

Diagnosing Pompe Disease (also known as Acid Maltase Deficiency)

When to Suspect Pompe Disease in Young Children and Adults

Pompe disease is a debilitating and often life-threatening neuromuscular disease characterized by progressive degeneration of skeletal, respiratory and, in infants, cardiac muscle. Early diagnosis and intervention are critical.

- Recognizing Pompe disease can be challenging as signs and symptoms may be heterogeneous and shared with those of other disorders
- Diagnostic delays have been reported to average 7 years in older children and adults¹

Confirming the Diagnosis of Pompe Disease

- Patients suspected to have any of the diseases listed in the table to the right may actually have Pompe disease
- Confirm the diagnosis by ordering a test to measure acid alpha-glucosidase (GAA) enzyme activity (see table on reverse)
- Absence of glycogen accumulation in muscle tissue does not rule out Pompe disease, since glycogen content can vary in muscle tissue¹
- Some individuals with relatively high residual GAA activity may need analysis of the GAA gene to distinguish affected from carrier status²

Measuring GAA Activity

Today, minimally invasive blood tests can accurately quantify GAA activity.

- Early blood tests were prone to error due to activity of an alpha-glucosidase isoenzyme³
- Newer assay methods address the problem by using acarbose to inhibit this alpha-glucosidase isoenzyme⁴⁻⁷
- Now it is possible to accurately measure GAA activity in dried blood spots, mixed leukocytes, and lymphocytes^{2,4-9}
- May save valuable time in patient care and treatment²

Common Differential Diagnoses in Early Childhood Through Adulthood^{2,10-13}

Differential Diagnosis	Shared Signs & Symptoms
Limb girdle muscular dystrophy (LGMD)	Progressive muscle weakness in the pelvis, legs, or shoulders, abnormal gait, elevated creatine kinase (CK)
Becker/Duchenne muscular dystrophy	Progressive proximal muscle weakness, respiratory impairment, difficulty walking, elevated CK
Polymyositis	Progressive, often symmetrical, muscle weakness, difficulty swallowing, elevated CK
Mitochondrial myopathies	Hypotonia, hyporeflexia, hepatomegaly. Some forms with exercise intolerance, muscle weakness, headache, breathlessness, elevated CK
Carnitine deficiency	Muscle weakness in the hips, shoulders, and upper arms and legs
Glycogen storage diseases (GSD) III and IV	Hypotonia, hepatomegaly, muscle weakness, elevated CK
Glycogen storage disease (GSD) V	Elevated CK, muscle cramps during exercise/exercise intolerance
Danon disease	Skeletal muscle myopathy, proximal muscle weakness, scapulo-peroneal muscular weakness, elevated CK
Rheumatoid arthritis	Generalized weakness, stiffness, fatigue, musculoskeletal symptoms
Spinal muscular atrophy	Asymmetrical muscle weakness, atrophy of voluntary muscles, elevated CK
Kennedy's disease	Bulbar muscle dysfunction/difficulty breathing and swallowing, elevated CK
Amyotrophic lateral sclerosis (ALS)	Progressive muscle weakness, respiratory impairment, elevated CK

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In the table below, options to determine GAA activity are listed from least invasive to most invasive (top to bottom).

Options to Determine Acid Alpha-Glucosidase (GAA) Activity			
Sample Type	Procedure for Sample Collection	Turnaround Time for Results*	Utility/Comments
Dried blood spot ^{6-9,14}	Blood draw, heel prick, or finger stick	2-10 days	<ul style="list-style-type: none"> Minimally invasive Rapid turnaround time Blood can be spotted directly on filter paper and shipped to lab easily Assay employed may use acarbose to remove interference by an alpha-glucosidase isoenzyme May preclude the need for more invasive testing (skin or muscle biopsy)
Lymphocytes ⁵	Blood draw	7-10 days	<ul style="list-style-type: none"> Minimally invasive Rapid turnaround time Assay employed may use acarbose to remove interference by an alpha-glucosidase isoenzyme May preclude the need for more invasive testing (skin or muscle biopsy)
Mixed leukocytes ^{4,5}	Blood draw	7-10 days	<ul style="list-style-type: none"> Minimally invasive Rapid turnaround time Assay employed may use acarbose to remove interference by an alpha-glucosidase isoenzyme May preclude the need for more invasive testing (skin or muscle biopsy)
Fibroblasts ^{3,15}	Skin biopsy	4-6 weeks	<ul style="list-style-type: none"> Invasive Commonly used assessment of enzyme activity Requires 4-6 weeks of cell culture Immune-based assay may be used to quantify GAA activity If culture is not successful, results will be delayed
Muscle tissue ^{3,5}	Muscle biopsy	1-4 weeks	<ul style="list-style-type: none"> Invasive and can require general anesthesia GAA activity can be measured directly Must be frozen in liquid nitrogen and shipped on dry ice

*Actual turnaround time will vary, depending on the laboratory.

Contact Genzyme Medical Information at 800-745-4447 (option 2) for more information on testing for Pompe disease or for a directory of laboratories.

References:

1. Winkel LP, Hagemans ML, van Doorn PA, et al. The natural course of non-classic Pompe's disease; a review of 225 published cases. *J Neurol* 2005; 252:875-84. 2. Kishnani PS, Steiner RD, Bali D, et al. Pompe disease diagnosis and management guideline. *Genet Med* 2006; 8:267-88. 3. Hirschhorn R, Reuser AJJ. Glycogen storage disease type II: acid alpha-glucosidase (acid maltase) deficiency. In: Scriver C, Beaudet A, Sly W, et al., eds. *The Metabolic and Molecular Bases of Inherited Disease*. New York: McGraw Hill, 2001:3389-420. 4. Okumiya T, Keulemans JL, Kroos MA, et al. A new diagnostic assay for glycogen storage disease type II in mixed leukocytes. *Mol Genet Metab* 2005; 88:22-8. 5. Jack R, Gordon C, Scott CR, Kishnani PS, Bali D. The use of acarbose inhibition in the measurement of acid alpha-glucosidase activity in blood lymphocytes for the diagnosis of Pompe disease. *Genet Med* 2006; 8:307-12. 6. Li Y, Scott CR, Chamoles NA, et al. Direct multiplex assay of lysosomal enzymes in dried blood spots for newborn screening. *Clin Chem* 2004; 50:1785-96. 7. Zhang H, Kallwass H, Young SP, et al. Comparison of maltose and acarbose as inhibitors of maltase-glucoamylase activity in assaying acid alpha-glucosidase activity in dried blood spots for the diagnosis of infantile Pompe disease. *Genet Med* 2006; 8:302-6. 8. Chamoles NA, Niizawa G, Blanco M, Gaggioli D, Casentini C. Glycogen storage disease type II: enzymatic screening in dried blood spots on filter paper. *Clin Chim Acta* 2004; 347:97-102. 9. Umaphysivam K, Hopwood JJ, Meikle PJ. Determination of acid alpha-glucosidase activity in blood spots as a diagnostic test for Pompe disease. *Clin Chem* 2001; 47:1378-83. 10. Gilbert-Barness E. Review: Metabolic cardiomyopathy and conduction system defects in children. *Ann Clin Lab Sci* 2004; 34:15-34. 11. Roe CR, Ding J. Mitochondrial Fatty Acid Oxidation Disorders. In: Scriver C, Beaudet A, Sly W, Valle D, editors. *The Metabolic and Molecular Bases of Inherited Disease*. New York, New York: McGraw-Hill; 2001. 12. Gilchrist JM. Overview of neuromuscular disorders affecting respiratory function. *Semin Respir Crit Care Med* 2002; 23:191-200. 13. Andres PL, Thibodeau LM, Finison LJ, Munsat TL. Quantitative assessment of neuromuscular deficit in ALS. *Neurol Clin* 1987; 5:125-41. 14. Meikle PJ, Grasby DJ, Dean CJ, et al. Newborn screening for lysosomal storage disorders. *Mol Genet Metab* 2006; 88:307-14. 15. Umaphysivam K, Hopwood J, Meikle P. Correlation of acid alpha-glucosidase and glycogen content in skin fibroblasts with age of onset in Pompe disease. *Clin Chim Acta* 2005; 361:191-98.

Labs Offering Diagnostic Testing for Pompe Disease

also known as Acid Maltase Deficiency and Glycogen Storage Disease Type II (GSD-II)

GAA Enzyme Activity Assay – Blood Tests

Laboratory	Ship-To Address	Contact Person
The Buffalo General Hospital www.rgbmgl.org	Robert Guthrie Biochemical Genetics Laboratory Room A-762, 100 High Street Buffalo, NY 14203	Georgirene D. Vladutiu PhD, Director 716-859-7741 Email: mitomaven@aol.com
Duke University Medical Center http://medgenetics.pediatrics.duke.edu	Glycogen Storage Disease Laboratory Biochemical Genetics Laboratory Pediatrics, Medical Genetics Duke University Medical Center 801, Suite - 6, Capitola Drive Durham, NC 27713	Deeksha Bali, PhD, FACMG 919-684-0025 Email: bali0001@mc.duke.edu or Sarah Young, PhD, FACMG 919-549-0445 ext.117 Email: young116@duke.edu
Emory University, Department of Human Genetics www.geneticslab.emory.edu	Emory Molecular Genetics Laboratory 2165 N. Decatur Road Decatur, GA 30033	Ymkje Cuperus, MS, GC 404-778-8550 Email: icuperu@emory.edu
Genzyme Genetics www.genzymegenetics.com	Genzyme Genetics 2000 Vivigen Way Santa Fe, NM 87505	Client Services 800-848-4436
Seattle Children's Hospital www.seattlechildrens.org/geneticslab	Seattle Children's Hospital Laboratory A6901 Attn: Rhona Jack, PhD 4800 Sand Point Way NE Seattle, WA 98105	Rhona Jack, PhD 206-987-2216 Email: rhona.jack@seattlechildrens.org

GAA Enzyme Activity Assay – Skin Biopsy

Laboratory	Ship-To Address	Contact Person
Duke University Medical Center http://medgenetics.pediatrics.duke.edu	Glycogen Storage Disease Laboratory Biochemical Genetics Laboratory Pediatrics, Medical Genetics Duke University Medical Center 801, Suite - 6, Capitola Drive Durham, NC 27713	Deeksha Bali, PhD, FACMG 919-684-0025 Email: bali0001@mc.duke.edu or Denise Peterson 919-684-2722 Email: pet01@duke.edu
Mayo Clinic www.mayomedicallaboratories.com/test-info/biochemical/index.html	Mayo Medical Laboratories 3050 Superior Drive NW Rochester, MN 55901-1995	Biochemical Genetics Laboratory Genetic Counselor on Call 800-533-1710 Email: biochemicalgenetics@mayo.edu
Seattle Children's Hospital www.seattlechildrens.org/geneticslab	Seattle Children's Hospital Laboratory A6901 Attn: Rhona Jack, PhD 4800 Sand Point Way NE Seattle, WA 98105	Rhona Jack, PhD 206-987-2216 Email: rhona.jack@seattlechildrens.org
University of Alabama at Birmingham	Metabolic Disease Laboratory University of Alabama at Birmingham 648 Kaul Building 720 20th St. South Birmingham, AL 35233	Paula Huffman, BS 205-934-6370 Email: phuffman@genetics.uab.edu

Contact the laboratories listed above for information on obtaining test requisitions, sample requirements, and turnaround time.

For additional information about laboratories that offer diagnostic testing for Pompe Disease, visit www.genetests.org

This listing includes only laboratories that have agreed to be listed by Genzyme and is not intended to be exhaustive. It is for informational purposes only, and no endorsement of or representations regarding the services offered are either intended or implied. Please note that, while Genzyme has endeavored to obtain information that is current as of the time of publication, it makes no representations as to accuracy, and physicians are directed to the individual laboratories for the specific details of the services provided.



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GAA Enzyme Activity Assay – Muscle Biopsy

Laboratory	Ship-To Address	Contact Person
Athena Diagnostics www.athenadiagnostics.com	Athena Diagnostics, Inc. 377 Plantation Street Worcester, MA 01605	Sat Dev Batish, PhD, FACMG Phone 508-756-2886 ext 3222 Fax 508-753-5601 Email: dev.batish@athenadiagnostics.com
The Buffalo General Hospital www.rgbmgl.org	Robert Guthrie Biochemical Genetics Laboratory Room A-762, 100 High Street Buffalo, NY 14203	Georgirene D. Vladutiu PhD, Director 716-859-7741 Email: mitomaven@aol.com
Duke University Medical Center http://medgenetics.pediatrics.duke.edu	Glycogen Storage Disease Laboratory Biochemical Genetics Laboratory Pediatrics, Medical Genetics Duke University Medical Center 801, Suite - 6, Capitola Drive Durham, NC 27713	Deeksha Bali, PhD, FACMG 919-684-0025 Email: bali0001@mc.duke.edu or Denise Peterson 919-684-2722 Email: pet01@duke.edu

GAA Enzyme Activity Assay – Prenatal Screening

Laboratory	Ship-To Address	Contact Person
Duke University Medical Center http://medgenetics.pediatrics.duke.edu	Glycogen Storage Disease Laboratory Biochemical Genetics Laboratory Pediatrics, Medical Genetics Duke University Medical Center 801, Suite - 6, Capitola Drive Durham, NC 27713	Deeksha Bali, PhD, FACMG 919-684-0025 Email: bali0001@mc.duke.edu or Denise Peterson 919-684-2722 Email: pet01@duke.edu

DNA Analysis

Laboratory	Ship-To Address	Contact Person
Cincinnati Children's Hospital www.cincinnatichildrens.org	Molecular Genetics Laboratory 3333 Burnet Avenue R-1042 Cincinnati, OH 45229	Laurie Bailey, CGC 513-636-4474 Email: laurie.bailey@cchmc.org
Duke University Medical Center http://medgenetics.pediatrics.duke.edu	Glycogen Storage Disease Laboratory Biochemical Genetics Laboratory Pediatrics, Medical Genetics Duke University Medical Center 801, Suite - 6, Capitola Drive Durham, NC 27713	Deeksha Bali, PhD, FACMG 919-684-0025 Email: bali0001@mc.duke.edu or Gwen Harmon Dickerson, FCMG 919-684-0338 Email: gharmon@duke.edu or Catherine Rehder, PhD, FACMG 919-613-8434 email: catherine.rehder@duke.edu
Emory University, Department of Human Genetics www.geneticslab.emory.edu	Emory Molecular Genetics Laboratory 2165 N. Decatur Road Decatur, GA 30033	Ymkje Cuperus, MS, GC 404-778-8550 Email: icuperu@emory.edu
Genzyme Genetics www.genzymegenetics.com	Genzyme Genetics 2000 Vivigen Way Santa Fe, NM 87505	Client Services 800-848-4436
Prevention Genetics www.preventiongenetics.com	Prevention Genetics LLC Attn: Diagnostics Lab 3700 Downwind Drive Marshfield, WI 54449	James Weber, PhD 715-387-0484 Email: jim.weber@preventiongenetics.com
Seattle Children's Hospital www.seattlechildrens.org/geneticslab	Seattle Children's Hospital Laboratory A6901 Attn: Rhona Jack, PhD 4800 Sand Point Way NE Seattle, WA 98105	Lisa Sniderman-King, M.Sc., CGC (206) 987-1406 Email: lisa.sniderman-king@seattlechildrens.org

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