CYSTIC FIBROSIS DIAGNOSIS AND NEWBORN SCREENING

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History of Cystic Fibrosis Newborn Screening

- 1970's: New Zealand
  - Developed method to **measure immunoreactive trypsinogen (IRT) on a dried blood spot specimen using radioimmunoassay.**
  - IRT is thought to be increased due to pancreatic duct dysfunction in both pancreatic-sufficient and pancreatic-insufficient infants and CF carriers in the first few weeks of life.
  - Screening by IRT was then adopted in U.K and Australia
- 1982, Colorado, first US state to initiate CF newborn screening,
  - followed shortly thereafter by ***"Wisconsin Cystic Fibrosis Neonatal Screening Project"-*** on going randomized trial, successfully demonstrated feasibility/long-term efficacy for nutritional outcomes.
- Uptake slow internationally due to lack of evidence to support benefit
- **After the 2004 CDC's statement of justification-rapid uptake from 8 states 2004 to 50 in 2010 and widespread international adoption**

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Impact of Early Diagnosis of Newborn Screening on Outcomes

- Most disorders on the newborn screening panel responsive to treatment in first weeks of life to avoid morbidity and mortality.
- Cystic Fibrosis is different:
  - At birth pancreatic disease leads to early malabsorption/malnutrition
  - Lung disease starts early in infancy
  - **Definitive treatment has not been available that would stop disease progression in infancy**

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Impact of Early Diagnosis on Outcomes- Benefits

- Clinical evidence 1980s-1990s lead to the CDC statement in 2004 that:
  - newborn screening for CF justified based on the *benefits of early intervention and treatment of early malabsorption and improved growth.*
- Additional reports, show *screened* infants:
  - have decreased pulmonary complications
  - can avoid early vitamin E deficiency associated with lower cognitive function
  - potential survival advantage

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Nutritional and Pulmonary Outcomes in the First Year

- Despite catch-up growth in weight following newborn screening **linear growth impairment continues to occur during the first year**
  - *earlier, more aggressive nutritional therapy necessary for normal growth.*
- **Guidelines for infant care and a more aggressive approach to preventative care are in place however:**
  - lung disease known to be present in the first months of life
  - ability to change the early course of lung disease in CF remains limited
  - *need for early therapies before onset of irreversible lung damage*
  - *long-term pulmonary benefits of CF newborn screening controversial*
- *Hope that CFTR modulators may offer hope*

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Broad Range of CFTR Dysfunction

- 1989: CFTR gene, long arm of chromosome 7 but **CFTR dysfunction encompasses a wide range of phenotypes** that can be challenging to diagnose:
  - classic pancreatic-insufficient CF
  - pancreatic sufficient CF
  - indeterminate diagnoses identified by newborn screening
  - single-organ-system manifestations identified in adulthood
- CFTR mutation analysis showing **2 CF-causing mutations in trans** is consistent with the diagnosis of CF however >2000 mutations identified only *minority* are disease causing.
- CFTR2 Web site (http://www.cftr2. org/) up-to-date information on CFTR mutations, phenotypic consequences.

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The Sweat Chloride Test:
cornerstone of diagnosis

- Sweat test directly measures CFTR dysfunction
- Proper performance critical: **requires skill and experience at accredited CF center "deceptively simple"**
- Involves:
  - transdermal administration of pilocarpine by iontophoresis to stimulate sweat gland secretion
  - sweat collection into a Macroduct coil/gauze/filter paper
  - analysis of chloride concentration (chloridometer).
- **Can be performed in healthy infants more than 2 kg and 2 weeks of age *ideally before 30 days of life***

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Cystic Fibrosis Screening Algorithms

- State public health systems responsible. Adoption/implementation/follow up is variable however based on local resources and legislative/regulatory constraints.
- **All state algorithms use an increased IRT level as the first stage**
- Increased IRT levels can also be seen in preterm infants and in African Americans
- Therefore all states use a **multistage algorithm to minimize false-positives with second stage testing using IRT/DNA for CFTR mutations**
- CFTR screening mutation panels *must cover the racial composition of population* screened, nonwhite populations problematic
- An **ultrahigh IRT algorithm** proposed in some states with ethnically diverse populations whereby:
  - Infants with no mutations identified, extremely increased IRT test recalled for sweat chloride testing

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Diagnosing CF in Newborn-screened Infants

- **Infants with 2 CF-causing mutations on the newborn screen still need a sweat chloride for diagnosis**
  - presumptive diagnosis of CF if initiation of therapies necessary
- **Value >= 60 mmol/L in an infant with a positive newborn screen is consistent with diagnosis**
- *Value < 30 mmol/L makes CF unlikely*
- *A value of 30 to 59 mmol/L is "indeterminate" and suggests "possible CF"-* extended CFTR mutation analysis required
- Meconium ileus:
  - false-negative screen possible
  - presumptive diagnosis of CF until further testing accomplished

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Cystic Fibrosis Transmembrane Regulator Metabolic Syndrome (CRMS)

- Described after NBS became widespread
- CRMS can only be diagnosed after a newborn screen not in later life
- Infant has a **positive newborn screen but indeterminate diagnosis** either:
  - sweat chloride <30 mmol/L with 2 CFTR mutations, (1 unclear phenotype) or
  - sweat chloride 30-59 mmol/L and < 2 CF-causing CFTR mutations.
- Most infants remain asymptomatic, small proportion ultimately develop CF and ***all should be followed on a regular basis by an CF Center and PCPs should refer to the CF Center staff should CF symptoms develop***

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Cystic Fibrosis Transmembrane Conductance Regulator–related Disorder (CFTR-RD)

- Indeterminate diagnosis can also arise in older patients
- CFTR-RD is associated with CFTR dysfunction that does not meet diagnostic criteria for CF:
  - >1 clinical features associated with CFTR dysfunction
  - patients are ***symptomatic***;
  - *tend to have* ***CFTR mutations result in diminished CFTR function, but not so reduced as to result in a full CF phenotype.***
  - Work up includes:
    - expanded genetic testing, lung function testing, chest imaging, respiratory culture, fecal elastase, genital evaluation in boys.

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Changing Landscape of Cystic Fibrosis over the last decade

- Instead of being diagnosis based on symptoms, after having endured long, difficult, expensive diagnostic odyssey **62% of U.S new diagnoses in 2013 were detected by newborn screening**
- Very different experience for parents
- Some individuals are still diagnosed symptomatically:
  - Born before implementation of NBS
  - False-negative newborn screen
  - Family refusal to screen

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Diagnosing Cystic Fibrosis: Symptomatic Individuals

- **Any child with signs/symptoms of CF or positive family history should have sweat testing regardless of CF newborn screen**
  - sweat chloride level less <39 mmol/L unlikely to be CF
  - indeterminate sweat chloride requires extended genetic testing

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Signs and symptoms suggestive of CFTR dysfunction in children and adolescents

Nutritional and gastrointestinal:

- Nutritional/metabolic: failure to thrive, hypoproteinemia, hypochloremic dehydration, chronic metabolic alkalosis
- Intestinal: meconium ileus, rectal prolapse, distal intestinal obstructive syndrome, steatorrhea
- Pancreatic: exocrine pancreatic insufficiency, recurrent pancreatitis
- Hepatic: protracted neonatal jaundice, biliary cirrhosis

Sinopulmonary:

- Chronic wet or productive cough
- Bronchiectasis on chest imaging
- Respiratory infection with *Pseudomonas aeruginosa* or other atypical gram-negative organisms
- Nasal polyposis in children
- Digital clubbing
- Allergic bronchopulmonary aspergillosis

Obstructive azoospermia in boys

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Summary

- The diagnosis of CF is straightforward in most patients.
- Rapid advances in CFTR genetics/CF NBS make clear the varying clinical manifestations of CFTR dysfunction that complicate diagnosis
- We balance the benefits of early detection and treatment of a life-shortening illness with the risks of inconclusive diagnoses in infants who are likely to remain healthy, but in whom there is a small risk of progression to CF.
- CF newborn screening/ diagnosis algorithms are likely to change in next decade based on advances in tandem mass spectrometry/extended genetic analysis, better understanding of genotype-phenotype.
- Critical to keep risks/benefits of detection of the wide range of CFTR dysfunctions in mind.

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