Newborn Screening for Pompe Disease in New York State: Outcomes and the Role of Long-term Follow-up
Beth Vogel, MS, CGC
Pilot Main Objectives

1. Validate and implement screening for Pompe disease
2. Determine confirmatory tests and procedures for out-of-range results
3. Perform short-term follow-up and track positive cases
4. Begin a mechanism to ensure individuals who are confirmed with Pompe disease are followed long-term to assess natural history and treatment outcomes
NYS NBS Pompe Advisory Committee

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   October 1, 2014 to May 25, 2016
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Cutoffs and Testing Algorithm

All specimens tested for Enzyme activity

< 20% of daily mean

Retested in duplicate (or more)

Average of 3 samples ≤ 15% (GAA/IDUA)

DNA testing GAA

1 or more mutations

Screen Positive Referral

Average of 3 samples > 15% (GAA/IDUA)

No mutations

Screen negative

364,555 Infants

Slide from J. Orsini

67 infants
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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
Pompe Disease Management Recommendations

1. Recommendations for Determining Cross Reactive Immunologic Material (CRIM) Status
2. Recommendations & Considerations for Initiating ERT
3. Table 1. Evaluations for Monitoring of Asymptomatic Patients with Pompe Disease
4. Table 2. Evaluations for Monitoring of Symptomatic Individuals with Pompe Disease
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# Role of Long-term Follow-up

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Role of Long-term Follow-up

• Public health Implications
  – Calculating positive predictive value
  – Without LTFU - assume all potential LOPD cases will develop symptoms
Role of Long-term Follow-up

- Clinical Implications
  - Variants of unknown significance
  - Decisions on monitoring and treatment
Variants of Unknown Significance

- p.V222M variant - 7 referrals
- 2 infants were homozygous
  - diagnostic GAA enzyme analysis: low GAA enzyme activity, but slightly above the late-onset disease range
  - The Erasmus MC GAA mutation database: variant is non-pathogenic
    - based on in vitro studies of GAA enzyme activity using site-directed mutagenesis and transient expression in cell lines (Kroos et al., 2012).
- Long-term follow-up to determine whether this variant is pathogenic or a pseudodeficiency allele
Case Study: Zoe

- Abnormal screen reported at 7 DOL
- GAA activity – 6.2%
- Genotype: Late onset / Infantile
- Diagnostic GAA results: 15.0 (Range: 67.7-706.4)
- Pediatrician and metabolic specialist: No symptoms noticed; cardiac evaluation normal
- Physical therapist (specializing in neuromuscular disorders): Some subtle delay identified
- What’s next for Zoe?
Case Study: Megumi

• Abnormal screen reported at 10 DOL
• GAA activity – 9.2%
• Genotype: Late onset / Variant of unknown significance + pseudo deficiency allele
• Diagnostic GAA results:
  • 3.8 (Range: 67.7-706.4)
  • 1.7 (Range: > 3.88)
• No symptoms; cardiac evaluation normal at of 6 months of age
• What’s next for Megumi?
Long-term Follow-up Process

- Identify Data Elements
- IRB approval and data collection tool
- Consent and data collection
NBSTRN Resources

Identify data elements – List developed by panel of experts led by NBSTRN

Data collection tool – Longitudinal Pediatric Data Resource
Status of LTFU for Pompe in NYS

- IRB approval from NYS DOH
- Working through IRB at each institution (9)
Barriers to LTFU Implementation

• IRB approval – Multi-site study
• Consent
• Data collection
Acknowledgements

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Thank you