Technical Workshop on Methods to Detect Pompe Disease and other Lysosomal Storage Disorders (LSDs) by Newborn Bloodspot Screening

April 16-17 | JW Marriott Atlanta Buckhead | Atlanta, GA

SUMMARY

CDC Initiatives

- **Bob Vogt:** NSTRI
  - possible extension of “Genzyme” reagent availability
  - PE reagents available now via “contract manufacturing”
  - QA, QC, PT
- **Harry Hannon:** CLSI Pompe report

  Provide input by end of April
- **Hui Zhou:**
  - Review of CDC’s LSD multiplex methods
  - Offering disease specific PT for Pompe, Krabbe and – by end of 2015 – MPS I

NBS for Pompe

- **Ron Scott:** Washington pilot
  - Pompe, Fabry and Gaucher
  - De-identified samples, FIA-MS/MS + molecular
  - Recently expanded to include 3 more LSDs with PE reagents
- **J. Liao and Sara Chiang:** Taiwan
  - Pompe and Fabry by FIA-MS/MS and fluorometry as of 2005
  - Using enzyme activity ratios to improve FPR and PPV
  - Moving towards FIA-MS/MS
- **Joe Orsini:** NY
  - Krabbe since 2006, XALD and Pompe since 2014/15
  - FIA-MS/MS method + molecular
  - Moving towards PE reagents
- **George Dizikes:** IL
  - LC-MS/MS for 5 (6) LSDs with PE reagents
  - Incubation time 3 vs. 17 hrs – no significant difference
  - Moving towards FIA-MS/MS with PE reagents
- **Pat Hopkins:** MO
  - Pompe + 3 LSD by digital microfludics (Baebies, Inc.); total FPR 0.08%
  - activity differences observed based on gestational age/birth weight, gender, age at collection
  - Benefit of multiplexing several enzymes
  - Krabbe (+ NPA/B) by stand-alone fluorometry (Baebies. Inc.) in validation
  - Krabbe in-house July 2015

NBS for Pompe

Table 1 – Summary of test methods, results, and performance metrics from screening studies of more than 30,000 newborns for Pompe disease.

Country/state	Taiwan	Taiwan	Taiwan	Taiwan	Austria	Hungary	WA	MO
Condition	Pompe	Pompe	Pompe	Pompe	Pompe	Pompe	Pompe	Pompe
Method	Fluorometry > MS/MS	Fluorometry	Fluorometry	MS/MS	MS/MS	MS/MS	MS/MS	DMF
# of NBS samples	402,281	132,538	473,738	191,786	34,737	40,024	111,544	43,702
TP	27	4	28	16	4	9	4	8
FP[a]	4184	1089	2213	858	1	55	13	10
FPR	1.04%	0.82%	0.47%	0.45%	0.003%	0.14%	0.012%	0.023%
PPV	0.64%	0.37%	1.25%	1.83%	80.00%	14.06%	23.53%	44.44%
Frequency: 1 in	14,899	33,135	16,919	11,987	8684	4447	27,886	5463
Follow-up	Clinical	Clinical	Clinical	Clinical	Mol. genetics[b]	Mol. genetics[b]	Mol. genetics[b]	Clinical
Patients	7 EIPD and 20 LOPD	No details	9 EIPD and 19 LOPD	5 EIPD and 11 LOPD	4 Likely later onset; FP has multiple sequence variants	8 EIPD, 2 LOPD, 25 carriers, and 3 uncertain	4 LOPD	3 EIPD, 3 LOPD, 2 uncertain, 2 pseudodef., and 3 carriers
Second tier test	No	Yes (NAG)	Yes (NAG)	No	No	No	No	No
References	25	23	73	74	38	39	75	42

DMF, digital microfluidics; EIPD, early-infantile Pompe disease; FP, false-positive cases; FPR; false-positive rate; LOPD, late-onset Pompe disease; MS/MS, flow-injection tandem mass spectrometry; PPV, positive predictive value; TP, true positive cases.

[a] False-positive cases (FP) are based on the first DBS sample and include non-carriers, carriers, and cases with pseudodeficient enzyme activity.

[b] Study used de-identified samples.

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SEMINARS IN PERINATOLOGY ▮ (2015)

NBS for LSD - Updates

- **Enzo Ranieri:** Adelaide, Australia
  - Preliminary confirmation that MS/MS with PE reagents works
  - Applied to clinical testing of at risk patients (not population screening)
- **Mei Baker:** WI
  - Applying DMF to pilot study of NBS for Pompe
  - Comparing very well to MO
- **Patrick Hopkins:** MO
  - Moving NBS for Krabbe from NY to MO
  - Will use standalone fluorometric assay developed by Baebies + in-house 2nd tier 30kbDel testing
  - So far comparing very well with NY FIA-MS/MS method
- **George Dizikes:** IL
  - LC-MS/MS for 5 (6) LSDs with PE reagents; FPR 0.24%
  - NBS for Krabbe pending due to logistics of external 2nd tier testing
- **John Thompson:** WA
  - Descriptionof process of adding condition to WA NBS panel
  - Focus on cost benetif/cost effectiveness studies that are required component of WA evidence review
- **Art Hagar:** GA
  - Applying DMF to pilot study of NBS for Pompe – not begun due to consent issue
- **Joe Orsini:** NY
  - Currently NBS for Krabbe, Pompe and X-ALD
  - Pilot for Fabry, Gaucher, NPA/B and (soon) MPS I
  - Pilot with informed (opt-in) consent (4 hospitals) – 72% opt-in rate

Things to Consider

- **Reagent availability**
  - possible extension of “Genzyme” reagents for MS/MS
  - single-source for MS/MS reagents likely
  - single-source for digital microfluidics
- **Currently no FDA approved tests for LSD screening and follow up**
  - FDA wants to add regulation to LDTs
  - FDA approval requires a lot of money and time (unless new requirements were implemented)
- **NBS Saves Lives** (or does it?) **Reauthorization Act**
  - Puts at risk ability to develop and implement new tests
  - We need to provide evidence that informed consent is not saving lives
  - Do we have data on how many patients would not have been saved if informed consent had been required 53 years ago?