe disease can be fatal. However, late-onset Pompe disease is variable in both age of onset and rate of progression. It is unknown whether presymptomatic treatment leads to better health outcomes for late-onset Pompe disease.

Returning to the key questions:

- **Do current screening tests effectively and efficiently identify cases of Pompe disease?**

The pilot study in Taiwan suggests that a highly sensitive enzyme assay using dried blood spots is available to identify cases of early infantile Pompe disease, but with a relatively high number of false positives. Other screening strategies (e.g., MS/MS) have not undergone prospective population-based pilot testing.

- **Does intervention in newborns or infants with pre-symptomatic or early symptomatic Pompe disease improve health outcomes?**

Treatment of infantile-onset Pompe disease is life saving. There is some concern that treatment may induce an immune reaction in those children who are CRIM negative that would decrease the benefit of treatment. However, without treatment, most children with infantile-onset Pompe disease would die between 12 and 24 months of life. Long-term treatment studies of treating infantile-onset Pompe disease are in progress. The optimal time to begin treatment (e.g., presymptomatic vs. after the development of symptoms) for late-onset Pompe disease is not known.

- **What is the cost-effectiveness of newborn screening for Pompe disease?**

We did not identify any cost-effectiveness data. Charge data are available for rhGAA. Other costs (e.g., costs of screening, treatment) are not available, and we are unaware of any data that quantify the costs or utilities (quality-of-life measure) associated with untreated Pompe disease, treated Pompe disease, the harms of false positives, and the relative benefits vs. harms of diagnosing late-onset Pompe disease during early infancy.

- **What critical information is missing that is needed to inform screening recommendations for Pompe disease?**

We identified several domains with deficient data, related to:

- **Prevalence of Pompe disease:** A more accurate way to determine prevalence would be through systematic case finding. Such a study would help determine the true distribution of infantile vs. late-onset Pompe disease.
- **Late-onset Pompe disease:** The relative distribution of late-onset to infantile Pompe disease is unknown. No data are available regarding the benefits or harms of detecting late-onset Pompe disease during infancy.
- **Accuracy of Screening:** The pilot screening project in Taiwan identified strategies to reduce the false positive rate. Prospective data are needed regarding this modified protocol. Data are also needed regarding the accuracy of other potential screening tests (e.g., ms/ms) when applied to a prospective population based screening.
- **Feasibility of Screening:** Data are needed regarding the ability of other newborn screening laboratories to offer Pompe disease screening.

- **Benefit of Early Diagnosis:** Indirect evidence supports the benefit of presymptomatic infantile-onset Pompe disease. Direct evidence will require evaluating long-term outcomes among populations of screened and unscreened neonates with Pompe disease.
- **Acceptability of Screening:** No data are available regarding the acceptability to consumers of screening. This is especially important because of the potential to diagnose late-onset disease.
- **Cost-Effectiveness:** We were unable to identify any cost-effectiveness data that were extrapolated to US screening centers; only charge data are available for enzyme replacement therapy.

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X. APPENDIX

Table 5. Key findings from selected articles (alphabetical by first author)

Author/Design	Sample Size/Population Characteristics	Interventions/Independent Variables	Significant Findings
Amalfitano 2001; Prospective Cohort	3 infants with Pompe disease	Treatment with rhGAA	All infants survived past one year; cardiac status and strength improved. One patient had decline in motor development associated with anti-rhGAA-antibodies
Ausems et al (1999); Cross-sectional	3,043 anonymous dried blood spots in the Netherlands	Gene mutations associated with Pompe disease	The frequency of infantile and late-onset Pompe disease was predicted to be 1/40,000.
Ausems et al (1999); Case Series	Case finding in the Netherlands between 1972 and 1996	Prevalence of Pompe disease	Birth prevalence of infantile Pompe disease: 1/101,000 (excluding prenatal diagnoses); juvenile (onset after 1-year but before 18-years): 1/53,000; adult: 1/53,000
Chien et al (2008); Prospective Cohort	132,538 newborns in Taiwan between Oct 2005 and Mar 2007, with comparison to the other children born in Taiwan during this period	Newborn screening for Pompe disease	Pompe disease identified in 4 of the newborns in the screened population. Although a similar proportion was identified in the unscreened population, diagnosis in this group was later (3-6 months vs. < 1 month). No false negative screens were identified. Among those screened, about 0.8% required a second blood spot of whom about 10% were referred for diagnostic testing. The authors suggest new test cut-offs that may decrease the false positive rate.
Chamoles et al (2000); Cross-sectional	Selected samples from individuals with Pompe disease and normal controls	Ability to measure GAA in dried blood spots	Technique is possible
Dajnoki et al (2008); Cross-sectional	Population-based samples to identify normal range and 229 adults with suspected Pompe disease, 14 with infantile-onset Pompe disease and 15 with late-onset Pompe disease	Ability to measure GAA by MS/MS in dried blood spots	Technique is possible
Hagemans et al (2005); Cross-sectional	255 children and adults with late-onset Pompe disease	Reported disease severity and duration	Disease duration predicted the need for respiratory support and wheel chair use more than the chronological age of the affected individual.
Jack et al (2006); Cross-sectional	14 patients with Pompe disease	Ability to measure GAA	13/14 cases were detected; 1 was intermediate
Kishnani et al (2006); Case Series	168 children with infantile Pompe disease	Natural history	The median age of symptom onset was 2 months (range 0 to 12 months) and of death is 8.7 months

			(range 0.3 to 73.4 months). Early symptom onset was associated with increased risk of early death.
Kishnani et al (2007); Prospective Cohort	18 patients with infantile Pompe disease	Treatment with enzyme replacement therapy (rhGAA from Chinese hamster ovary cells)	All patients survived to 18 months of age, the study endpoint. Treatment reduced the risk of 99% and the risk of death or invasive ventilation by 92%. CRIM-negative patients may develop a higher immunologic response to rhGAA, which could limit its effectiveness.
Klinge et al (2005); (<i>Neuromuscular Disorders</i>) Prospective cohort	2 patients with infantile Pompe disease	Treatment with rhGAA (rabbit milk)	Dramatic improvement in cardiomyopathy and some improvement in motor skills. Antibody formation was not associated with motor declines
Klinge et al (2005); Prospective cohort	As above	As above	Survival at the end of this report was > 20 months
Kroos et al (2008); Cross-sectional	Database of mutations	Mutation analysis	The database has 189 unique mutations, bringing the total number of reported mutations to 289
Li et al (2004); Cross sectional	Selected population of blood spots from individuals with lysosomal storage disorders, including Pompe disease and normal controls	Ability to measure lysosomal enzymes in dried blood spots	The laboratory technique is feasible and accurate.
Martiniuk et al (1998); Cross-sectional	928 randomly selected adults in New York.	Gene mutations associated with Pompe disease	The frequency of infantile and late-onset Pompe disease was predicted to be 1/40,000.
Meikle et al (1999); Case Series	Cases of lysosomal storage disorders in Australia from 1980-1996	Incidence of lysosomal storage disorders	21 cases of Pompe were diagnosed in the postnatal period, yielding a carrier frequency of 1 in 191 and a prevalence of 1/146,000
Meikle et al (2006); Cross-sectional	30 blood spots from individuals with Pompe disease (3 infantile-onset), blood spots from 173 adults and 426 newborns, and blood spots from 81 individuals with other lysosomal storage disorders	Test characteristics of a multiplexed immune-quantification assay to detect lysosomal storage disorders	For Pompe disease (infantile and late-onset), the sensitivity is 90% and the specificity is >99%
Okumiya et al (2006); Cross-sectional	25 patients with Pompe disease	Ability to assay GAA	Technique is possible
Pinto et al (2004); Case Series	Population of Portugal between 1982-2001	Prevalence of lysosomal storage disorders, including Pompe disease	The prevalence of Pompe disease was 1/50,000
Poorthuis et al (1999); Case Series	Population of the Netherlands between 1970-1996	Prevalence of lysosomal storage disorders, including Pompe disease	Birth prevalence of infantile Pompe disease 1.3/100,000 and overall 1/50,000
Slonim et al (2000);	12 infants with Pompe	Natural history	Some infants may have an atypical

Case Series	disease		course with survival beyond 12 months
Umapathysivam et al (2000); Cross-sectional	Selected samples from individuals with lysosomal storage disorders and normal controls	Ability to measure enzyme activity in dried blood spots	Technique is possible
Van den Hout et al (2003); Case Series	20 cases of infantile Pompe disease and 133 cases from the literature	Natural history	Symptoms start around 1.6 months with a median age of death between 6 and 7.7 months. Cardiomyopathy is significant.
Van den Hout et al (2004); Case Series	4 cases of infantile Pompe disease	Outcomes of treatment with rhGLU	All children reached the age of 4 years. There was motor improvement, but respiratory improvement was variable. CRIM-negative status was not associated with worse outcomes.
Winkel et al (2004); Prospective Cohort	3 patients with late-onset Pompe disease (11-, 16-, and 32-years)	Treatment with enzyme replacement therapy (rhGAA from rabbit milk)	Pulmonary function stabilized, fatigue improved, and the least affected patient had marked improvement in strength.
Winkel et al (2005); Systematic Review of Case Reports	225 case reports of late-onset Pompe disease	Age of onset, symptoms, cause of death	Most patients (62%) had an age of onset of 18-years or older. Motor/muscle problems are the most common first symptom (79.9%). The median age of death is 24.5 years (range (0.9-66). Respiratory failure is the most frequent cause of death (72%).
Zhang et al (2006); Cross-sectional	Dried blood spots from patients with Pompe disease, heterozygotes, and normal controls	Ability to measure GAA in dried blood spots	Technique is possible