Newborn Screening for Cystic Fibrosis in Texas
Giving Little Texans with CF a Chance for Better Outcomes

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Review: Texas NBS Program

- 2008: Received ~796,000 specimens
  - Specimens Assayed and Reported: ~791,000
  - ~4,800 unsatisfactory specimens (~0.60%)
  - Avg: 2,527 specimens/day

- Linking of specimens - overall success rate
  - 2008: 84.8%
  - 2009: 87.4%

- Two screening tests for each baby born in Texas
  - 24 – 48 hours of age
  - 1 – 2 weeks of age

Infants testing positive receive prompt confirmatory testing.

Newborn Screening for Cystic Fibrosis: Overarching Assumptions

- DSHS workload estimates:
  - FY10: 818,000 screens
  - FY11: 828,000 screens
- IRT/IRT/DNA model
  - Measure IRT levels on both 1st and 2nd screens
  - Elevated IRT levels on both screens triggers a DNA test
- Fail safe protocol:
  - If 2nd screen not received within 30 days after birth, reflex to DNA
  - Estimate 82-94 diagnosed cases annually

“Indeterminate” First Screen Screening Result Notes

- Many unaffected infants have an elevated immunoreactive trypsinogen (IRT) level on the first specimen.
- The second screening specimen (collected after 7 days of age) is required to determine if result is significant.
- Please repeat the newborn screen.

Prospective Specimen Numbers Using Data from Colorado and Utah

1st Screen Blood Spot (409,000)

- Normal IRT (396,730)
- Elevated IRT (12,270)

- Normal CF Screen
- Indeterminate CF Screen

2nd Screen Blood Spot

- Normal IRT
- Elevated IRT (1,200 – 1,840)

- 0 mutation (950 – 1,590)
- 1 mutation (~170)
- 2 mutations (~80)

- Inconclusive CF Screen
- Abnormal CF Screen
**CFTR Mutation Panel**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆F508</td>
<td>R334W</td>
</tr>
<tr>
<td>∆F508</td>
<td>R347F</td>
</tr>
<tr>
<td>G542X</td>
<td>711+1G&gt;T</td>
</tr>
<tr>
<td>G551D</td>
<td>3849+4A&gt;G</td>
</tr>
<tr>
<td>N1303K</td>
<td>4152H</td>
</tr>
<tr>
<td>R553X</td>
<td>3849+10kbD&gt;T</td>
</tr>
<tr>
<td>P1102D</td>
<td>1999+1G&gt;A</td>
</tr>
<tr>
<td>R117H</td>
<td>3659delC</td>
</tr>
<tr>
<td>R117H</td>
<td>3120+1G&gt;A</td>
</tr>
<tr>
<td>A455E</td>
<td>554R</td>
</tr>
<tr>
<td>R560T</td>
<td>3876delA</td>
</tr>
<tr>
<td>R1162X</td>
<td>Y122X</td>
</tr>
<tr>
<td>G85E</td>
<td>3120+1G&gt;A</td>
</tr>
</tbody>
</table>

**Mutation Detection Rate**

<table>
<thead>
<tr>
<th>Category</th>
<th>Total # of Identified CF Alleles</th>
<th>% of Identified CF Alleles</th>
<th>% of Total CF Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Texas Data*</td>
<td>2132</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>ACMG Panel (23)</td>
<td>2016</td>
<td>94.56%</td>
<td>70.69%</td>
</tr>
<tr>
<td>Hologic Extended Panel (40+2)</td>
<td>≥ 2055</td>
<td>≥ 96.39%</td>
<td>≥ 72.05%</td>
</tr>
</tbody>
</table>

*Data from 1,426 CF patients in Texas (total 2,852 alleles)

**“0 Mutation” Screening Result Notes**

- Inconclusive
  
  No further evaluation necessary unless clinically indicated. Although there is a minimal risk for Cystic Fibrosis (CF) in the absence of detected mutations, an elevated immunoreactive trypsinogen (IRT) result may be indicative of CF due to a mutation not included in the 40-mutation panel.
  
  Recommend sweat testing and possible genetic evaluation only if clinically indicated.

**“1 Mutation” Screening Result Notes**

- Abnormal
  
  One mutation, ∆F508, in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene was identified. Cystic Fibrosis can not be ruled out due to a possibility of a second mutation which is not included in the 40-mutation panel.
  
  Recommend referral for confirmatory sweat testing and consider genetic counseling.

**“2 Mutations” Screening Result Notes**

- Abnormal
  
  Two potential Cystic Fibrosis-causing mutations, ∆F508 and R117H (7T/9T), in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene were identified.
  
  Recommend referral for confirmatory sweat testing and consider genetic counseling.

**Prospective Specimen Numbers Using Data from Colorado and Utah**

- 0 mutation: (950 – 1590)
- 1 mutation: (~170)
- 2 mutations: (~80)
- Both Extremely Elevated IRTs: (<40)
- Sweat Test: (~300)
- CF: (84-92)
“0 Mutation”
Result Report Screening Notes

- Abnormal (Extremely elevated IRT )
  Although there is a minimal risk for Cystic Fibrosis (CF) in the absence of detected mutations, a very elevated immunoreactive trypsinogen (IRT) result may be indicative of CF due to mutations not included in the 40-mutation panel.

  Recommend referral for confirmatory sweat testing and consider genetic counseling.

Normal Screen Report

Abnormal Screen Report

DSHS case will be created for case management if:
- 2 very elevated IRT levels detected
- 2 elevated IRT results and one or two mutations on DNA analysis OR
  Single elevated IRT and one or two mutations on DNA if only one screen received
- Case will be handled similar to other newborn conditions:
  - Parent will receive a letter with notification of screen results
  - PCP will receive a fax from laboratory with results
  - NBS Nurse will call PCP with results and FAX follow up info
- CF center M.D. will be notified of child referred for sweat test

What happens after the screen comes back positive?
- DSHS case manager will inform physician and family that patient should be referred to an accredited CF Center for sweat testing.
- Tri-Services Military Cystic Fibrosis Center
  Lackland AFB, TX 78236
  Appointments: (210) 292-7329
  Director: John M. Palmer, M.D.
- CHRISTUS Santa Rosa Children’s Hospital
  333 North Santa Rosa
  Appointments: (210) 704-2338
  Director: Donna Beth Willey-Courand, M.D.
Sweat Test

- Gold standard
  - Pilocarpine Iontophoresis
- Collection Methods:
  - Gibson Cook Method
    - Collect sweat on dry gauze with direct measurement of chloride concentration
    - Need 75 mg of sweat
  - Macroduct Coil Collection System with direct measurement of chloride concentration
    - Need 50 mcg of sweat
  - Measure chloride concentration in sweat
- Test should only be performed at an accredited CF Center

Sweat Tests-Age Related Interpretation of Results

<table>
<thead>
<tr>
<th></th>
<th>&lt;6 months</th>
<th>&gt;6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30 meq/l</td>
<td>&lt;40 meq/l</td>
</tr>
<tr>
<td>Borderline</td>
<td>30-70 meq/l</td>
<td>40-70 meq/l</td>
</tr>
<tr>
<td>Abnormal</td>
<td>&gt;70 meq/l</td>
<td>&gt;70 meq/l</td>
</tr>
</tbody>
</table>

CSRCH CF Center Approach

- All newborn screen positive infants will be scheduled for sweat testing
- Once sweat test results are available, genetic counselor will meet with family and go over results
- All patients with borderline or elevated sweat tests will be seen in CF Center

?s……..Call (210)704-2338

- Donna Beth Willey-Courand MD
- Lisa Matasovsky RN, PNP
- Michelle Stress RN
- Melanie Drummond RN
- Vicky Enciso MA, CGC
- Kay Batzer RRT
- Sarah Fryer RD