Cystic Fibrosis in Children

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Presenter Disclosure

D.B. Sanders, MD, MS

The following relationship(s) exists related to this presentation:

CF Foundation, Consulting and Research Funding (Institution)

Objectives

- Describe the incidence and genetics of CF
- Understand the impact of newborn screening
- Discuss the pathophysiology of CF lung disease
- Describe approaches to treating the underlying defect in CF

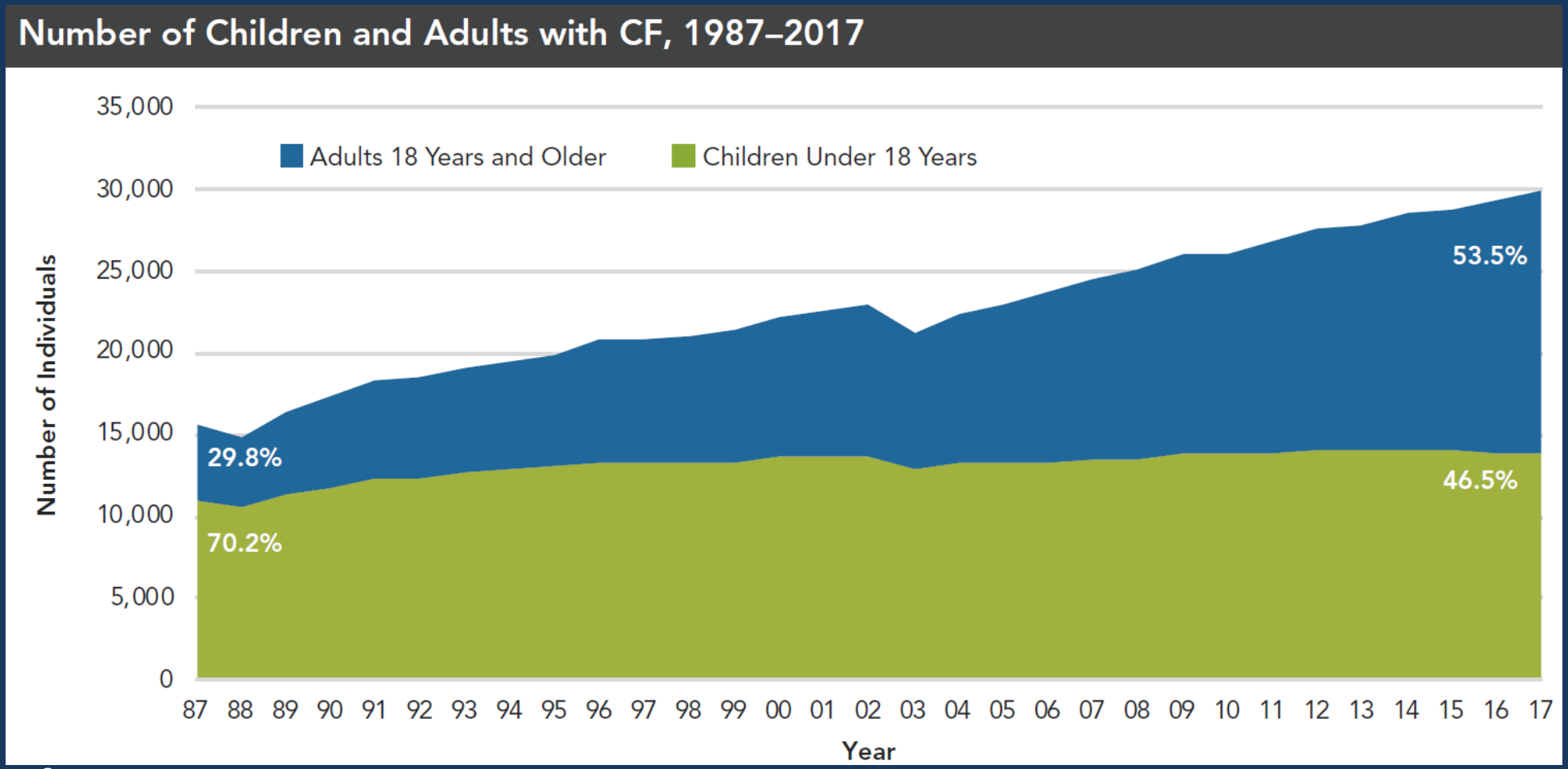
CF EPIDEMIOLOGY AND GENETICS

Incidence and Prevalence

- Most common fatal genetic disorder in Caucasians
  - 1 in 3,600 Caucasian births
  - 1 in 17,000 African-Americans
  - 1 in 31,000 Asian-Americans
- 30,000 people in US and 70,000 worldwide

- Carrier rate 1:30

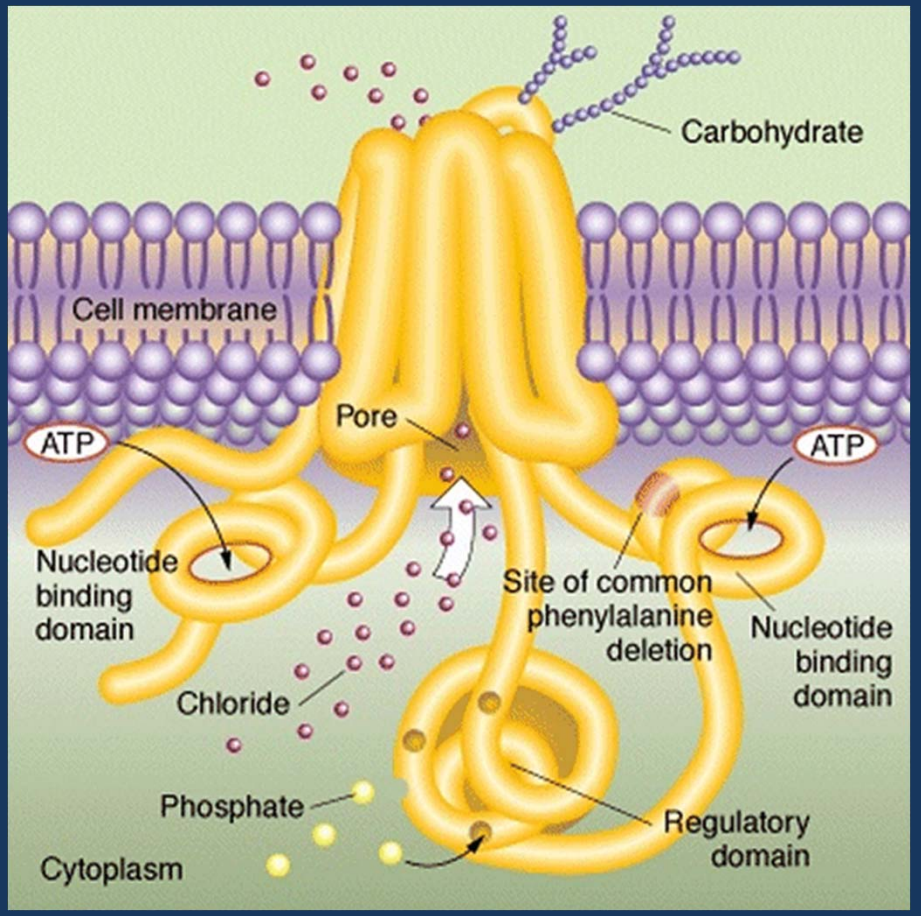
Proportion of People with CF Reaching Adulthood



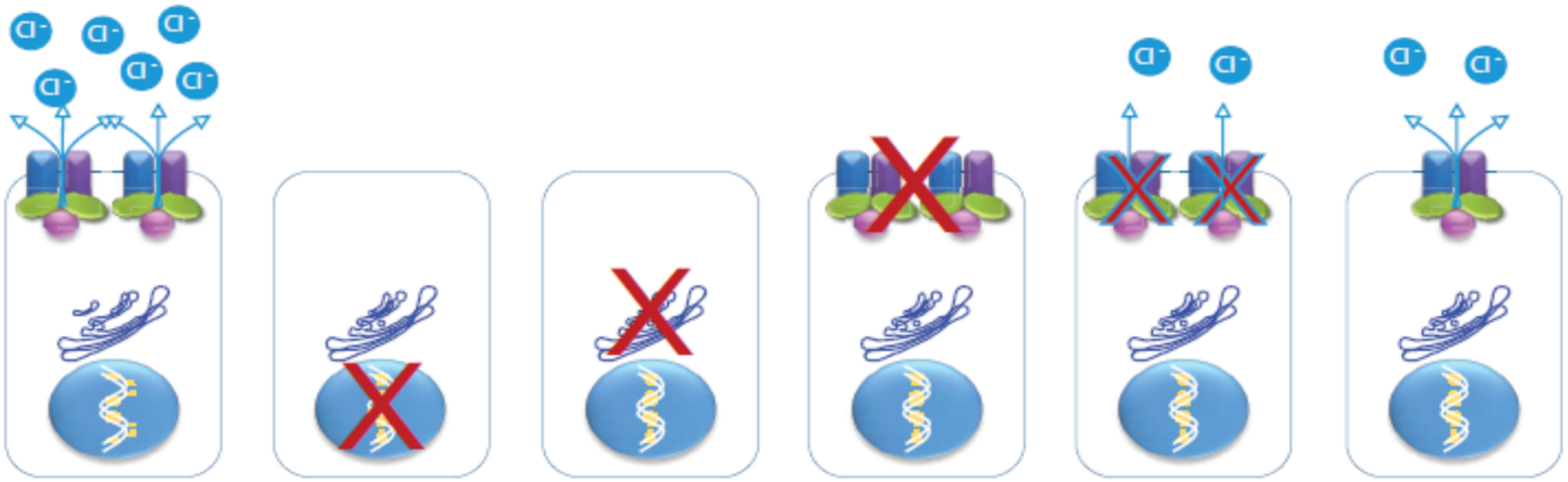
CF Foundation Patient Registry 2017

Genetics

- CF Transmembrane Conductance Regulator (CFTR) protein
  - Long arm of Chromosome 7
  - Controls the movement of salt and water
- Over 1,900 mutations
  - F508del most common



One Way of Classifying CFTR Mutations



Class VI

	Production Mutations	Processing Mutations	Gating Mutations	Conduction Mutations	Insufficient Quantities	Increased Turnover at cell surface
			Reduced CFTR function			
	G542X	F508del	G551D	R117H	3849+10kbC->T	N287Y

CF Foundation Patient Registry 2016

Airway hydration

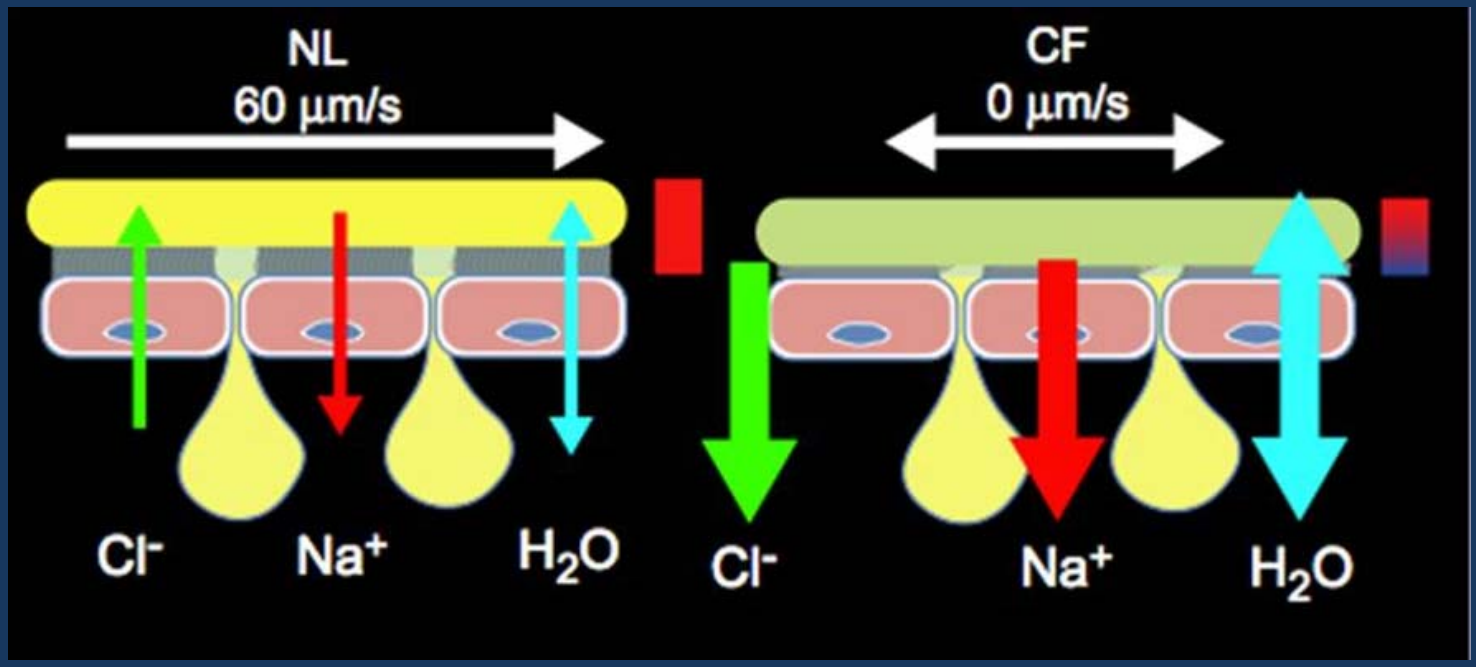


Image courtesy of R Boucher

NEWBORN SCREENING

Question 1

- Newborn screening for a healthy, full-term baby girl reveals CFTR mutations F508del and R117H
- Sweat chloride levels are 37 and 44 mmol/L, respectively

Question 1: Which of the following results would increase suspicion that this child has cystic fibrosis?

A. Sweat test = 55 mmol/L

B. Fecal elastase level of 395 mcg/g stool

C. Presence of the 5T form of the poly-T sequence of intron 8

D. Presence of the 9T form of the poly-T sequence of intron 8

E. Sputum culture with *Staphylococcus aureus*

Question 1: Which of the following results would increase suspicion that this child has cystic fibrosis?

C. Presence of the 5T form of the poly-T sequence of intron 8

R117H and poly-T sequence

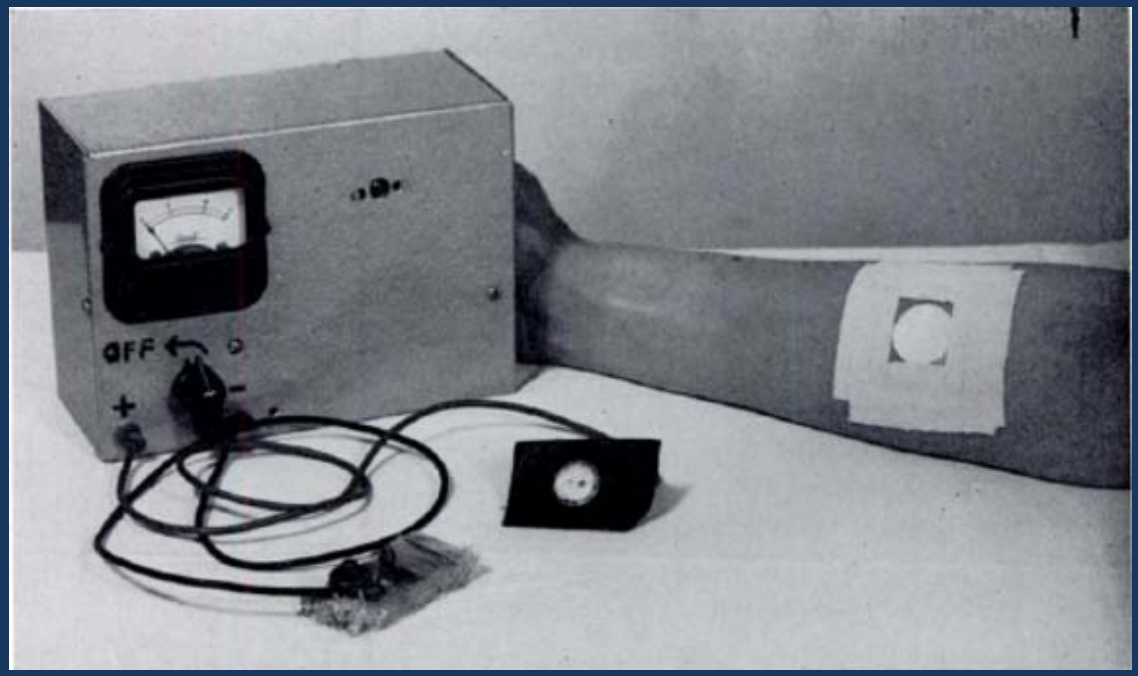
- Found in intron 8 of the *CFTR* gene
- Can impact CFTR function by aberrant splicing of exon 9
- 5T alleles are considered mutations
  - Decrease the efficiency of intron 8 splicing
- 7T and 9T alleles are considered polymorphic variants

R117H and poly-T predicted outcomes

One mutation:	Second mutation: R117H + ?	Predicted outcome:
CF-causing mutation, e.g., F508del	R117H + 5T	R117H will **likely** act as a disease-causing mutation
	R117H + 7T	R117H is **unlikely** to act as a disease-causing mutation. May result in male infertility
	R117H + 9T	R117H is **highly unlikely** to act as a disease-causing mutation. Male infertility is typically not affected

The Sweat Test

- Pilocarpine iontophoresis is the only approved method
- Ranges of Chloride Concentration
  - < 30 mM/L, normal range
  - > 60 mM/L suggestive of CF
- Minimum acceptable sweat volume
  - Filter paper: 75 mg
  - Microbore tubing: 15 microliters



Question 2

- Newborn screening results come back for a healthy, full-term baby boy
- Initial immunoreactive trypsinogen (IRT) levels are in the highest 5% of IRT values obtained that day
- DNA mutation analysis reveals one copy of G551D
- Sweat test results are 35 mmol/L and 38 mmol/L at 3 weeks
- Complete gene sequencing detects a missense mutation in *cis*

Which of the following is the most likely diagnosis?

A. Cystic fibrosis

B. Cystic fibrosis transmembrane conductance regulator-related metabolic syndrome (CRMS)

C. False positive NBS result

D. CFTR-related disorder

E. Atypical cystic fibrosis

Which of the following is the most likely diagnosis?

B. Cystic fibrosis transmembrane conductance regulator-related metabolic syndrome (CRMS)

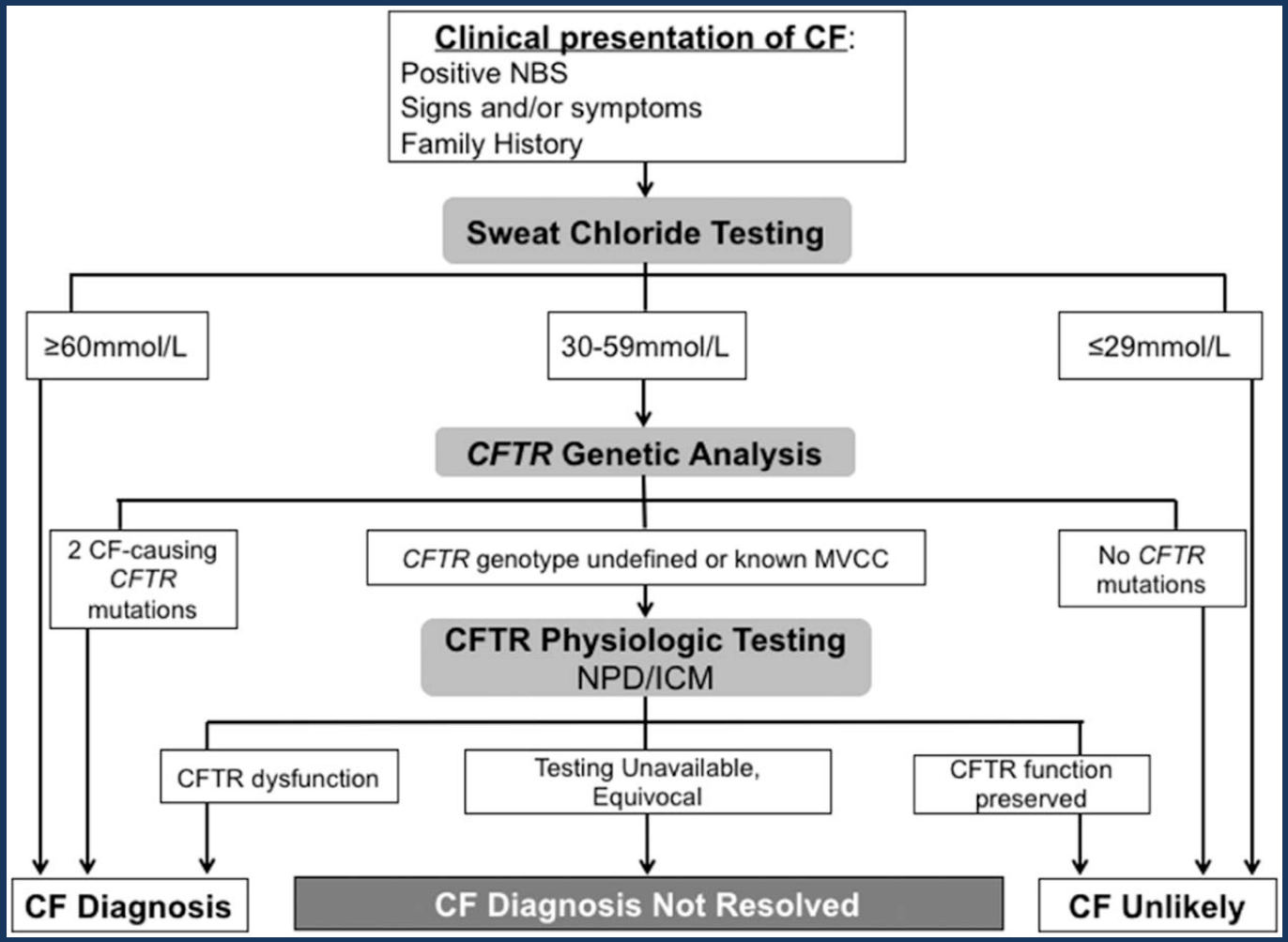
CRMS/CFSPID

CFTR-Related Metabolic Syndrome (CRMS) Follow at CF Center			
SC (mmol/L)	Number of CFTR Mutations		
	Group A**		Group B or D**
< 60 ***	1		1
< 60 ***	0		2
40-59	1	or	1
Unresolved: Possible CRMS			
40-59	0		0

Group A	Group D
"CF-Causing"	"Unknown or Uncertain Significance"
1078delT	Many missense mutations *
1677delTA	
1717-1G>A	
1898+1G>A	
2184delA	
2184insA	
2789+5G>A	
3120+1G>A	
3659delC	
3849+10kbC>T	
621+1G>T	
711+1G>T	
A455E	
E822X	
F508del	
G542X	
G551D	

Borowitz *J Pediatr* 2009

Cystic Fibrosis: Diagnosis



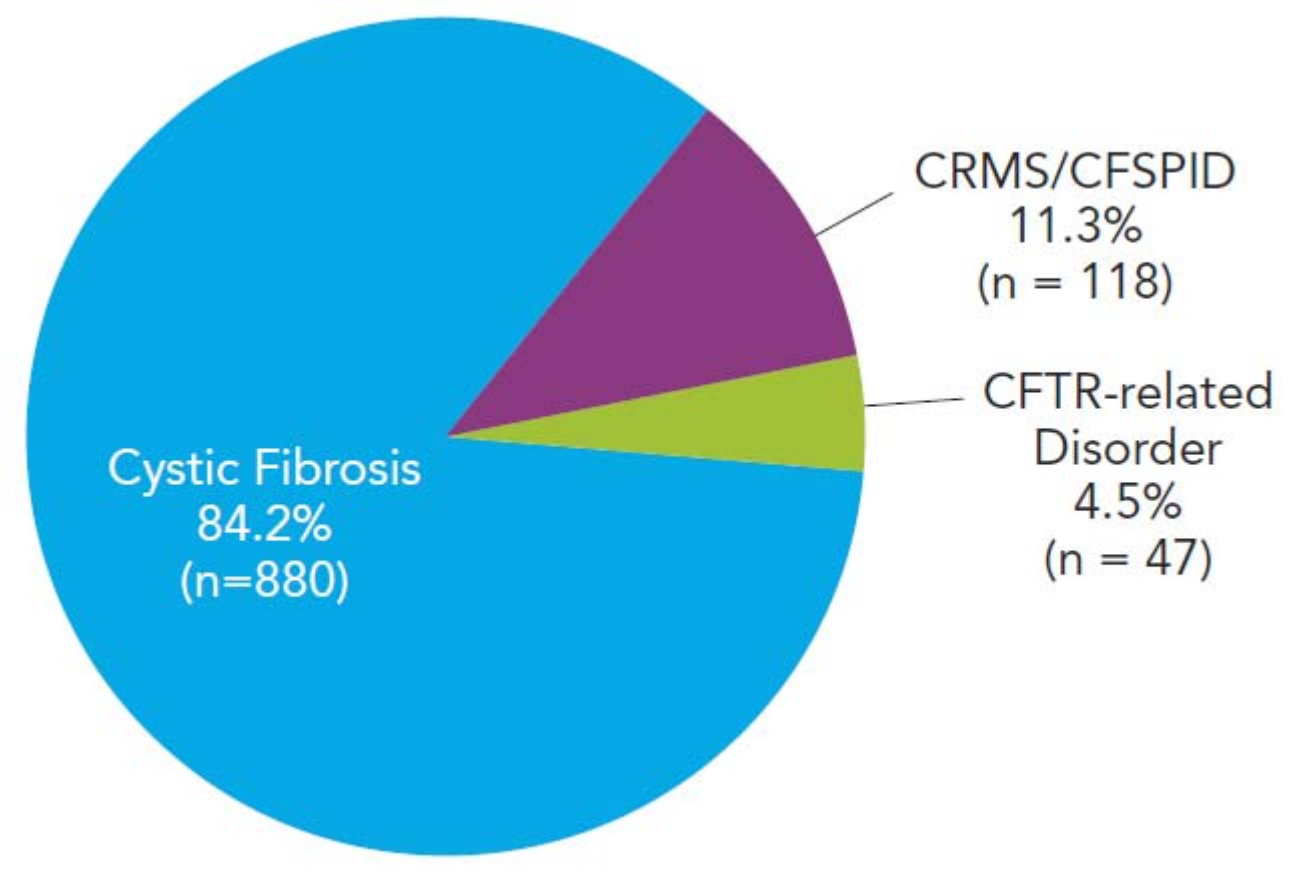
MVCC: Mutation of varying clinical consequence

NPD: Nasal potential difference

ICM: Intestinal current measurement

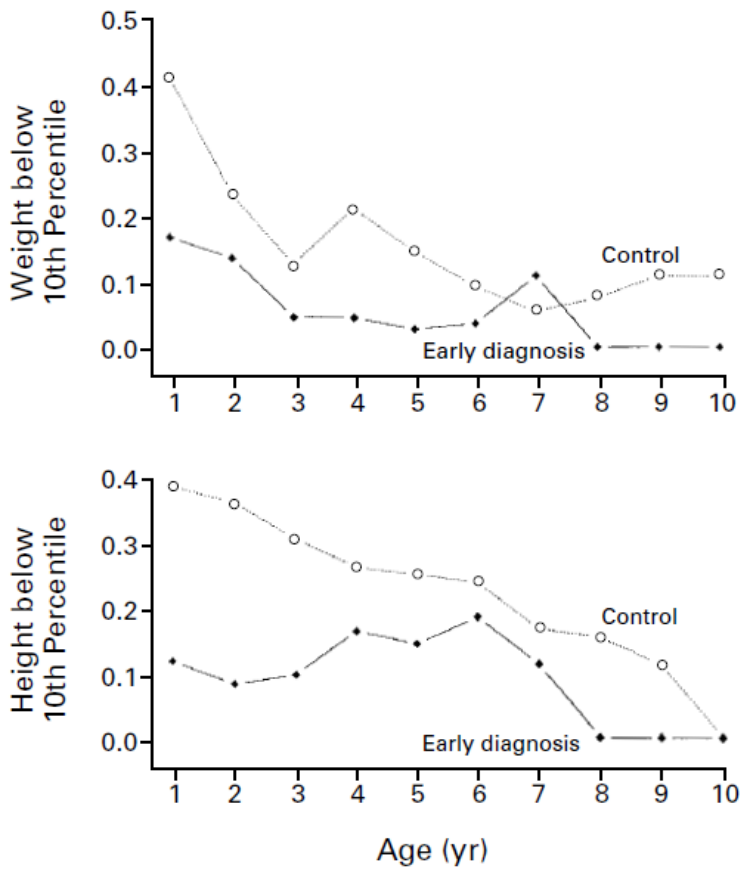
Farrell *J Pediatr* 2017

Cystic Fibrosis: Diagnosis



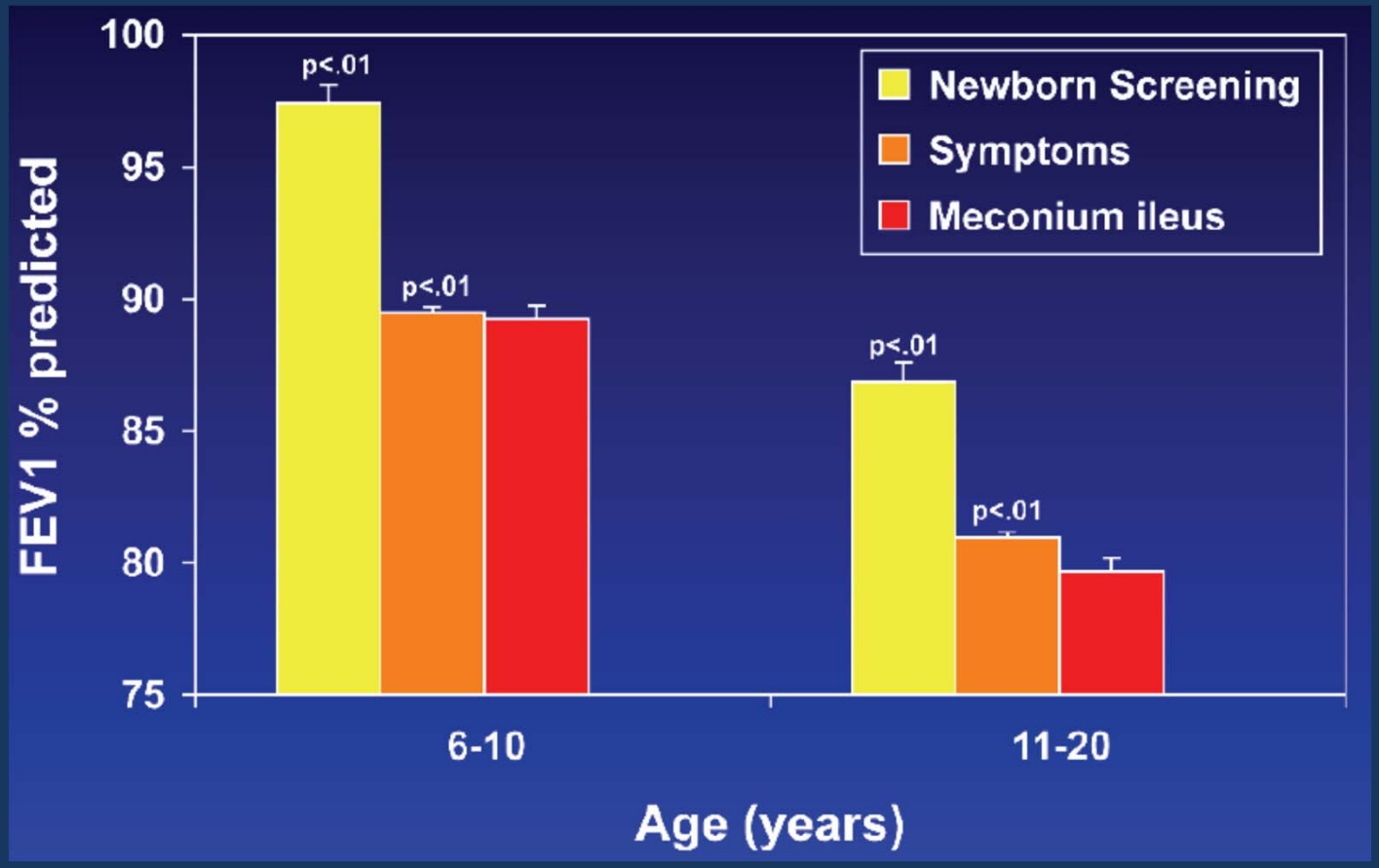
CF Foundation Patient Registry 2017

Early diagnosis improves growth



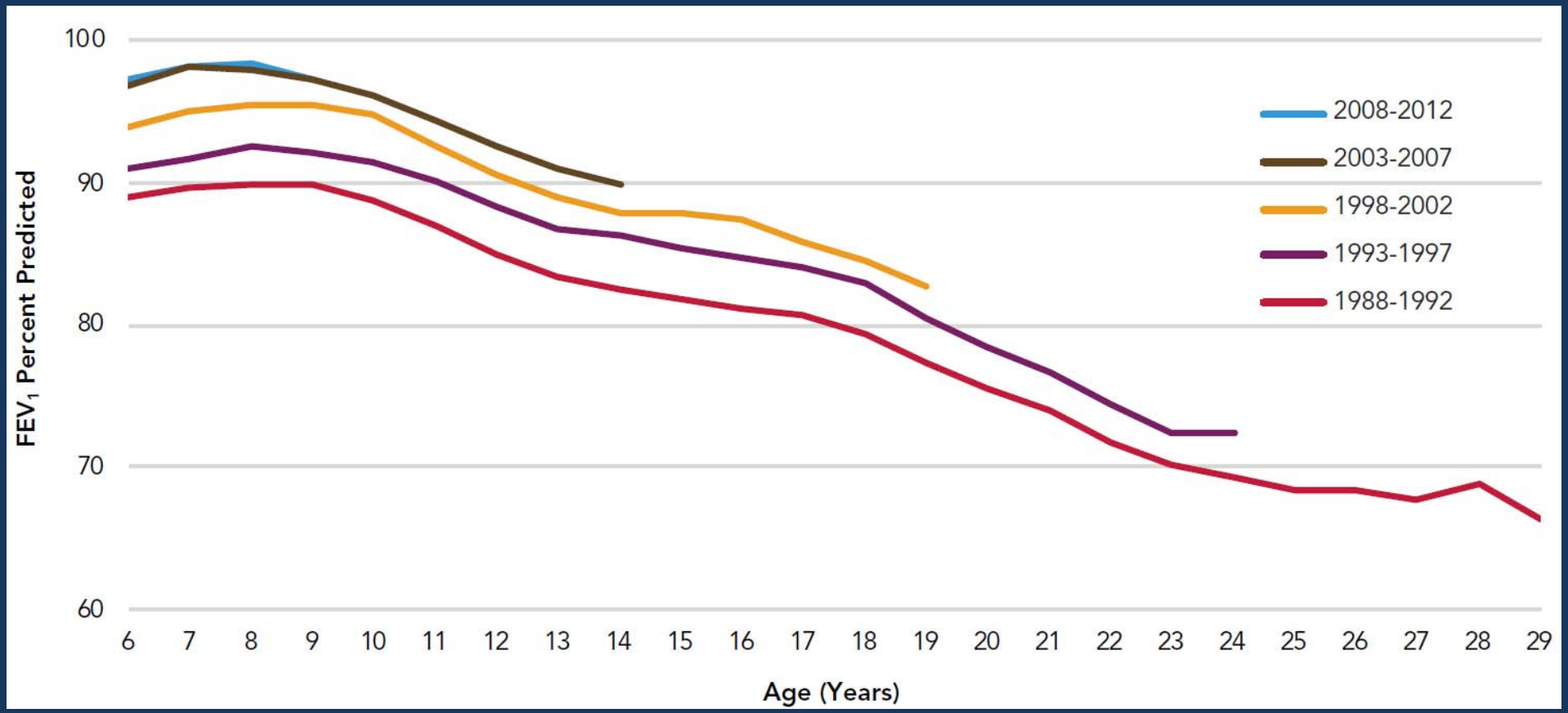
Farrell *J Pediatr* 2005

Lung function according to mode of diagnosis



Accurso *J Pediatr* 2005

FEV_1 vs Age by Birth Cohort



CF Foundation Patient Registry 2017

Complications from Late Diagnosis

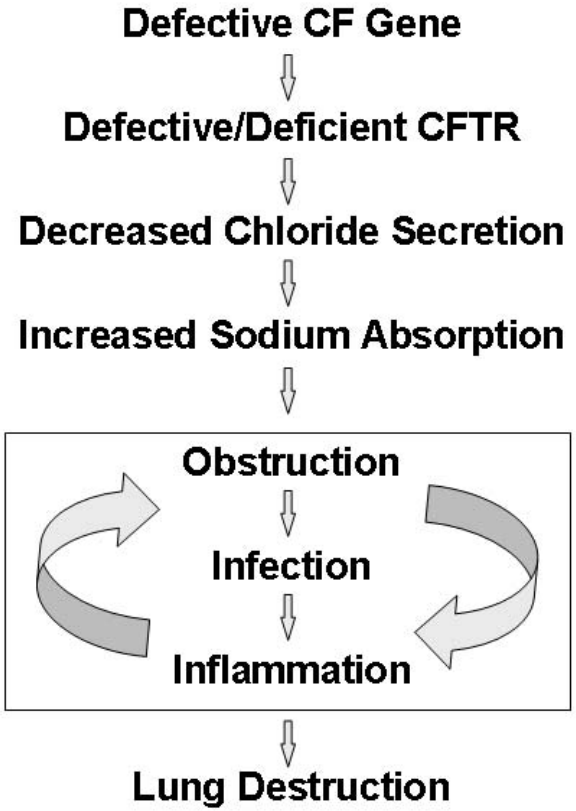
- Electrolyte abnormalities
  - Hypochloremia
  - Hyponatremia
- Growth
  - Failure to thrive
  - Hypoproteinemia
  - Kwashiorkor
- Rectal prolapse
- Vitamin deficiencies
  - E: Hemolytic anemia
  - K: Bleeding diathesis
  - Zinc: Acrodermatitis
- Hepatobiliary
  - Focal biliary cirrhosis
    - Cirrhosis occurs in ~5% of patients
- Portal hypertension
  - Hypersplenism and esophageal varices
    - Bleeding can be life-threatening

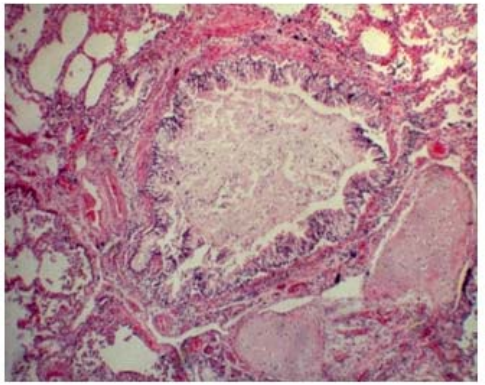
CF LUNG DISEASE

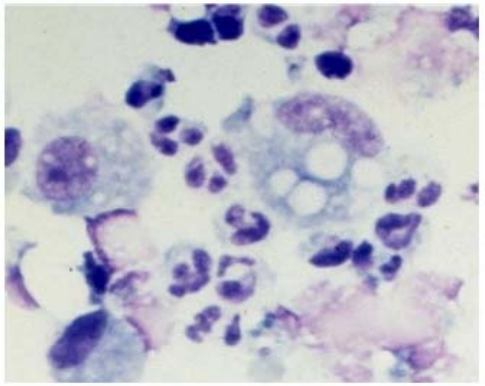
Etiology of CF lung disease

- Lungs appear grossly normal at birth
- Begins with small airways

- Decreased mucociliary clearance
  - Dehydration of mucus
  - Altered mucins

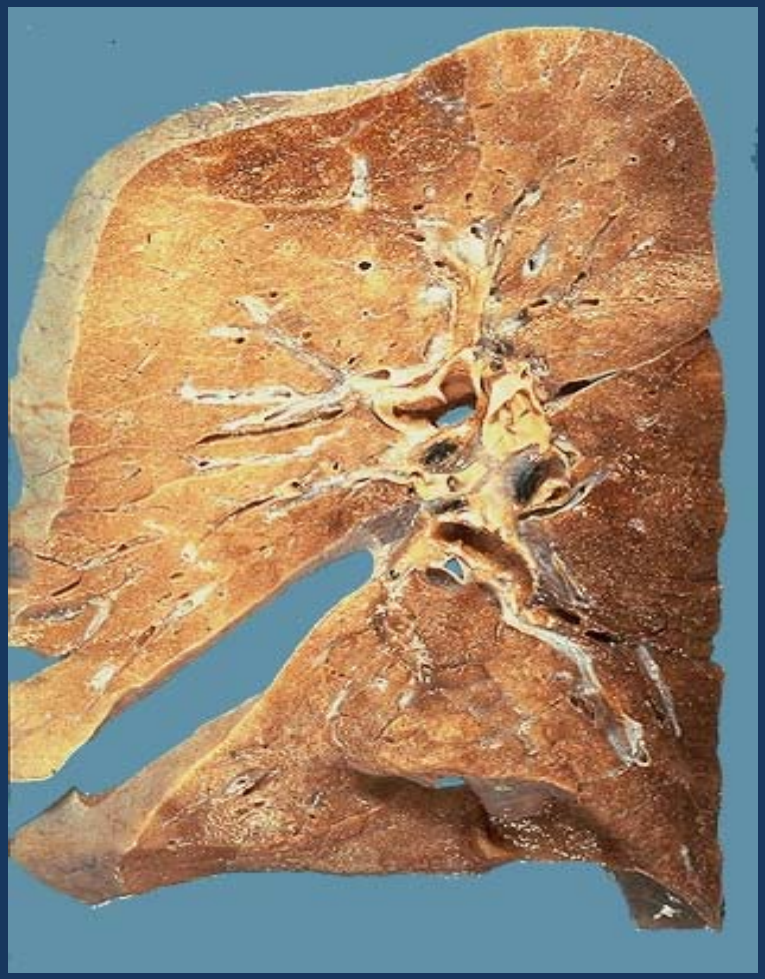




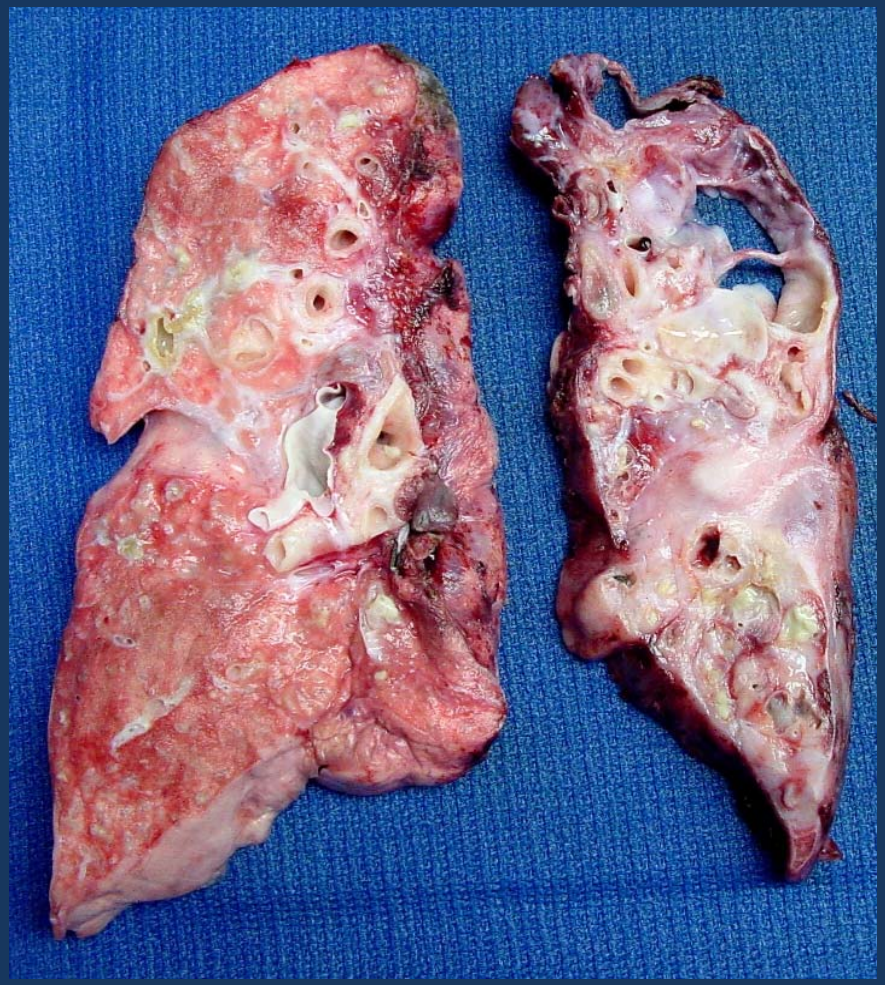


Konstan *Pediatr Pulmonol* 2008

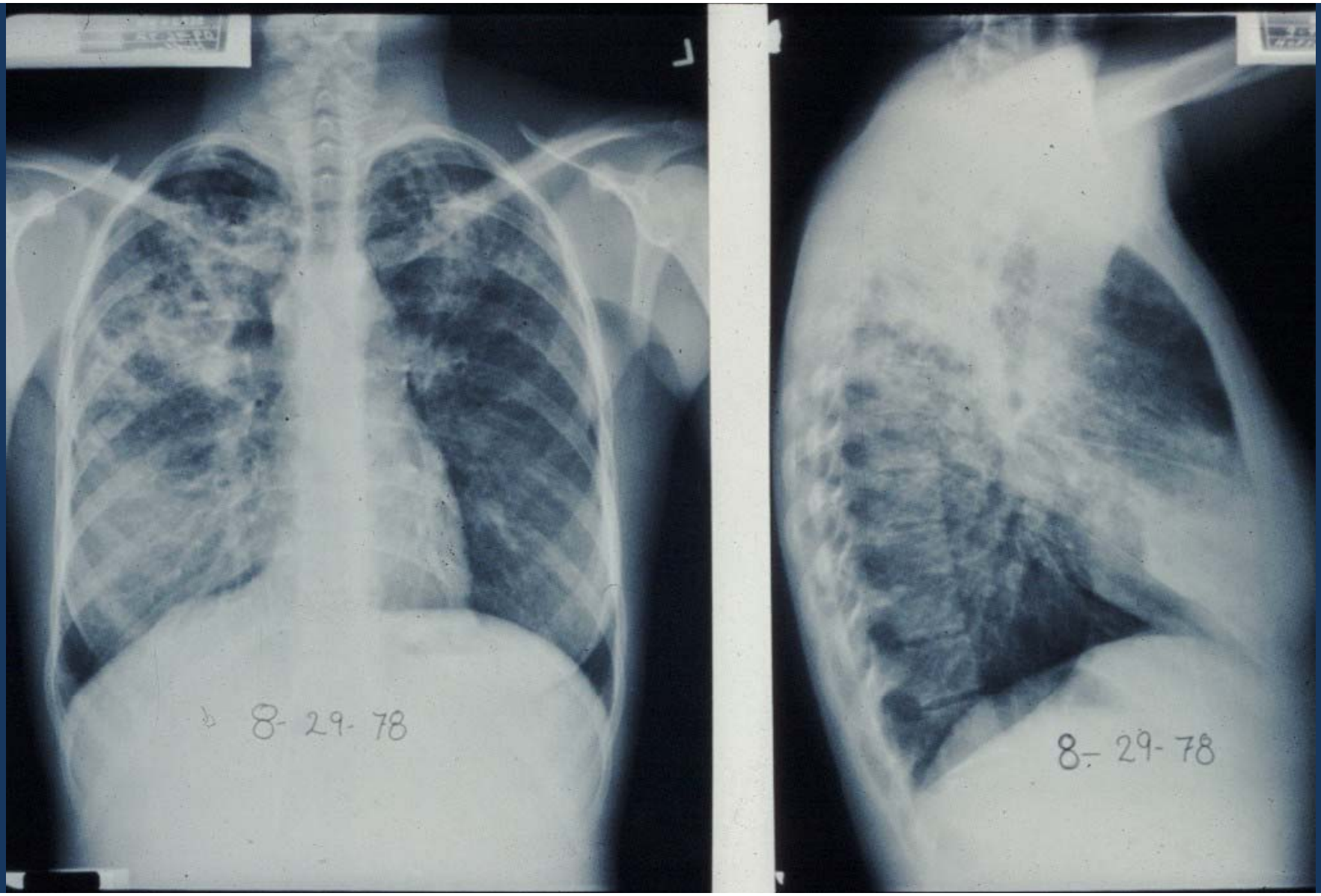
Normal



Cystic Fibrosis



Courtesy of Jim Chmiel

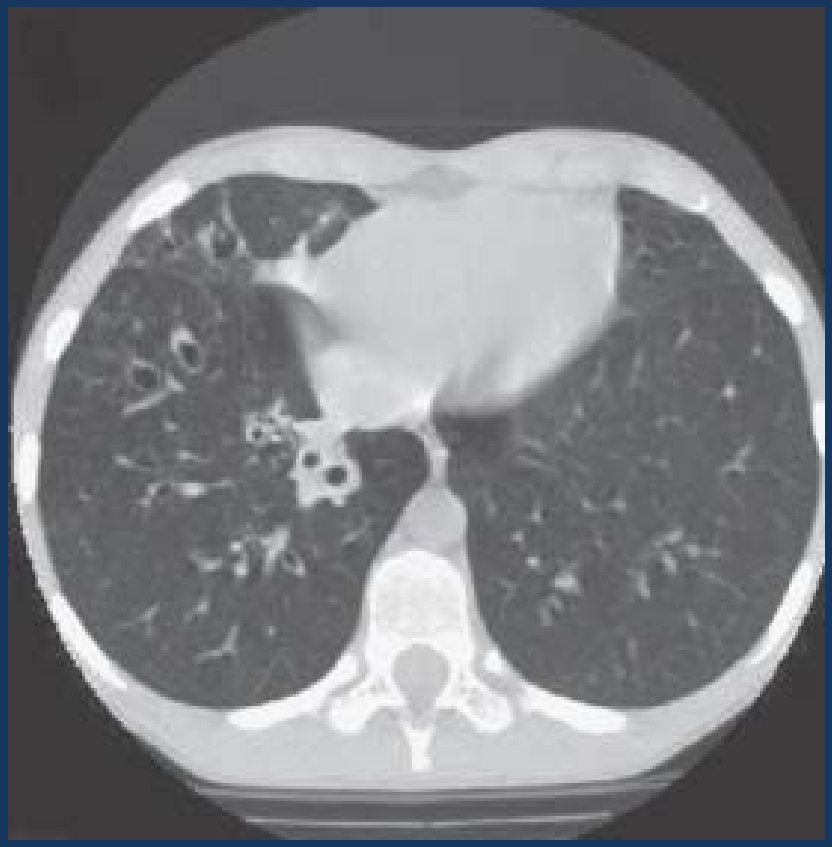


Courtesy of Jim Chmiel

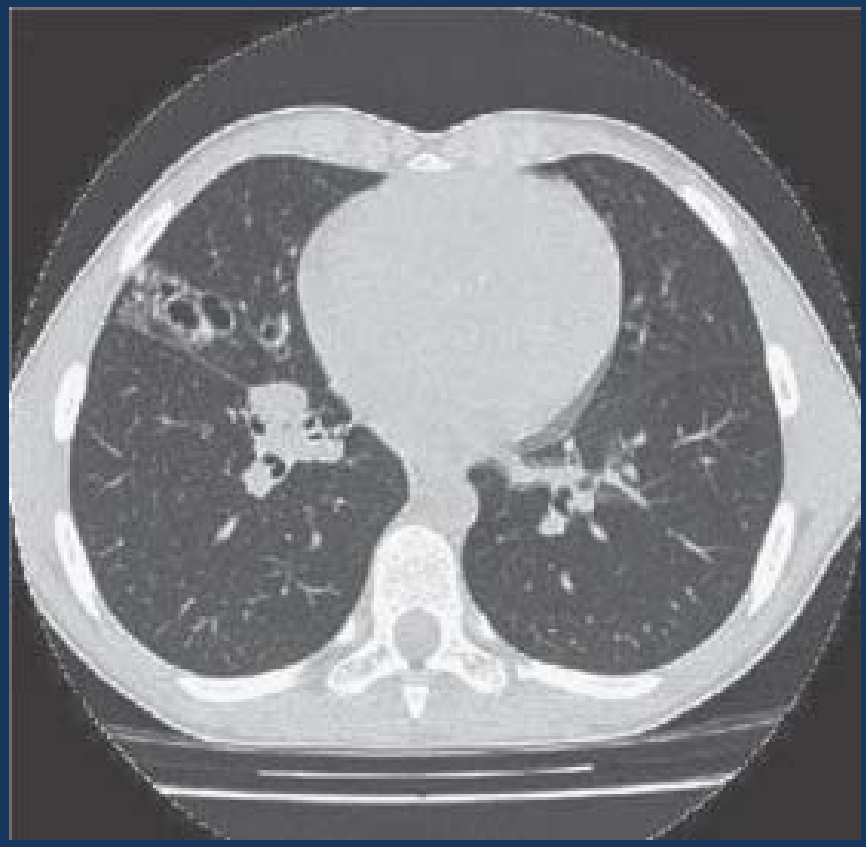
Detecting Lung Disease

- Functional
  - Spirometry
  - Multiple breath washout (MBW)
  - MRI scan (perfusion and ventilation, active inflammation)
- Structural
  - Chest radiograph
  - CT scan
  - MRI Scan

CT imaging of CF lungs



10 year old, FEV_1 = 86% predicted



13 year old, FEV_1 = 96% predicted

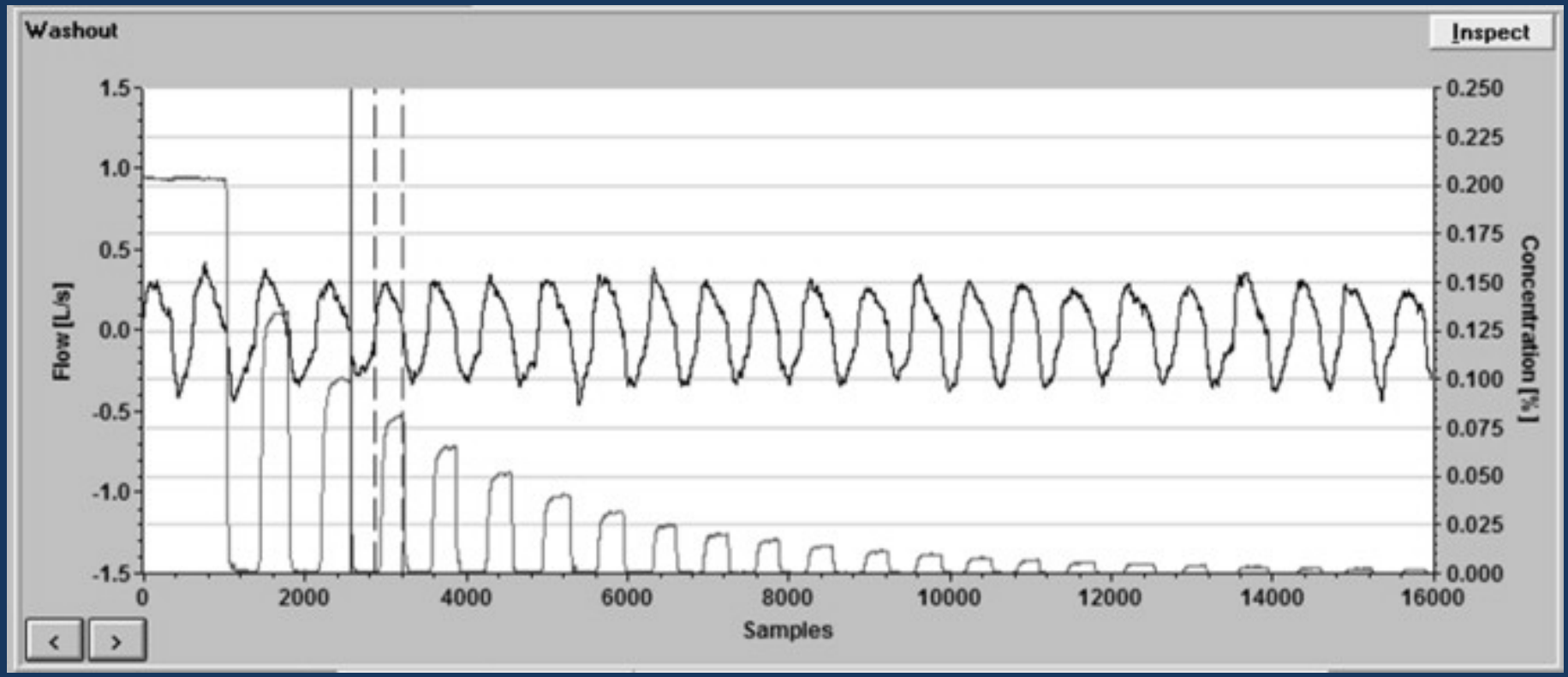
De Jong *Eur Respir J* 2004

Multiple breath washout

- Measure of ventilation inhomogeneity
- Lung clearance index = ventilation required to clear inert gas
- ↑LCI indicates inefficient gas mixing
- Sensitive to changes in lung disease
- Tracks with later lung function
- Several limitations

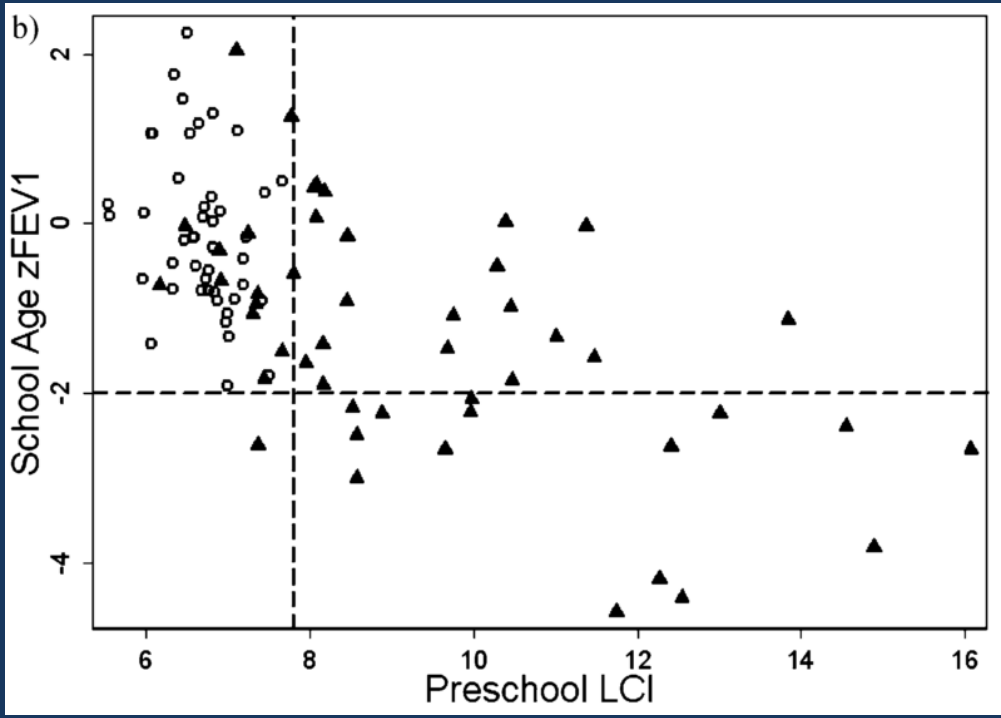
Aurora *Am J Respir Crit Care Med* 2011

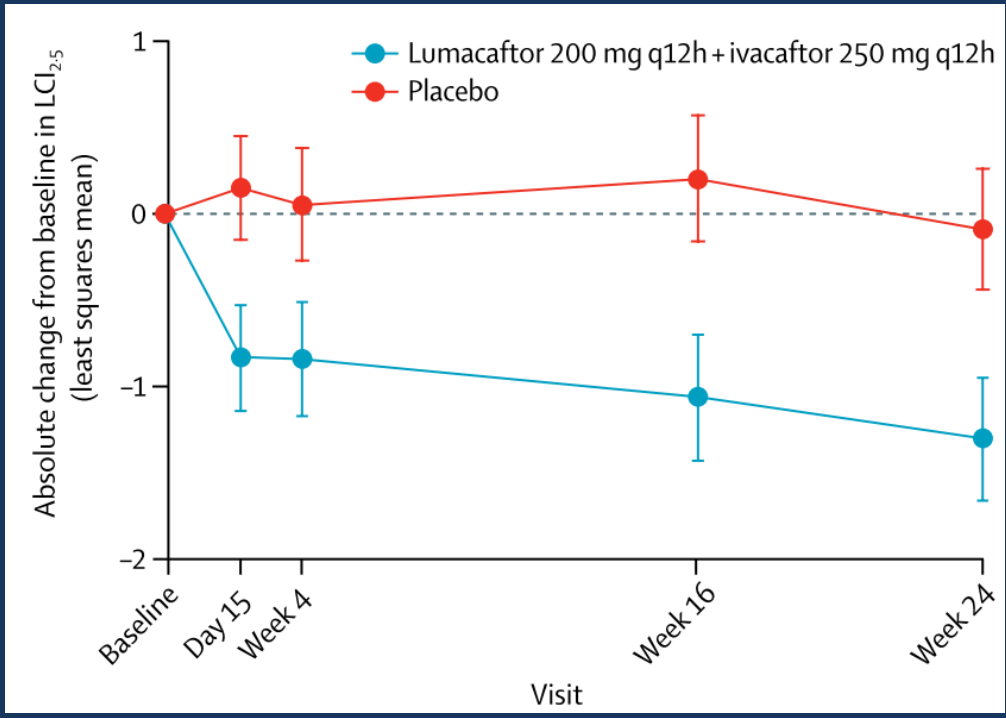
MBW Read out



Aurora *Am J Respir Crit Care Med* 2011

MBW can be used to detect early lung disease





Aurora *Am J Resp Crit Care Med* 2011, Ratjen *Lancet Resp Med* 2017

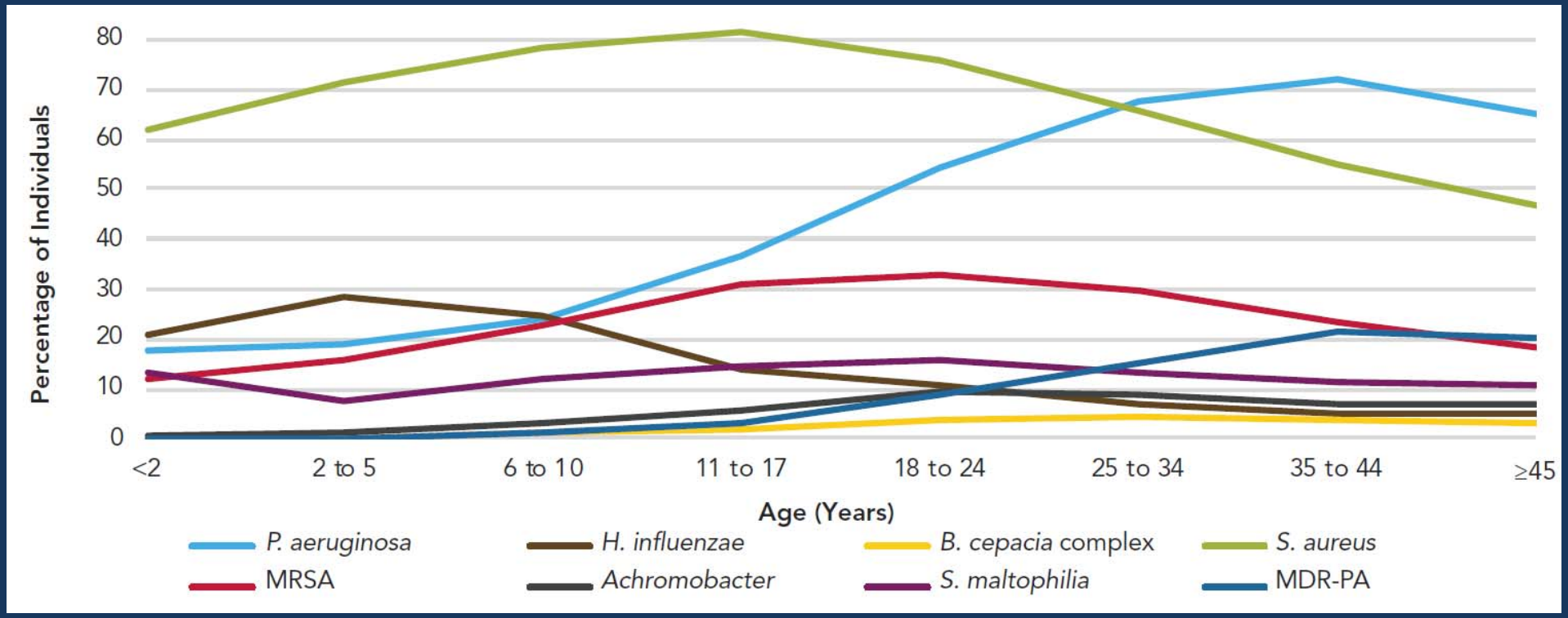
Inflammation in CF

- Occurs early in life
- Excessive relative to the burden of bacteria
- Persistent even in the absence of detectable organisms
- Contributes to lung damage
- Neutrophils release
  - Oxidants and proteases → damage the lung
  - DNA → increases secretion viscoelasticity
- May be directly linked to the basic defect in CF

Inflammation in CF (Continued)

- Lung inflammation leads to bronchiectasis
- Other complications follow:
  - Hypoxemia
  - Hemoptysis, pneumothorax
  - Chronic hypoxemia and pulmonary vasoconstriction
  - Pulmonary hypertension and right ventricular hypertrophy (cor pulmonale)
- Respiratory insufficiency eventually leads to death

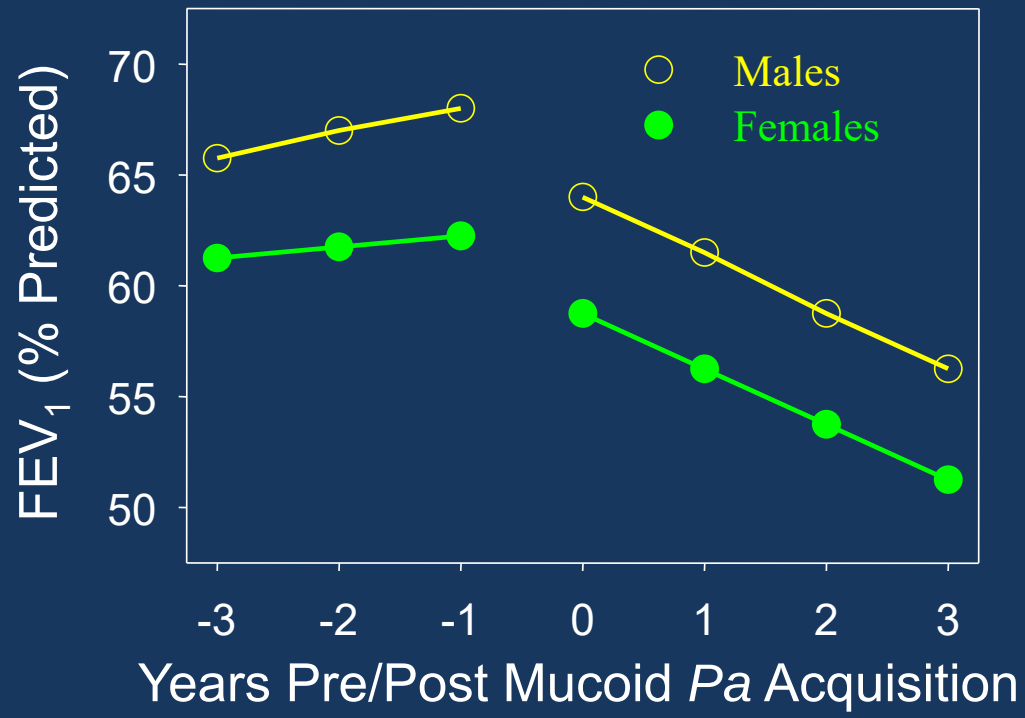
Lung infections



CF Foundation Patient Registry 2017

Pseudomonas aeruginosa (*Pa*) is associated with poor outcomes

- Acquisition is associated with
  - Proinflammatory response
  - Lower lung function
  - Increased cost of care
  - Decreased survival
- Biofilm protects from host defenses and antibiotics



Demko *J Clin Epidemiol* 1995

Eradication of *Pa*

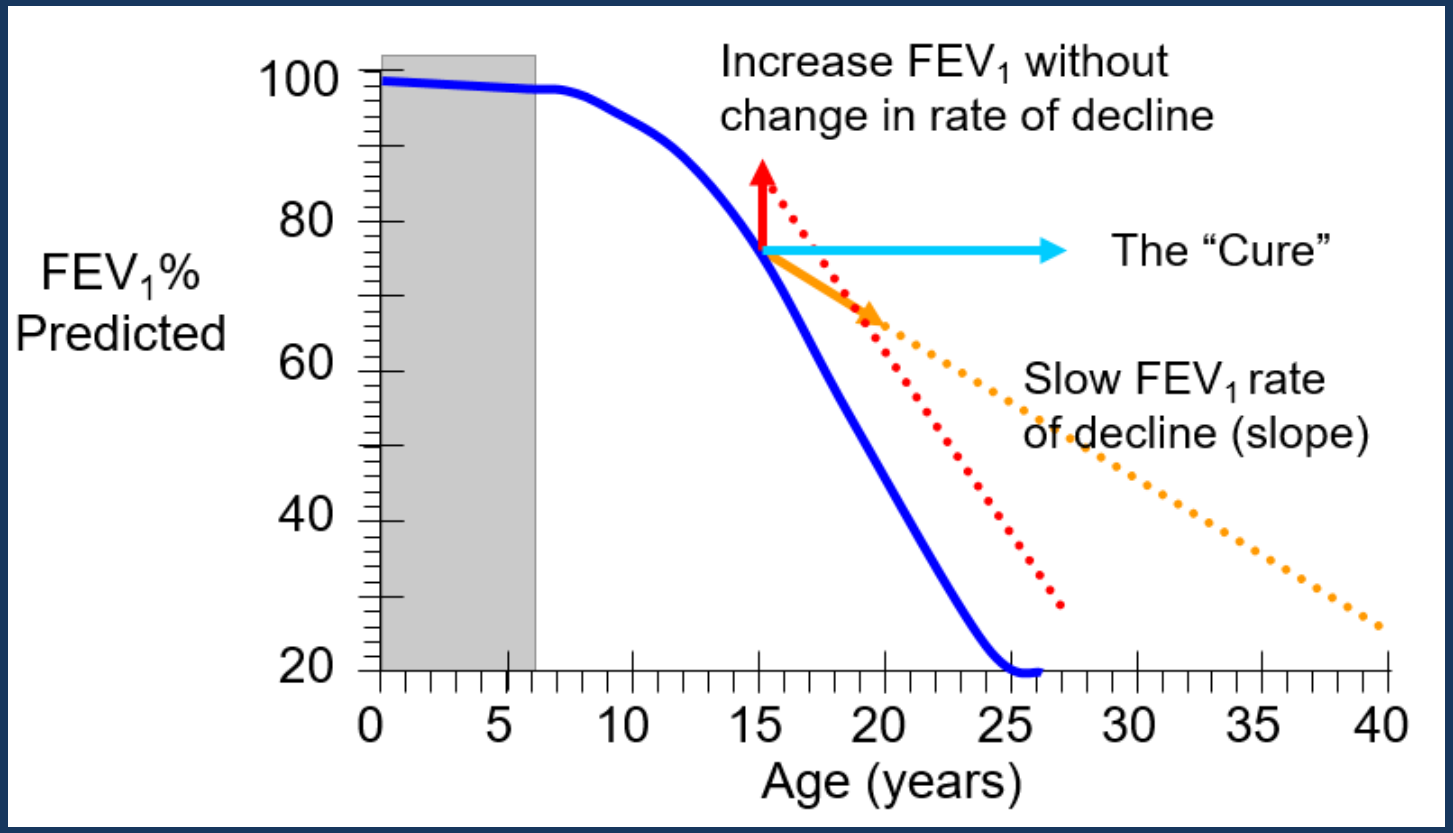
- 72-90% of eradication attempts are successful
- *Pa* recurs in ~33% within 18–27 months
- *Pa* recurrence is associated with the risk of IV-treated pulmonary exacerbations
- No clear evidence for treatment of *Pa* recurrence

Ratjen *Thorax* 2010, Treggiari *Arch Pediatr Adolesc Med* 2011

MEDICATIONS AND THEIR IMPACT ON DISEASE PROGRESSION

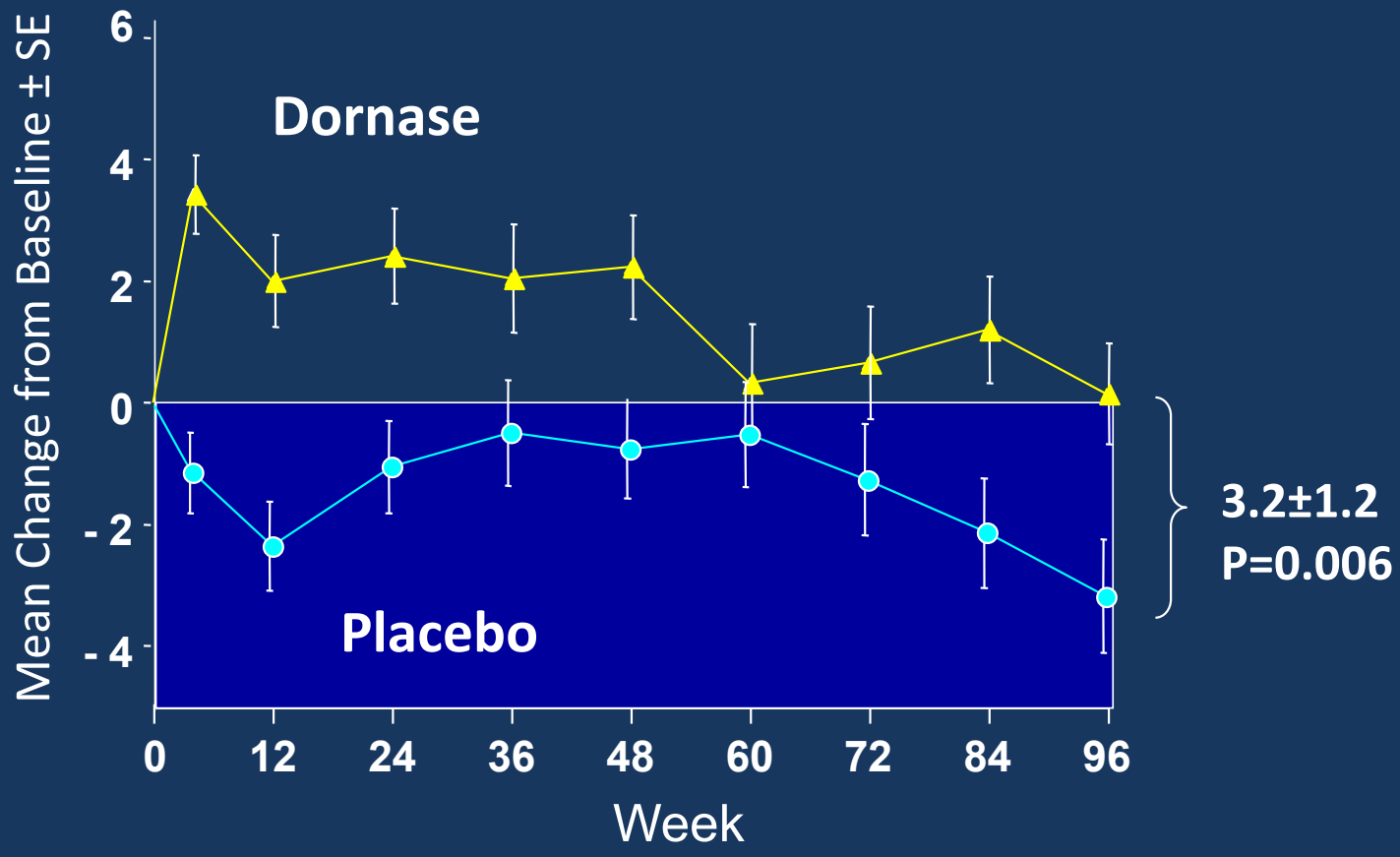
Extrapolating Relative Benefit

Improvement in FEV_1 vs. Slowing the Rate of Decline



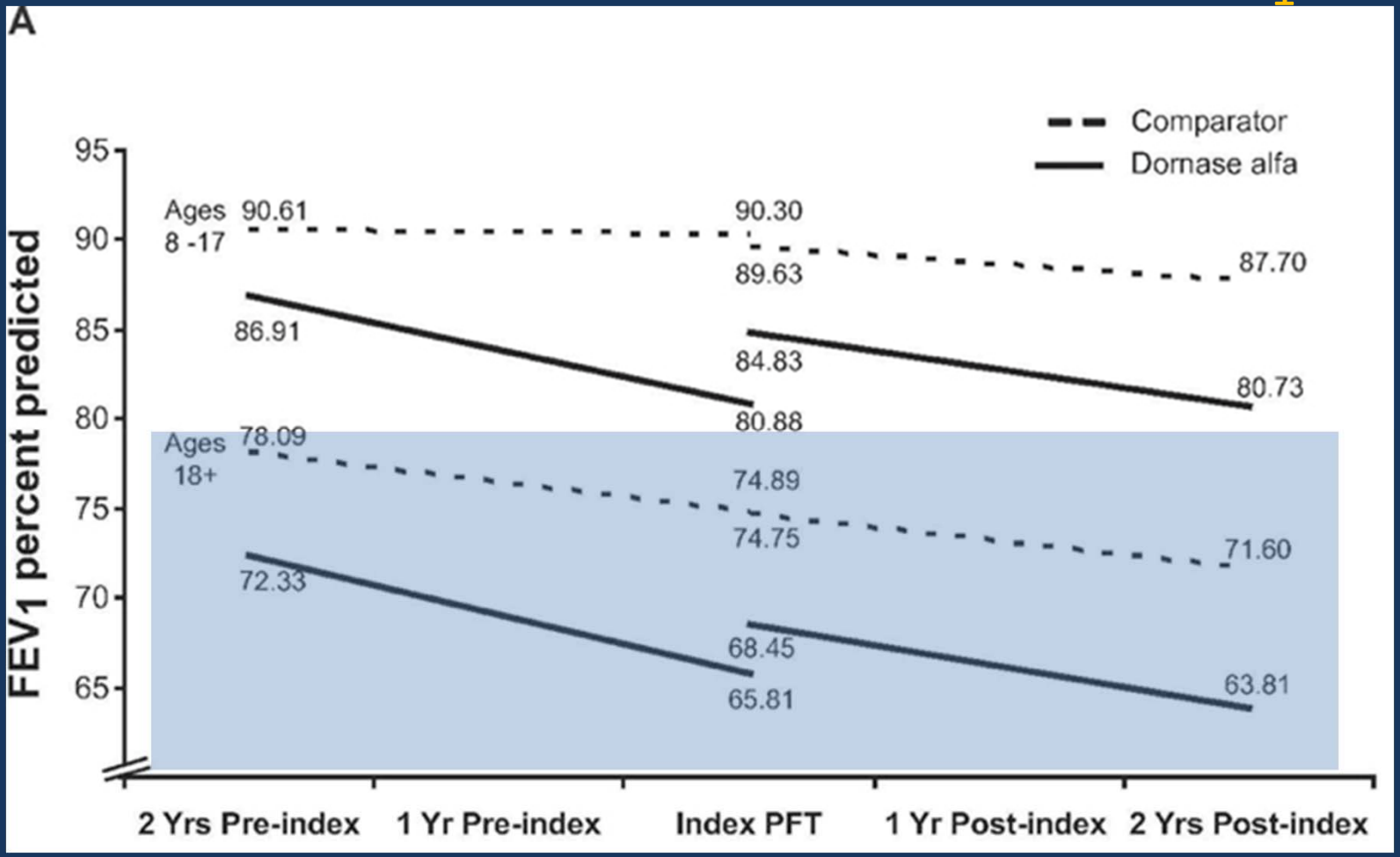
Corey *J Pediatr* 1997, Schluchter *Stat Med* 2002

Change in FEV_1 % predicted with dornase alfa



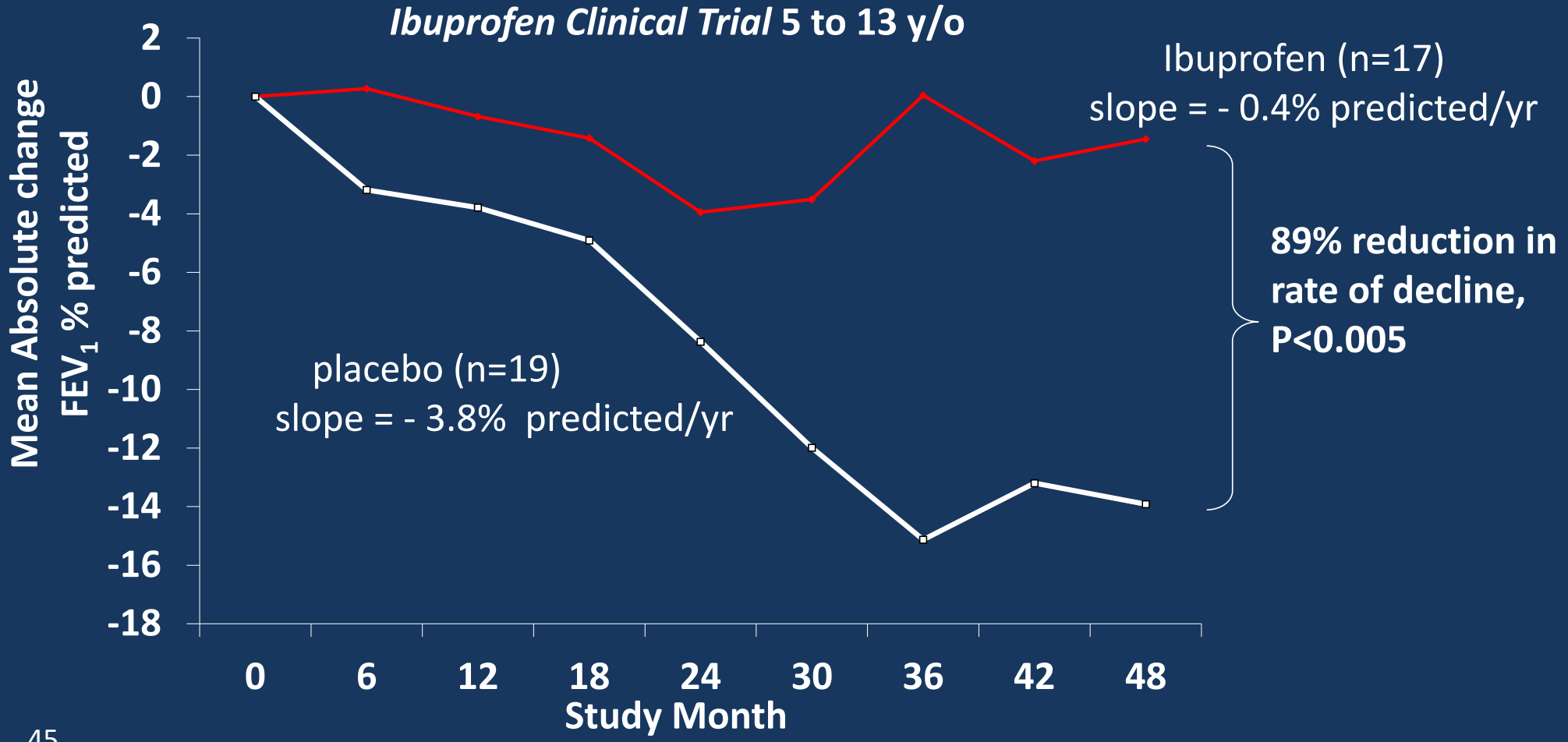
Quan *J Pediatr* 2001

Dornase alfa slows the decline of FEV_1



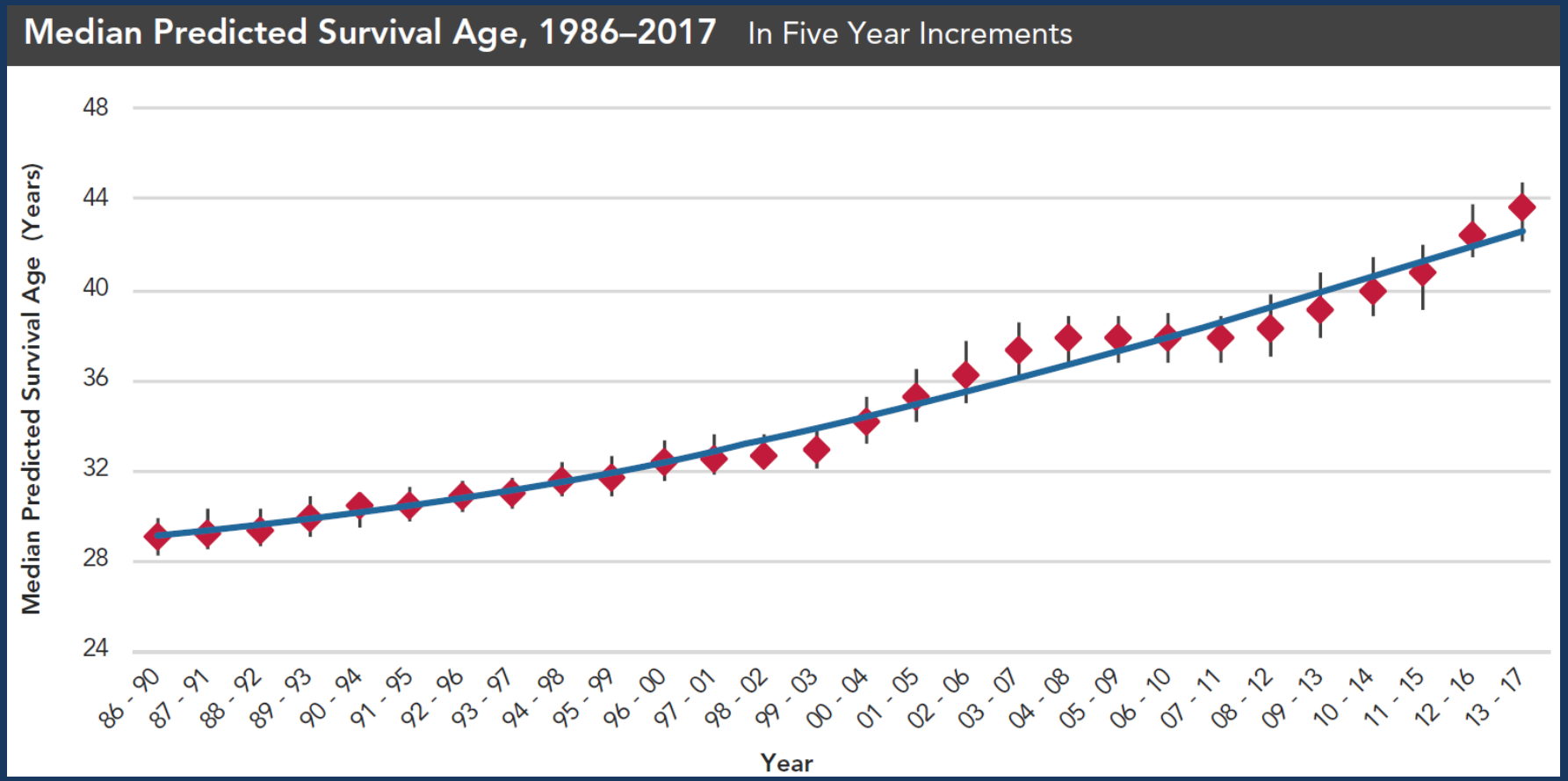
Konstan *Pediatr Pulmonol* 2011

Annualized Rate of Decline of FEV_1 % predicted



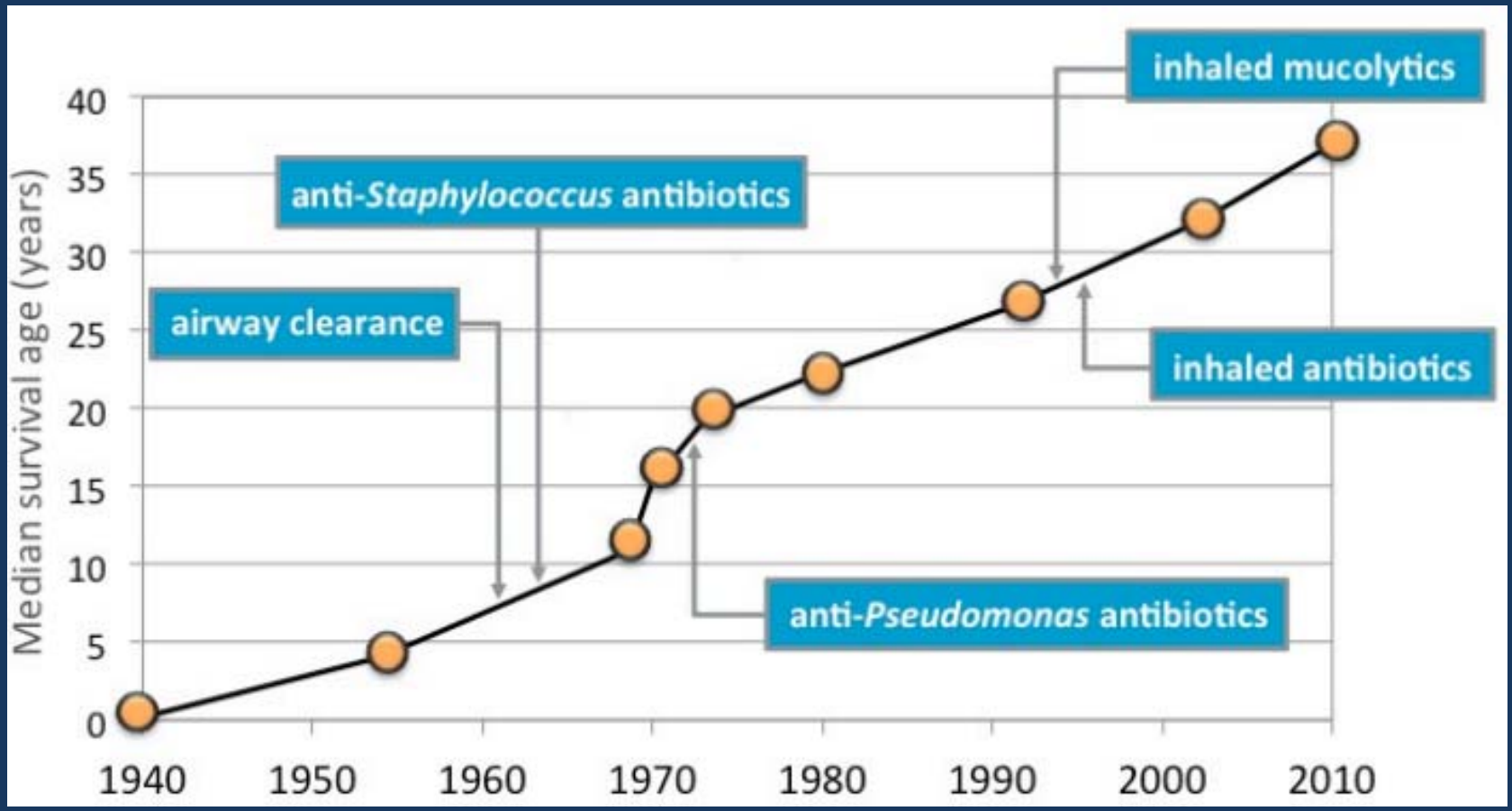
Konstan *N Engl J Med* 1995

Median Predicted Survival Age



CF Foundation Patient Registry 2017

Advances in survival in the US and in CF care



Courtesy of Tom Ferkol

Chronic Medication Guidelines (≥6 y/o)

Strongly Recommend	Recommend	Case-by-Case basis	Recommend against	Insufficient evidence
INH tobramycin (Mod-severe disease)	INH tobramycin (In mild disease)	AZM (no *Pa*)	Inhaled steroids	Other INH ABX
Dornase alfa (Mod-severe disease)	Dornase alfa (In mild disease)		Oral steroids	Leukotriene modifiers
INH aztreonam (Mod-severe disease)	INH aztreonam (In mild disease)		Prophylactic anti-Staph antibiotics	Chronic anti-Staph antibiotics
Ivacaftor	Hypertonic saline			PO or INH N-acetylcysteine
	AZM (with *Pa*)			PO or INH glutathione
	Ibuprofen (<18 y/o)			Ibuprofen (>18 y/o)
				β-agonists
				INH anticholinergics

Mogayzel *Am J Respir Crit Care Med* 2013

Question 3: Which of the following reduces pulmonary exacerbations in infants and toddlers with CF?

A. Hypertonic saline

B. Dornase alpha

C. Ivacaftor

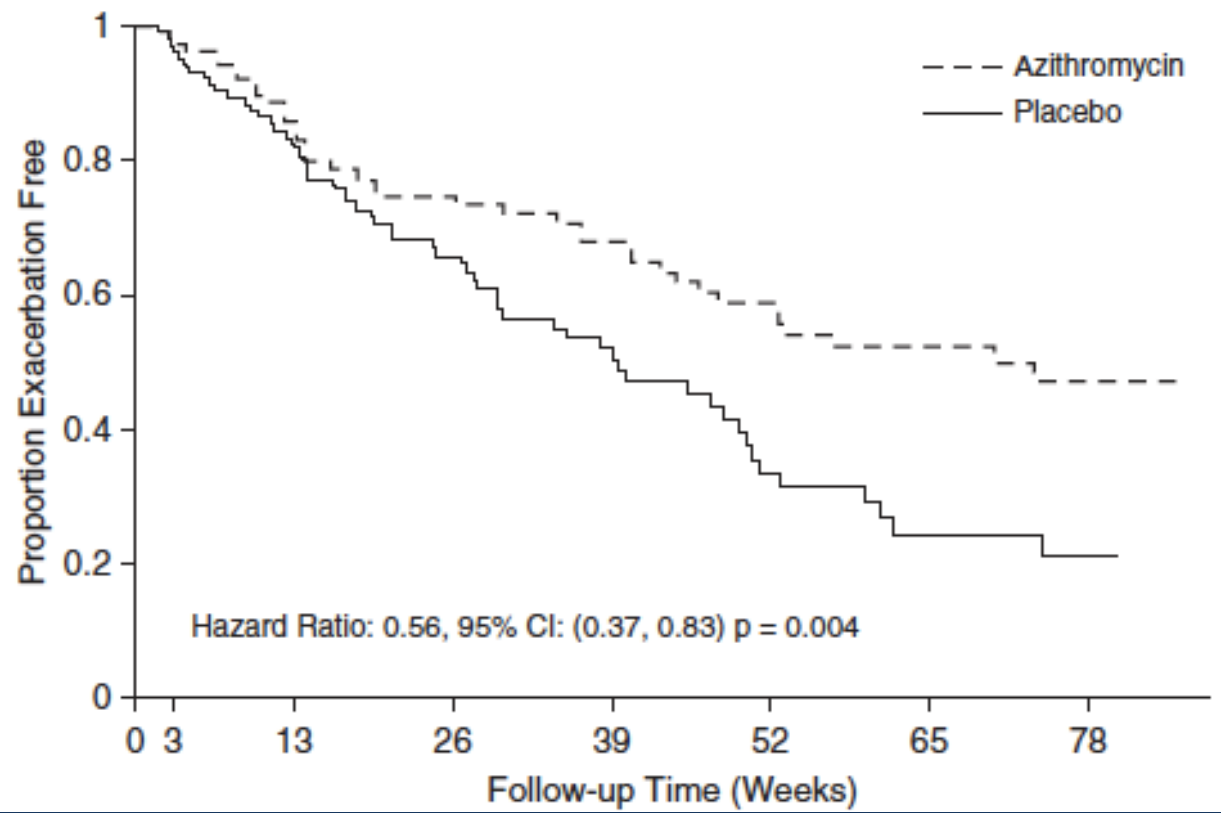
D. Azithromycin

E. Inhaled tobramycin

Question 3: Which of the following reduces pulmonary exacerbations in infants and toddlers with CF?

D. Azithromycin

Decreased risk of pulmonary exacerbations



Participants	Hazard ratio	95% CI
Overall	0.6	0.4, 0.8
6 months – 3 years	0.4	0.2, 0.7
>3-6 years	0.6	0.3, 1.5
>6-12 years	0.8	0.4, 1.8
>12-18 years	0.6	0.2, 1.8

Mayer-Hamblett *Am J Respir Crit Care Med* 2018

Pulmonary exacerbations

Marked by changes in

- Cough
- Sputum production
- Weight
- Physical exam
- Energy level
- Appetite
- Lung function

Treatment

- Antibiotics
- Chest physiotherapy
- Attention to nutrition

Associated with

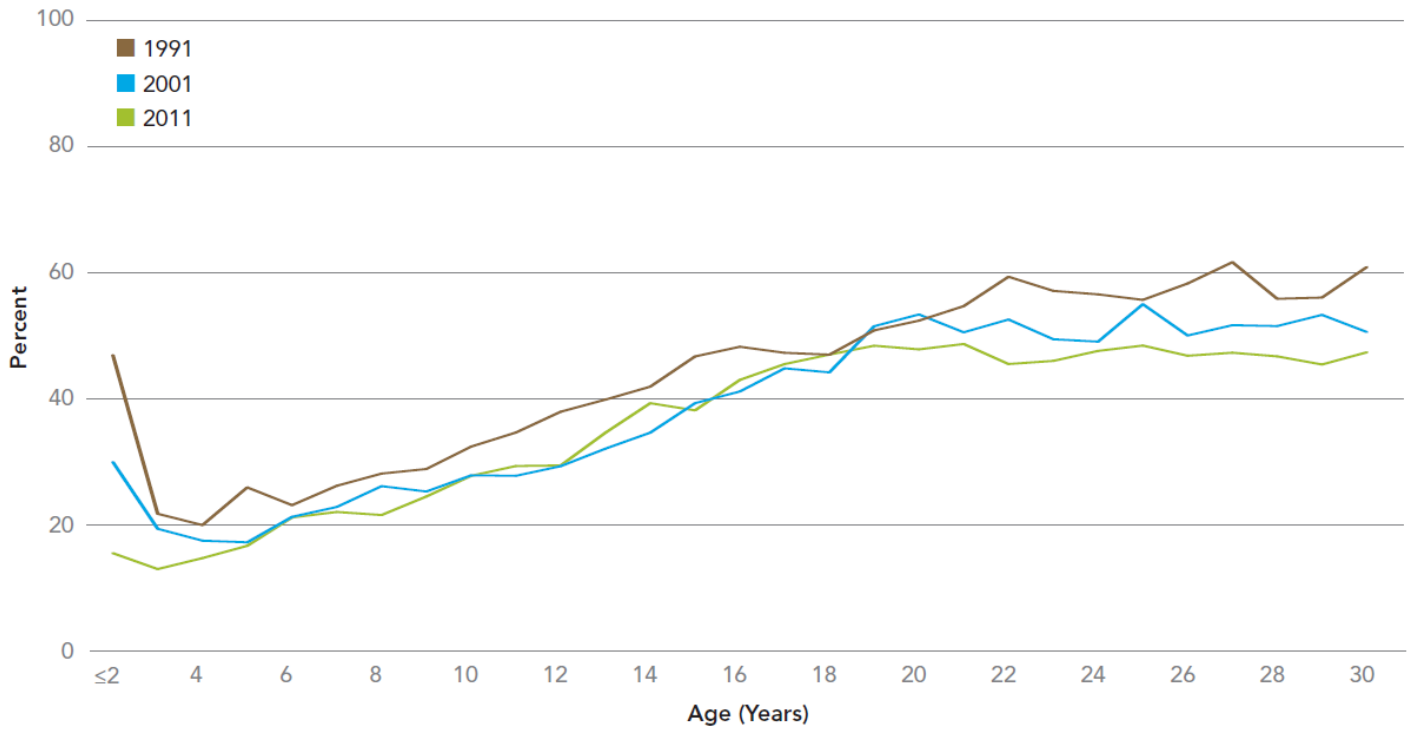
- Poor quality of life
- Lower FEV_1
- Higher healthcare costs
- Mortality

Ferkol *J Pediatr* 2006

Pulmonary exacerbation frequency

~33% of patients are treated annually with IV antibiotics for an exacerbation

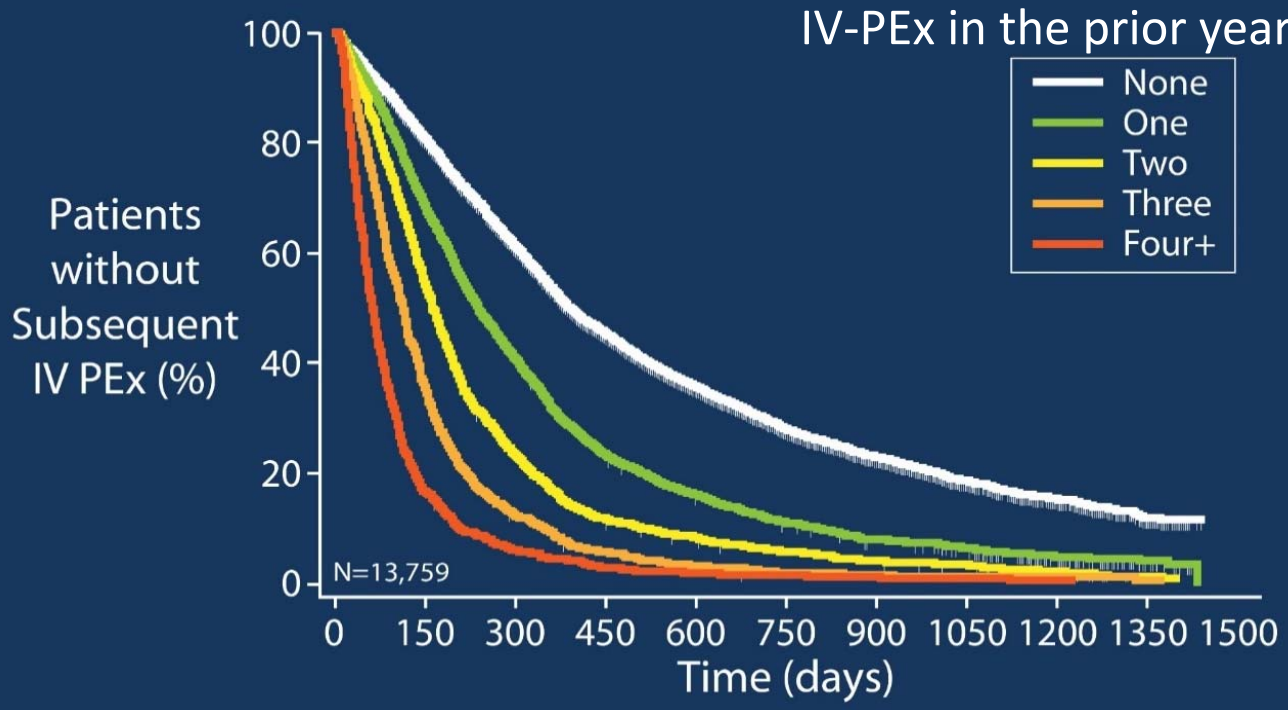
Figure 64: **Pulmonary Exacerbations vs. Age**



CF Foundation Patient Registry 2012

Outcomes after pulmonary exacerbation treatment

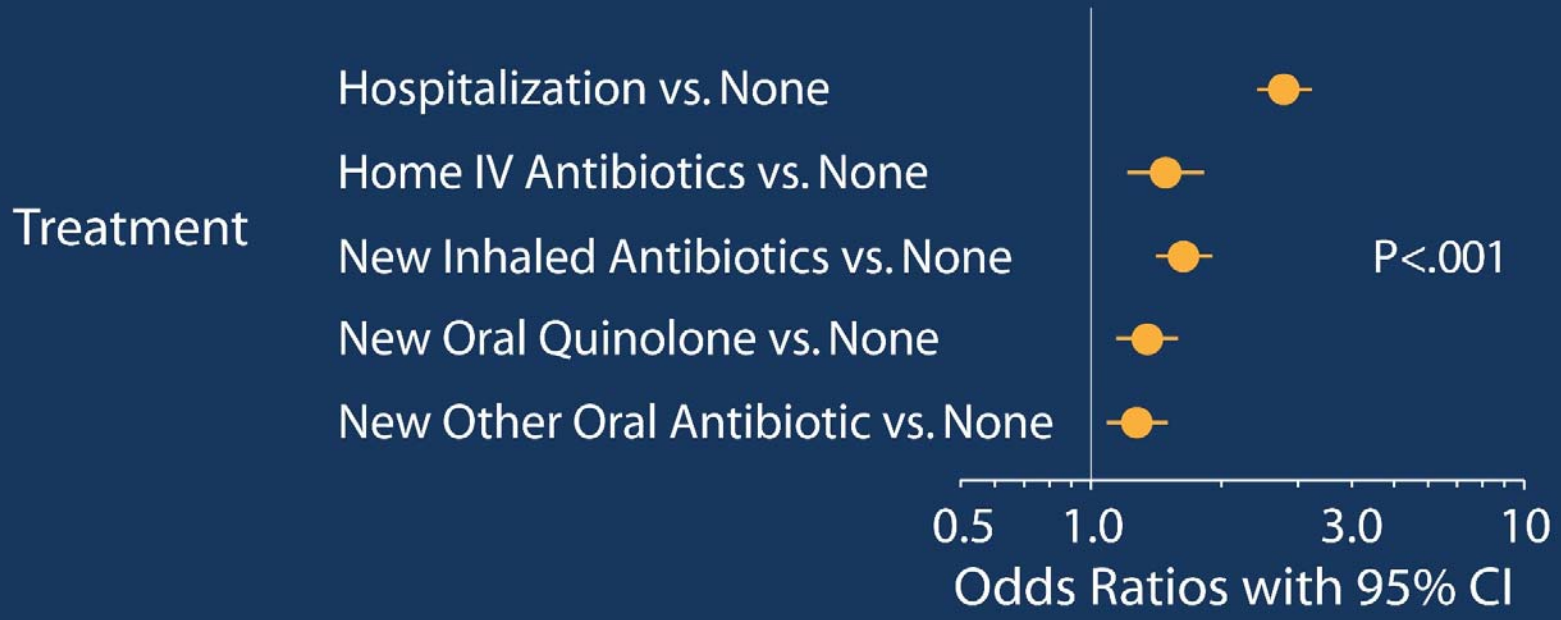
- Poor improvement in spirometry
- Prolonged courses of IV antibiotics
- Accelerated decline in pulmonary function
- Re-treatment



Sanders *Am J Respir Crit Care Med* 2010, de Boer *Thorax* 2011, Parkins *Chest* 2012, Waters *Eur Respir J* 2012, Heltshe *Thorax* 2016

Treatment decisions are associated with FEV_1 recovery

- Response to ≥10% acute decline in FEV_1
- 64% of acute declines in FEV_1 were treated



Morgan *Ann Am Thorac Soc* 2017

When all else fails: Lung Transplant

Who to refer

- Psychosocial stability
- Demonstrated adherence to therapy
- Trading one disease for another

When to refer

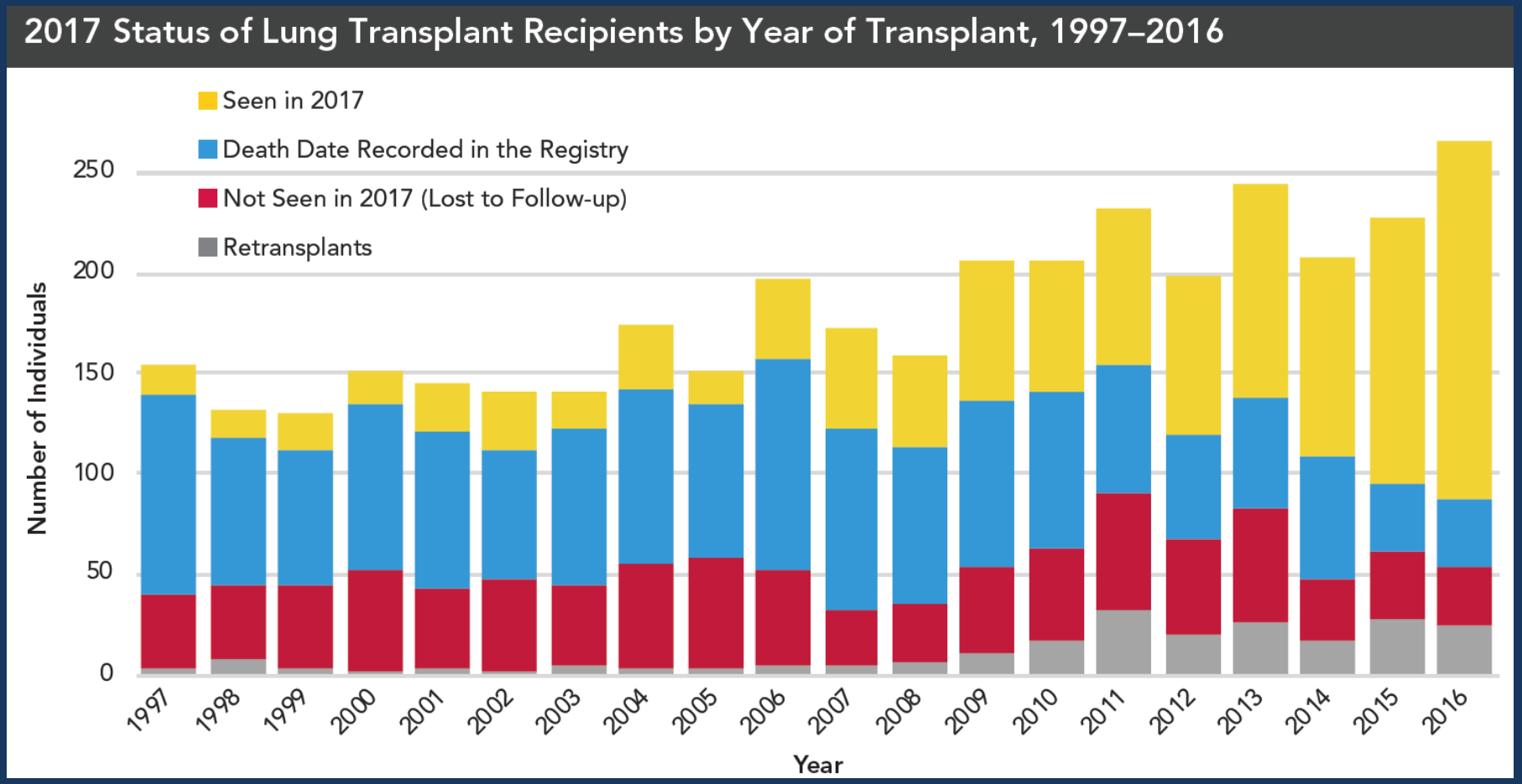
- FEV_1 vs clinical status

Lung transplantation and survival

- ~250 people with CF receive lung transplantation annually
  - 9% in pediatric patients
- Median survival = 6.6 years with FEV_1 <30% predicted without a lung transplant
  - Risk factors: oxygen, frequent pulmonary exacerbations, FEV_1, pulmonary hypertension, abnormal 6 minute walk test, massive hemoptysis, recurrent pneumothorax
- Median survival following lung transplant:
  - Adults = 9.5 years
  - Pediatrics = 5.4 years

CF Foundation Patient Registry 2017, Ramos *Chest* 2017, Yusen *J Heart Lung Transplant* 2016, Khush *J Heart Lung Transplant* 2018

Lung Transplantation



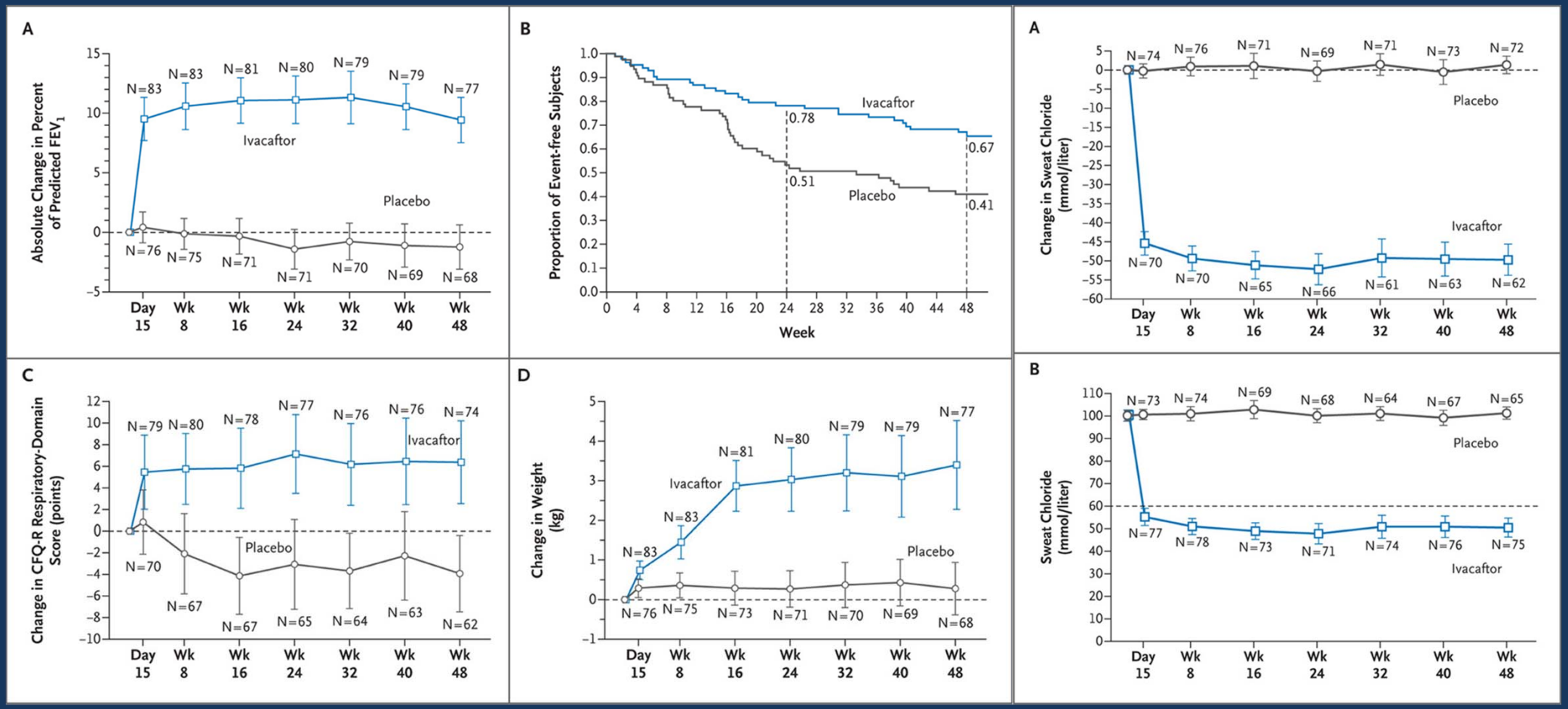
CF Foundation Patient Registry 2017

CFTR MODULATORS

Modulator therapy

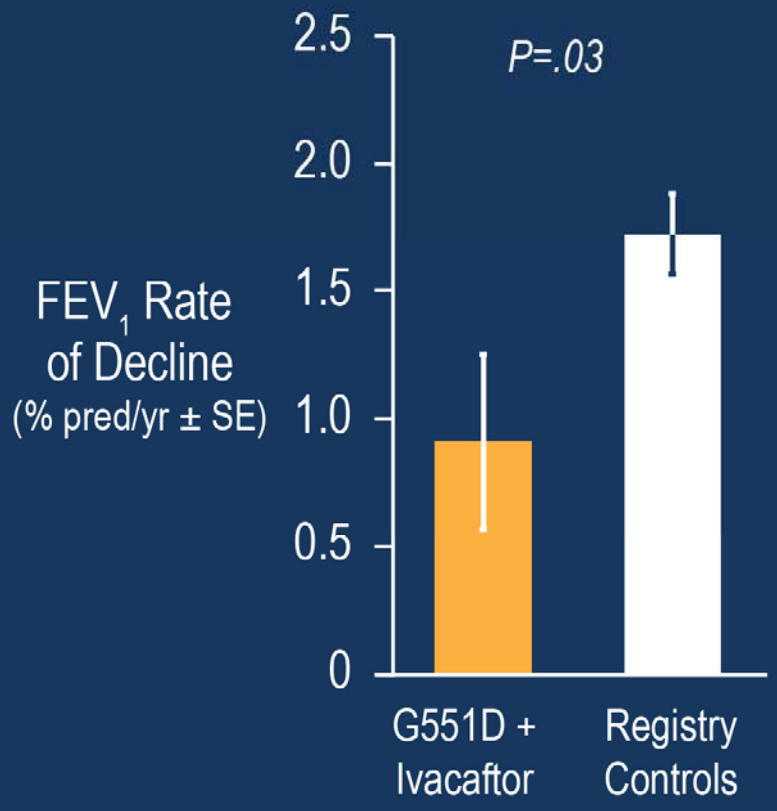
- Potentiators
  - Increases the open probability of the CFTR chloride channel
- Correctors
  - Helps misshaped CFTR to fold into the correct 3-D conformation
- Amplifiers
  - Increase the amount of CFTR protein produced
- Stabilizers
  - Decreases CFTR protein channel turnover at the cell surface

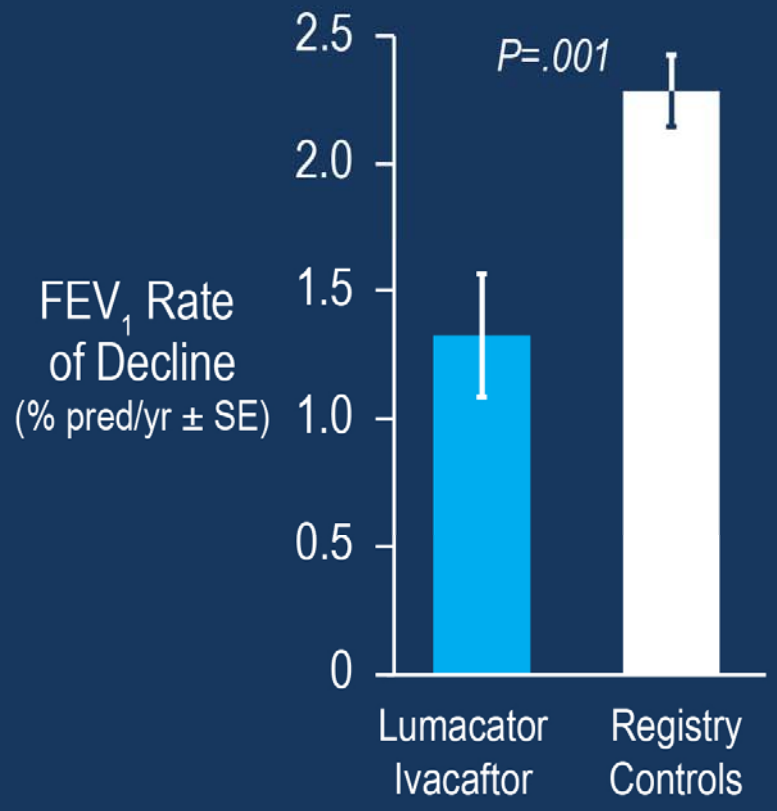
Ivacaftor in People with CF and G551D



Ramsey *N Engl J Med* 2011

CFTR Modulators and slowing of FEV_1 decline





Sawicki *Am J Respir Crit Care Med* 2015, Konstan *Lancet Resp Med* 2017

Question 4: What is the mechanism of action of "triple combination" CFTR modulators?

A. Potentiator/Potentiator/Corrector

B. Potentiator/Corrector/Amplifier

C. Potentiator/Corrector/Corrector

D. Potentiator/Corrector/Stabilizer

E. Potentiator/Corrector/Read through suppressor

Question 4: What is the mechanism of action of "triple combination" CFTR modulators?

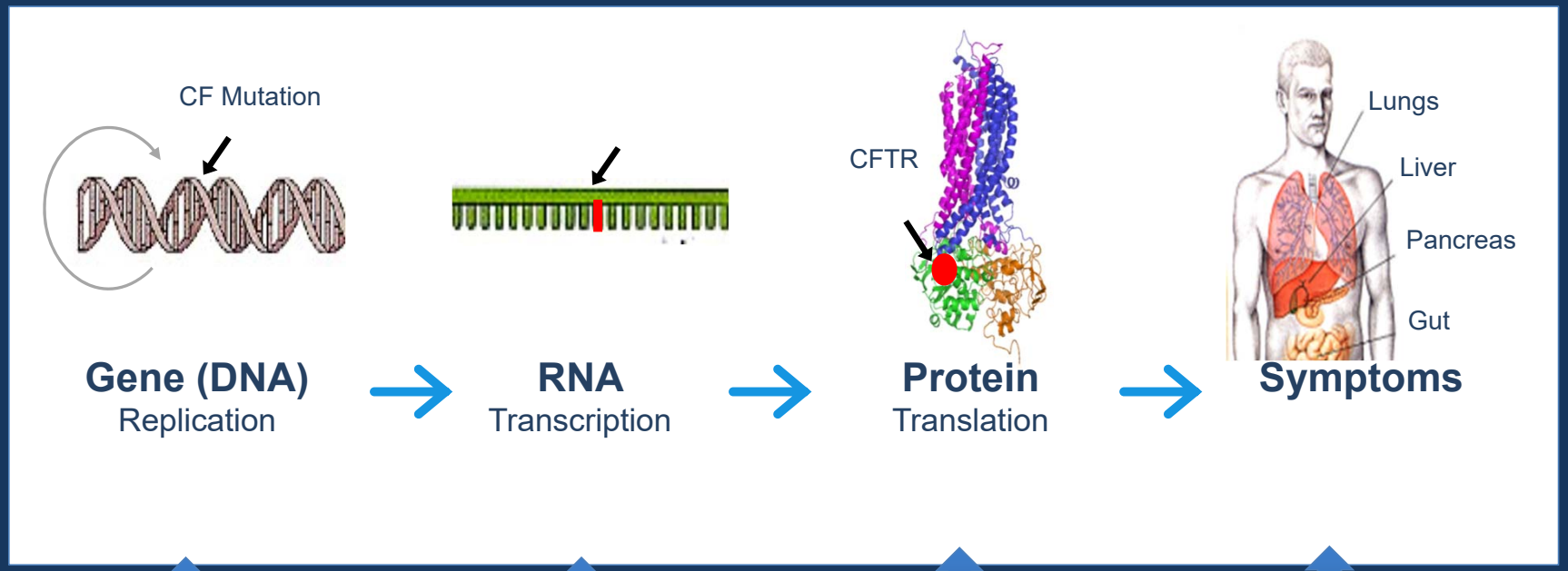
C. Potentiator/Corrector/Corrector

Triple-combination therapy phase 3 clinical trials

- People with CF ≥12 years of age treated with elexacaftor-tezacaftor-ivacaftor
- 113 patients with 2 F508del mutations
  - → 10% increase in FEV_1 vs tezacaftor/ivacaftor alone
- 403 patients with 1 F508del mutation + 1 minimal function
  - → 14% increase in FEV_1 vs placebo
  - → 63% decrease in rate of pulmonary exacerbations

Heijerman Lancet 2019; Middleton *N Engl J Med* 2019

Goal is to restore CFTR function in all people with CF



Gene editing
Gene delivery
Stem cell biology

Transcription
Translation
RNA repair
RNA replacement

Protein repair
(CFTR modulators)

Antimicrobials
Mycolytics
Anti-inflammatories
Nutrition

Courtesy of Jim Chmiel

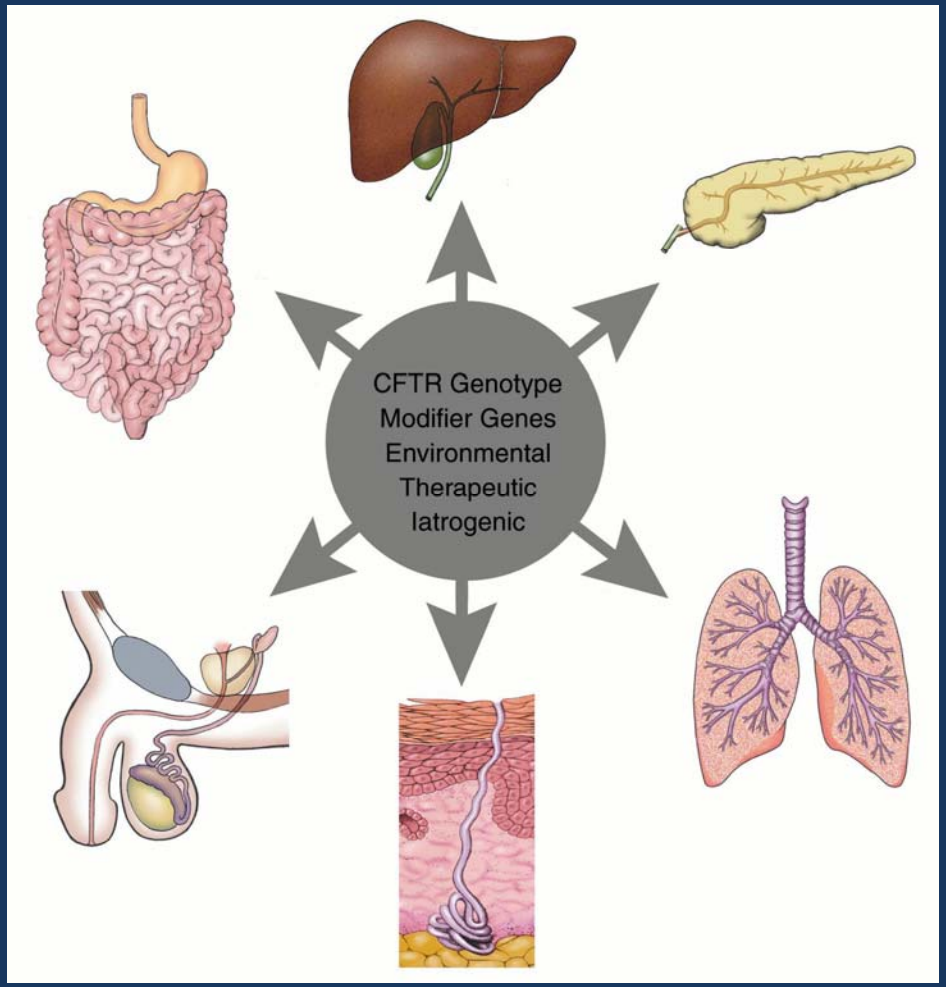
OTHER DISEASE FEATURES

Organ Dysfunction in CF

Liver
Focal cirrhosis

Intestine
Meconium ileus
Constipation
DIOS

Vas deferens
Failure to develop



Pancreas
Exocrine insufficiency
CF Related Diabetes

Respiratory
Sinusitis
Nasal polyps
Endobronchitis
bronchiectasis

Sweat gland
Salt-losing dehydration

Meconium ileus and DIOS

- Meconium ileus
  - ~15% of infants with CF
  - Inspissated fecal material and mucus, mostly in the small bowel
- Distal intestinal obstruction syndrome (DIOS)
  - Annual prevalence of 2-3%
  - Thick intestinal secretions, malabsorption, and decreased gut motility

Pancreatic insufficiency

- ~85-90% of patients with CF, usually within the first year of life
- Signs and symptoms
  - Large and greasy stools, flatulence, abdominal bloating
  - Poor weight gain and malnutrition
- Leads to vitamin (A, D, E, and K) deficiencies
  - Acrodermatitis, anemia, neuropathy, night blindness, osteoporosis, and bleeding disorders

Diagnosing pancreatic insufficiency

- 72 hour stool collections for fat absorption determination
- Recommended laboratory test is fecal elastase
  - Levels < 100 µg/g stool have an excellent predictive value
  - Enzyme replacement recommended for levels <200 µg/g stool

O'Sullivan *J Pediatr* 2015

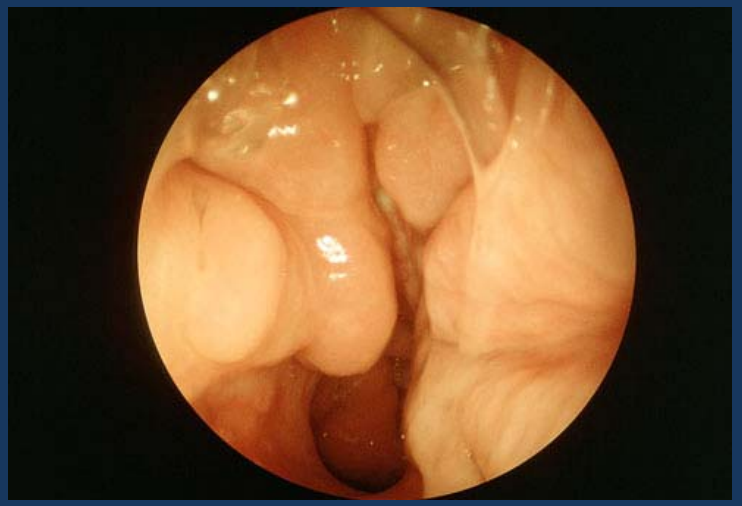
Pancreatic enzyme replacement therapy

- CF Foundation guidelines
  - 500-2,500 lipase units/kg/meal, titrated based on symptoms and growth
  - Infants enrolled in BONUS: 1,880 lipase units/kg/meal
- Fibrosing colonopathy
  - Limit to <2500 lipase units/kg/meal and <10,000 units lipase/kg/day
  - Infants enrolled in BONUS: up to 12,400 lipase units/kg/day
- Supplemental fat soluble vitamins
  - A, D, E, K
- High-calorie diet
  - May be >120% of recommended intake

Gelfond *J Pediatr Gastroenterol Nutr* 2018, Shoff *J Pediatr* 2006

Nose and sinus disease

- Nasal polyposis and pansinusitis
- Associated with poor quality of life
- Polyps may indicate a sweat test for non-CF patients

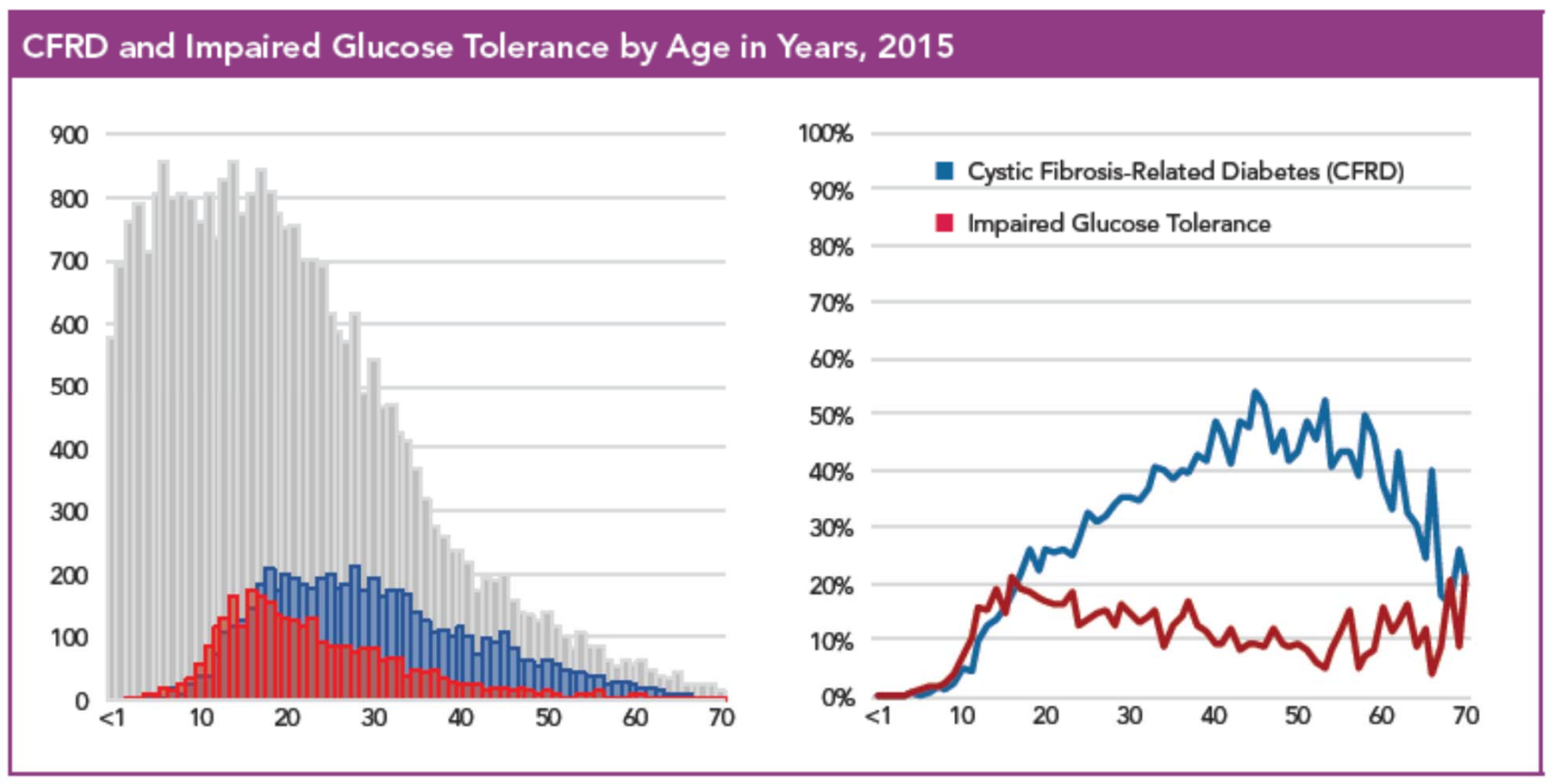


http://curesinusproblems.com/chronic-sinusitis-treatment/

CF-related diabetes mellitus (CFRD)

- Insulin insufficiency/resistance leads to carb intolerance
- Different from type I or type II diabetes mellitus
  - DKA is rare
  - Do not restrict diet
- Pancreas becomes replaced by fat
  - Autodigestion of the pancreas by pancreatic enzymes
  - Islet cells eventually disappear
- A yearly oral glucose tolerance test for ≥10 years of age

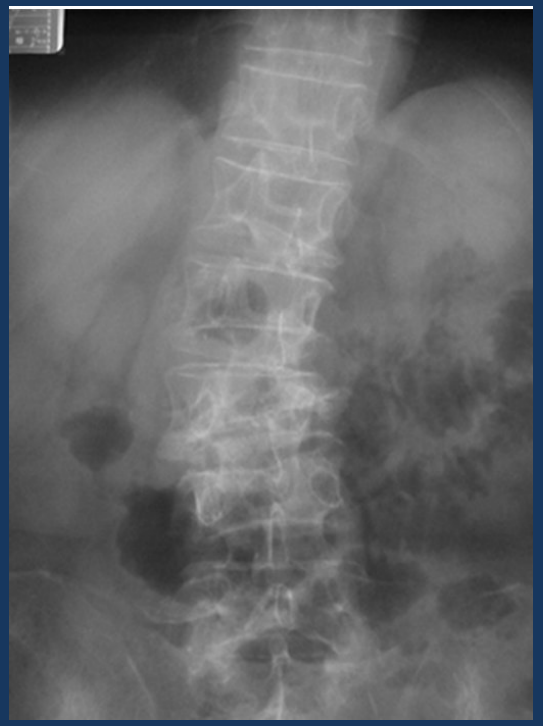
Prevalence of CFRD



CF Foundation Patient Registry 2015

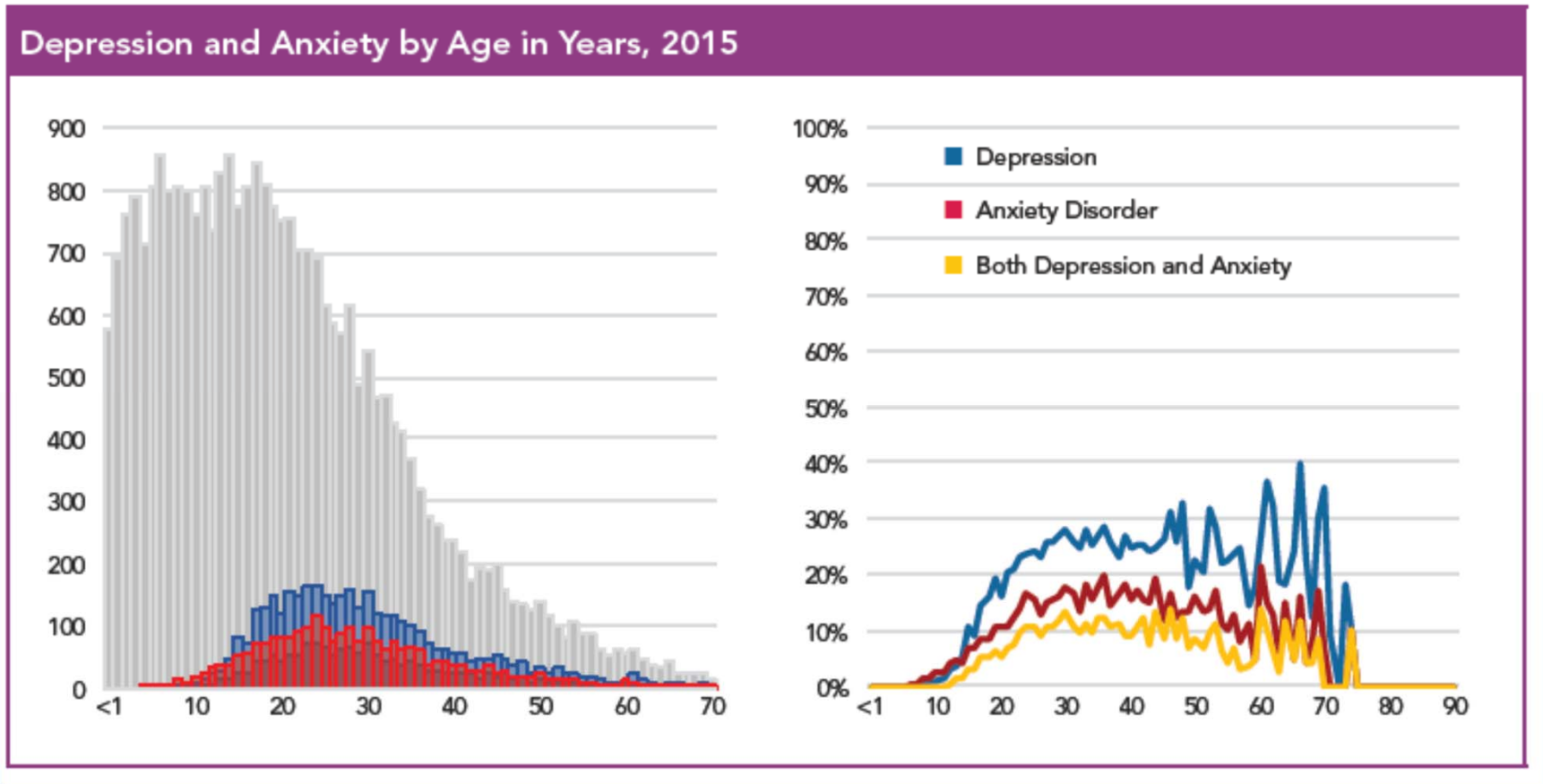
CF osteoporosis

- Common in CF
- Secondary to vitamin D deficiency, medications
- Vertebral and rib fractures are increasingly being seen as more CF patients survive into adulthood



The Internet Journal of Spine Surgery 2007 : Volume 3 Number 1

Prevalence of Depression and Anxiety



CF Foundation Patient Registry 2015

CF reproductive abnormalities

- Virtually all males with classic CF are infertile
  - Congenital bilateral absence of the vas deferens
- 1-2% of infertile men have CFTR dysfunction
  - Most men with obstructive azoospermia carry 1-2 CFTR mutations
- Most women with CF are fertile
  - Thickened cervical mucus may be present

Take home points

- Newborn screening has changed CF care
- Frequent monitoring and early detection of disease progression is key
- Inflammation and pulmonary exacerbations will still occur
- CFTR modulators and other “next-gen” therapies offer significant benefits