Does IRT/IRT/DNA Really Work?
Review of Cystic Fibrosis Newborn Screening in Texas

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TX NBS Specimen Load

• To test each infant twice:
  • 24 to 48 hours of age &
  • 1 to 2 weeks of age

• 2013: Received ~753,000 specimens
  • ~ 2,450 specimens per day (6 days per week)
  • ~ 7,400 unsatisfactory specimens (0.99%)
Cystic Fibrosis NBS

- Implemented statewide December 1, 2009
- IRT/IRT/DNA methodology
  - 1st screen elevated IRT/2nd screen elevated IRT/DNA
  - IRT fixed cutoff:
    - 60 ng/mL in blood for infants <21 days at the time of specimen collection
    - 46.5 ng/mL in blood for infants 21 days or older at the time of specimen collection
  - CFTR mutation panel – Hologic (40+2)
    - 1 or 2 mutations identified – Abnormal CF screen
    - 0 mutation identified - Normal
‘Failsafe’ Protocols

- Ultra-high IRT levels (>150 ng/mL blood) but 0 mutations
- If 1st screen is elevated & no or unacceptable second specimen received by 30 days of age, the first screen is reflexed to DNA
- 1st normal IRT or no 1st screen with 2nd screen elevated IRT is reflexed to DNA
### Cystic Fibrosis Screening

December 1, 2009 – December 31, 2013

2.4% of the total 1st newborn specimens were elevated for IRT.

0.8% of the total follow-up specimens were elevated for IRT.

<table>
<thead>
<tr>
<th></th>
<th>Specimen Received</th>
<th>IRT Screen Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Screen</td>
<td>1,570,933</td>
<td>37,821</td>
</tr>
<tr>
<td>Follow-up Screen</td>
<td>1,534,469</td>
<td>12,360</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,105,402</td>
<td>50,181</td>
</tr>
</tbody>
</table>
IRT/IRT/DNA Algorithm
December 1, 2009 – December 31, 2013

1st Screen (1,570,933)

- Normal IRT
- Elevated IRT (37,821)

Repeat IRT on 2nd Screen (30,371)

- Normal IRT (26,566)
- Elevated IRT (3,805)

No 2nd Screen (7,450)

CF DNA Mutational Analysis
CF DNA Specimen Type
(December 1, 2009 – December 31, 2013; Total DNA tests performed = 19,056)

- 36.74% 2nd screen with normal 1st (7,002)
- 39.10% 1st elevated IRT, no 2nd (7,450)
- 4.19% 2nd screen with elevated 1st (3,805)
- 19.97% 2nd screen with no 1st (799)
### Cystic Fibrosis DNA Test

December 1, 2009 to December 31, 2013

<table>
<thead>
<tr>
<th></th>
<th># of newborns</th>
<th># of diagnosed cases</th>
<th># of missed cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mutations found</td>
<td>199</td>
<td>176</td>
<td>4</td>
</tr>
<tr>
<td>1 mutation found</td>
<td>915</td>
<td>64</td>
<td>2</td>
</tr>
<tr>
<td>0 mutation, very</td>
<td>468</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>elevated IRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 mutation found</td>
<td>17,474</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0 mutation found</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19,056</td>
<td>249</td>
<td>9</td>
</tr>
</tbody>
</table>

- 1,582 newborns had presumptive positive CF screening results.
- “0 mutation found” is reported as normal CF screening results.
Mutation Distribution
(249 CF cases)

<table>
<thead>
<tr>
<th>Mutation Name</th>
<th># of Alleles</th>
<th>Mutation Name</th>
<th># of Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>deltaF508</td>
<td>316</td>
<td>3120+1G&gt;A</td>
<td>3</td>
</tr>
<tr>
<td>G542X</td>
<td>16</td>
<td>3849+10kbC-&gt;T</td>
<td>3</td>
</tr>
<tr>
<td>R117H</td>
<td>14</td>
<td>D1152H</td>
<td>3</td>
</tr>
<tr>
<td>G551D</td>
<td>10</td>
<td>S549N</td>
<td>3</td>
</tr>
<tr>
<td>1717-1G-&gt;A</td>
<td>6</td>
<td>3876delA</td>
<td>3</td>
</tr>
<tr>
<td>N1303K</td>
<td>5</td>
<td>3905insT</td>
<td>3</td>
</tr>
<tr>
<td>621+1G&gt;T</td>
<td>4</td>
<td>W1282X</td>
<td>2</td>
</tr>
<tr>
<td>deltaI507</td>
<td>4</td>
<td>A455E</td>
<td>1</td>
</tr>
<tr>
<td>R1162X</td>
<td>4</td>
<td>R347P</td>
<td>1</td>
</tr>
<tr>
<td>R553X</td>
<td>3</td>
<td>3659delC</td>
<td>1</td>
</tr>
<tr>
<td>2789+5G-&gt;A</td>
<td>3</td>
<td>2183A A-&gt;G</td>
<td>1</td>
</tr>
<tr>
<td>R334W</td>
<td>3</td>
<td>394delTT</td>
<td>1</td>
</tr>
<tr>
<td>1898+1G&gt;A</td>
<td>3</td>
<td>V520F</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TOTAL</td>
<td>417</td>
</tr>
</tbody>
</table>

- Mutation detection rate using Hologic 40+2 panel is ~84% (417/498).
- 32 other mutations were identified. L206W, A559T, and W1089X were the most prevalent.
‘Failsafe’ Protocols

• Ultra-high IRT levels (>150 ng/mL blood) but 0 mutations = 6

• If 1st screen is elevated & no or unacceptable second specimen received by 30 days of age, the first screen is reflexed to DNA = 29

• 1st normal IRT or no 1st screen with 2nd screen elevated IRT is reflexed to DNA = 13
Age of Presumptive Positive Result Notification (Days)

Range = 0-186 Days
Medium = 22 Days
82% (203/249) notified within 30 days of age
98% (243/249) notified within 40 days of age
Range = 0-182 Days
Medium = 30 Days
52% (129/249) diagnosed within 30 days of age
87% (217/249) diagnosed within 60 days of age
9 Missed Cases

- **Definition** - Cystic Fibrosis cases with normal screening results
  - 7 due to IRT below cutoff
  - 2 due to mutation panel (both African American)
- 4 with history of Meconium Ileus
- Age of Diagnosis ranged from 6 days to 173 days (average 69 days)
- Based on data from two missed cases, older baby cutoff was re-evaluated and changed from 30 days to 21 days (DOB to DOC) using cut off ≥46.5 ng/mL
Summary

- # of newborn screened: 1,570,933
- # of newborn tested by CF DNA: 19,056 (1.2%)
- # of newborn with presumptive positive results: 1,582 (0.1%)
- # of newborn diagnosed with CF: 249
- # of missed cases: 9
- # of carriers identified: 851
- # of CFRMS identified: 23
• Positive Predictive Value - 15.7%
• Sensitivity - 96.4% (False negative rate – 3.6%)
• Specificity - 99.9%
• Overall Incidence Rate – 1 in 6,308
  • White - 1 in 3,505
  • Hispanic – 1 in 10,150
  • African American – 1 in 11,803
  • Others – 1 in 19,888
• Need system-wide education on timing of specimen collection, esp. 2nd screens.
Thank you