Nationwide Newborn Screening for Cystic Fibrosis: Finally Creating an Opportunity for All Patients to Have Better Outcomes

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*No disclosures other than CFF.

Learning Objectives

1. Describe the new strategy of diagnosing cystic fibrosis early through newborn screening, including the plans for implementation of IRT/RT/RT/DNA testing in Texas.

2. Interpret the latest clinical evidence regarding airway infections and their impact on the CF population.

3. Discuss QoL assessment using the CF Questionnaire.

4. Summarize data on the current pharmacologic options and products in development (mutation-specific therapy).
**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 poly/vincent disease, liver disease, rectal prolapse, etc

[Ju et al, AJE 2002;156:165-173 (11,275 CFF patients)]

**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

**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

**Consequences in Texas of Diagnosing CF without NBS during 2005-2009**

(assuming ~100/yr new CF diagnoses)

- ~20 preventable deaths of undiagnosed patients*
- ~200 children with preventable, severe malnutrition (probably “stunted” forever)
- ~100 CF patients with irreversible lung disease at diagnosis
- ~130 CF children with Pseudomonas aeruginosa at diagnosis
- Parental anger, frustration, and uninformed reproduction
- Widespread medical malpractice risk

*Potentially ~5% of CF patients die undiagnosed

**CF NBS Historical Perspective:**

The Beginning in Auckland, NZ

1979: IRT* discovery in NZ—“the shot heard around the world” for CF NBS
(Crossley JR, Elliott RB, Smith PA, Lancet 1:472, 1979)

*Immunoreactive trypsinogen

Result: Potential of IRT recognized (retrospectively)

Discovery of the ΔF508 CFTR Mutation

Research teams led by Lap-Chee Tsui, Jack Riordan, and Francis Collins
Demonstration of Benefits from Early Diagnosis through CF NBS


“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…”

Neonatal Screening for CF

Risks
- Medical
- Psychosocial
- Psychological

Benefits
- Nutritional
- Pulmonary
- Psychosocial
- Psychological

Children of early diagnosis

Status of CF NBS in 2004

- Universally required
- Universally offered, but not required
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 procedures linked to clinical follow-up systems.


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 multiple technologies.

Diagnosis Through Newborn Screening

This ~0.4 ml dried blood specimen supports numerous screening tests!

Evolution of Cystic Fibrosis Newborn Screening Tests

IRT → IRT/DNA → IRT/DNA (CFTR)

1979 → 1991 → 2003

Follow-up Responsibilities of Cystic Fibrosis Centers

1. False positive families*
2. Diagnosed patients
3. Uncertain cases (eg, CRMS)
4. False negative patients

*May be shared or delegated

Goals of CF Neonatal Dx & Rx

- 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

CFTR Mutant Alleles in U.S. Patients*

(Cystic Fibrosis Foundation Registry, 1998)

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*Bobadilla et al, Human Mutation 2002; 19:575-606. These 20 alleles and 5 others are included in the 25 mutation ACMG panel.
**Found in specific ethnic populations.
***Associated with CF when the 5T variation is present.
Three Preventive Goals

- Prevent misunderstandings (effective risk communication)
- Prevent malnutrition (support normal growth)
- Prevent mucoid PA (identify acquisition and treat)

“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…”

Huang, Nancy N et al

The Flora of the Respiratory Tract of Patients with Cystic Fibrosis of the Pancreas

J. Pediatrics 1961;59:512-521
(demonstrated the importance of Pseudomonas aeruginosa)

Stages of PA Infection

- No PA by culture*
  ↓ ↑
- Non-mucoid PA (initial infection)
  ↓
- Mucoid PA (MPA)

*may be infected by serologic Dx
Quality of Life in Children with CF

- Evaluated by the CF Questionnaire
- Measures the subjective and objective impact of dysfunction with an illness
- Includes the dimensions of physical health, role limitations, emotional state, energy, and social limitations as well as CF-specific dimensions of body image, eating disturbances, treatment constraints, and embarrassment.

CF lung disease based on WCXR scores showed a strong negative relationship with the QOL Respiration and Physical scales (p<0.006). FEV-1/FVC showed a strong positive relationship with Respiration scale (p<0.005). Percent FEV-1 predicted the Social scale (p=0.010) but no other health scales. Among participants age 14 and older, WCXR scores significantly

Therapeutic Strategy: Increase Mutant CFTR Function
Amount of mutant CFTR function correlates to disease severity

Directly Targeting the Core Defects in Mutant CFTR
Orally Bioavailable Small Molecule Therapies

The New Era for CF Patients

1. A “paradigm shift” (predicted by CDC)
2. Routine early Dx and prevention
3. Much better patient outcomes (safer, more effective care)
4. Better quality of life
5. Transition of healthy adults to Adult CF Centers