Georgia NBS Implementation Studies for Pompe and MPS-I: Interpretation and Performance

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NBS in Georgia

• Currently screening for all conditions on the RUSP, except for the 3 most recently added

• Testing performed at state Public Health Lab; follow-up mainly coordinated through Emory University (all except hemoglobinopathies)
  – 140,000 – 150,000 births / year
  – Most common disorders identified: sickle cell, hypothyroidism, MCAD, PKU, CF

• Implementation studies in process / planned for 3 most recently added conditions
Addition of New Conditions

• Submitted to and approved by Georgia NBSAC
  – Most recently: SCID, CCHD
• NIH funding has allowed us to perform implementation studies for Pompe, MPS-I and X-ALD
Currently in Progress

• 2-Plex 1\textsuperscript{st} tier screening for Pompe and MPS-I
  – MS/MS
  – Abnormal results trigger a 2\textsuperscript{nd} tier test, which is done from NBS card, does not require additional patient contact

• X-ALD screening – validation complete; finalizing documentation and reporting structure
Workflow

Pre-analytical:
- Samples
  - GA Public Health Lab

Post-analytical:
- Normal
  - Emory F/U Database
- 2nd Tier Test
  - GA Public Health Lab
- Abnormal
  - Emory F/U Team

Demographics Data
- GA Public Health Lab
- Emory NBS F/U Program

EGL Genetics
Interpretation of Results

- Data files are processed (QC, review checklists, combined with demographic data) and saved on server for interpretation
- MPS-I / Pompe Application in CLIR
GA Post-Analytical Tools

• 1\textsuperscript{st} Tier Testing:
  – Primary - 2-plex, results are adjusted for age at collection
  – Secondary – 2-plex, results are not adjusted for any covariate
  • Used for missing ages or extremes (particularly older babies)
Post-Analytical Tools

• Output for single condition tools is similar to what is used for Region 4 tools:
  – Not informative
  – Possible
  – Likely
  – Very Likely

• For first tier test results – any informative score was sent to 2\textsuperscript{nd} tier testing

• Interpretation with 2\textsuperscript{nd} tier 6-plex utilized single condition tools for Pompe and MPS-I; as well as dual scatter plots
Current Performance

• 36,095 samples completed
  – 197 samples gave informative scores for both conditions:
    • Sample condition issue or prep issue – referred for 2\textsuperscript{nd} tier testing to expedite resolution
  – 297 cases with missing / invalid demographics
    • Age at collection = 0 hours or > 8760 hours (1 year)
      – Early samples: referred for 2\textsuperscript{nd} tier testing
      – After 04/17: resolved with unadjusted tools
  – Abnormal by single condition tool for a single condition:
    • MPS-I: 9 (1 very likely; 2 likely; 6 possibly)
    • Pompe: 188 (2 very likely, 1 likely, 185 possibly)
Performance and Outcomes

• 35,404 (98.1 %) resolved as normal by 1\textsuperscript{st} tier test
  – 1.9 % sent for 2\textsuperscript{nd} tier test (predicted 1 – 2 \%)
  – 1.1 % with complete switch to unadjusted tools for missing or invalid age at collection

• 4 cases reported out:
  – 3 positive for MPS-I
    • Confirmatory enzyme testing was low for all cases, urine screening incomplete, molecular testing pending
    • Pseudodeficiencies suspected
  – 1 positive for Pompe
    • Decreased enzyme, molecular pending
Abnormal – MPS-I

- IDUA Enzyme Activity: 0.20 nmol/mL/hr (1st percentile in CLIR = 3.16 nmol/mL/hr); sample collected @ 32 hours
- MPS-I Single Condition Tool: Likely MPS-I
Other Approaches

• 36,095 samples analyzed using tools which did not require demographic data
  – 197 samples gave informative scores for both conditions (same cohort of sample condition or sample prep issues)
  – 0 errors with missing or invalid demographics
  – Abnormal by single condition tool for a single condition:
    • MPS-I: 14 (2 likely; 12 possible)
    • Pompe: 41 (2 very likely; 5 likely; 34 possible)
Cutoffs / Daily Mean

• Setting the cutoff as $< 10\%$ of daily mean:
  – Low GAA: 199
  – Low IDUA: 218

• Setting the cutoff as $< 1^{\text{st}}$ percentile of the reference population:
  – Both enzymes low: 238
  – Low GAA: 158
  – Low IDUA: 147
Challenges

• Integration of 3 (4) unique IT environments
• Laboratory move
• Missing covariates added to interpretation time
Lessons Learned

• All four interpretive strategies identified the same group of samples that were reported out as abnormal
  – Varying levels of presumptive false positives with each strategy

• Any interpretive strategy should strongly consider 2\textsuperscript{nd} tier testing to reduce false positives, unless 1\textsuperscript{st} tier test is comprehensive
Moving Forward

- Adding X-ALD to the screening panel – “alternative 6-plex” for post-analytical tools
- Working with GA NBSAC to review study results and make decisions:
  - Addition of conditions to state panel
  - Methodology
  - Interpretation strategy (+/- 2nd tier tests)
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