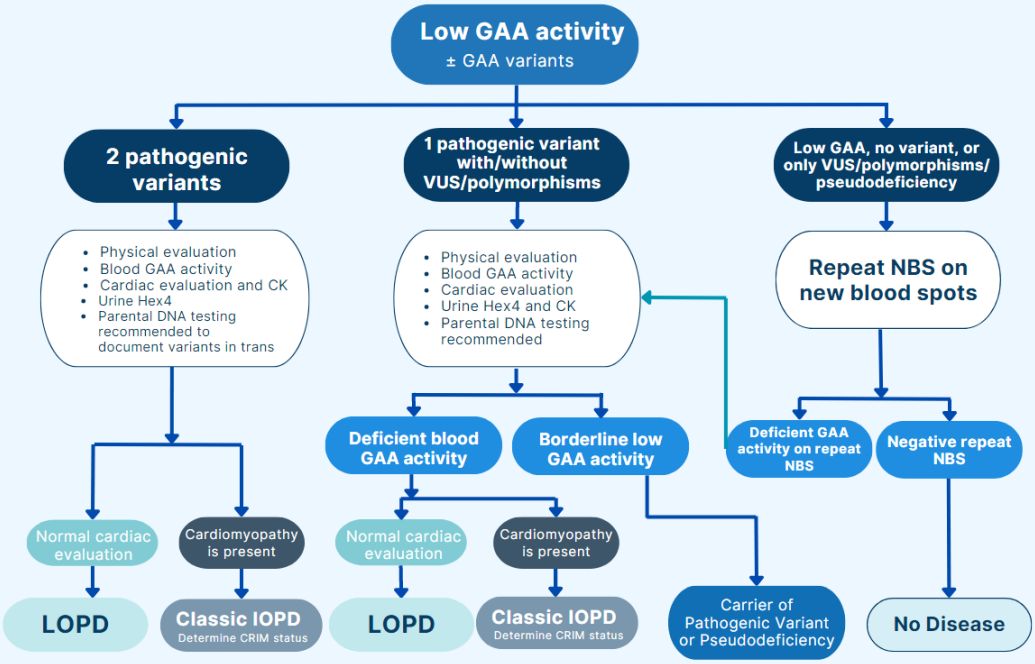
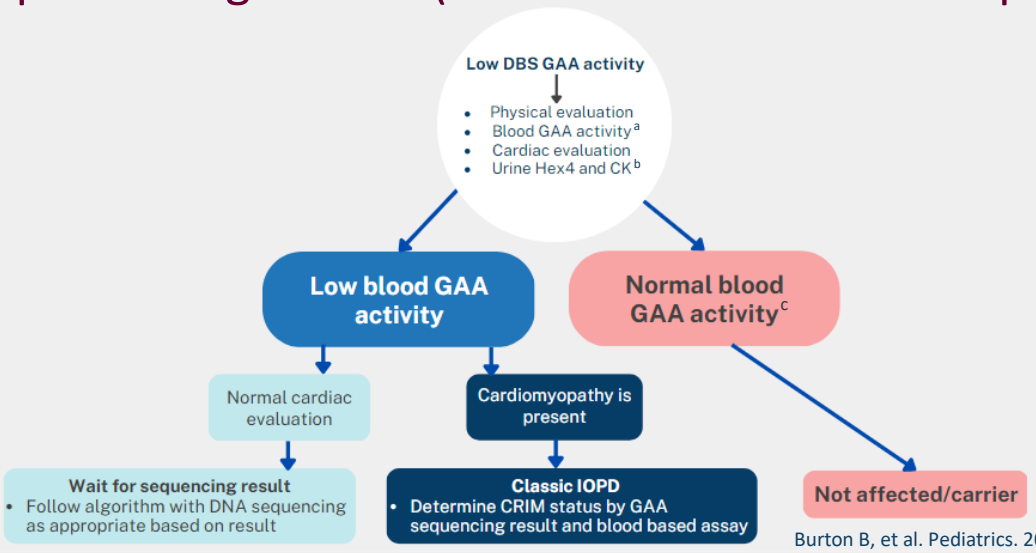
Pompe Disease Newborn Screening: Algorithms and Minimum Evaluation Schedule from Peer-Reviewed Literature

Pompe disease - Pompe disease is a lysosomal storage disease caused by deficiency of acid α-glucosidase. Individuals with Pompe disease have pathogenic variants in the *GAA* gene which codes for production of acid α-glucosidase, which typically degrades glycogen in cardiac, skeletal, and smooth muscle. Pompe disease is heterogenous with 2 subtypes – **Infantile-onset Pompe Disease (IOPD)** which presents within the first year of life with cardiomyopathy, and **Late-onset Pompe Disease (LOPD)** which presents without cardiomyopathy at any age.

Pompe NBS Algorithms (Protocol with DNA sequencing)



Pompe NBS Algorithms (Protocol without DNA sequencing)



Burton B, et al. Pediatrics. 2017 Jul; 140 Suppl 1:S14

a. Blood-based assays include DBSs, purified lymphocytes, and mixed leukocyte assay methods
b. Obtain as a baseline, can also be postponed until a definitive diagnosis is obtained
c. Need to ensure assay is being done in a laboratory with appropriate enzyme assay experience and capabilities and that the patient has not received a blood transfusion or other interventions that would result in normal GAA enzyme levels

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Infantile-Onset Pompe Disease Recommended Minimum Evaluation Schedule

The listed recommendations were obtained from peer reviewed publications cited below. Physicians and health care providers will determine the assessments and their actual frequency according to the patient's individual needs.

	Assessment Timepoint & Frequency				
	Initial newborn referral	2-4 weeks of age	Monthly to 4 months of age	Every 2 months (4–12 months of age)	Every 3–6 months (>12 months of age)[a]
Demographics	✓	-	-	-	-
Diagnosis (GAA and Variants)	✓	-	-	-	-
CRIM Status[b]	✓	-	-	-	-
Medical history	✓	✓	✓	✓	✓
Clinical follow-up	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓
Height, weight, head circumference, BMI	✓	✓	✓	✓	✓
CK/CK-MB, HCO_3	✓	✓	✓	✓	✓
Urine Hex_4	✓	✓	✓	✓	✓
Chest radiographs	✓	-	-	-	-
ECG (PR, QRS, QTc, WPW)	✓	✓	✓	✓	✓
ECHO (LVMI, EF, SF)	✓	✓	✓	✓	✓
Audiology	✓(BAER)	-	-	✓	✓
Developmental assessments[c]	✓	-	✓	✓	✓
Video fluoroscopic swallow study	✓	-	✓a	✓a	✓a
Pulmonary evaluation	✓	-	✓a	✓a	✓a
Motor status	✓	-	-	-	✓
Early intervention	-	-	-	✓	-
Cardiac evaluation	✓	✓	✓	✓	✓

A change in clinical status may indicate a need for additional intervention. regimen, including ALT, AST, and complete blood count, should be done. BAER, brainstem auditory-evoked response; CK-MB, CK myocardial band; ECG, electrocardiogram; EF, ejection fraction; LVMI, left ventricular mass index; SF, shortening fraction; WPW, Wolff–Parkinson–White. [a]As clinically indicated. [b]Varies with patient's genotype. [c]Denver; Bailey; TIMP; AIMS; Gross Motor Function Measure-88; CHOP INTEND. Videotaping can be done and used to assess patients.

Kronn D, et al. Pediatrics. 2017 Jul; 140 Suppl 1:S24-S45

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Late-Onset Pompe Disease Recommended Minimum Evaluation Schedule

The listed recommendations were obtained from peer reviewed publications cited below. Physicians and health care providers will determine the assessments and their actual frequency according to the patient's individual needs.

	Symptomatic Late-onset Pompe Disease					Asymptomatic Late-onset Pompe Disease							
	Assessment Timepoint & Frequency					Assessment Timepoint & Frequency							
						Age in months							
	Initial newborn referral	1 month	Monthly to 4 months	Every 3 months (4-12 months of age)	Every 3-6 months [a] (>12 months of age)	Initial newborn referral	1	3	6	9[a]	12	Every 3-12 months[b] (1-3 years of age)	Annually[e] (after 3 years of age)
Demographics	✓	-	-	-	-	✓	-	-	-	-	-	-	-
Diagnosis (GAA and variants)	✓	-	-	-	-	✓	-	-	-	-	-	-	-
Medical history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Feeding/swallowing						-	-	-	-	-	✓	✓	✓
Clinical follow-up	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height, weight, head circumference, BMI	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CK/CK-MB, HCO_3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine Hex_4	✓	✓	✓	✓	✓	✓	✓[f]	✓	✓	✓[f]	✓	✓	✓
Chest radiograph	✓	-	-	-	✓	✓	-	-	-	-	-	-	-
ECG	✓	✓	✓[b]	✓[b]	✓	✓	✓[a]	✓[a]	✓[a]	-	✓	✓[a]	✓
ECHO[c]	✓	-	✓[b]	✓[b]	✓	✓	-	✓[a]	✓[a]	-	✓	✓[a]	✓
Audiology	✓ (BAER)	-	-	-	✓	✓ (BAER)	-	-	-	-	✓	✓	✓
Developmental assessments[d]	✓	-	-	-	✓	✓	✓	✓	✓	✓	✓	✓	✓
Whole-body MRI/ultrasound	-	-	✓[b]	✓[b]	✓[b]								
Swallow study	-	-	✓[b]	✓[b]	✓								
Pulmonary evaluation	-	-	✓[b]	✓[b]	✓								
Motor Status	-	-	-	-	✓								
Early intervention	-	-	-	✓[b]	✓								
Cardiac evaluation[c]	-	-	✓[b]	✓[b]	✓								

Initial assessments as for asymptomatic Pompe patients. BAER, brainstem auditory evoked response; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram. [a]Varies with patient's genotype. [b]As clinically indicated. [c]For patients with IVS splice site variant in heterozygosity, an initial ECHO cardiogram and follow-up at 6 months of age are recommended. If normal, the frequency of ECHO evaluations can be reduced and eliminated after 6 months for patients with the IVS splice site variant in heterozygosity because the variant may be cardioprotective. [d]Denver; Bailey; TIMP; CHOP INTEND; AIMS; Gross Motor Function Measure-88. Videotaping can be done and used to assess patients.

Any change in status may indicate a need for additional evaluation. BAER, brainstem auditory evoked response; ECG, electrocardiogram. [e]For milder genotypes. [f]If CK levels are elevated at these assessment time points.

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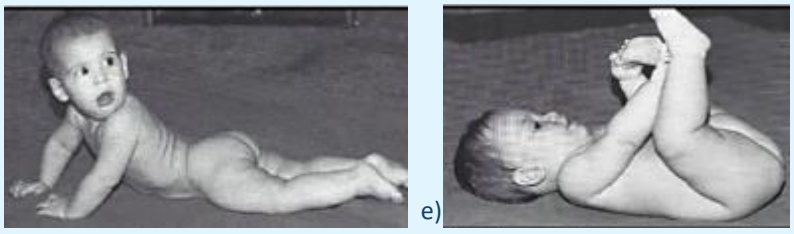
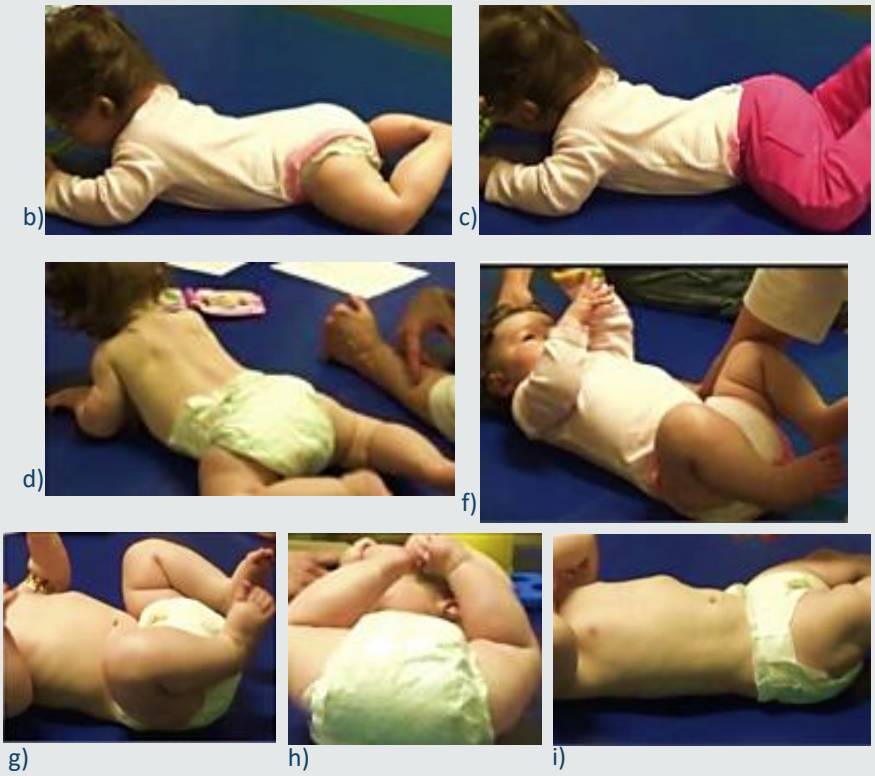
Postural Tendencies in LOPD Diagnosed by Newborn Screening[1]

6 months old typical function

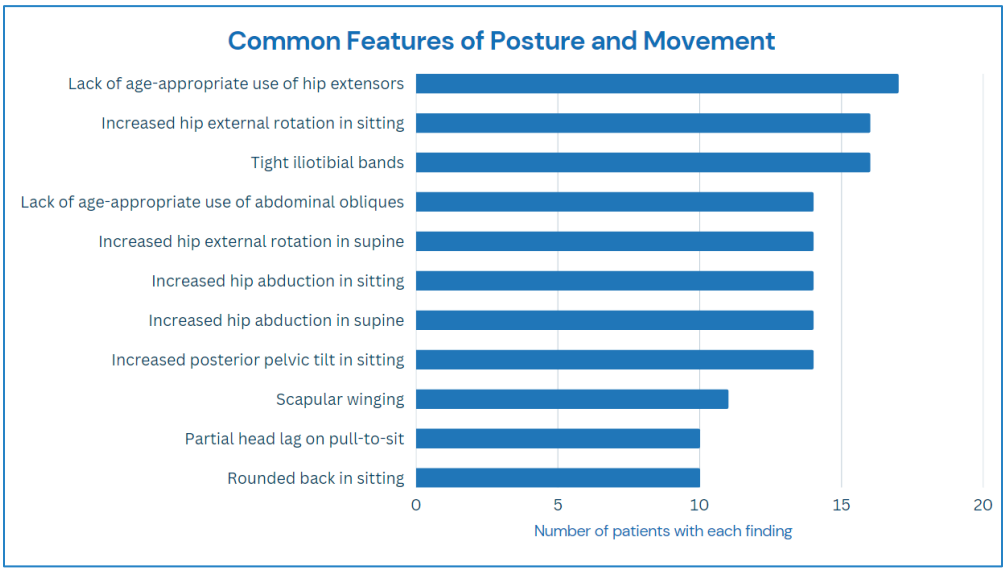


6-month-old infant with c.-32-13T>G "late-onset" GAA variant



Prone	
Typical Function[a]	• Active hip extension & adduction • Shoulder girdle stability & depression • Humeral adduction • Upper Extremity weight bearing with elbow extension • Balanced neck flexion/extension • Abdominal muscle activity
LOPD Function[b, c, d]	• Excessive hip flexion, abduction, external rotation • Excessive lumbar vs thoracic extension • Increased hip and knee flexion with increased activity • Decreased hip extension, adduction, internal rotation • Decreased shoulder girdle depression • Lack of upper extremity weight-bearing with elbows placed under shoulders. • Can maintain propping but with scapular winging and lack of shoulder girdle stability
Supine	
Typical Function[e]	• Use of abdominals for pelvic lifting • Hip flexion with emerging knee extension • Reaching with elbow extension
LOPD Function[f, g, h]	• Less use of abdominals, including abdominal obliques • Greater hip abduction and external rotation • Less pelvic lifting • Less use of adductors • Greater knee flexion • Less active knee extension • Lower rib flaring[i] • Iliotibial band tightness[i]

Postural Tendencies in LOPD Diagnosed by Newborn Screening[2]



Kinematic analysis of 20 infants with LOPD identified on NBS showed 11 gross motor findings that were present in at least 50% of all patients

Alberta Infant Motor Scale testing was completed in 18/20 patients and revealed a wide range of scores

1. Rairikar MV et al. Mol Genet Metab. 2017; 122(3):99-107
2. Huggins E et al. Mol Genet Metab. 2022 Mar;135(3):179-185

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