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

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

Low GAA, 2 known mutations

Leukocyte GAA activity, urine Glic4 assay, perform cardiac evaluation, parental samples for DNA phasing

Determine CRIM status Refer to page 2 of mgmt recommendations

Normal cardiac evaluation

Pompe Disease: Consider clinical presentation and skin biopsy to further characterize

Abnormal cardiac evaluation, other clinical symptoms (hypotonia, feeding difficulty) or mutations consistent with IOPD

Infantile onset Pompe disease (IOPD)

Low GAA, at least 1 known mutation with or without VUS/polymerisms

Leukocyte GAA, CK, parental samples for DNA phasing

Determine CRIM status Refer to page 2 of mgmt recommendations

Low leukocyte GAA activity: Perform cardiac evaluation and urine Glic4 assay

Normal cardiac evaluation

Pompe disease

Infantile onset Pompe disease

No disease (if one mutation – carrier)

No disease

Screen negative, different report

Screen negative
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>
<thead>
<tr>
<th>Evaluation</th>
<th>At diagnosis</th>
<th>As clinically indicated*</th>
<th>If abnormal, consider initiating ERT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical examination with attention to muscle tone</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Establish medical home for patient</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Determination of CRIM status (via GAA genotype and/or measuring GAA activity in fibroblasts)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiology evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>• ECG and 24-hour ECG, If indicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Blood GAA enzyme analysis (skin as needed)</td>
<td>X</td>
<td>X</td>
<td>X**</td>
</tr>
<tr>
<td>• GAA gene sequencing</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>• Urine Glc₄</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>• CK</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>• ALT</td>
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<td>• AST</td>
<td>X</td>
<td></td>
<td></td>
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<td>Pulmonary evaluation</td>
<td>X</td>
<td>X</td>
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<td>Swallow study</td>
<td>X</td>
<td>X</td>
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<td>Nutrition/GI evaluation</td>
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<td>X</td>
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<tr>
<td>Ophthalmology evaluation</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Audiology evaluation</td>
<td>via NBS</td>
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<tr>
<td>Developmental Pediatrics/Early Intervention evaluation</td>
<td>X</td>
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<td>Bone density</td>
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<td>Anesthesiology</td>
<td>X</td>
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<td>Genetic counseling</td>
<td>X</td>
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CASE DEFINITIONS
<table>
<thead>
<tr>
<th>Category</th>
<th>Mutation Status</th>
<th>GAA Enzyme Activity</th>
<th>Cardiac Involvement</th>
<th>Clinical Symptoms/Lab Findings</th>
<th>CRIM Status</th>
<th>Diagnosis Code</th>
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<tbody>
<tr>
<td>Definite, early-onset Pompe disease</td>
<td>2 disease-causing mutations or positive skin or muscle bx</td>
<td>Low</td>
<td>Yes</td>
<td>Present</td>
<td>Negative</td>
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<td>2 disease-causing mutations or positive skin or muscle bx</td>
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<td>Positive</td>
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<td>Yes</td>
<td>Not present</td>
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<td>Yes</td>
<td>Not present</td>
<td>Positive</td>
<td>POMP13</td>
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<td>2 disease-causing mutations or positive skin or muscle bx</td>
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<td>No</td>
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<td>Negative</td>
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<td>No</td>
<td>Present</td>
<td>Positive</td>
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<td>Negative</td>
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<td>Not present</td>
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<td>Negative</td>
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<td>1 disease-causing mutation*</td>
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<td>Positive</td>
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<td>Diagnosis</td>
<td>Mutation Type</td>
<td>Activity</td>
<td>Presence</td>
<td>Status</td>
<td>Panel ID</td>
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<td>----------------------------------------</td>
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<tr>
<td>Definite, early-onset Pompe disease</td>
<td>1 disease-causing mutation*</td>
<td>Low</td>
<td>Yes</td>
<td>Not present</td>
<td>Negative</td>
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<td>1 disease-causing mutation*</td>
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<td>Yes</td>
<td>Not present</td>
<td>Positive</td>
<td>POMP21</td>
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<td>1 disease-causing mutation*</td>
<td>Low</td>
<td>No</td>
<td>Present</td>
<td>Negative</td>
<td>POMP22</td>
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<td>Definite, early-onset Pompe disease</td>
<td>1 disease-causing mutation*</td>
<td>Low</td>
<td>No</td>
<td>Present</td>
<td>Positive</td>
<td>POMP23</td>
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<tr>
<td>Possible disease</td>
<td>1 disease-causing mutation*</td>
<td>Low</td>
<td>No</td>
<td>Not present</td>
<td>N/A</td>
<td>POMP30</td>
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<tr>
<td>Possible disease</td>
<td>≥ 1 VUS</td>
<td>Low</td>
<td>No</td>
<td>Not present</td>
<td>N/A</td>
<td>POMP31</td>
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<td>No disease</td>
<td>No disease-causing mutations</td>
<td>Normal</td>
<td>No</td>
<td>Not present</td>
<td>N/A</td>
<td>POMP40</td>
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<tr>
<td>No disease</td>
<td>1 or 2 pseudodeficiency alleles only (no mutation)</td>
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<td>No</td>
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<td>N/A</td>
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</table>

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

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