Duke Clinical Research Institute

Newborn Screening for Pompe Disease: Condition Review Update

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September 13, 2012

Condition Review Workgroup (2012 – 2013)

Members	Institution
Alex R. Kemper, MD, MPH, MS (*Chair*)	Duke University
Anne M. Comeau, PhD	New England NBS Prog /UMass Med School
Aaron Goldenberg, PhD	Case Western Reserve
Nancy S. Green, MD	Columbia University
Scott D. Gross, PhD	Centers for Disease Control and Prevention
Lisa A. Prosser, PhD	University of Michigan
K.K. Lam, PhD (*Project Leader*)	Duke University
Advisory Committee Representatives	
Charles Homer, MD, MPH	Nat'l Initiative for Children's Healthcare Quality
Andrea M. Williams, BA	The Children's Sickle Cell Foundation

Pompe Evidence Review

- Technical Expert Panel Teleconferences (2)
- Developed Scope of Review
  - *Case Definition*
  - *Newborn Screening & Diagnosis Procedures*
  - *Key Questions*
  - *Key Sources of Information*
- Drafted Preliminary Evidence Review Protocol
- Initial Literature Search (PubMed, EMBASE)

Condition Review: Pompe Disease

Pompe NBS - Technical Expert Panel				
Member	**Institution**	**Expertise**	**TEP1**	**TEP2**
Olaf A. Bodamer, MD, PhD, FAAP, FACMG	University of Miami Miller School of Medicine	Biochemical Geneticist; Pilot NBS Program-Austria	√	
Barry J. Byrne, MD, PhD	University of Florida	Clinician-Researcher		√
Sharon L. Kardia, PhD	University of Michigan School of Public Health	Genetic Epidemiologist	√	
***Priya Kishnani,** MD, MBBS	Duke University Medical Center	Clinician-Researcher; **Nominator*	√	√
Muhammad Ali Pervaiz, MD, FACP, FACMG	Emory University School of Medicine	Clinician		√
C. Ronald Scott, MD	University of Washington	Biochemical Geneticist; State NBS Advisor; Multiplex TMS	√	

Technical Expert Panel Teleconferences

TEP 1 (July 10, 2012)

Aims:

- Develop case definition
- Refine key questions
- Identify key sources of information

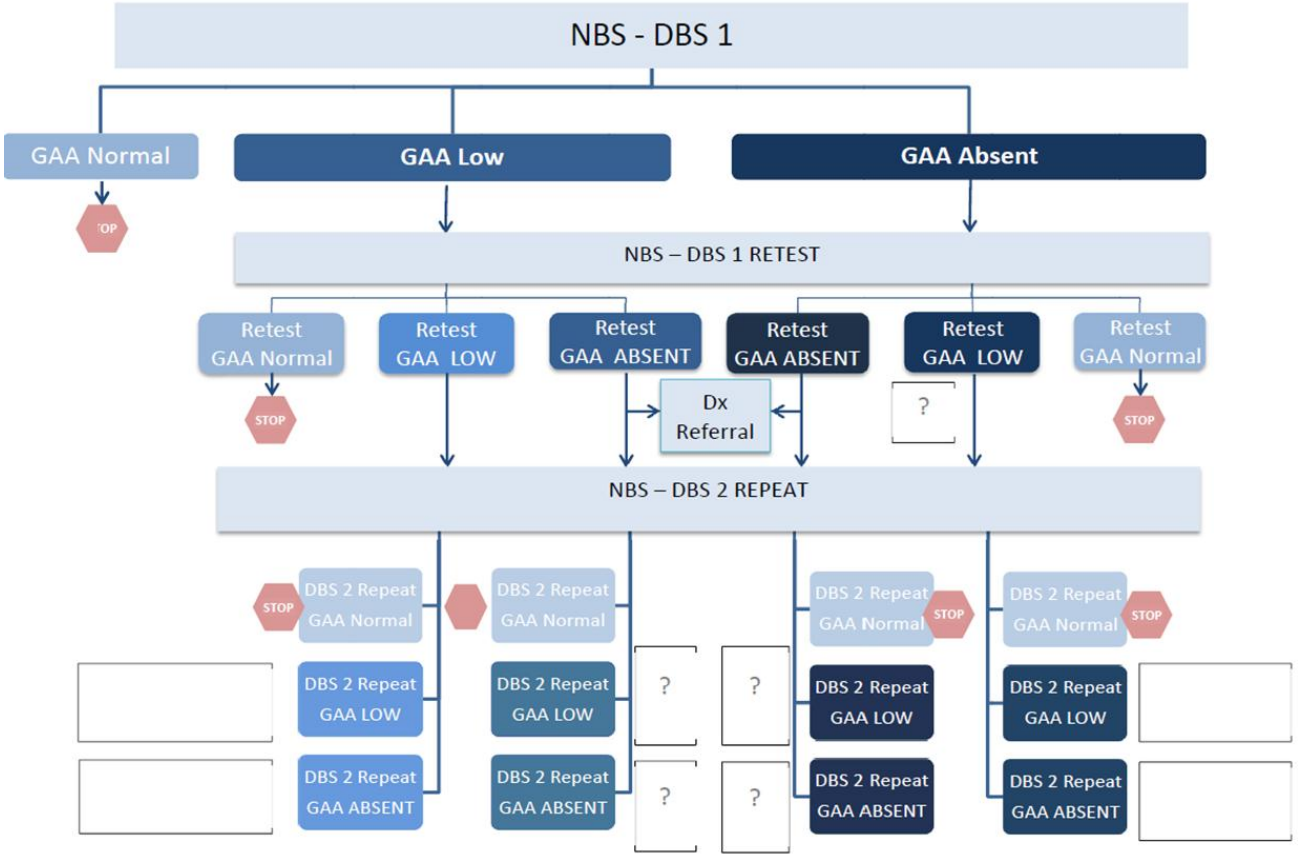
TEP 2 (July 25, 2012)

Aims:

- Delineate standard care screening, diagnosis process
- Review decision-making practices regarding treatment initiation
- Describe process and timing of immune therapy relative to ERT

Findings from TEP Calls

- Variability in approaches to screening.



Findings from TEP Calls

- Treatment Initiation
  - *Treatment can be started for those with very low GAA levels pending genetic confirmation*
  - *Genotyping can inform whether CRIM status will affect treatment response*
  - *Immunomodulation may begin after more certainty regarding CRIM status*
  - *CRIM + individuals can develop antibodies*

Findings from TEP calls

- No standard protocol for the management of those with later-onset Pompe disease.

Scope of Review

- Case Definition
- Screening and Diagnostic Procedures
- Key Questions
- Other Relevant Sources of Information

Pompe Disease: Case Definition

- Infantile form:
  - *Classic: rapidly progressive disease characterized by prominent cardiomegaly, hepatomegaly, weakness and hypotonia, and death due to cardiorespiratory failure usually in the first year of life*
  - *Nonclassic: slower progression and significantly less severe cardiomyopathy than the classic form.*
- Later-onset form exists on a wide spectrum
  - *childhood, juvenile, or muscular variant: presents after infancy, and typically does not include cardiomyopathy.*
  - *adult-onset form: slowly progressive myopathy predominantly involving skeletal and respiratory muscle that can present as late as the second to sixth decade of life.*

Key Questions

1. What factors present in newborns affect the age of onset or disease course of individuals with Pompe disease?
2. What is the direct evidence from the pilot newborn screening studies that screening for Pompe disease reduces morbidity or mortality? How does this vary by form of Pompe disease? Are there factors (e.g., CRIM status) that modify outcomes?

Key Questions

3. What is the analytic validity and clinical utility of the screening approaches used in the pilot studies to diagnose Pompe disease? Does screening distinguish the different forms? What diagnostic testing methods are available? Can diagnostic testing differentiate between the forms of Pompe disease in a timely manner?

Key Questions

4. What are the most important intermediate outcomes related to treatment of Pompe disease? Does early initiation of enzyme replacement make a difference in intermediate health outcomes when the condition is caught early or through screening? Do follow-up protocols exist for the management of Pompe disease that does not require immediate initiation of enzyme replacement therapy? What is known about the effectiveness of follow-up protocols? Are their factors that modify the effect of treatment (e.g., CRIM status)?

Key Questions

5. What are the most important health outcomes related to the treatment of Pompe disease? Does early initiation of enzyme replacement make a difference in health outcomes when the condition is caught early or through screening? Do follow-up protocols exist for the management of Pompe disease that does not require immediate initiation of enzyme replacement therapy? Are there factors that modify the effect of treatment (e.g., CRIM status)?
6. How strong is the association between intermediate outcomes of improvement for Pompe disease and health outcomes?

Key Questions

7. What are the harms of a false positive screening result to both the individual and the family? How does this vary by form of the disease? Is early identification of later-onset Pompe disease harmful?
8. What are the harms of treatment for Pompe disease? Does this vary by form? Are their patient factors associated with increased risk of harm?

Literature Search

- Initial Literature Search
  - *PubMed, EMBASE (1966 – July 16, 2012)*
  - *MeSH Terms/Associated key words:*
    - Glygogen storage disease Type II
    - Pompe Disease
    - Pompe's Disease

PubMed: 1229 abstracts

EMBASE: 862

Initial Abstract and Title Screening (*August 2012*)

- Screening Criteria

Inclusions:	Relevant to key questions
	Infantile and Later-Onset Forms
	All study designs (n ≥ 1)
	English language abstracts
Exclusions:	Non-human studies
	Non-English or no abstract available
	No new empirical data/analyses

- Two independent reviewers
- Discussion and/or 3rd reviewer to resolve conflicts

Observations from the Literature Review

- More recent reports on immunomodulation
- Many reports on later-onset Pompe disease, which were not included in the original report

Grey Literature Search

- The American College of Medical Genetics
- The American Academy of Pediatrics
- The National Newborn Screening Resource Center
- The March of Dimes
- The Acid Maltase Deficiency Association
- The International Pompe Association
- The United Pompe Foundation
- The FDA
- Genzyme Corporation/Pompe disease registry
- OMIM

Other Relevant Sources of Information

- The Pompe Registry
- Pilot screening programs – Europe (Austria), Taiwan, Washington State
- Interviews with experts in the field
  - *Dr. Kishnani - database of patient CRIM status and associated factors.*
- Dr. Bodamer - Austrian validation study of multiplex screening for 3+ lysososomal disorders with anonymous DBS only

Next Steps

- Posting protocol
- Completing abstract/literature review
- Key informant interviews
- Grey literature analysis
- Net Benefit Modeling – underway (Dr. Prosser)
- Public health readiness and feasibility to be conducted by APHL

Questions?