Nomination and Prioritization Reports: MPS I and Pompe Disease

Nancy S. Green, MD
Associate Dean for Clinical Research Operations
Associate Professor of Pediatric Hematology
Columbia University

May 17, 2012
Nomination and Prioritization Work Group

- Dr. Joseph Bocchini, Jr., MD – Chair
- Fred Lorey, PhD
- Dietrich Matern, MD
- Andrea Williams
- Nancy Green, MD
Outline of Presentation

- **MPS I:**
  - Present review by Nomination and Prioritization Work Group
  - Discussion and Vote by Committee: Move forward to Evidence Review?

- **Pompe:**
  - Present review by Nomination and Prioritization Work Group - update
  - Discussion and Vote by Committee: Move forward to Evidence Review?
MPS I: Nomination

- **Nominator:** National MPS Society
  - Barbara Wedehase, MSW, GCG, Executive Director

- **Medically serious condition:**
  - Defective glycosaminoglycan catabolism (↓α-Iduronidase)
  - Debilitating < 1 yr: multi-system (cardiac, pulmonary, CNS, other)
  - Fatal within 1st decade of life; considerable CNS impairment (Hurler Syndrome); Absent enzyme.
    - 40-60% of cases; Symptoms by 6 months
  - Attenuated forms with slower, later progress;
    - Symptoms by 5 years; Less or no CNS; some enzyme activity

- **Estimated incidence** 1:100,000 in the U.S.,
  - including those within the spectrum of disease.
  - Actual U.S. incidence is unknown.
MPS I: Case Definition & Disease Spectrum

- Case definition and disease spectrum - Yes
- Attenuated forms: Broader spectrum of age and onset:
  - Later symptoms and slower progression;
  - Approximately half of cases
- All forms: little or absent enzyme activity
  - Depends on tissue tested
- Molecular analysis provides good correlation with protein function
- Some uncertain genotype-phenotype correlates:
  - Some variants have unclear impact on enzyme
  - Pseudo-deficiency variant = rare
MPS I: Population-based Newborn Screening & Diagnosis

Recently established algorithm*

• Screen by enzyme activity (MS/MS): low/absent
  - Absent activity: severe form
  - Low activity: generally less severe but serious, but levels are imperfect predictors of severity
    [Multiplex with other LSDs]

• DNA sequencing of \( \alpha \)-Iduronidase
  - Predict severity (if mutation is obvious known)
  - May need to sequence gene in family members (e.g. for novel mutations)
  - Technical challenges for some states? (Fine for Krabbe - NY)

*Wang, et al. ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Genetics in Medicine, 2011
MPS I: Analytic Validity

• Washington State: 75,000 screened (anonymous) by multiplex (3 enzymes):
  • 5 identified below cutoff value: 1 early; 1 attenuated; 1 heterozygote; 2 no identifiable mutation.
    - False positive rate approx. 1:14,000.

• Missouri: Assay development is underway

• Several states (e.g. New Jersey, CA):
  - Currently deliberating about their screening approach
MPS I: Clinical utility

- Treatment improves outcomes:
  - HSC* transplant for the severe form
    - Best < Age 2 yrs;
    - Arrests disease impact on CNS;
    - Lifespan if transplanted vs. not: 15.6 vs. 7.9 yrs (2008)
    - 10-15% mortality, plus 10-15% GVHD, other complications
  - FDA approved therapy: ERT
    - Milder forms: enzyme replacement therapy or pre-BMT.
    - Does not cross the blood–brain barrier, thus does not improve CNS effects for severe form (Intermediate?).

* Hematopoietic stem cell transplant
MPS I: Issues & Recommendation

- **Established overall**: Case definition, Screening and diagnostic protocol, Treatment protocols
  - Appeal of multiplex testing

- **Recommend**: *Move forward to Evidence Review*

  **BUT WITH RESERVATIONS**
  - Uncertain: Identifying various forms of MPS, though each type is serious and treatable: Phenotypic spectrum and genotypic mutations
  - Uncertain: Impact of treatment with HSCT and ERT, especially for variants (50% of those identified)
  - Uncertain: Acceptability to parents (e.g. Krabbe experience, other non-oncologic disorders)
  - Uncertain: State NBS laboratory and program challenges
  - Uncertain: Public health impact
MPS I
Nomination and Prioritization: Comments and Questions?
Columbia University Medical Center
Previously nominated & reviewed in 2008
- Nominator: Priya S. Kishnani, MD, Duke University

Pompe Disease is medically serious:
- Deficient enzyme Acid α-glucosidase (GAA): Hydrolyzes lysosomal glycogen → accumulates in muscle
- Progressive muscular disease: skeletal +/- cardiac
- 1/3 have the infant form (early & rapid Sx, cardiac too)
- Infantile: Symptoms at ~2 months
- 100% mortality in the first year of life

Estimated incidence: 1/40,000
- Including Infantile and later onset forms
Infantile versus later onset

• Later onset: more variable in timing of onset, its impact on health, treatment issues
• Distinguishing infantile onset from late-onset:
  - Can be challenging
• Pseudo-deficiency: low efficiency enzyme
  – Prevalent among Asian populations
  – Would need to be discerned
1st tier screening: GAA enzyme activity level
- Fluorometry or MS/MS - perform similarly
- Enzyme levels differ by tissue

Newly clarified for diagnostic testing*:

- Leukocyte GAA activity
- Followed by GAA gene sequencing
  - Likely to detect infantile, but some uncertain mutations
  - (Technical challenges for some state labs? NY: Fine for Krabbe)
  - CRIM status (Western Blotting)

*Wang, et al. ACMG Work Group on Diagnostic Confirmation of Lysosomal Storage Diseases. Genetics in Medicine, 2011
Pompe: Analytic validity

- DBS Screen: GAA Enzyme activity
  - Different methods appear comparable (multiplex)
- Prospective pilot data from Washington State (false positive rate: 0.01%).
- Illinois: 8002 screened - 2 false positives (BB 2/20/2012)
- Taiwan: 130,000 infants screened – 4 Diagnosed
  - Repeat blood testing rate: 0.82%;
  - Clinical recall rate 0.091%
- Austria (35,000 babies screened):
  - False positive rate: 0.006%
Pompe: Clinical utility

- Taiwan: 130,000 infants screened
  - 4 diagnosed by NBS in 1st month;
  - 3 diagnosed clinically between 3-6 months

- Children who would benefit from newborn identification and therapy = 1/3 of those identified
- Clinical utility for children in the later onset group: not addressed by the Nominator
Pompe: Treatment

- Defined treatment protocols exist using enzyme replacement therapy (ERT)
- Earlier diagnosis and treatment has been shown to improve outcomes.
- C/W European consensus (2011)
- Open issues: CRIM = cross-reactive immunologic material
  - Some with limited response to treatment
    (CRIM negative) – 20-30% of infantile on treatment (Kishnani 2010)
    - African American common
  - Sensitization: Antibodies to GAA replacement (“Anti-CRIM”)
Pompe: Open Issues

• Identifying late onset disease – 2/3 of cases.
• Challenges in DNA sequencing:
  How clinically predictive
  Technical challenges for some state labs.
• ERT: Sensitization to enzyme replacement.
Pompe: Work Group Recommendation

- Move forward to Evidence Review
- Review of the specific areas previously deficient:
  - Improved screening test specificity for infantile form
  - Standardized method of diagnosis of pre-symptomatic infants
  - Benefit and harm of diagnosing late-onset Pompe disease during infancy
  - Review any cost or cost-effectiveness data
  - Impact on State Health Departments
  - New: Public health impact
Pompe
Nomination and Prioritization: Comments and Questions?