2017 Alabama Newborn Screening Conference

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Prattville, Alabama
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Cystic Fibrosis

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Outline

- **What is CF?**
- **How we diagnose CF?**
- **What are the clinical manifestations of CF?**
- **How do we treat CF?**
- **New and future treatments for CF**

WHAT IS CYSTIC FIBROSIS?

Cystic fibrosis (CF) is a progressive, genetic disease that causes persistent lung infections and limits the ability to breathe over time.
In people with CF, a defective gene causes a thick, sticky buildup of mucus in the lungs, pancreas, and other organs.

WHAT IS CYSTIC FIBROSIS?

In the lungs, the mucus clogs the airways and traps bacteria leading to infections, extensive lung damage, and eventually, respiratory failure. In the pancreas, the mucus prevents the release of digestive enzymes that allow the body to break down food and absorb vital nutrients.

WHAT IS CYSTIC FIBROSIS?

Symptoms of CF
People with CF can have a variety of symptoms, including:
•Very salty-tasting skin
•Persistent coughing, at times with phlegm
•Frequent lung infections including pneumonia or bronchitis

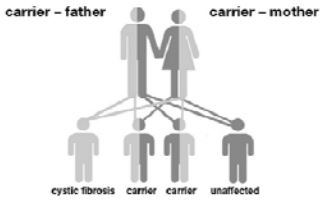
WHAT IS CYSTIC FIBROSIS?

- Wheezing or shortness of breath
- Poor growth or weight gain in spite of a good appetite
- Frequent greasy, bulky stools or difficulty with bowel movements

GENETICS of CF

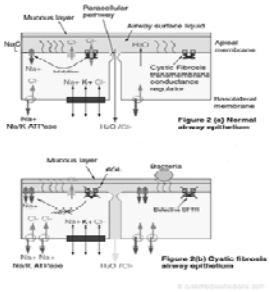
- **Autosomal recessive**

The disorder is inherited by two copies of a defective cystic fibrosis gene. One from each parent.



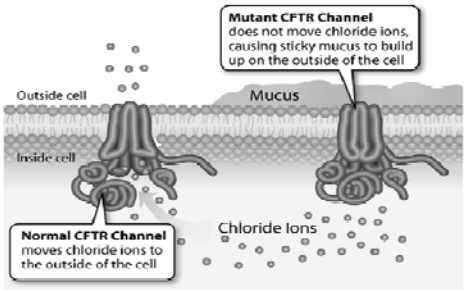
www.cysticfibrosis.org.uk

FUNCTIONAL CONSEQUENCE OF CF MUTATIONS



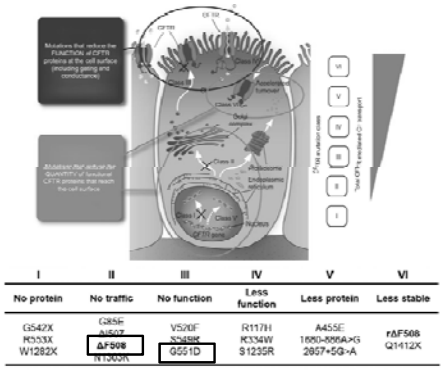
http://www.cfmedicine.com/htmldocs/images/iontransport.jpg

FUNCTIONAL CONSEQUENCE OF CF MUTATIONS

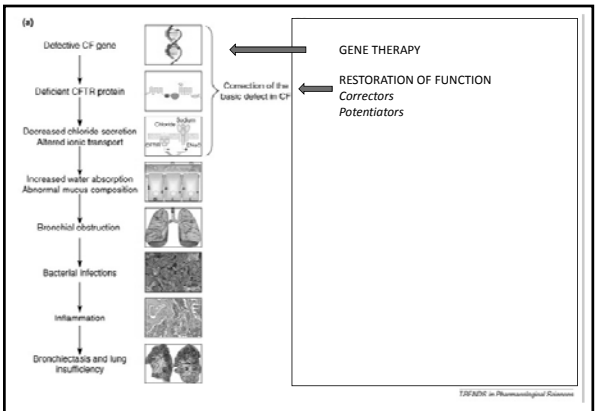


http://learn.genetics.utah.edu/content/disorders/singlegene/cf/images/cf-channel.jpg

FUNCTIONAL DEFECT in CF



I	II	III	IV	V	VI
No protein	No traffic	No function	Less function	Less protein	Less stable
G542X R553X W1282X	G85E ΔI507 ΔF508 N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	rΔF508 Q1412X



http://www.cell.com/cms/attachment/586391/4450266/gr1.jpg

HOW DO WE DIAGNOSE CF?

Blood Spot Screen

Newborn Screening for CF

From Blood spot screen:

1. IRT measurement
2. DNA analysis (Mutation Panel)
3. Sweat Test

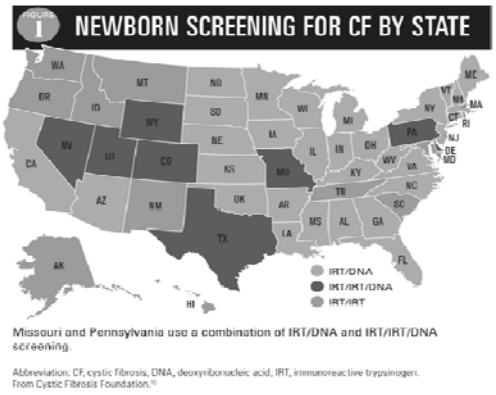
NOTES:

1. *IRT level is considered POSITIVE if above a cutoff level*
2. *Mutation panel does NOT test of all known CFTR mutations*

Blood Spot Screen

AL Confirmed NBS CF Diagnoses

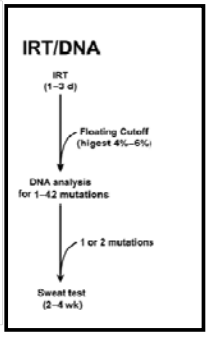
Year	2008	2009	2010	2011	2012	2013	2014	2015	2016
Cases	7	23	13	19	14	12			



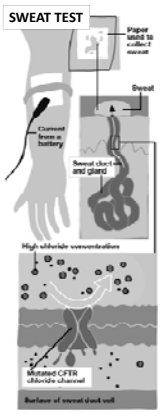
Missouri and Pennsylvania use a combination of IRT/DNA and IRT/IRT/DNA screening.

Abbreviation: CF, cystic fibrosis; DNA, deoxyribonucleic acid; IRT, immunoreactive trypsinogen.
From Cystic Fibrosis Foundation.[10]

DIAGNOSIS of CF



http://pediatrics.aappublications.org/content/123/2/e338.figures-only



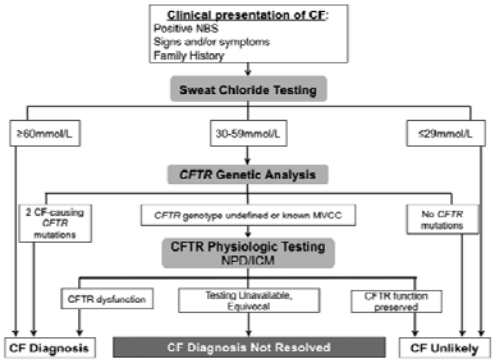
Interpretation of sweat test results (2017)

For newborns, a chloride level of:

- Less than 30 mmol/L (negative) = CF is very unlikely

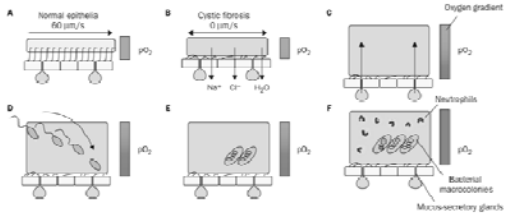
For all populations, a chloride level of:

- Less than 30 mmol/L (negative) = CF is very unlikely
- Between 30 - 59 mmol/L (intermediate) = may have CF
- Greater than or equal to 60 mmol/L (positive) = CF is likely to be diagnosed



WHAT ARE THE CLINICAL MANIFESTATIONS OF CF?

PATHOPHYSIOLOGY of LUNG DISEASE in CF

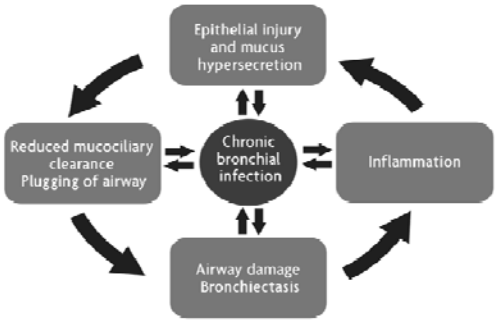


Triad of LUNG DISEASE in CF:

- AW Obstruction
- AW Inflammation
- Infection

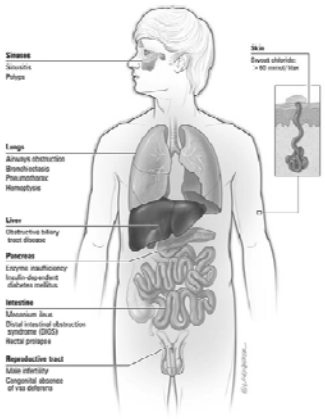
http://www.thelancet.com/cms/attachment/2002696134/2009454142/gr1_lrg.jpg

PROGRESSION OF LUNG DISEASE IN CF. A VICIOUS CYCLE

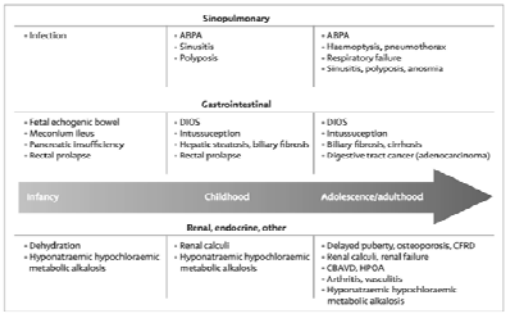


SYSTEMS or ORGANS INVOLVED in CLINICAL MANIFESTATIONS of CF

Most common Manifestations:
Chronic cough
Failure to thrive
Recurrent "bronchitis/ pneumonia"



AGE of ONSET of CLINICAL MANIFESTATIONS of CF

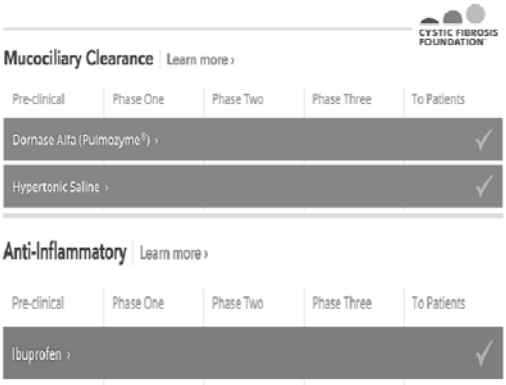


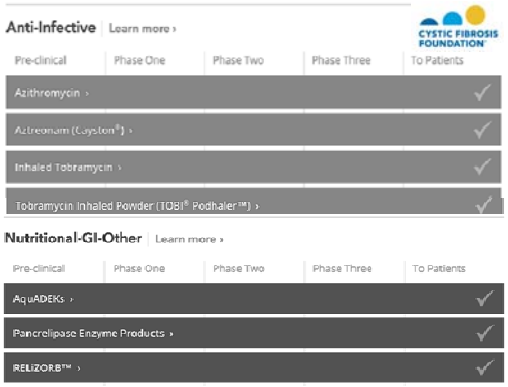
TREATMENT OF CYSTIC FIBROSIS

LUNG DISEASE:
Inflammation
Infection
Obstruction

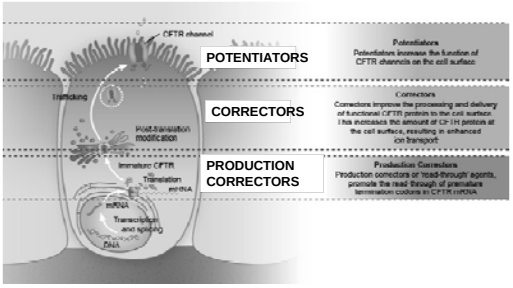
Airway clearance
Antibiotics
Bronchodilators
Mucolytics

GI DISEASE (FTT)
Enzyme replacement
Vitamin supplements

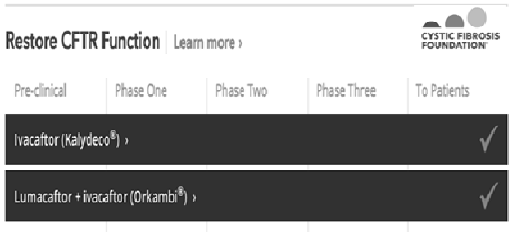




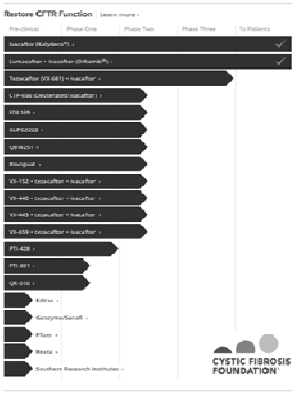
NEW AND FUTURE TREATMENTS FOR CF



http://www.cftr.info/wpcontent/uploads/m1_s2_03_01_012.jpg

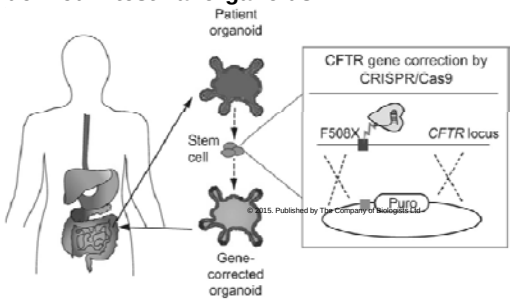


CURRENT INVESTIGA-TIONAL DRUGS AIMED TO RESTORE CFTR FUNCTION



THE FUTURE..? Gene Editing

Gene correction in cystic fibrosis patient-derived intestinal organoids.



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