

and/or Immunology specialists. These assessments may help determine when treatment should be initiated. The infant's cross reactive immunologic material (CRIM) status should be determined by GAA genotype or by measuring GAA enzyme activity in fibroblasts.

### Treatment:

Enzyme replacement therapy (ERT)- This entails replacement of the defective GAA enzyme with a recombinant form called alglucosidase alfa (this is also called recombinant human GAA, or rhGAA), which is administered via biweekly infusions. Babies with early-onset Pompe disease in whom ERT is initiated before six months of age demonstrate improved survival, are less likely to need ventilator assistance. They acquire more developmental milestones and show improvement in cardiac size and function. In individuals with late-onset disease, ERT stabilizes ventilatory function and motor ability.

An individual's CRIM status is an important predictor of his or her clinical response to ERT. CRIM is the endogenous GAA protein produced by most patients with Pompe disease. CRIM negative (CN) means there is no residual GAA enzyme activity. Pompe patients who are CN produce anti-rhGAA antibodies and do not respond to ERT unless immune tolerance induction (ITI) is done prior to the start of or concurrent with ERT. Approximately 20% of earlyonset Pompe disease patients are CRIM negative. CRIM positive means there is residual GAA enzyme activity of at least 1%. These individuals usually do not produce anti-rhGAA antibodies and tend to have a better response to ERT.

**Prognosis:** Prognosis is variable and dependent on multiple factors including the severity of disease and response to treatment, however clinical outcomes have improved substantially since the advent of ERT, cardiomyopathy, and also a test for urine tetrasaccharide (Glc4). Babies with a confirmed diagnosis will be referred to Pediatric Cardiology, and may require assessments by Pulmonology, Ophthalmology, Gastroenterology/ Nutrition, Developmental

### Links:

#### Genetics Home Reference

<http://ghr.nlm.nih.gov/condition/pompe-disease>

#### Gene Reviews

<http://www.ncbi.nlm.nih.gov/books/NBK1261/>

#### National Institute of Neurological Disorders and Stroke Pompe Disease Information Page

<http://www.ninds.nih.gov/disorders/pompe/pompe.htm>

## Newborn Screening For Your Baby's Health



## Overview of Pompe Disease



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## Definition

Pompe disease is a genetic disorder caused by mutations in the GAA gene. It is a progressive metabolic condition that causes muscle weakness.

The GAA gene codes for an enzyme called acid alpha-glucosidase (GAA) which is necessary for the degradation of glycogen in the lysosome. Mutations in GAA result in an accumulation of glycogen in the lysosomes. It is therefore considered a Lysosomal Storage Disorder.

Pompe disease is also referred to as: Glycogen Storage Disease Type II, Acid Maltase Deficiency, Acid Alpha-glucosidase Deficiency

## How inherited

Pompe disease is inherited in an autosomal recessive pattern. Normally a person has two functional GAA genes. In people with Pompe disease, both copies of this gene have a mutation and there is a deficiency of the critical enzyme activity. Each parent of a newborn with Pompe disease typically has one functional and one mutated gene and is considered a carrier. When both parents are carriers, the chance of a newborn inheriting two mutated genes is 25%.

## Symptoms in carriers

None known.

## Symptoms

The symptoms of Pompe disease vary in terms of age of onset and severity, and correspond to the degree of GAA enzyme activity.

- **Early-onset:** Results from complete or near absence of GAA enzyme activity. Symptoms begin at birth or shortly thereafter, with hypotonia, hypertrophic cardiomyopathy, failure to thrive, and respiratory insufficiency. Without treatment progression is rapid and most babies die from

cardiac or respiratory complications before a year of age.

- **Late-onset:** Results from partial deficiency of GAA enzyme. The age of onset is variable; symptoms may appear as early as the first few months of life, or as late as adulthood. The primary symptom is a slowly progressive myopathy primarily involving skeletal muscle. There is not usually cardiac involvement with the late onset form of Pompe disease.

## Newborn Screening

**Incidence:** The overall incidence of Pompe disease is approximately 1 in 17,000 births. It is panethnic. **New York State Method of Screening (First Tier):** Screening for Pompe disease is accomplished by analysis of GAA enzyme activity by mass spectrometry. If concentrations are normal, the sample is deemed within acceptable limits. If abnormal, second tier screening is performed.

**Second Tier Screening:** Sequencing of the GAA gene.

**Testing can be affected by:** GAA enzyme activity may be low in healthy newborns, thus giving a false positive result. Within the GAA gene, at least one pseudodeficiency allele has been identified which results in lower GAA enzyme activity but no clinical symptoms of Pompe disease.

**Interpretation/Reporting of data:** Results are reported as within acceptable limits, repeat specimen required or as a referral. Prompt consultations with specialists are required for each referral.

- When two GAA mutations are identified in an infant, it is consistent with a diagnosis of Pompe disease. The baby will be referred to a Metabolic Geneticist at one of the designated Specialty Care Centers.
- When one mutation is identified in an infant, additional testing by a Metabolic Geneticist is needed in order to determine if the baby is affected by Pompe disease or is a carrier. This is

because DNA sequence analysis may not detect all possible mutations in the GAA gene. These evaluations include analysis of leukocyte GAA enzyme and creatine kinase (CK). If low GAA activity persists, follow recommendations for reaching a diagnosis (see below). If GAA activity is normal in leukocytes, the baby is a carrier of Pompe disease.

- When no mutation is identified in GAA gene, but one or more variants of uncertain significance or polymorphisms are found, a repeat newborn screen is requested. If low GAA enzyme activity persists, follow recommendations for one mutation (see above).
- When GAA gene sequencing reveals a pseudodeficiency allele only, which results in lower GAA enzyme activity but no clinical symptoms of Pompe disease, this is considered screen negative. The presence of the pseudodeficiency allele will be indicated on the report, but no follow-up testing is recommended.

**Referral to Specialty Care Center:** Babies with an abnormal newborn screen for Pompe disease with an identified GAA mutation are referred to an Inherited Metabolic Disease Specialty Care Center for a diagnostic evaluation.

## Diagnosis

All babies who have a positive Pompe newborn screen with at least one GAA gene mutation should be assessed with leukocyte GAA enzyme analysis, and babies with two mutations will require a cardiac evaluation (echocardiogram and EKG) to look for signs of cardiomyopathy, and also a test for urine tetrasaccharide (Glc4). Babies with a confirmed diagnosis will be referred to Pediatric Cardiology, and may require assessments by Pulmonology, Ophthalmology, Gastroenterology/ Nutrition, Developmental Pediatrics, Audiology