

Newborn Screening for Pompe Disease

Status of Long-term Clinical Follow-up Efforts

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Disclosures

- Genzyme - paid consultant and site PI for Genzyme Registry
- I am a child neurologist who is interested in improving long-term clinical outcomes in those diagnosed with rare disorders via NBS.



Objective

- Outline how those of us involved in Pompe disease NBS are addressing two critical needs:
 - To engage in ongoing discussions of best practices in those with “non-infantile Pompe disease” or LOPD
 - To ensure that LOPD patients are receiving appropriate clinical follow-up with evaluation of outcomes

Background

- Pompe disease NBS was added to the Recommended Uniform Screening Panel (RUSP) in 2015 based on compelling evidence of improved outcomes with early initiation of treatment in those with infantile Pompe disease.
- Pompe NBS also identifies those who may develop weakness and need treatment later in life (i.e., late-onset Pompe disease, [LOPD]), anytime from early childhood to adulthood.

Pompe Disease NBS Pilots

- NICHD supported pilot of Pompe
 - Georgia
 - Wisconsin
 - New York
- NBSTRN Resources
 - Monthly Calls
 - Pilot states
 - States that have implemented
 - Missouri, Illinois, Kentucky
 - States that are planning to implement
 - Clinician focused call
 - Specimens – VRDBS
 - Analytical and Clinical Validation – R4S/CLIR 2.0
 - Long-Term Follow-Up Tool and Data Sets - LPDR

ACMG ACT Sheets

- Newborn Screening ACT Sheets and Confirmatory Algorithm
 - Condition Description
 - Diagnostic Evaluation
 - Clinical Considerations
- Emergency Management
 - *You should take the following actions*
- Referrals for
 - Testing
 - Clinical Services
 - Find Genetic Services

American College of Medical Genetics **ACT SHEET**

Newborn Screening ACT Sheet Pompe Disease (Glycogen Storage Disease II)

Condition Description: Pompe disease is a lysosomal storage disorder (LSD) caused by a defect in acid alpha-glucosidase (GAA), resulting in glycogen accumulation primarily in cardiac and skeletal muscle. There is wide variability in severity and age of onset. Pompe disease is an autosomal recessive disorder.

YOU SHOULD TAKE THE FOLLOWING ACTIONS:

- Consult with genetic metabolic specialist.
- Contact family to inform them of the newborn screening result.
- Evaluate the newborn with attention to hypotonia, feeding difficulties and clinical evidence of heart disease.
- Provide the family with basic information about Pompe disease.
- Report confirmatory findings to newborn screening program.

Diagnostic Evaluation: Confirmatory alpha-glucosidase enzyme assay. Patients with low enzyme activity should have GAA gene analysis and immediate assessment for cardiomyopathy.

Clinical Considerations: The clinical presentation of Pompe disease ranges from a rapidly progressive infantile form, which is uniformly lethal if untreated, to a more slowly progressive late-onset form. All forms of the disorder are eventually associated with progressive muscle weakness and respiratory insufficiency. Cardiomyopathy is associated almost exclusively with the infantile form. Enzyme replacement therapy (ERT) is available for both forms. ERT should be started as soon as possible for patients with the infantile form and at the first signs of muscle weakness in the late-onset form. ERT is highly complicated and should only be given under the guidance of a specialist with expertise in lysosomal storage disorders.

Additional Information:
[Genetics Home Reference](#)
[OMIM](#)

Referral (local, state, regional and national):
[Testing](#)
[Clinical Services](#)
[Find Genetic Services](#)

ACMG Practice Guideline

- “Pompe disease diagnosis and management guideline” May 2006
 - Diagnostic Confirmation
 - Differential Diagnosis
 - Clinical Evaluation
 - Laboratory Testing
 - Diagnostic Algorithm
 - Management
 - Cardiology
 - Pulmonary
 - Gastrointestinal
 - Musculoskeletal
 - Neurological
 - Surgery
 - Care Coordination
 - Genetic Counseling
 - Therapies

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ACMG Practice Guideline

Pompe disease diagnosis and management guideline

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Key Words: Pompe disease, acid maltase deficiency, lysosomal storage disease, glycogen storage disease type II, management guidelines

Disclaimer: ACMG standards and guidelines are designed primarily as an educational resource for physicians and other health care providers to help them provide quality medical genetic services. Adherence to these standards and guidelines does not necessarily ensure a successful medical outcome. These standards and guidelines should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, the geneticist should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these standards and guidelines.

Pompe disease is a rare, progressive, and often fatal muscular disease. The underlying pathology is a deficiency of the enzyme acid alpha-glucosidase (GAA) that hydrolyzes lysosomal glycogen. Pompe disease is a single disease which manifests as a clinical spectrum that varies with respect to age at onset, rate of disease progression, and extent of organ involvement. The advent of enzyme replacement therapy for this condition will necessitate early diagnosis. This guideline for the management of Pompe disease was developed as an educational resource for health care providers to facilitate the prompt and accurate diagnosis and treatment of patients. An international group of experts in various aspects of Pompe disease met to review the evidence base from the scientific literature and their expert opinions. Consensus was developed in each area of diagnosis, treatment and management in the development of this guideline. This management guideline specifically addresses evaluation and diagnosis across multiple organ systems (cardiology, pulmonary, gastrointestinal/nutrition, musculoskeletal, neurological) involved in both infantile and late-onset Pompe disease. Conditions to consider in a differential diagnosis stemming from presenting features and diagnostic algorithms are provided. Aspects of functional assessment, rehabilitation, nutritional management, emerging therapeutics, care coordination, nursing, genetic counseling, prenatal diagnosis and screening also

are addressed. A guideline that will facilitate the appropriate diagnosis, treatment and management of patients with Pompe disease was developed. It will raise awareness of this condition and the presentation of patients across the disease spectrum in order to expedite their diagnosis so they can take advantage of emerging therapeutics such as enzyme replacement therapy (ERT).

GENERAL/BACKGROUND

Pompe disease, also referred to as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid- α -glucosidase (GAA).¹ It was the first recognized lysosomal storage disease and is the only glycogen storage disease that is also a lysosomal storage disease. In Pompe disease, lysosomal glycogen accumulates in many tissues with skeletal, cardiac, and smooth muscle most prominently involved.^{2,3}

All patients with Pompe disease share the same general disease course, namely the steady accumulation of glycogen substrate in target tissues leading to progressive debilitation, organ failure and/or death; resulting in a spectrum of disease severity. Severity varies by age of onset, organ involvement including degree and severity of muscular involvement (skeletal, respiratory, cardiac), and rate of progression. Due to the presence of weakness and hypotonia, it has also been classified as a neuromuscular disease or metabolic myopathy. Great phenotypic variability has led to the creation of types based on the age of onset and degree of organ involvement. These subtypes have been referred to inconsistently in the literature by various terminologies such as infantile, late-infantile, childhood, juvenile, and adult-onset form. Heretofore, we have considered Pompe

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ACMG Practice Guideline

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ACMG Standards and Guidelines

“Lysosomal Storage Diseases: Diagnostic Confirmation and Management of Presymptomatic Individuals” May 2011

- Diagnosis and ascertainment
- Treatment of LSDs
- Newborn screening
- Purpose
- Target audience

Pompe

Fabry

Gaucher

Krabbe

Metachromatic
Leukodystrophy

Niemann Pick
Type A and B

MPS Type I

MPS Type II

MPS Type VI

ACMG STANDARDS AND GUIDELINES

Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals

Raymond Y. Wang, MD¹, Olaf A. Bodamer, MD, PhD², Michael S. Watson, MS, PhD³, and William R. Wilcox, MD, PhD^{4,5}; on behalf of the ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases

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CONSENSUS TREATMENT RECOMMENDATIONS FOR LATE-ONSET POMPE DISEASE

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ON LATE-ONSET POMPE DISEASE

MUSCLE & NERVE March 2012

Table 1. Treatment recommendations for the musculoskeletal element of late-onset Pompe disease.

Provide patient with information on the following resources:

Muscular Dystrophy Association, Acid Maltase Deficiency Association, Pompe Registry, Association for Glycogen Storage Disease, International Pompe Association

Physical examination and assessments

Patients should be examined by a cardiologist and pulmonologist before beginning an exercise program

Screen all patients diagnosed with Pompe disease, regardless of age and wheelchair use, with dual-energy x-ray absorptiometry (DEXA); follow-ups can be considered on a yearly basis

Patients with late-onset Pompe disease and reduced bone density should undergo medical evaluation, including laboratory testing and medication review by an endocrinologist or bone density specialist

Conduct fall risk assessment followed by a formal evaluation for balance and safe gait training for patients at increased risk for osteoporosis and falls

Recommend adaptive equipment, such as a cane or walker, to reduce risk of falls

Physical/occupational therapy

A physical or occupational therapist should develop an exercise program that may include one or more of the following: walking, treadmill, cycling, pool-based program, swimming, submaximal aerobic exercise, or muscle strengthening, that follows the guidelines for other degenerative muscle diseases

Avoid overwork weakness, excessive fatigue, disuse, strenuous exercises, and eccentric contractions

Emphasize submaximal aerobic exercise

Incorporate functional activities when possible

Teach patient to monitor heart rate and breathing in relation to exertion

Integrate energy conservation techniques and biomechanical advantages

A preventive stretching regimen should be started early and performed as part of the daily routine to prevent or slow the development of muscle contractures and deformities

Management of contractures

Manage contractures by using orthotic devices, appropriate seating position in the wheelchair, and standing supports

Surgical intervention

Surgical intervention should be considered for scoliosis when the Cobb angle is between 30° and 40°

Vitamins and mineral supplements

Recommend vitamin D, calcium, and bisphosphonates, following the guidelines for other neuromuscular disorders



Clinical Follow-up Initiatives

- There are ongoing discussions taking place among providers who see Pompe disease NBS referrals
 - NBSTRN sponsored provider calls (began in June, 2016)
 - State-based provider calls
 - Industry-sponsored (e.g. Genzyme) workshops
- The discussions tend to be expert opinion driven and standardized approaches are evolving

From NYS Pompe Disease Guidelines...

long-term follow-up

Table 1. Evaluations for Monitoring of Asymptomatic Patients with Pompe Disease

Evaluation	At diagnosis	As clinically indicated*	If abnormal, consider initiating ERT
Clinical examination with attention to muscle tone	X	X	X
Establish medical home for patient	X		
Determination of CRIM status (via GAA genotype and/or measuring GAA activity in fibroblasts)	X		
Cardiology evaluation <ul style="list-style-type: none"> ECG and 24-hour ECG, If indicated Echocardiogram 	X	X	X
Laboratory studies <ul style="list-style-type: none"> Blood GAA enzyme analysis (skin as needed) GAA gene sequencing Urine Glc₄ CK ALT AST 	X X X X X X	X X X X	X**
Pulmonary evaluation		X	X
Swallow study		X	X
Nutrition/GI evaluation		X	X
Ophthalmology evaluation		X	X
Audiology evaluation	via NBS	X	
Developmental Pediatrics/Early Intervention evaluation		X	X
Bone density		X	
Anesthesiology		X	
Genetic counseling	X	X	

Pompe Disease NBS Clinical Follow-up Registry

- Could help refine existing clinical care guidelines and protocols
 - Optimal surveillance frequency & testing?
 - At what point should treatment be started?
- There are Pompe disease NBS registry efforts underway:
 - NBSTRN and individual states
 - Genzyme

Recent Questions Raised About LOPD Longterm Follow-up (LTFU)

- How frequently should LOPD patients be followed?
- When isolated abnormalities arise, how should they be addressed?
 - Elevations in CK?
 - Complaints of fatigue, weakness, headache, pain
 - Minor – mild findings suggesting cardiac, pulmonary, or muscle involvement
- How much do we know about certain genotypes? E.g., should those who are homozygous for the GAA splicing mutation, “-32-13T>G” have a simpler and less frequent follow-up regimen?

When Public Health Meets Rare Disease Care



Cystic Fibrosis (CF) NBS is frequently cited as the model for improving clinical outcomes following NBS. CF's successes are due to:

- Ongoing evaluation of clinical outcomes using a centralized national registry
- Registry oversight by an advocacy organization committed to quality improvement
- Access to steady sources of funding unheard of in other rare disorders screened in newborns

Pompe disease NBS

Conclusion about LTFU efforts

- Pompe disease NBS LTFU Registries are being developed in pilot-screening states, with NBSTRN and with industry
- There are ongoing efforts to clarify genotype-phenotype correlations using resources like ClinGen and to develop better biomarkers
- The NBSTRN sponsored provider calls are a resource for clinicians grappling with immediate LTFU questions