Developing a Follow-up Framework for Pompe Disease

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Outline

- Review of Pompe disease
- Newborn screening for Pompe
- New York State (NYS) method
- Follow-up preparations
  - Diagnostic algorithm
  - Management recommendations/considerations
  - Case definitions

Pompe Review

- Pompe disease is a lysosomal storage disorder
- Caused by mutations in the *GAA* gene, which codes for the alpha-glucosidase (GAA) enzyme
- AKAs: Glycogen storage disorder type II, Acid Maltase Deficiency, Acid Alpha-glucosidase deficiency
- Autosomal recessive
- Incidence: ~ 1 in 17,000 births, panethnic

Pompe Review

- Two phenotypic sub-types:
  - Early-onset: results from complete or near absence of GAA enzyme
    - Symptoms begin at birth or shortly thereafter
    - Symptoms: hypotonia, hypertrophic cardiomyopathy, failure to thrive, and respiratory insufficiency
  - Late-onset: results from partial deficiency of GAA enzyme
    - Age of onset if variable from first few months of life to adulthood
    - Symptoms: slowly progressive myopathy primarily involving skeletal muscle
    - Usually no cardiac involvement with this form

Pompe Review

- Treatment is enzyme replacement therapy (ERT)
  - Myozyme or Lumizyme
  - Improved survival and function
- CRIM status is important consideration
  - Cross Reactive Immunologic Material
  - It is the endogenous GAA enzyme produced by most Pompe patients
  - CRIM negative = no residual GAA activity
    - 20% of patients
    - They produce anti-rhGAA antibodies and do not respond to ERT unless immune tolerance induction is done prior to or concurrent with ERT
  - CRIM positive = GAA enzyme activity > 1%
    - These patients usually do not produce anti-rhGAA antibodies and have better response to ERT

Newborn Screening For Pompe Disease

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Discretionary Advisory Committee on
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June 3, 2013

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, DC 20201

Dear Secretary Sebelius:

The Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (the Committee) is charged with making systematic evidence-based and peer-reviewed recommendations that include heritable disorders that have the potential to significantly impact public health for which all newborns should be screened. During the Committee's May 2013 meeting, the Committee reviewed the objective evidence report for the nominated heritable disorder –Pompe disease (also known as glycogen storage disease type II or acid maltase deficiency). Based on this report which included a public health impact assessment and Committee deliberations, the Committee voted to recommend that you update and expand the Recommended Uniform Screening Panel (RUSP) to include the addition of Pompe Disease.

NYS Method of Screening for Pompe

- 1st tier: measure GAA enzyme activity via MS/MS
- 2nd tier: sequencing of *GAA* gene

Follow-up Preparations

- New York-Mid-Atlantic Consortium for Genetic and Newborn Screening Services (NYMAC) sponsored a Pompe disease symposium November 1-2, 2013 in Valhalla, NY

- Attendees included metabolic geneticists from mid-Atlantic region, genetic counselors, and newborn screening personnel from several states, as well as an expert on Pompe disease, Dr. Priya Kishnani from Duke University

Follow-up Preparations

1. Preliminary diagnostic algorithms and management recommendations were created by NBS staff prior to NYMAC Pompe symposium
2. These were reviewed with the group at the meeting
3. They were revised using the group's feedback
4. Revised versions were sent to the attendees after the meeting via email for additional feedback
5. The documents were revised again
6. One final review with Dr. Priya Kishnani and Dr. David Kronn
7. Final edits made

Diagnostic Algorithm

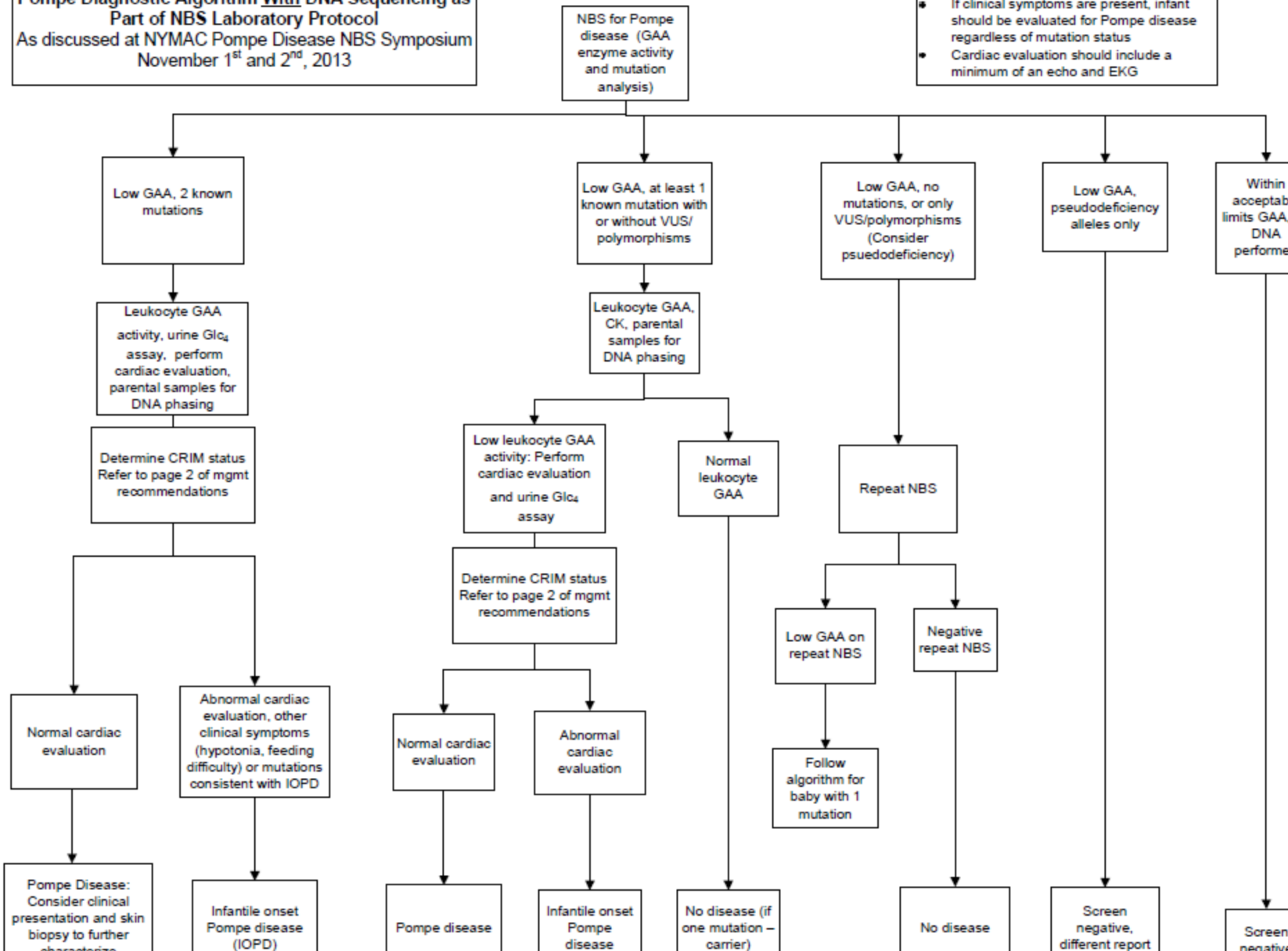
- Goals of the algorithm:
  - To answer the question, does this baby have Pompe disease?
  - To recommend the minimum lab work and evaluations necessary in order to answer that question

Pompe Diagnostic Algorithm With DNA Sequencing as Part of NBS Laboratory Protocol

As discussed at NYMAC Pompe Disease NBS Symposium November 1st and 2nd, 2013

Special considerations:

- If clinical symptoms are present, infant should be evaluated for Pompe disease regardless of mutation status
- Cardiac evaluation should include a minimum of an echo and EKG



Management Protocols

- Goals of the recommendations:
  - To provide medical management recommendations for infants and children with Pompe disease identified on newborn screening
    - These are intended to cover what is minimally needed, and are not a substitute for good clinical judgment
    - The most recent published guidelines were from 2006 when the diagnosis most often occurred because an infant or child was symptomatic, and when ERT was still considered an emerging treatment (Kishnani PS, Steiner RD, Bali D et al. (2006))
  - To ensure that recommended tests and evaluations are feasible

Management Protocols

- Recommendations for Determining Cross Reactive Immunologic Material (CRIM) Status
- Recommendations & Considerations for Initiating ERT
- Table 1. Evaluations for Monitoring of Asymptomatic Patients with Pompe Disease
- Table 2. Evaluations for Monitoring of Symptomatic Individuals with Pompe Disease

EXAMPLE: Recommended Evaluations for Monitoring of Asymptomatic Patients with Pompe Disease

Table 1. The following are evaluations for consideration when providing medical care for asymptomatic individuals (no cardiac involvement or other signs/symptoms at birth) with Pompe disease identified on NBS:

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 • ECG and 24-hour ECG, If indicated • Echocardiogram	X	X	X
Laboratory studies • Blood GAA enzyme analysis (skin as needed) • *GAA* gene sequencing • Urine Glc_4 • 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	

Case Definitions

Pompe Disease Newborn Screening Case Definitions

Pompe Disease (aka Acid Alpha-Glucosidase Deficiency)	Category	Mutation Status	GAA Enzyme Activity	Cardiac Involvement	Clinical Symptoms/Lab Findings	CRIM Status	Diagnosis Code
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	Yes	Present	Negative	POMP10
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	Yes	Present	Positive	POMP11
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	Yes	Not present	Negative	POMP12
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	Yes	Not present	Positive	POMP13
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	No	Present	Negative	POMP14
	Definite, early-onset Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	No	Present	Positive	POMP15
	Definite, Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	No	Not present	Negative	POMP16
	Definite, Pompe disease	2 disease-causing mutations or positive skin or muscle bx	Low	No	Not present	Positive	POMP17
	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	Yes	Present	Negative	POMP18
	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	Yes	Present	Positive	POMP19

	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	Yes	Not present	Negative	POMP20
	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	Yes	Not present	Positive	POMP21
	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	No	Present	Negative	POMP22
	Definite, early-onset Pompe disease	1 disease-causing mutation*	Low	No	Present	Positive	POMP23
	Possible disease	1 disease-causing mutation*	Low	No	Not present	N/A	POMP30
	Possible disease	≥ 1 VUS	Low	No	Not present	N/A	POMP31
	No disease	No disease-causing mutations	Normal	No	Not present	N/A	POMP40
	No disease	1 or 2 pseudodeficiency alleles only (no mutation)	Low	No	Not present	N/A	POMP41
	No disease	1 disease-causing mutation	Normal	No	Not present	N/A	POMP42
	No disease	Polymorphisms only (no mutations)	Normal	No	Not present	N/A	POMP49

* With or without variants of uncertain significance (VUS) or pseudodeficiency allele.

Questions?

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