Workshop: Pulmonology

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Associate Professor of Pediatrics
I have no relevant financial disclosures.

I may mention off-label use of FDA approved medication.
Objectives

1. Review cystic fibrosis newborn screening, interpretation of results....and learn what the heck is CRMS?
2. Review various inhaler devices
3. Introduce a dramatic paradigm shift in asthma management proposed in GINA guidelines 2019
4. Consider some random fun pulmonary cases (if there’s time)
Newborn Screening for CF in Virginia

• Screening for CF since March 1, 2006

  • Initial methodology was IRT/IRT (2 specimens)

  • Changed to IRT/DNA protocol (single specimen) starting December 1, 2011 to improve detection
CF Newborn Screening Methods

• IRT: immunoreactive trypsinogen
  - *Enzyme precursor made by pancreas*
  - *Detectable in blood of normal and CF newborns*
  - *Elevated in CF newborns, even those with pancreatic sufficiency (approx. 10-15% of CF patients)*
  - *Damaged pancreatic acinar cells “leak” this enzyme into bloodstream*
  - *Nonspecific elevation with perinatal stress*

• DNA: CFTR mutations
  - *Over 2,000 known mutations*
  - *Virginia protocol tests for 39 CFTR mutations and 4 polymorphisms*
Bloodspot IRT at 24-48h of age

Elevated (≥ top 4% of the day)

Reflex: DNA for CF - 45-mutation panel (from same sample)

- No mutations
  - Report as "negative screen"

- 1 mutation "Possible CF"
  - Sweat chloride
    - < 30: Carrier counseling
    - > 30: CF consult/referral

- 2 mutations "Probable CF"
  - CF consult/referral
Fun Facts on the IRT/DNA Algorithm

• How many samples will have “elevated” IRT?
  • By definition, 4% (because cutoff is set at 96th percentile)

• Of those with elevated IRT, how many will be normal on DNA testing (ie., No Mutations)?
  • About 94%

• Of those with elevated IRT and One Mutation, how many will have CF?
  • About 3% ....thus the need for the sweat test (as there could be a second mutation that was not in test panel)

• Of those with elevated IRT and Two Mutations, how many will have CF?
  • Most will have CF, but some will classify as CRMS/CFSPID
About that IRT

- Population incidence of CF 1:4,000 0.025%
- IRT “abnormal” 4%

Remember: Only a small fraction of the “abnormal IRT” babies actually have CF.

Non-CF factors associated with elevated IRT
- Contamination of filter paper card with traces of meconium
- Neonatal stress, low Apgars
- African-American
- CF carrier (approx. 10% of the elevated IRT group vs. 3% of population)
- Upper end of normal distribution
Does the height of initial IRT value predict the likelihood of CF?

Our daily top 4% cutoff usually falls around 45-50 ng/mL.

<table>
<thead>
<tr>
<th>IRT Level (ng/mL)</th>
<th>No. CF/No. Infants</th>
<th>CF Risk, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 to 139</td>
<td>2/1404</td>
<td>0</td>
</tr>
<tr>
<td>140 to 179</td>
<td>1/387</td>
<td>0.25 (0 to 0.7)</td>
</tr>
<tr>
<td>180 to 219</td>
<td>12/333</td>
<td>3.6 (1.6 to 5.6)</td>
</tr>
<tr>
<td>220 to 259</td>
<td>13/122</td>
<td>10.7 (5.2 to 16.2)</td>
</tr>
<tr>
<td>260 to 299</td>
<td>11/59</td>
<td>18.6 (8.7 to 28.5)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>20/83</td>
<td>24.1 (14.9 to 33.3)</td>
</tr>
</tbody>
</table>

Gregg RG et al, Pediatrics 1997, 99: 819-824 (data from Wisconsin RCT)
Distribution of IRT values: CF patients in relation to normal newborn population (MoM= multiple of the median for IRT value)

Median IRT for CF is 7X median for normals

“Biologic False Neg:” CF cases with low IRT

Massie, J et al. Arch Dis Child 2006; 91:222-225
Age-related decline of IRT in non-CF infants with elevated initial IRT

*Infants with CF may also show IRT decline with time

Some reasons for “false negative” initial IRT

• **Meconium ileus**: Infants with meconium ileus have a high rate of false negative IRT (approx. 26%). Meconium ileus is almost always due to CF (>98%) and further testing and consultation is indicated regardless of a negative NBS.

• **“Biologic False Negative”**: Some IRTs will fall at the low end of distribution among CF infants, even below the 4%ile cutoff of the screening protocol. It’s a screening test and will not detect every case. If there is clinical concern for CF, test or refer to CF Center.
Anatomy of a CF-NBS Report after Top 4% IRT

• IRT top 4%, and No Mutations: “Negative Screen”
  • No further action required unless clinical concern
  • If IRT was “ultrahigh” (>170 ng/ml), and there is no obvious reason (e.g., severe neonatal problems, congenital anomalies, etc.), consider calling CF consultant. Some ultrahigh IRT cases may merit sweat testing even with no mutations.
  • IRT level notation of “abnormal” may remain on report.

• IRT top 4%, and One Mutation: “Possible CF”
  • Needs sweat test (accredited CF Center) to discern carrier vs CF-- target w/in 1 week
  • Recommend professional genetic counseling

• IRT top 4%, and Two Mutations: “Probable CF or CRMS”
  • Contact CF center without delay
  • CF center will arrange sweat test plus clinical visit within 1-3 days
How could a 2 mutation result **not** represent CF?

- Sample mixup at birth hospital or state lab: wrong baby

- 2 different CF mutations are in *cis* (within the same chromosome), and balanced by a normal CFTR gene on the other chromosome

- Presence of at least one identified CF mutation of potentially subclinical severity: e.g., R117H
  - 4\(^{th}\) most common CF-associated allele (1.3%)
  - PolyT variant in Intron 8 affects pathogenicity (5T > 7T/9T)
  - Variable clinical manifestations (possibly none)- thus “CRMS” label
**Example report arrives**

### ABNORMAL TEST RESULTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystic Fibrosis Screen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* IRT</td>
<td>89.5</td>
<td>&lt; Daily 4% ng/mL</td>
</tr>
<tr>
<td>CFTR Mutation Analysis</td>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

*Mutations screened (ACMG/ACOG panel in bold; 4 variants in italics) for:
## ABNORMAL TEST RESULTS

<table>
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<tbody>
<tr>
<td><strong>Cystic Fibrosis Screen</strong></td>
<td>Abnormal *</td>
<td></td>
</tr>
<tr>
<td>* IRT</td>
<td>56.4</td>
<td>&lt; Daily 4% ng/mL</td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation</td>
<td>No Mutations Found</td>
<td></td>
</tr>
</tbody>
</table>

**Abnormal Cystic Fibrosis Screen:**

**INTERPRETATION:** In view of finding no mutations and the IRT > 96th percentile, the NEGATIVE predictive value for CF is very high. However, there is the very rare possibility that an elevated trypsinogen (IRT) result may be indicative of CF associated with mutations not included in this screening.

**PLEASE NOTE:** Regardless of screening test results, a physician should immediately evaluate any infant or child who exhibits findings consistent with cystic fibrosis. Newborn screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic.

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*Mutations screened (ACMG ACOG panels in bold, 4 variants in italic)*:

- M1192X-GC
- M1192X-GG
- H1224X (T.567G)
## ABNORMAL TEST RESULTS

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<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis Screen</td>
<td>Abnormal ^</td>
<td>&lt; Daily 4% ng/mL</td>
</tr>
<tr>
<td>* IRT</td>
<td>48.4</td>
<td></td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation</td>
<td>3120+1G&gt;A</td>
<td></td>
</tr>
</tbody>
</table>

**Abnormal Cystic Fibrosis Screen:**

**INTERPRETATION:** The presence of one Cystic Fibrosis (CF) mutation is indicative of a CF gene carrier state, which would not carry adverse health consequences. However, CF disease cannot be ruled out, due to the possibility of a second mutation that is not included in the mutation testing panel.

**RECOMMENDED ACTION:** Infants should be referred to a CF Center for diagnostic evaluation to determine whether the child is a carrier or has CF disease.

Cynthia Epstein, MD  
Children's Hospital of the King's Daughters  
Norfolk  
757-668-7137

James Clayton, MD  
Pediatrics Lung Center  
Fairfax  
703-289-1410

Deborah K. Fish, MD  
UVA Hospital  
Charlottesville  
434-924-2250

H. Joel Schmidt, MD  
VCU Hospital  
Richmond  
804-828-2982

**PLEASE NOTE:** Newborn Screening tests are intended to provide an early opportunity to detect disorders before symptoms.
**Report: Two Mutations**

### CRITICAL TEST RESULTS

<table>
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<tr>
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<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cystic Fibrosis Screen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interpretation: The results below for the Cystic Fibrosis Screen are suggestive of Cystic Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*RT</td>
<td>89.5</td>
<td>&lt; Daily 4% ng/mL</td>
</tr>
<tr>
<td>*Cystic Fibrosis Mutation ^</td>
<td>dF508</td>
<td></td>
</tr>
<tr>
<td>*Cystic Fibrosis Mutation 2 ^</td>
<td>dF508</td>
<td></td>
</tr>
</tbody>
</table>

**Critical Cystic Fibrosis Screen:**

**INTERPRETATION:** The presence of multiple Cystic Fibrosis (CF) mutations is consistent with Cystic Fibrosis.

**RECOMMENDED ACTION:** Infant should be promptly referred to a CF Center for diagnostic evaluation and consultation with a CF specialist.

<table>
<thead>
<tr>
<th>Name</th>
<th>Hospital</th>
<th>City</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cynthia Epstein, MD</td>
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<td>Richmond</td>
<td>804-828-2982</td>
</tr>
</tbody>
</table>

**PLEASE NOTE:** Newborn Screening tests are intended to provide an early opportunity to detect disorders before symptoms appear. These tests are not diagnostic, and require further confirmation.

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"Mutations screened: (ACMG/ACOG/pediatric hold) 5 variants in total for:

Current Follow-up Reporting Process

IRT --

1 Mutation

IRT -->
Mutation
Analysis*

Lab report mailed to PCP

1 month: CF Letter faxed to PCP

2 Mutation

Report Critical

Call PCP, fax report

Fax CF Center

* Sample to mutation analysis when: IRT in top 4% of daily sample OR > 170
### Case 1

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</thead>
<tbody>
<tr>
<td>Cystic Fibrosis Screen</td>
<td>Abnormal</td>
<td>&lt; Daily 4% Ng/mL</td>
</tr>
<tr>
<td>* IRT</td>
<td>64.0</td>
<td></td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation</td>
<td>No Mutations Found</td>
<td></td>
</tr>
</tbody>
</table>

### Case 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis Screen</td>
<td>Abnormal</td>
<td>&lt; Daily 4% Ng/mL</td>
</tr>
<tr>
<td>* IRT</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation</td>
<td>1717-1G&gt;A</td>
<td></td>
</tr>
</tbody>
</table>
## Case 3- Repeat Sample Sent

<table>
<thead>
<tr>
<th></th>
<th>Sample 1, DOL 2</th>
<th>Sample 2, DOL 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRT</td>
<td>52 ng/ml (&quot;Abnormal,&quot; &gt;96th %)</td>
<td>27 ng/ml (Normal)</td>
</tr>
<tr>
<td>CF mutation</td>
<td>df508</td>
<td></td>
</tr>
<tr>
<td>Other results</td>
<td>Report directs you to send repeat blood spot care due to abnormal amino acid screen.</td>
<td>Repeat amino acid screen is normal.</td>
</tr>
</tbody>
</table>
**Case 4**

### Cystic Fibrosis Screen

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>* IRT</td>
<td>Abnormal</td>
</tr>
<tr>
<td>CFTR Mutation Analysis</td>
<td>244.3</td>
</tr>
<tr>
<td>Pending</td>
<td></td>
</tr>
</tbody>
</table>

### Critical Test Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Interpretation</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis Screen</td>
<td>The results below for the Cystic Fibrosis Screen are suggestive of: Cystic Fibrosis</td>
<td>Critical</td>
</tr>
<tr>
<td>* IRT</td>
<td></td>
<td>244.3</td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation</td>
<td></td>
<td>dF508</td>
</tr>
<tr>
<td>* Cystic Fibrosis Mutation 2</td>
<td></td>
<td>N1303K</td>
</tr>
</tbody>
</table>
Case 5

Day 11 weight at 0.4%ile

- Notice sent by FAX to PCP and CF Center.
- Received on baby’s DOL 10.
Sweat Chloride Results

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Sweat Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30-59</td>
</tr>
<tr>
<td>Abnormal</td>
<td>&gt; 60</td>
</tr>
</tbody>
</table>

Babies with a positive NBS and intermediate sweat test should be followed at a CF Center.

Tentative label for such infants is “CRMS” or CFTR-related metabolic syndrome. With serial sweat testing and clinical followup, these infants may ultimately be reclassified as normal or as CF.
Sweat test results after Abnormal NBS

<table>
<thead>
<tr>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>60+</td>
<td>Positive</td>
</tr>
<tr>
<td>30-59</td>
<td>Intermediate</td>
</tr>
<tr>
<td>&lt;30</td>
<td>Negative</td>
</tr>
</tbody>
</table>

What to do?
Infants with “Borderline” Sweat Tests

- Initial sweat tests in the intermediate range (30-59 mEq/L) should be followed up

- **Example shown (Colorado):**
  5 infants with NBS positive and initial sweat test borderline: 3 later proven CF, 2 healthy

**New diagnostic term- 2009:**

**CRMS** = CFTR related metabolic syndrome

Or

**CFSPID** = CF Screen Positive Inconclusive Diagnosis

CRMS/CFSPID: 2 Scenarios

Example 1:
IRT positive
df508

Intermediate SC
(30-59)

One or No Definite CF causing Variant

Abnormal NBS

Example 2:
IRT positive
df508/R117H-7T

Definite disease causing mutation

Mutation/Variant of varying clinical significance

Bottom Line:
Follow clinically for signs of CF and sweat test conversion

Normal or Intermediate SC

- Unable to exclude CF by negative SC
- Unable to confirm CF by 2 definite disease causing variants after extended genotyping

- Variant of unknown significance may or may not ultimately cause clinical disease
Following a Child with CRMS

• Followup at CF Center at least twice in first year of life, then yearly

• Reinforce that child is healthy, does not have CF diagnosis, and needs no special health precautions- BUT needs annual CF Center checkup

• Be alert to potential symptoms of conversion to CF:
  • Not gaining weight
  • Persistent loose stools, extremely bad gas, or constipation
  • Very bad, frequent stomach aches
  • Persistent coughing or wheezing

Approximately 10% of CRMS babies ultimately develop CF.
Pearls on CF-NBS

• IRT/DNA protocols detect >95% of CF cases but can still miss a small %. Order sweat testing if you note symptoms concerning for CF.

• Babies with meconium ileus may have false negative CF-NBS due to low IRT.

• The finding of IRT top 4%/No Mutations constitutes a negative screen; no further action needed unless clinical concern or sometimes if ultrahigh IRT.

• Promptly follow up NBS positive screen results, even if they suggest that a carrier situation is most likely and there are no obvious CF symptoms.

• Sweat testing should occur at a CF center.

• Recommend genetic counseling if any CF mutation is found.

• Some positive screens cannot upon followup testing be resolved as CF or not, and these are termed CRMS/CFSPID and merit long term observation.

• Call your state NBS program or CF center for advice when needed, and consult cff.org website (CF Foundation) for additional info or parent-oriented materials.
My oh my, it’s an MDI

- Optimal use without a spacer requires a slow, deep inhalation commencing immediately after activation, followed by breath hold of 4-10 sec.
- Using spacer (VHC, valved holding chamber) reduces need for coordinating the maneuver.
- At best, pMDI without spacer delivers only 20% of emitted dose to lower airways, with 80% deposited onto the oropharynx (potential for topical effects - thrush or dysphonia, and more systemic absorption).
- Use of spacer slows down the aerosol cloud coming out of the pMDI, which may improve lung deposition of fine particles, and filters out larger particles more likely to deposit in pharynx or be swallowed.
- With pMDI, we **always** recommend use of spacer.
-Small mask: young infant (up to 6-9 mo)
-Medium mask: older infant to about 5y
-Large mask: older children who can’t switch to mouthpiece style (devel delay, oral anomaly, etc)

1. Hold the mask to the face so that both the nose and mouth are covered. It is important to between the face and mask so that all medication will be delivered to the airways.
2. Press the inhaler once. The medication will be delivered into the AeroChamber®.
3. Breathe in and out at least 6 times. The diaphragm should move with each breath.
4. Remove the mask from the face.
5. Repeat steps 1-4 when more than one puff is prescribed.
Spacer with Mouthpiece-
Usually ~age 5 and up

Steps for Using a Spacer with an MDI

1. Insert the Inhaler/canister into spacer and shake.
2. Breathe out.
3. Put the spacer mouthpiece into your mouth.
4. Press down on the inhaler once.
5. Breathe in slowly (for 3-5 seconds).
6. Hold breath for 10 seconds.
Diskus inhalers: Dry Powder

Issues:

- Difficulty with shallow mouthpiece fitting between lips, powder escaping
- No feel of puff since no propellant, thus lack of confidence in medication
- Dry powder may leave bad taste/film
- Confuses patient used to traditional pMDI

Esp for kids--Beware of pharmacy substitution of dry powder form instead of pMDI form of some medications!
2019: A Major Shift in Strategy for Adolescents and Adults with Asthma

- Never use SABA alone: safety issues due to increased risk of exacerbations

- ICS/LABA combo as the recommended product for both maintenance and rescue inhaler for this age group
  - Mild intermittent asthma: no daily med with prn low dose ICS-LABA (and no plain albuterol inhaler); or daily ICS plus prn low dose ICS-LABA

  - Moderate or severe asthma: daily controller is low dose ICS-LABA, with use of extra ICS-LABA as the rescue inhaler. For more severe asthma, use higher dose ICS component.

- Recommended ICS-LABA product is budesonide-formoterol (Symbicort)

- If have only individual inhalers of SABA and ICS, always start ICS with SABA as prn reliever

- Note, use of prn ICS-LABA is not approved by FDA as asthma reliever medication