Cystic Fibrosis Newborn Screening – An Opportunity to Improve the Health of Children Through Early Diagnosis and Treatment

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With

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On the basis of a preponderance of evidence, the health benefits to children with CF outweigh the risk of harm and justify screening for CF.

Newborn screening systems should ensure parental and provider education…
Learning Objectives

1. Describe the epidemiology of cystic fibrosis and challenges associated with diagnosis and treatment.

2. Explain the principles of newborn screening tests and how to interpret both positive and negative results.

3. Review the benefits and risks of newborn screening for cystic fibrosis using either the trypsinogen method with repeated testing or the trypsinogen/DNA strategy.

4. Describe the follow-up system needed in CF Centers and the early interventions that can facilitate better outcomes through preventive therapies.
Newborn Screening Promotes a Paradigm Shift

From:
Intervention in Individuals with Illness or Injury (4 I’s)

To:
Prevention in Presymptomatic Populations (3 P’s), e.g., CF
Lung Disease
(Chronic infection, inflammation, airways obstruction)

Salt Loss
(high sweat electrolytes--diagnostic test)

Gastrointestinal Abnormalities
(pancreatic insufficiency, malabsorption, and malnutrition)

CYSTIC FIBROSIS
Autosomal recessive disorder
(1/4000)*

Other Clinical Manifestations
(intestinal obstruction, cirrhosis, diabetes, etc.)

Sweat chloride ≥60 mEq/L traditionally used for diagnosis, although lower levels are compatible with CF
(Farrell and Koscik, Pediatrics 1996;97:524-528)

*Estimated incidence by ethnic/genetic background:
  White Americans ~ 1/3000
  Hispanic Americans ~1/6000
  African Americans ~1/10,000
(Comeau et al, Pediatrics 2004;113:1573-1581)
Discovery of the $\Delta$F508 CFTR Mutation
Milestones in Diagnosis of CF

1938: Andersen
   (Am J Dis Child 1938;56:344-399)
   Autopsy-based identification

1953: di Sant’Agnese
   (Pediatrics 1953;12:549-563)
   “Sweat electrolyte disturbances”

1959: Gibson and Cooke
   (Pediatrics 1959;23:545-549)
   Quantitative pilocarpine
   iontophoresis

1970: Shwachman
   (Pediatrics 1970;46:335-343)
   Value of early recognition (<3 months)

1979: Crossley, Elliott, Smith
   (Lancet 1979;1:472-474)
   Trypsinogen screening (IRT test)

1989: Tsui, Riordan, Collins
   (Science 1989;245:1073-1080)
   DNA analysis for ∆F_{508}

IRT/IRT → IRT/DNA (∆F_{508}) → IRT/DNA (CFTR)*

Early diagnosis through newborn screening

*IRT/DNA (CFTR) = Multimutation panel of 25 or more mutant alleles
Traditional Method of Diagnosis (at an average age of 4 years)

Sweat test by pilocarpine iontophoresis after recognizing signs/symptoms or family history; expensive because of ~100 negative tests per CF patient diagnosed.

Presenting Manifestations:

- 25% Respiratory and GI
- 22% Meconium ileus
- 15% GI (malabsorption or FTT)
- 15% Respiratory (acute or chronic)
- 13% Other signs or symptoms, i.e., electrolyte imbalance, nasal polyps/sinus disease, liver disease, rectal prolapse, etc

[Lai et al, AJE 2002;156:165-173 (11,275 CFF patients)]
Onset of Cystic Fibrosis Disease

- Variable age depending on genotype/phenotype (but generally manifest during infancy)

- At birth in ~20% with Meconium ileus (may have false negative newborn screening results)

- Malnutrition is often early (by 2 months) (Sokol et al, Am J Clin Nutr 1989; 50:1064-1071) (Bronstein et al, J Pediatr 1992; 120; 533-540)

Age at Diagnosis: 21,588 CF Patients (1999 CFF Patient Registry)

Diagnosis by symptoms (Lai et al, AJE 2004;159:537-546):
Mean/median age: Males = 43/9; Females = 49/13 months
Problems Associated with Delayed Diagnosis*

- Potentially preventable deaths and shortened survival
- Severe, potentially fatal malnutrition or electrolyte imbalance
- Possible pulmonary complications (pneumonia, atelectasis, etc)
- Disparities associated with delays in some populations
- Parental anxiety and frustration
- Parental uninformed reproductive decision-making

*Suffering of patients, parents, and siblings

**Potentially ~5% of CF patients die undiagnosed
Long Term Implications of Early Prolonged Malnutrition in CF

Failure to achieve genetic growth potential
(Farrell et al, J Pediatr 2005;147 S30-S36)

Impaired development of cognitive function
(Koscik et al, Pediatrics 2004;113:1549-1558)

Increased risk of early lung disease
(Konstan et al, J Pediatr 2003;142: 624-630)
Severe CF Malnutrition at Diagnosis
(3 month old diagnosed during 2001 in a nonscreening state)

Potentially fatal protein-energy malnutrition with salt depletion

Photo courtesy of Frank J. Accurso, MD
Newborn screening for cystic fibrosis
Newborn Screening Definition*

Population-based public health program applying preventive medicine in defined regions to reduce infant morbidity and mortality from certain biochemical and genetic disorders by using presymptomatic detection/diagnosis with dried blood specimens from newborns analyzed in central laboratories employing automated computerized procedures linked to clinical follow-up systems.

Principle of Achieving Better Outcomes Through Newborn Screening

- Screening/Follow-up/Diagnosis
- Effective Therapy

- Birth
- Biologic Onset
- Symptomatic Onset
- Life Threatening or Irreversible Disease
- Death

Preclinical Stage

Time/Event
Newborn Screening System Components
(from the ACMG-MCHB/HRSA Report)*

1. Education of professionals and parents.
2. Screening—specimen collection, submission, and testing.
3. Follow-up of abnormal and unsatisfactory test results.

4. Confirmatory testing and diagnosis.
5. Medical management and periodic outcome evaluation.

*Recommends mandated screening for 29 genetic conditions and multiplex technologies.
Diagnosis Through Newborn Screening

This ~0.4 ml dried blood specimen supports numerous screening tests!
# States | Disease
---|---
51 | Phenylketonuria
51 | Congenital Hypothyroidism
51 | Galactosemia
51 | Sickle Cell Disease (plus “trait”)
41 | Congenital Adrenal Hyperplasia
36 | Biotinidase Deficiency
39 | Maple Syrup Urine Disease
35 | Homocystinuria
19++ | Cystic Fibrosis (plus CF-HZ carriers)

**Also:**

34 | Tandem Mass Spec for 11 fatty acid oxidation defects, 11 organic acidemias, and 8 amino acidemias
NBS Financing Mechanisms Vary

1. Revenue producing functions (e.g., “selling” Guthrie cards as in Wisconsin and Ohio)

2. Governmental budgetary allocations (e.g., line item fiscal commitments annually as in New York and Texas)

Economic Aspects of CF Newborn Screening

(Lee et al, J Pediatr 2003;142:617-23)

1. Diagnosis by traditional method is expensive due to the high number of sweat tests ($16,846 per patient).

2. IRT/DNA (__F508) at $2.66 per screened baby can be cost effective with savings to finance regional costs.

3. IRT/DNA (CFTR) is more expensive ($4.16) but provides significant added value ($9,390 → $12,817 per patient).

4. Reducing the need for hospitalizations is the greatest cost-saving potential economic benefit of CF/NBS.

5. Further study is needed on cost effectiveness and other economic aspects of CF diagnosis/treatment.

* Financial data are provided as year 2000 dollars
Distribution of IRT Values in 10,000 Screened Newborns
(Farrell et al, unpublished data)
## CFTR Mutant Alleles in U.S. Patients*
*(CFF Registry, 1998)*

<table>
<thead>
<tr>
<th>Allele</th>
<th>% Mutations</th>
</tr>
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<tbody>
<tr>
<td>ΔF508</td>
<td>68.6</td>
</tr>
<tr>
<td>G542X</td>
<td>2.4</td>
</tr>
<tr>
<td>G551D</td>
<td>2.1</td>
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<tr>
<td>W1282X</td>
<td>1.4</td>
</tr>
<tr>
<td>N1303K</td>
<td>1.3</td>
</tr>
<tr>
<td>R553X</td>
<td>0.9</td>
</tr>
<tr>
<td>621+1G → T</td>
<td>0.9</td>
</tr>
<tr>
<td>3849+10kbC → T</td>
<td>0.7</td>
</tr>
<tr>
<td>1717-1G → A</td>
<td>0.7</td>
</tr>
<tr>
<td>R117H</td>
<td>0.7</td>
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<table>
<thead>
<tr>
<th>Allele</th>
<th>% Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔI507</td>
<td>0.3</td>
</tr>
<tr>
<td>2789+5G → A</td>
<td>0.3</td>
</tr>
<tr>
<td>G85E</td>
<td>0.3</td>
</tr>
<tr>
<td>R347P</td>
<td>0.2</td>
</tr>
<tr>
<td>R334W</td>
<td>0.2</td>
</tr>
<tr>
<td>R1162X</td>
<td>0.2</td>
</tr>
<tr>
<td>R560T</td>
<td>0.2</td>
</tr>
<tr>
<td>A455E</td>
<td>0.2</td>
</tr>
<tr>
<td>2184delA</td>
<td>0.1</td>
</tr>
<tr>
<td>711+1G → T</td>
<td>0.1</td>
</tr>
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* Bobadilla et al, Human Mutation 2002; 19:575-606
IRT level as a predictor of CF in infants with positive IRT/DNA (ΔF508) screen* 
(Gregg et al, Pediatrics 1997;99:819-824)

<table>
<thead>
<tr>
<th>IRT level (ng/ml)</th>
<th># CF / # Infants</th>
<th>CF Risk, %(95% C.I.)</th>
</tr>
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<tbody>
<tr>
<td>100-140</td>
<td>0/1404</td>
<td>0</td>
</tr>
<tr>
<td>140-180</td>
<td>1/387</td>
<td>0.25 (0-0.7)</td>
</tr>
<tr>
<td>180-220</td>
<td>12/333</td>
<td>3.6 (1.6-5.6)</td>
</tr>
<tr>
<td>220-260</td>
<td>13/122</td>
<td>10.7 (5.2-16.2)</td>
</tr>
<tr>
<td>260-300</td>
<td>11/59</td>
<td>18.6 (8.7-28.5)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>20/83</td>
<td>24.1 (14.9-33.3)</td>
</tr>
</tbody>
</table>

*Estimates are based on observed rates of non-meconium ileus diagnosis

“Ultrahigh” IRT values
Screening Algorithms for Cystic Fibrosis

IRT/IRT (Colorado)

IRT @ 24-48 hours
> cutoff (~140 ng/ml)
  Recall* (0.6%) 600
IRT @ 2 weeks
> cutoff (~100 ng/ml)
  Notify PCP/parents (0.2%) 200
Sweat test @ 3 weeks

IRT/DNA (WI and MA)

IRT @ 24-48 hours
> cutoff (variable)
  Highest 4-6% 5000
DNA analysis for 1-86 mutations
Ultrahigh IRT
  1 or 2 mutations*
  1 mutation: ~250
  2 mutations: 12-20
  IRT > 170 ng/ml: 60
Sweat test @ 3 weeks


* If 2 mutations are detected, notification is immediate; sweat chloride of >30 mEq/L is “abnormal” and potentially diagnostic (Farrell and Koscik, Pediatrics 1996;97:524-528)
## Sensitivity, Specificity and Positive Predictive Value of Three Screening Methods

*(Rock et al, J Pediatr 2005;147:S73-S77)*

<table>
<thead>
<tr>
<th>Method</th>
<th>PPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cost/Baby</th>
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<tbody>
<tr>
<td>IRT (99.8 percentile)</td>
<td>12.5%</td>
<td>87%</td>
<td>99%</td>
<td>$1.41</td>
</tr>
<tr>
<td>IRT/DNA (ΔF508)</td>
<td>10%</td>
<td>94%</td>
<td>99%</td>
<td>$2.27</td>
</tr>
<tr>
<td>IRT/DNA (CFTR)</td>
<td>9%</td>
<td>99%</td>
<td>99%</td>
<td>$3.55</td>
</tr>
</tbody>
</table>

* Genetic diagnosis from 2 CFTR mutant alleles in 41% (ΔF508/ ΔF508)

** Presumptive diagnosis from 2 CFTR mutant alleles in 67% (25 allele test)
Advantages of CFTR Multimutation Panel* vs. ΔF508 Analysis Alone
(Comeau et al, Pediatrics 2004;113;1573-1581)

• Immediate (genetic) diagnosis in 75% vs. 50% of patients
• Greater sensitivity (98.2% vs. 92.7%)
• Lower risk of true positives in group with positive IRT/DNA and one mutation (1:37 vs. 1:17)

*Also detects more CF heterozygote carrier infants (43% increase)
Sweat Test Considerations

- Follow up sweat test should be scheduled immediately
- Most infants produce adequate sweat by 2-3 weeks (if > 2 kg)
- CFF guidelines should be followed for sweat testing infants
- QPIT should be used at certified centers with a 75 mg requirement or 15 µl by macroduct method
- Chloride concentrations above 30 mEq/L are compatible with a CF diagnosis and above 40 mEq/L levels are diagnostic
- Requiring ≥ 60 mEq/L for diagnosis is inappropriate
- “Borderline” concept may be confusing to parents and caregivers

Farrell and Koscik, Pediatrics 1996; 97:524-528
Parad et al, J Pediatr 2005;147:S69-S72
Benefits of Early Diagnosis Through CF Neonatal Screening

1. Prevent deaths of ~5% undiagnosed patients--save lives!
2. Improve access--avoid geographic and fiscal barriers
3. Avoid disparities related to gender, race and ethnicity
4. Provide genetic counseling for parents, etc.
5. Reduce costs for diagnosis and possibly treatment
Benefits of Early Diagnosis Through CF Neonatal Screening

6. Prevent protein-energy malnutrition and stunted growth

7. Prevent micronutrient deficiencies such as vitamin E

8. Reduce risk for cognitive dysfunction due to malnutrition

9. Delay onset of PA infection and progression of lung disease*

10. Enhance quality of care and quality of life

* Create the opportunity to initiate respiratory treatment before irreversibility develops ("point of no return"), which will eventually facilitate prevention of lung disease when correction of the basic defect becomes available (i.e., lung "cure")
Wisconsin Randomized Clinical Trial Results: Anthropometric Indices at Diagnosis
(Farrell et al, Pediatrics 2001;107:1-2)

- **Screened Group (n=57); \( \bar{x} \) age = 13 weeks**
  - Length or Height Percentile: 25%
  - Weight Percentile: 24%
  - Head Circumference: 32%
  - **44%**
  - **p < 0.01**

- **Control Group (n=51); \( \bar{x} \) age = 107 weeks**
  - Length or Height Percentile: 25%
  - Weight Percentile: 24%
  - Head Circumference: 32%
  - **52%**
  - **p = 0.003**

- **Weight Percentile**
  - **p = 0.018**
Wisconsin CF Neonatal Screening RCT = Growth of Screened and Traditionally Diagnosed Patients

(Farrell et al, J Pediatrics 2005;147:S30-S36)
Head Circumference and Cognitive Score Values

(Koscik et al, J Pediatr 2005;147:S51-S56)  
(Koscik et al, J Pediatr 2004;113:1549-58)

Control, vitamin E < 300 (n=16)  
Control, vitamin E ≥ 300 (n=13)  
Screened, vitamin E < 300 (n=17)  
Screened, vitamin E ≥ 300 (n=20)

GEE p = 0.019

Cognitive Score

p<.05

Cognitive Skills Index
Wisconsin Randomized Clinical Trials Results:
Chest Radiographic Scores at Diagnosis

- **Screened Group (n=49)**: Mean age = 13 weeks
- **Control Group (n=40)**: Mean age = 107 weeks

The bar graph shows the WCXR (Worsening Chest Radiography) scores comparing the two groups. The screened group has a mean score of 7, while the control group has a mean score of 8.

- **p = .012** (age adjusted)
- **p = .014** (age adjusted)

The scores indicate a statistically significant difference between the two groups, with the control group having worse scores compared to the screened group.
Pulmonary Function in CF Patients by Diagnostic Category and Age Calculated from CFF registry data of 2002 (Accurso et al, J Pediatr 2005;147:S37-S41)
Neonatal Screening for CF
More good than harm? YES

Risks
Medical: Pseudomonas acquisition (nosocomial; antibiotics)
Psychosocial: False positive families (misunderstandings)
Insurance: Potential loss of coverage

Benefits
Nutritional Pulmonary Psychosocial
Provide genetic counseling
Prevent malnutrition
Preempt lung disease
Provide psychosocial support
"The net balance of benefits and risks is contingent on how newborn screening for CF is implemented."

"Newborn screening for CF should be accompanied by rigorous infection control practices..."
Excellent Implementation is the Key to Ensuring More Good than Harm*

The benefits of early diagnosis through CF newborn screening can only be accomplished with the essential elements sustained.

1. Organize a collaborative program involving CF centers and the regional screening lab(s).
2. Establish excellent follow-up mechanisms, including high quality communications methods, sweat testing and multidisciplinary care.
3. Be prepared when parents first visit (IRT/DNA results predict most patients).
5. Improve respiratory management aimed at prevention of chronic infections (especially Pseudomonas aeruginosa acquisition and infection).

See also, “10 Steps to Success” (Adv Pediatr 47;79-115, 2000)
**Goals of CF Neonatal Screening**

- Initiate CF center care in newborns
- Provide genetic counseling
- Prevent severe malnutrition
  - Vitamin E deficiency (hemolytic anemia)
  - Vitamin A deficiency
  - Essential fatty acid deficiency
  - Protein energy malnutrition*
  - Growth failure
- Prevent hyponatremia/hypochloremia
  - Salt loss in sweat*
  - Associated with breast feeding
- Prevent early progression of lung disease
  - Recurrent bacterial infections
  - Obstructive pulmonary disease
  - Atelectasis with mucus plugs

*Potentially fatal
Three Preventive Goals

- Prevent misunderstandings
  (effective risk communication)

- Prevent malnutrition
  (support normal growth)

- Prevent mucoid PA
  (identify acquisition and treat)
CF Infant Nutrition Management

1. Diagnose before malnutrition begins
2. Commit to preventing malnutrition
3. Assess pancreatic function
4. Pancreatic therapy, as indicated
5. High caloric intake, as needed
6. Essential fatty acid supplementation
7. Fat soluble vitamin supplements
8. Salt supplements, as indicated
9. Ensure excellent compliance
10. Monitor growth frequently
CF Infant Pulmonary Care:
The CF lung is normal at birth—great opportunity!

1. Segregated/PA-free clinic and/or hospital care is ideal.

2. Observation for symptoms/signs is needed from diagnosis.

3. Recurrent cough is an early sign of chronic respiratory infection.

4. Chest radiographs, preferably obtained serially, may reveal subtle signs of infection (e.g., peribronchial thickening).

5. The roles of infant pulmonary function testing and chest HRCT scans are evolving.
6. Respiratory secretion cultures are helpful but not as sensitive as pseudomonas serology for adequate reliability.

7. Anti-Staph therapy used intermittently can be quite effective.

8. Anti-PA therapy, when indicated, should be employed for eradication of non-mucoid PA, including aerosolized tobramycin.

9. Chest physiotherapy is helpful when bronchial drainage is needed for secretions but may be risky (eg, GER).

10. Other therapies such as RSV prophylaxis, DNase, bronchodilators, and anti-inflammatory agents may help but need further investigation.
Summary of Advantages of Newborn Screening

- Avoid diagnostic “odyssey” and parental anxiety
- Early, specific & proper care at a CF Center
- Prevent rather than treat malnutrition
- Lung function preservation = better survival
- Improved pharmacoeconomic benefit
- Systematic, proactive strategy of care
- Improved quality of life likely
- Improved parental learning
Status of CF Newborn Screening

US annual births - 4,000,000

<table>
<thead>
<tr>
<th>Year</th>
<th>% births screened</th>
<th>New dx</th>
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<tbody>
<tr>
<td>2000</td>
<td>5%</td>
<td>50</td>
</tr>
<tr>
<td>2006</td>
<td>25%</td>
<td>250</td>
</tr>
<tr>
<td>2007</td>
<td>70%</td>
<td>700</td>
</tr>
<tr>
<td>2010</td>
<td>100% (CFF target)</td>
<td>1,000</td>
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