



# Cystic Fibrosis

## In the Era of Highly Effective Modulators

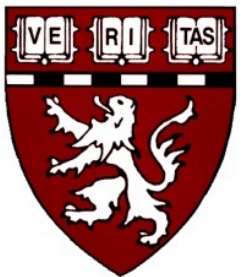
**Ahmet Uluer, DO MPH**

**Director, Adult CF Program**

**Adult Director, Therapeutic Development Network, Adult CF Program**

**Assistant Professor, Harvard Medical School**

Boston Children's Hospital and  
Brigham & Women's Hospital Cystic Fibrosis Center  
Boston, MA, USA



# Disclosures

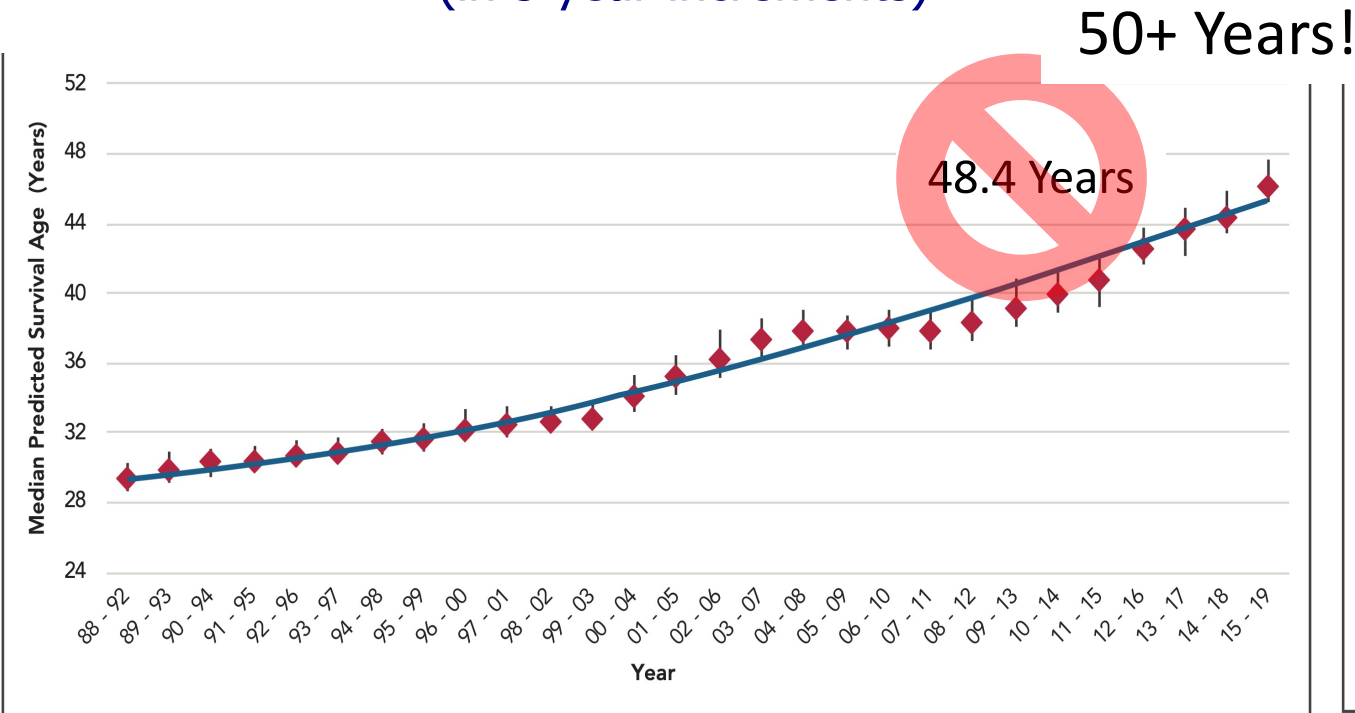
- Cystic Fibrosis Foundation Therapeutic Development Network
- Adult CF Program Principal Investigator
- North American Lead Principal Investigator
  - Vertex VX121-101
  - Eloxx-012

# Outline

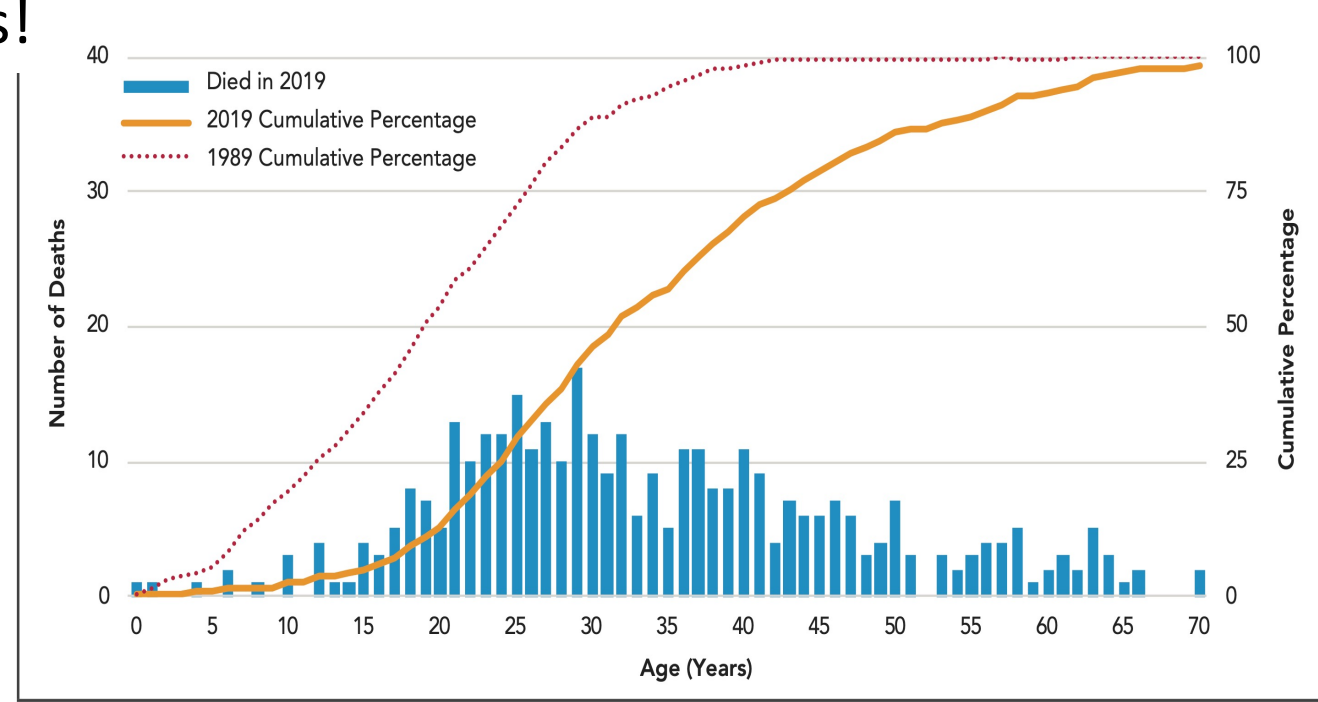
- Introduction to CF and Brief Overview
- Patient Case: 62 year old presenting with bronchiectasis and recurrent exacerbations
- CF Pathophysiology
- Diagnosis and Outpatient Management
- CFTR Modulators and Future
- Conclusion and Questions

# Improving Survival

Median Predicted Survival Age, 1988-2019  
(in 5 year increments)



Median Age of Death - 2019



**373 deaths reported, median age at death 32.4 years**

# A Story of Progress

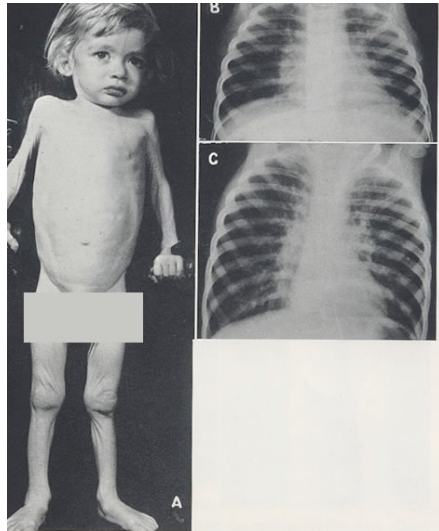
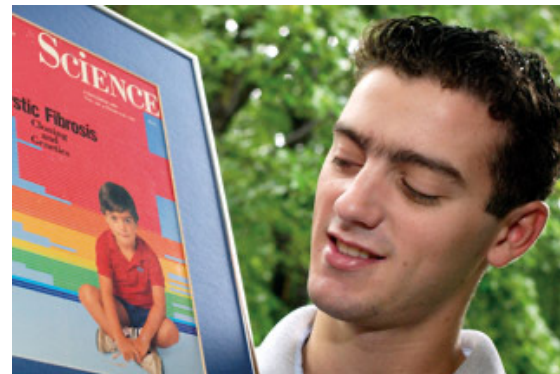
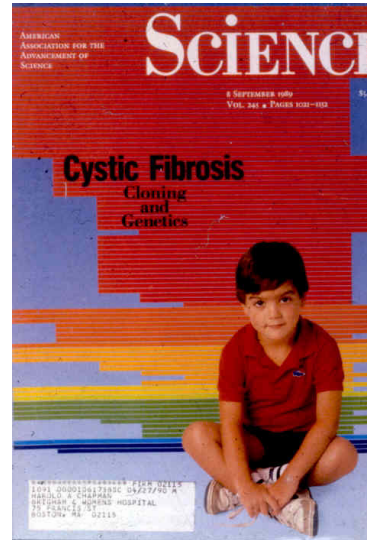
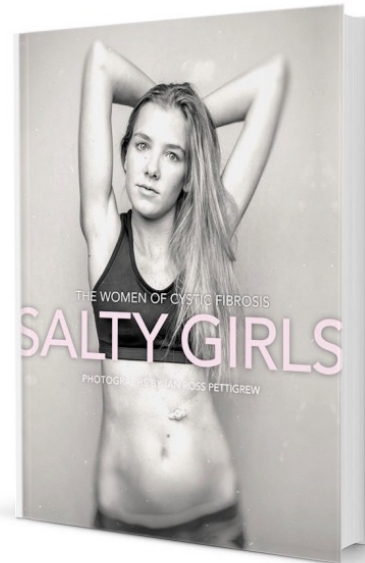


Figure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, five months. B. Lungs at one year, two months. C. Lungs at two years, five months. When infection becomes established in the viscous secretion in the bronchioles at an early age, and persists, the lungs show progressive development of peribronchial infiltration and emphysema. The nutritional state deteriorates with advance of the infection. (Reproduced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the pancreas in Infants and Children, *J. Pediat.*, 34:663 (1949) with permission of C. V. Mosby, St. Louis.)

1950



1989



2015



2020

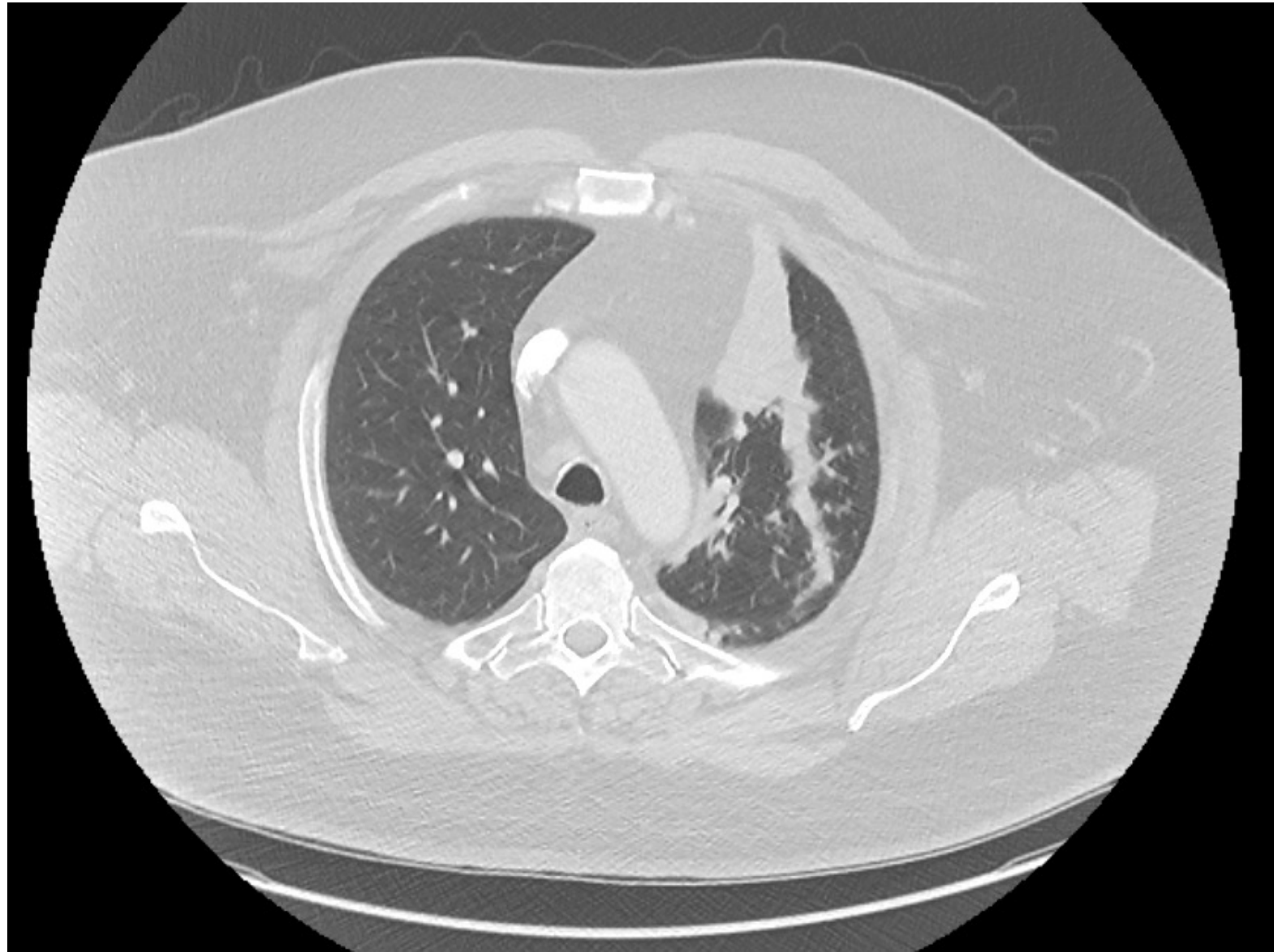
# Patient Case

General information	
Age at diagnosis:	--
Current age:	62 years
Sex (M/F):	M
Genotype:	--
Sweat chloride:	--
Lung function:	71% (initial visit)
Medical background (e.g. exacerbations/infection history):	
Pneumonia and recurrent bronchitis since age 14 (yearly) Exacerbations increased to 3-4x/year and chronic cough  <b>Chest CT in 2016 with diffuse nodular opacities and bronchiectasis</b>  <b>TB testing negative</b>	

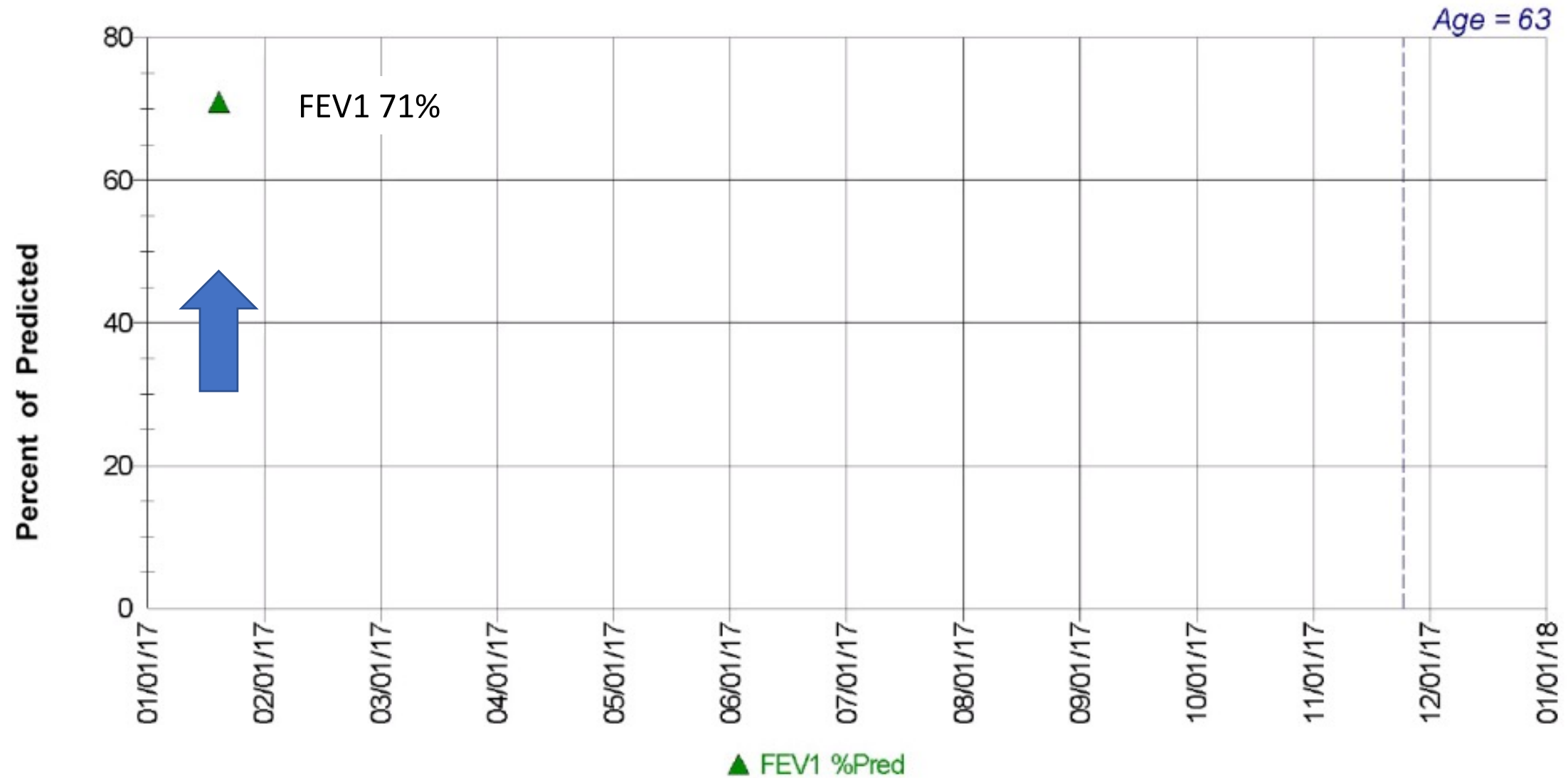
Comorbidities:
Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity
Lifestyle/circumstance:
Decreased activity, desk job
CFTR Treatment:
Other
Never smoked No Children Family History of Colon cancer

CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

## Patient Case



# Patient Case

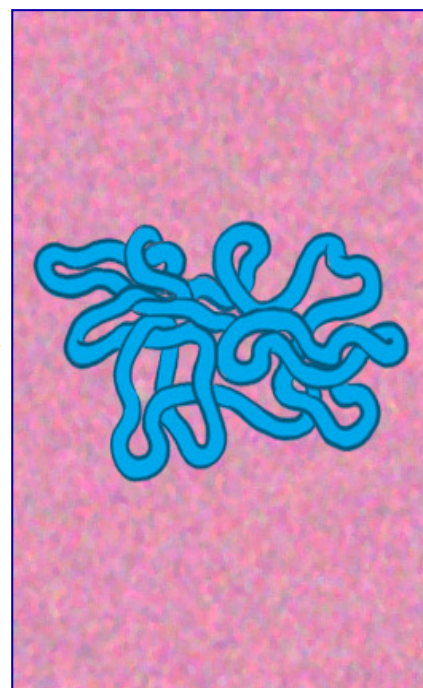


# CF Pathophysiology

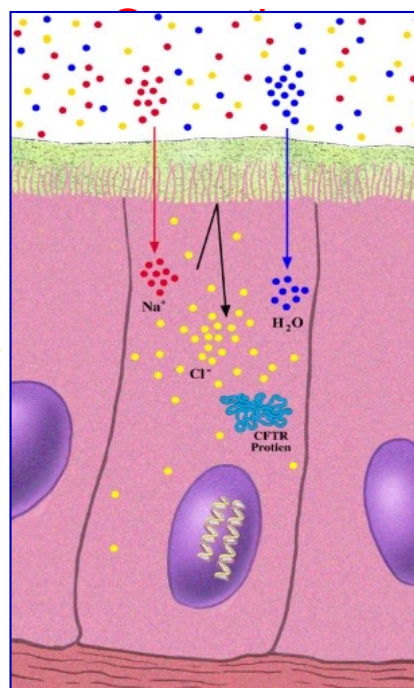
Abnormal Gene



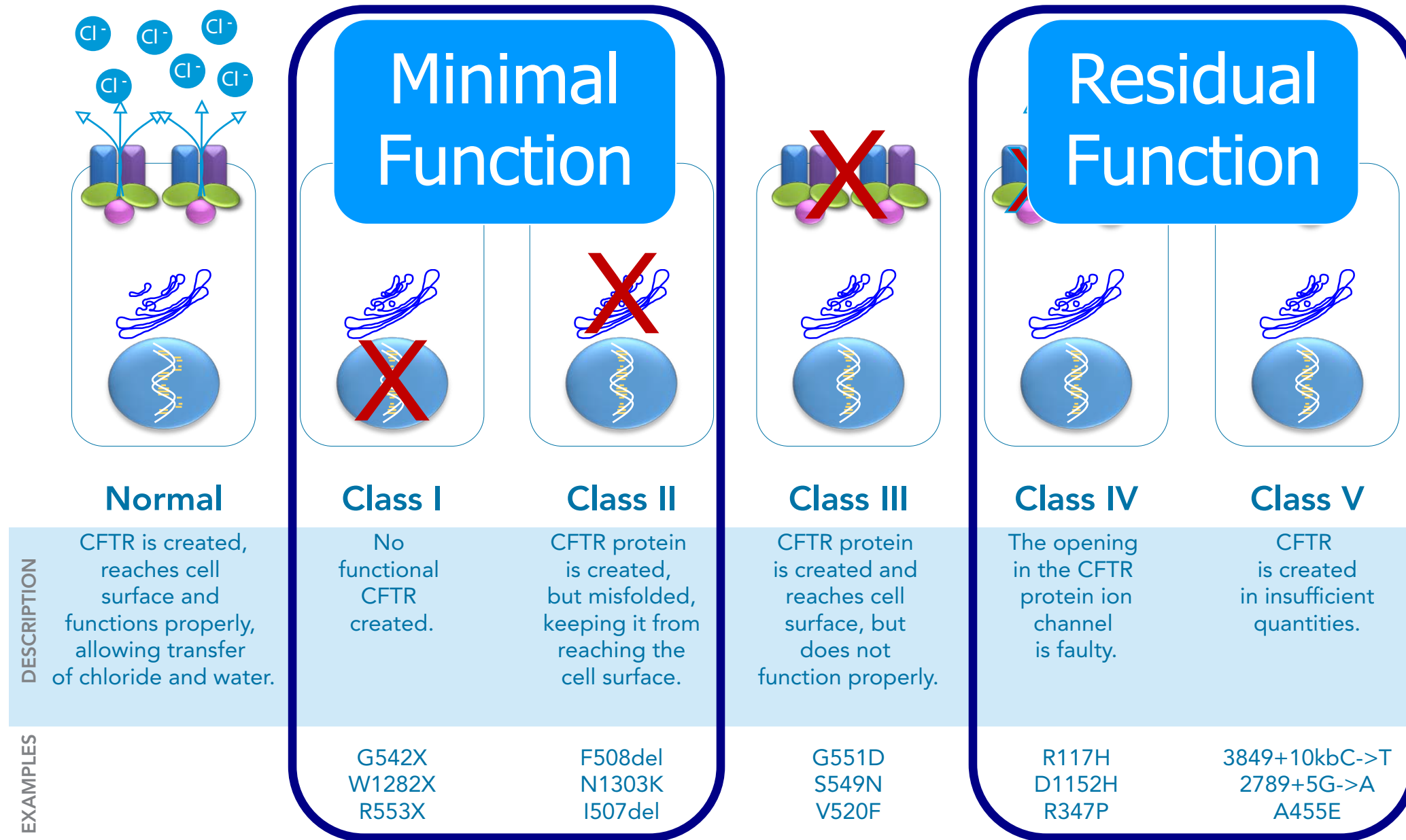
Abnormal Protein



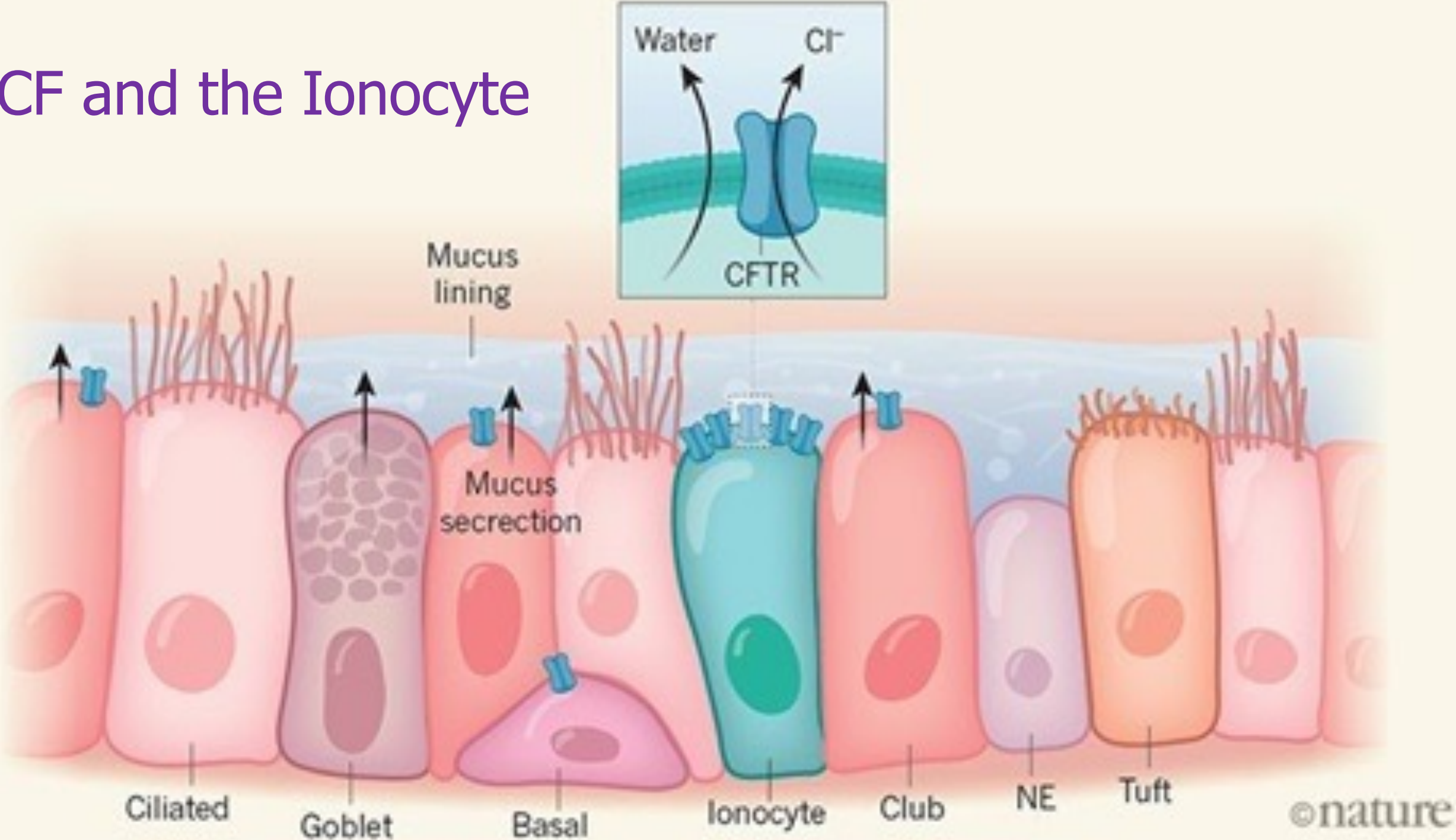
Altered Ion Transport ( $\text{Cl}^-$  and  $\text{HCO}_3^-$ ) & Abnormal Mucus



# 5 (or 6) Classes of CFTR Mutations



# CF and the Ionocyte

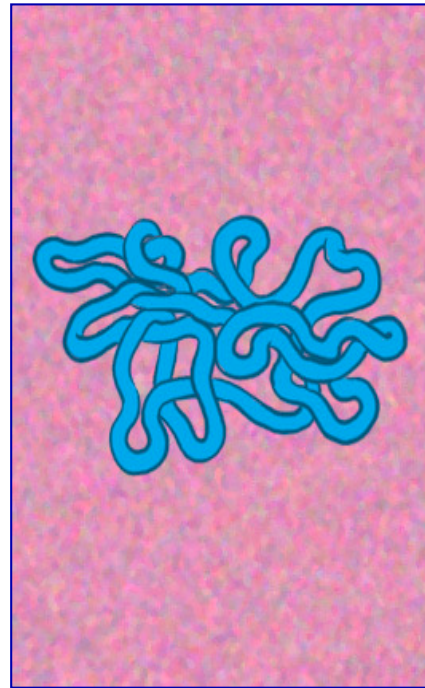


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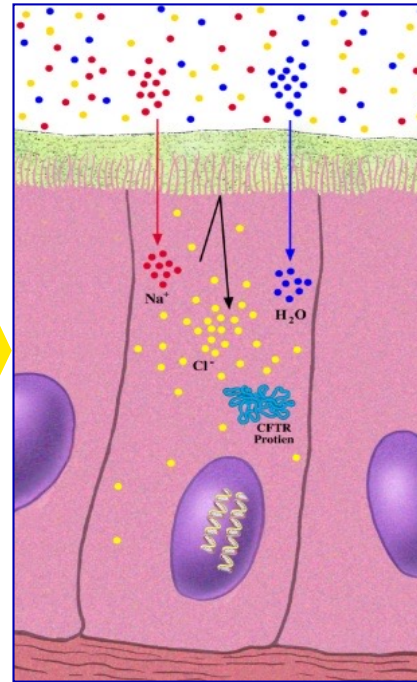
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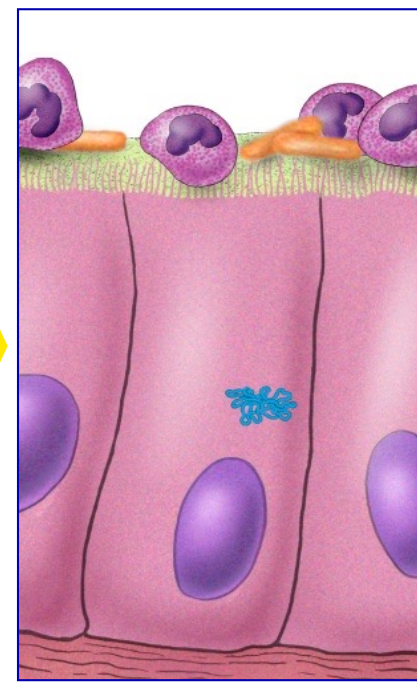
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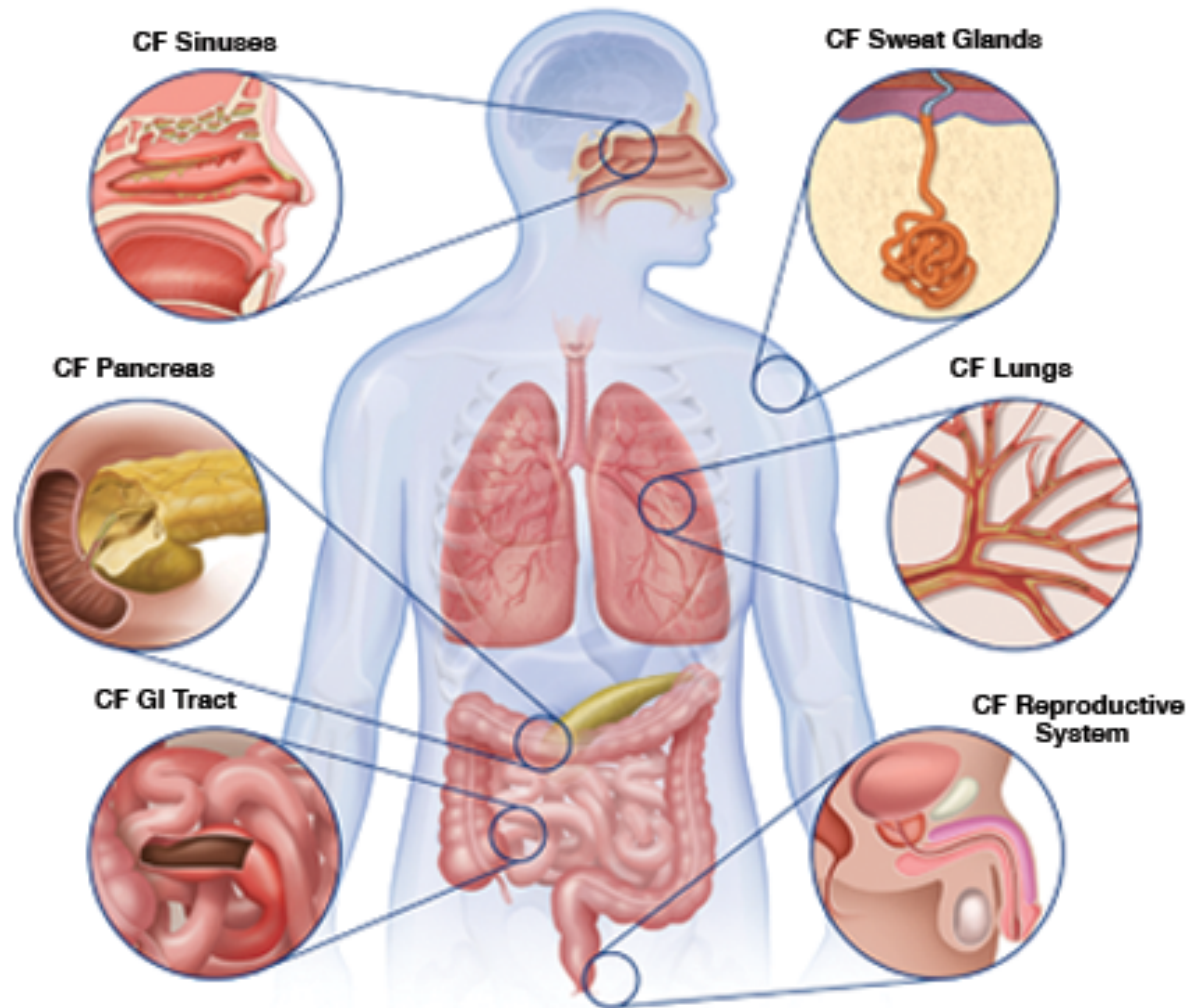
Infection & Inflammation



Organ Destruction & Respiratory Failure



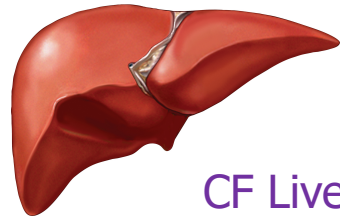
# CF - Multi-Organ Involvement



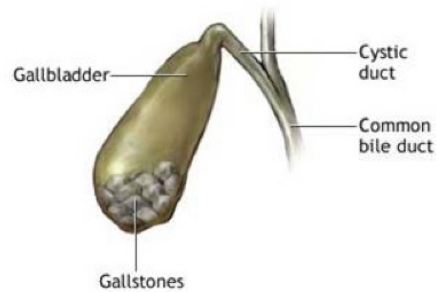
Pulmonary Disease is major cause of morbidity and mortality

<https://www.cftrscience.com/?q=CF-morbidity>

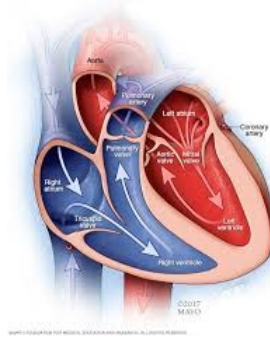
# CF - Multi-Organ Involvement (Cont'd)



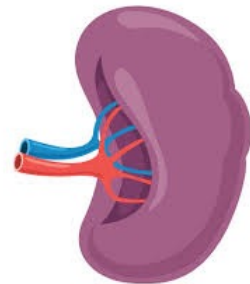
CF Liver Disease



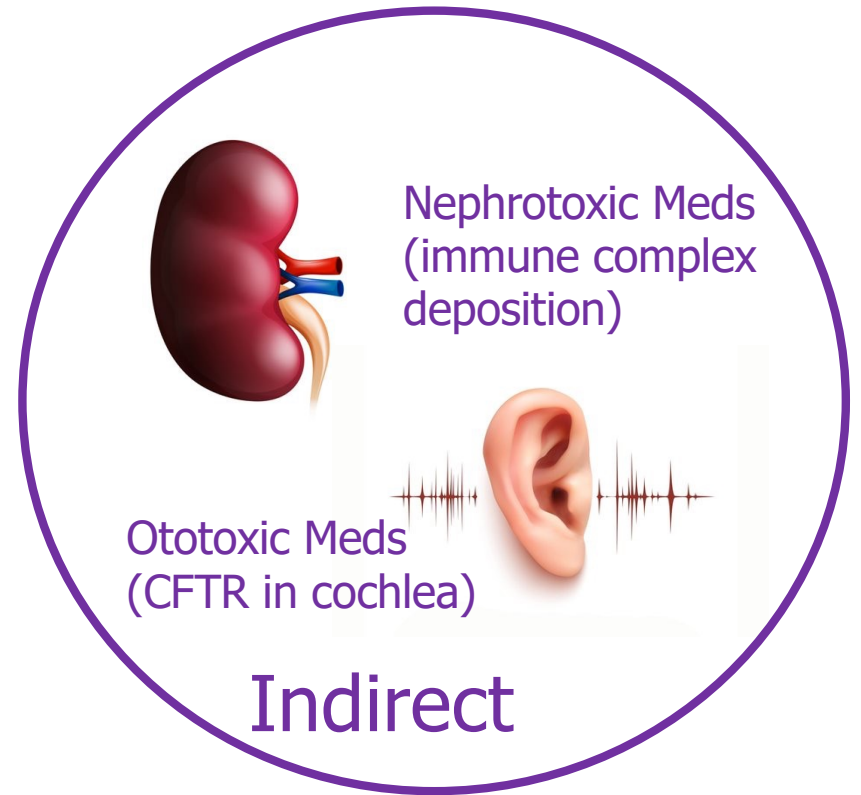
CF Gall Bladder



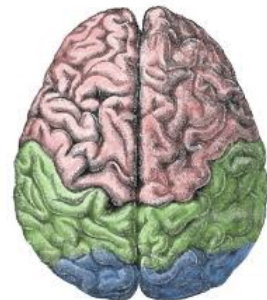
Pulmonary HTN and Cor pulmonale



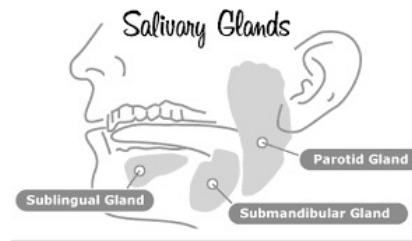
Splenomegaly and splenic infarcts



CF Bone Health



Arnold-Chiari Malformation



Salivary duct plugging and stones



CF Mental Health

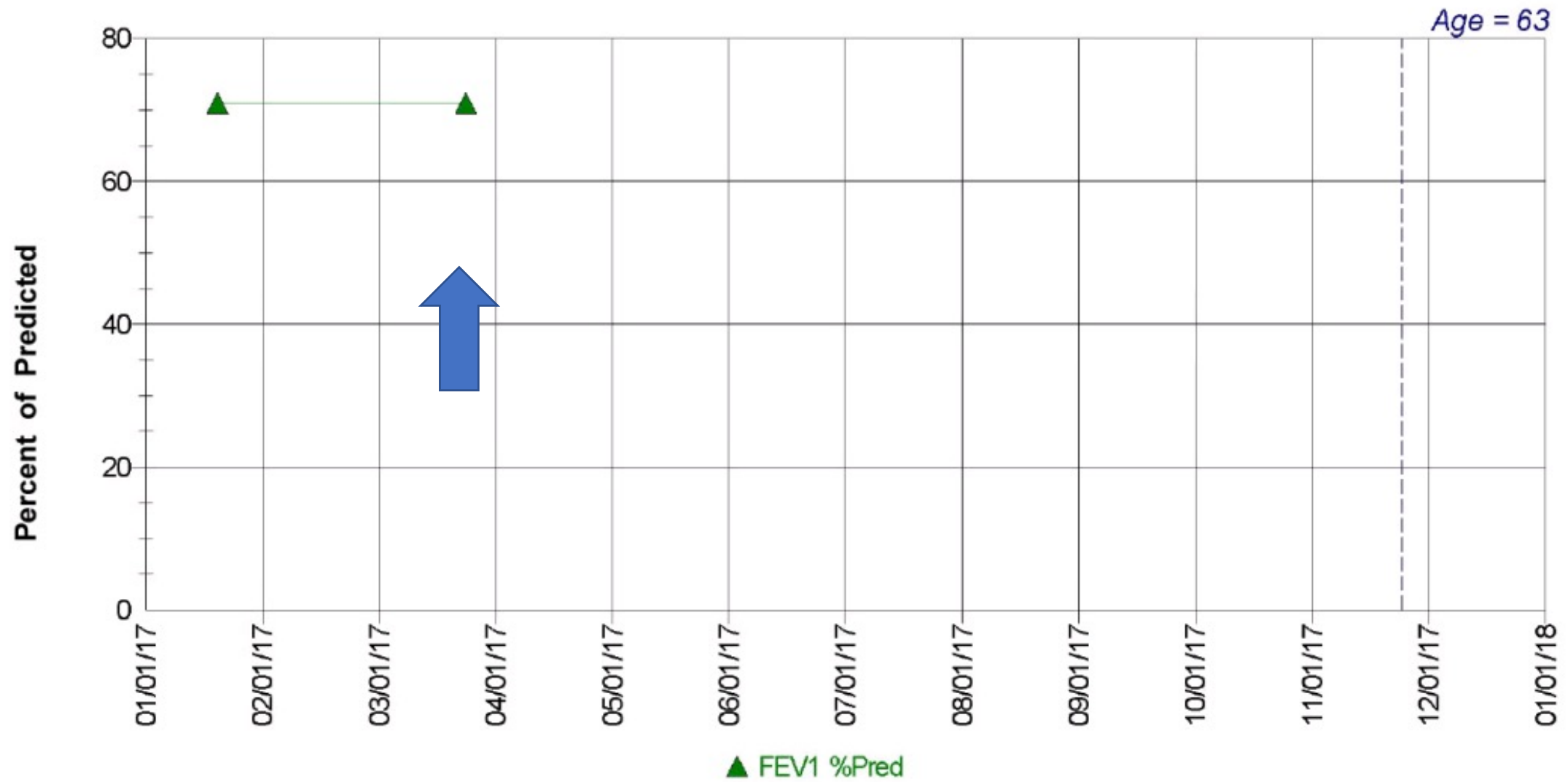
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Lung function:	71% (initial)
Medical background (e.g. exacerbations/infection history):	
Last 2 years	
Hemoptysis 1-2 teaspoon with exacerbations	

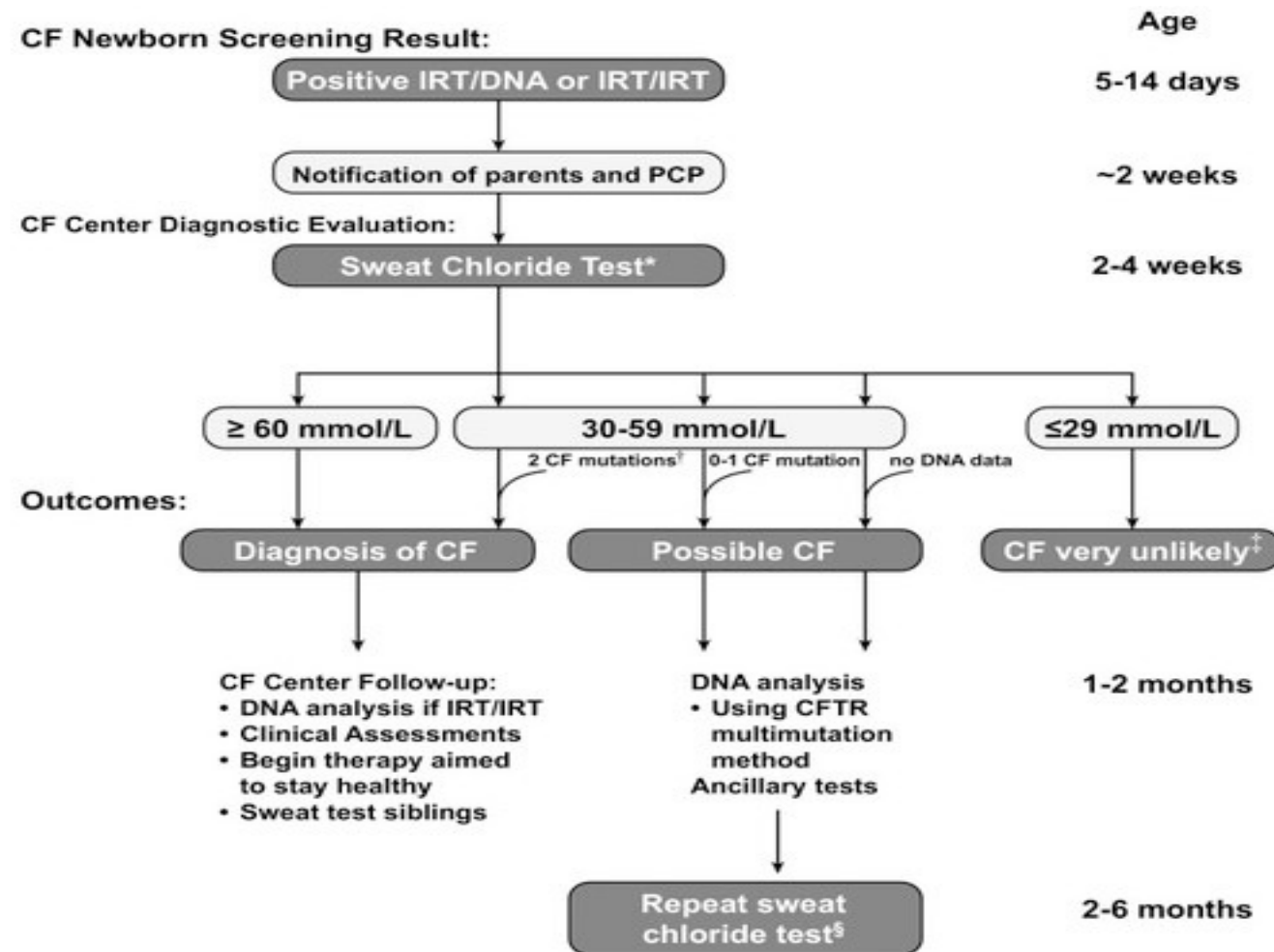
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CFTR Treatment:
Eligible for ivacaftor, a CFTR modulator (prior to elexacaftor/tezacaftor/ivacaftor approval)
Other
Never smoked No Children Family History of Colon cancer

CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

# Patient Case



# Diagnosis of Cystic Fibrosis



(J Pediatr 2008;153:S4-S14)

\* If the baby is at least 2kg and more than 36 weeks gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 µl, respectively.

† CF mutation refers to a CFTR mutant allele known to cause CF disease.

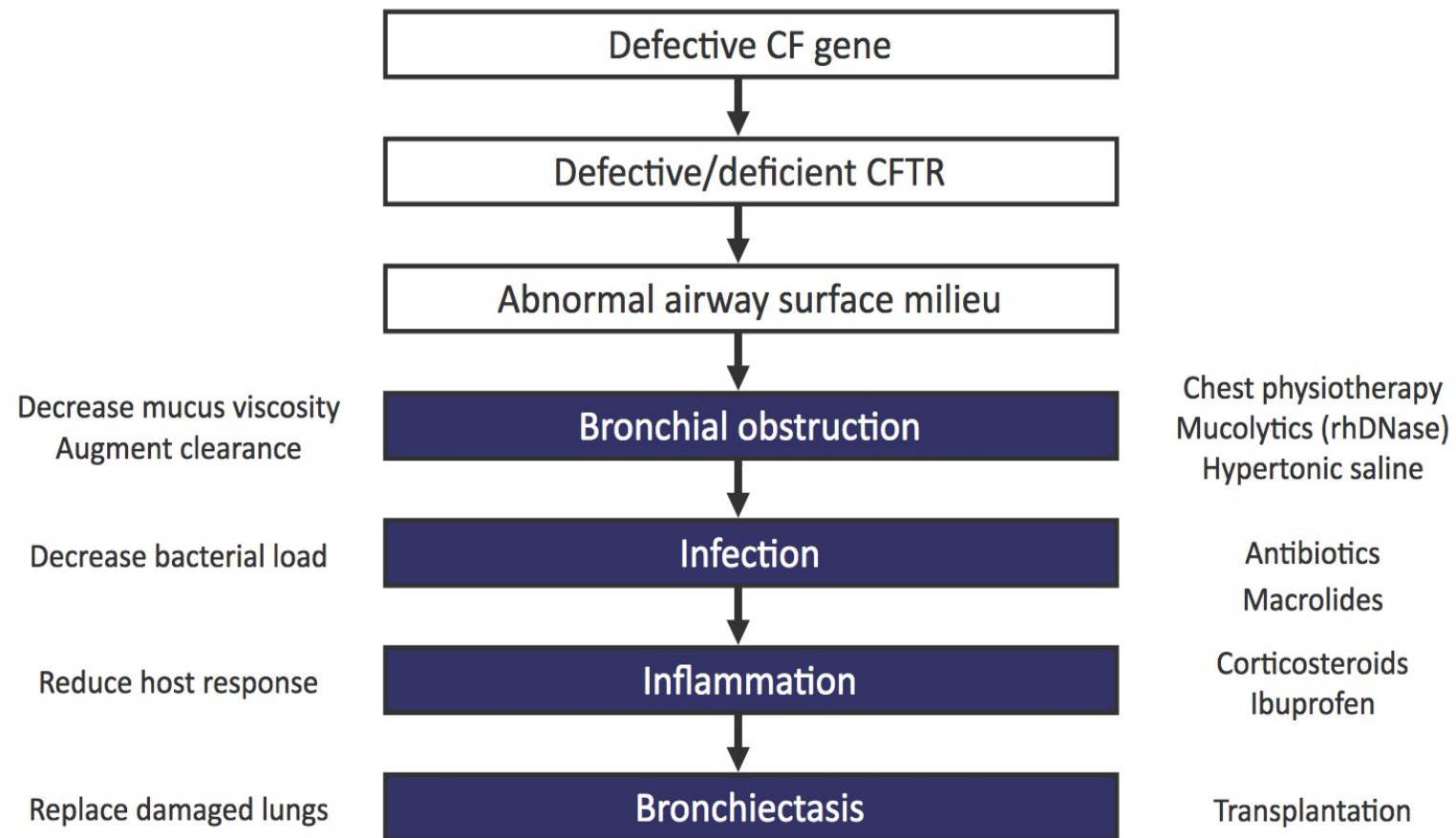
‡ The disease is very unlikely; however, if there are 2 CF mutations in trans, CF may be diagnosed.

§ After a repeat sweat test, further evaluation depends on the results as implied above.

# Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.

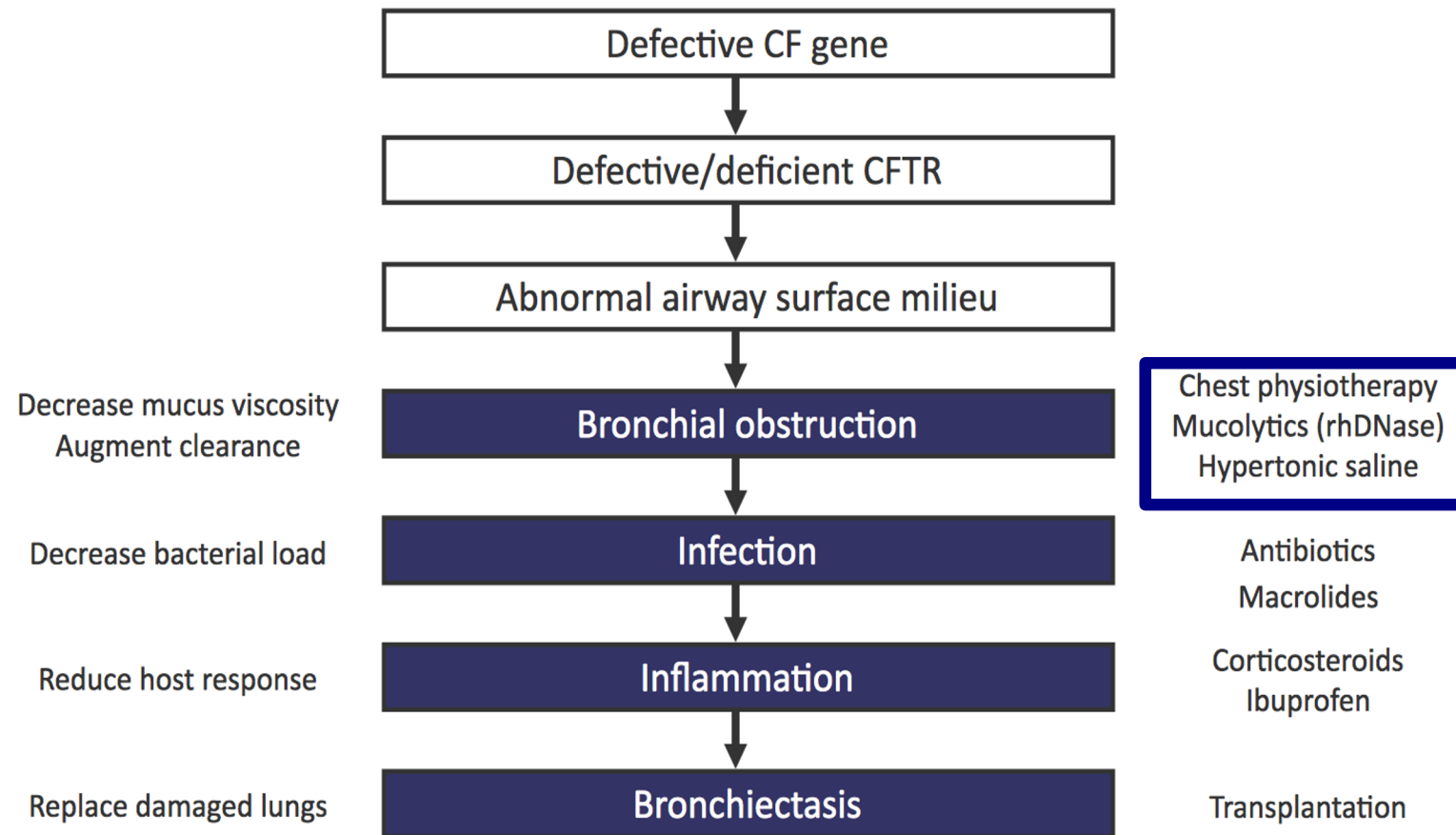
## Treatment of cystic fibrosis lung disease



# Therapeutic Approaches for CF Lung Disease

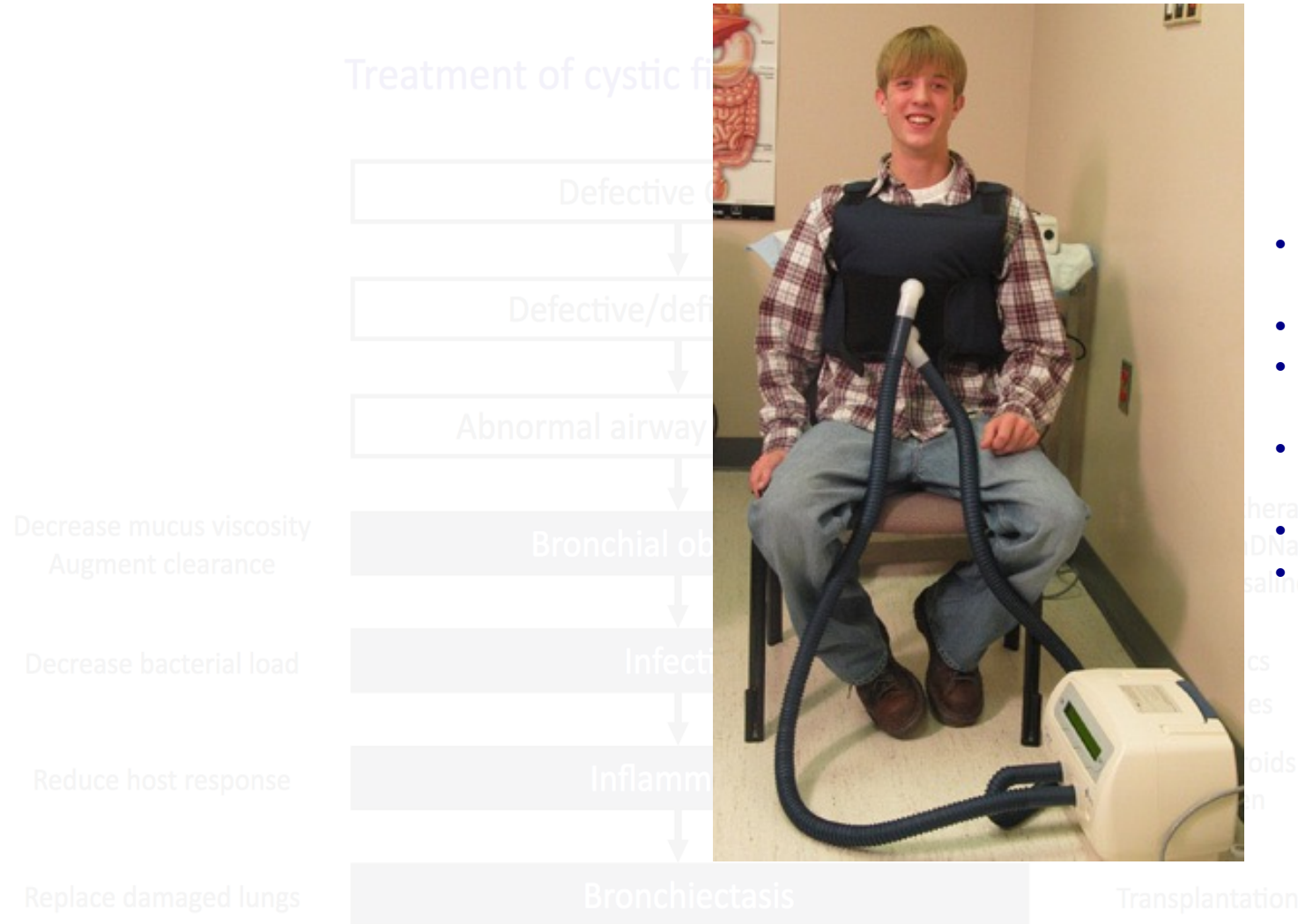
Davis PB, et al J Respir Crit Care Med. 1996;154:1229.

## Treatment of cystic fibrosis lung disease



# Therapeutic Approaches for CF Lung Disease

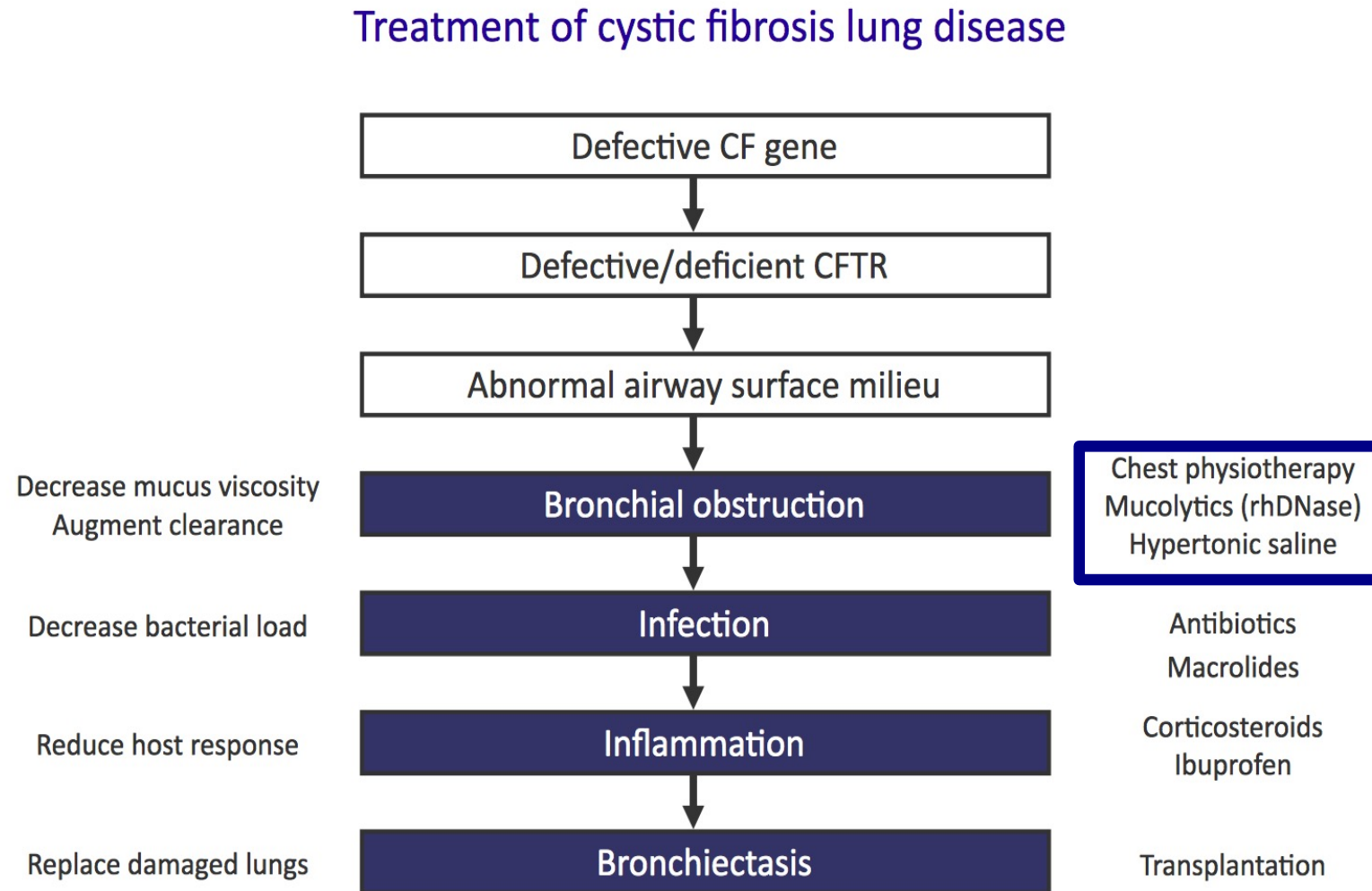
Davis PB, et al J Respir Crit Care Med. 1996;154:1229.



- High Frequency Chest Wall Compression (Vest)
- Manual Percussion and Drainage
- Positive Expiratory Pressure Device (PEP)
- Active Cycle Breathing and Autogenic drainage
- Exercise
- Others

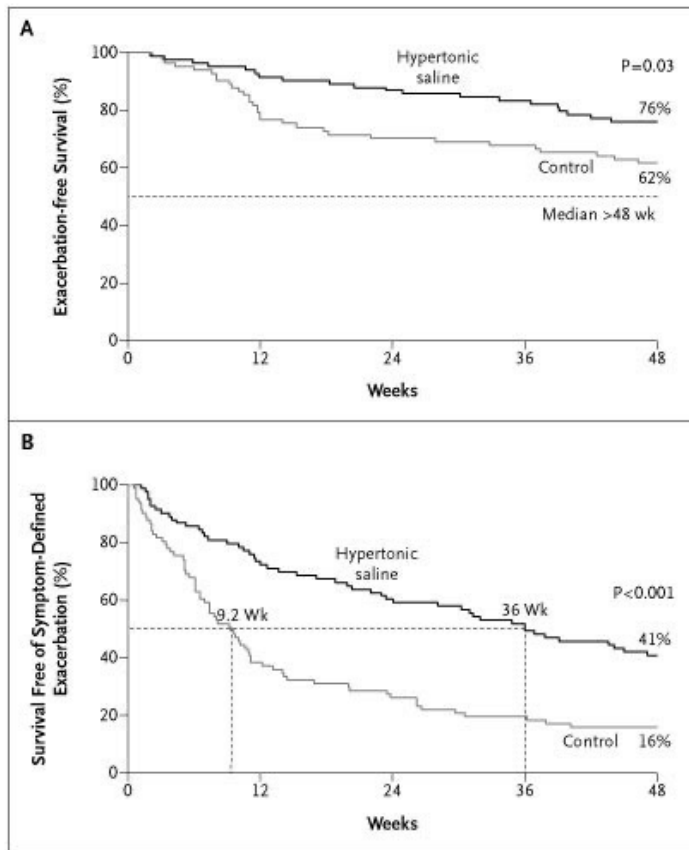
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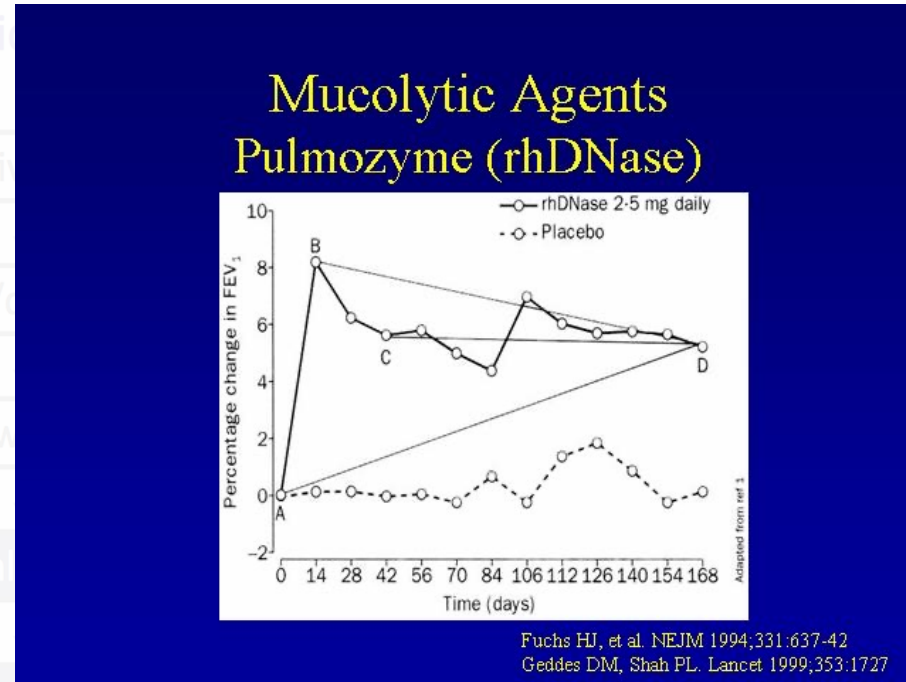


# Therapeutic Approaches for CF Lung Disease

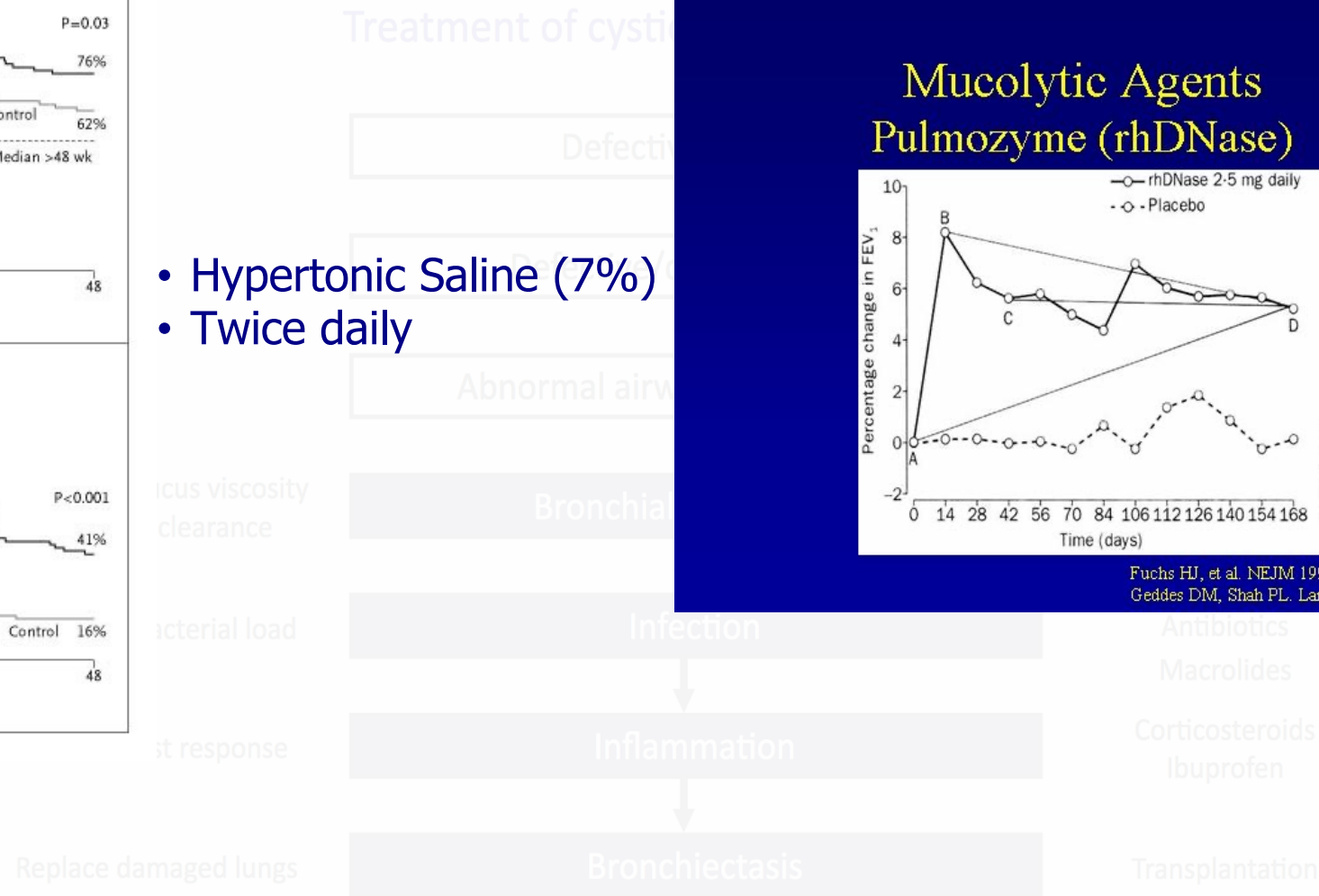
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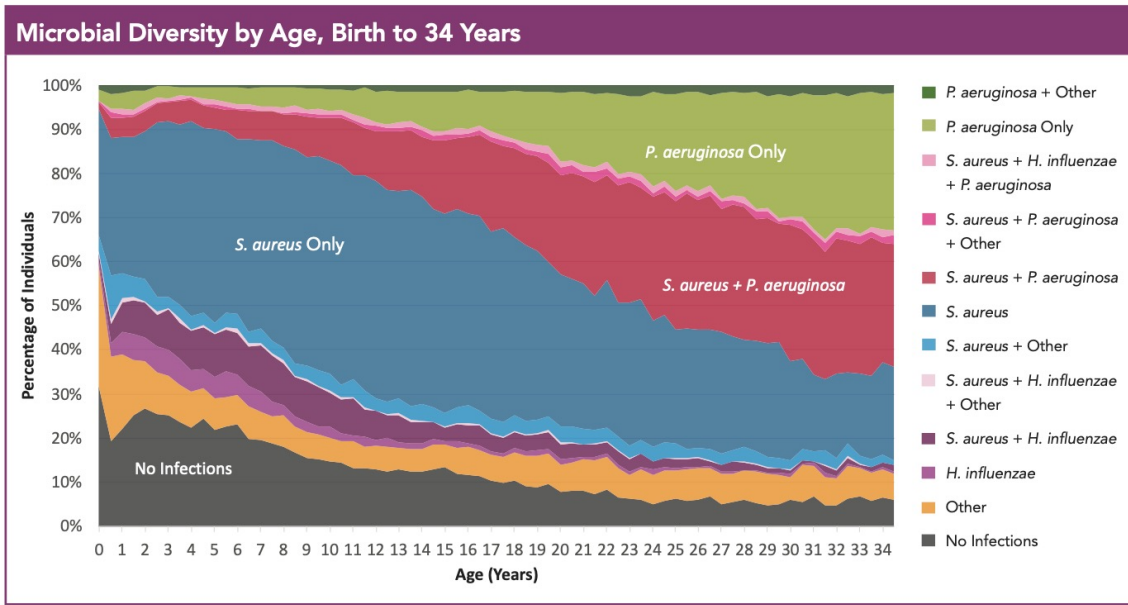
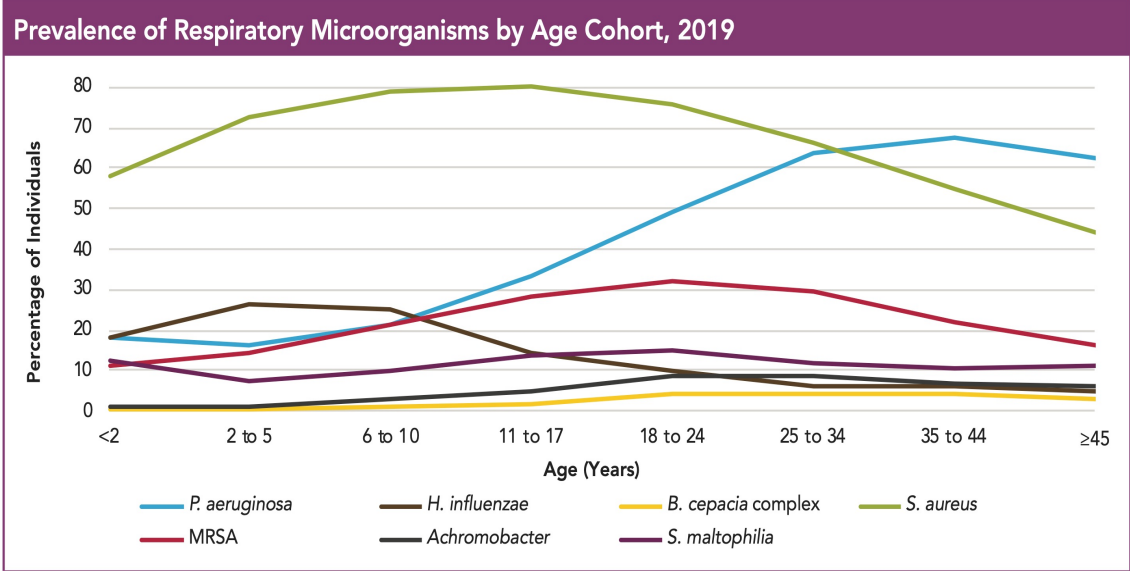
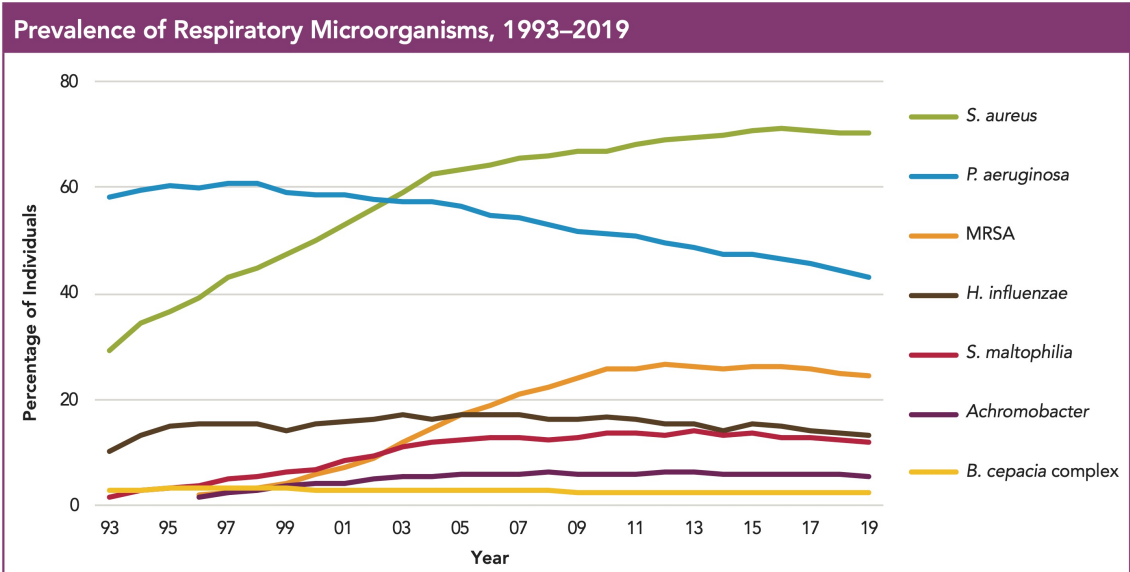
- Hypertonic Saline (7%)
- Twice daily



- Dornase alpha
- Once daily



# Bacterial Epidemiology in CF

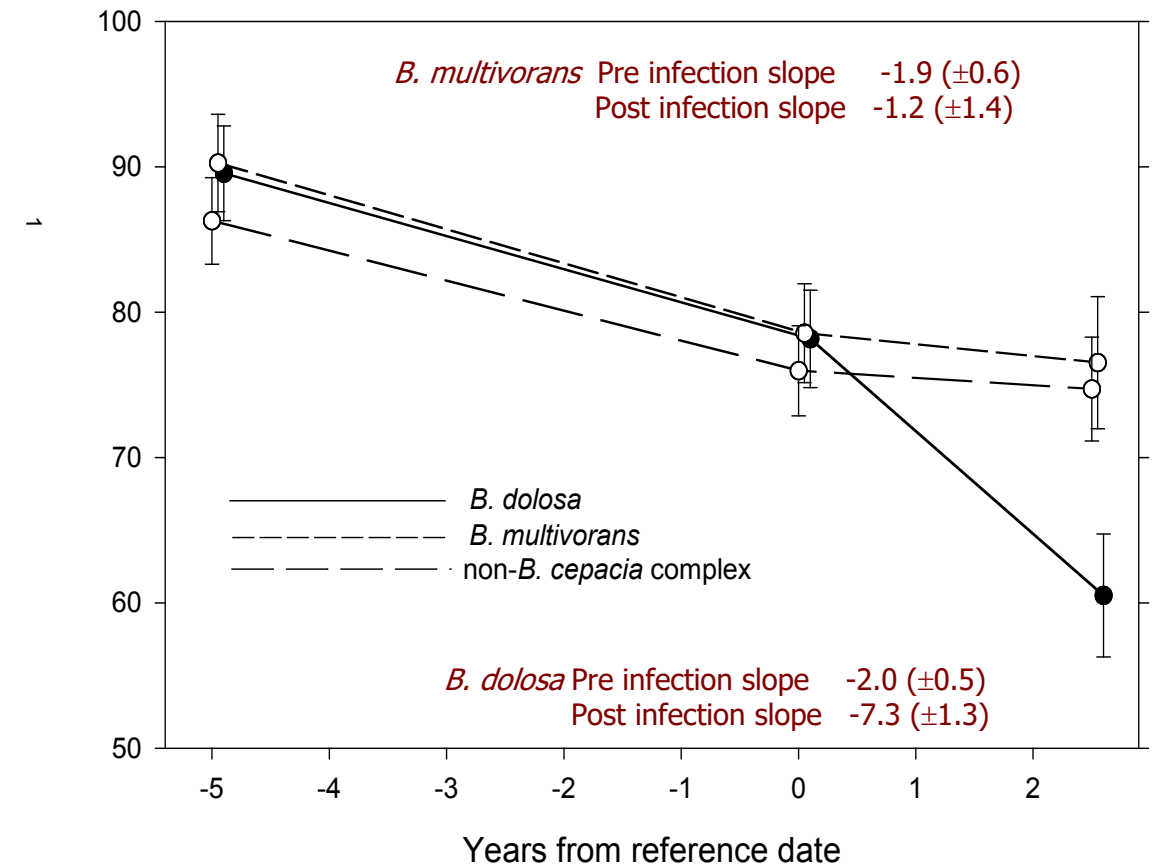


CFF 2019 Annual Registry Report

# Preventing Infection and consequences of *B. dolosa* transmission



- Infection prevention and control is the most effective way to prevent new infections in CF

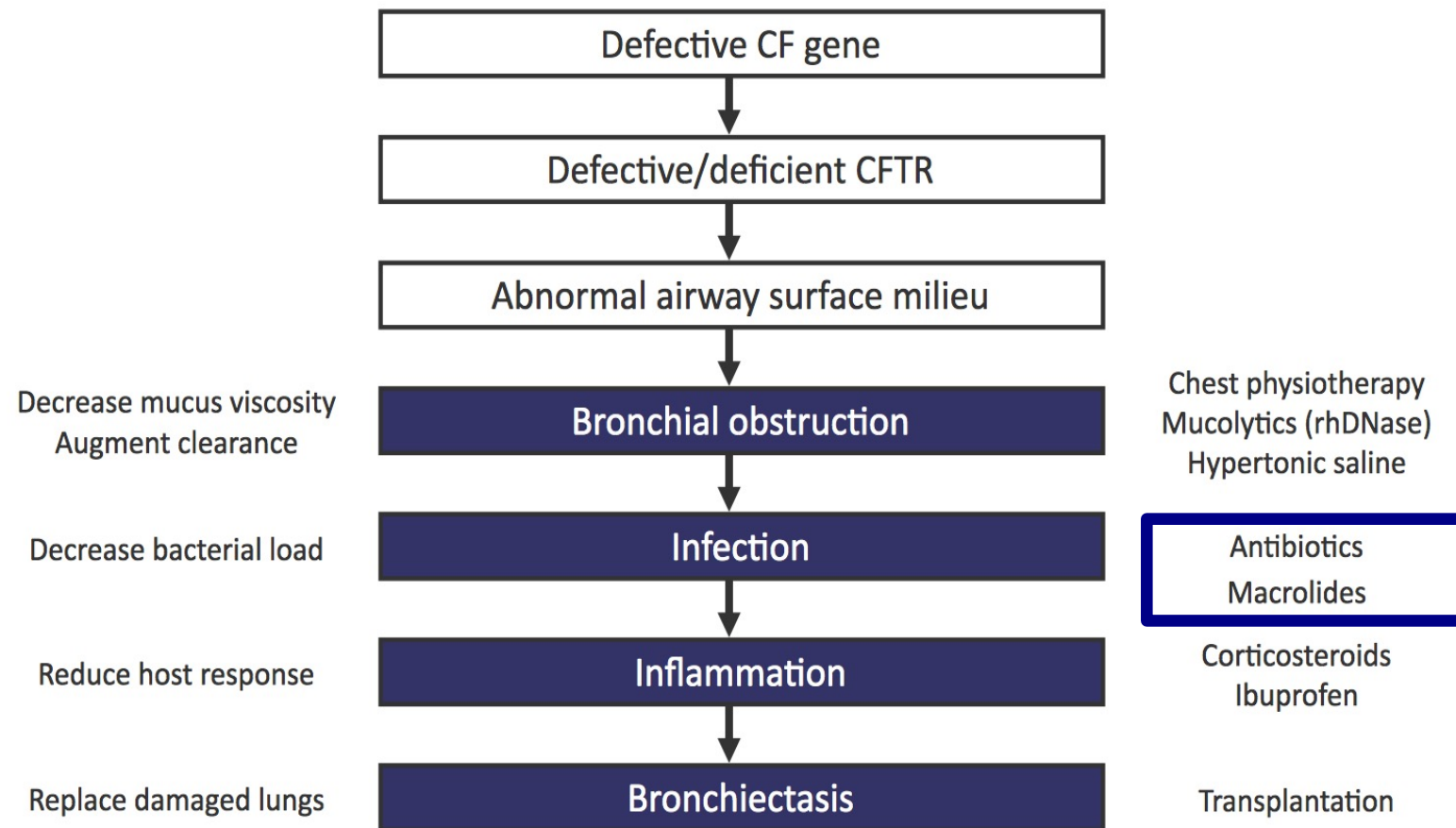


Kalish, Waltz et al. AJRCCM 2006

# Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.

## Treatment of cystic fibrosis lung disease



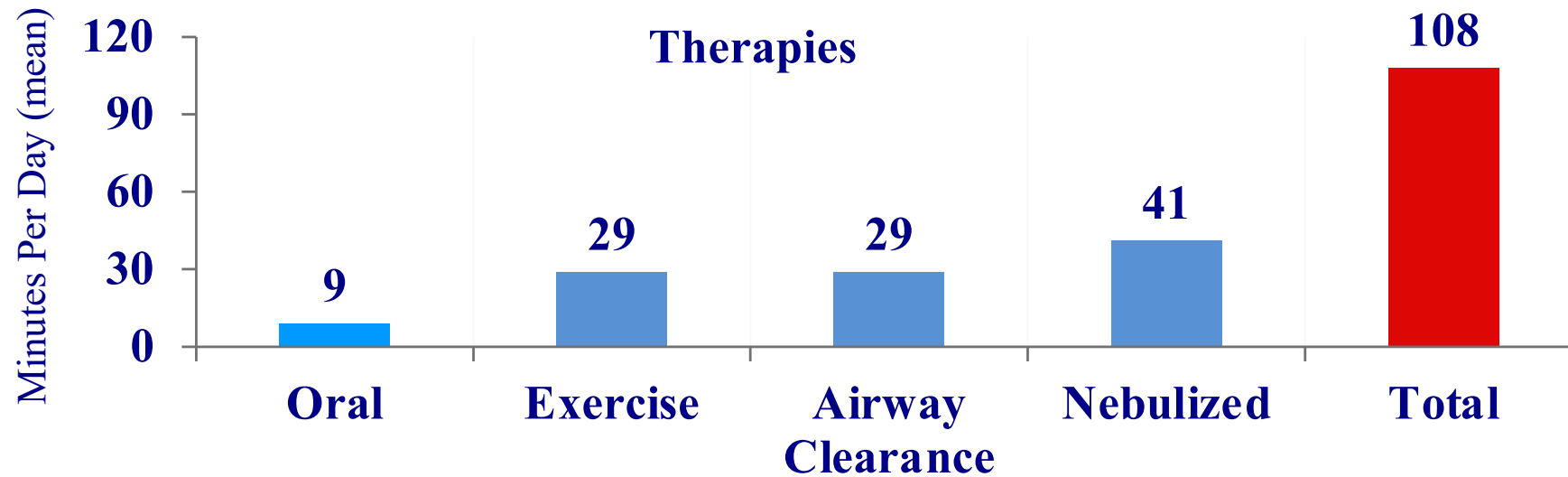
# Chronic Therapies for Maintenance of Lung Health

<u>Grade A Recommendation</u> <u>(High Benefit/Substantial)</u>	<u>Grade B Recommendation</u> <u>(Mod Benefit/Substantial)</u>	<u>No Recommendation</u> <u>(Insufficient Evidence)</u>
<ul style="list-style-type: none"> <li>• Inhaled Tobramycin                             <ul style="list-style-type: none"> <li>• Mod-severe disease</li> </ul> </li> <li>• Dornase Alfa                             <ul style="list-style-type: none"> <li>• Mod-severe disease</li> </ul> </li> <li>• Inhaled aztreonam                             <ul style="list-style-type: none"> <li>• Mod-severe disease</li> </ul> </li> <li>• CFTR Modulators (<i>modified</i>)                             <ul style="list-style-type: none"> <li>• (F508del and other eligible mutations)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Inhaled Tobramycin                             <ul style="list-style-type: none"> <li>• Mild disease</li> </ul> </li> <li>• Dornase Alfa                             <ul style="list-style-type: none"> <li>• Mild disease</li> </ul> </li> <li>• Inhaled aztreonam                             <ul style="list-style-type: none"> <li>• Mild disease</li> </ul> </li> <li>• Hypertonic Saline</li> <li>• Macrolides (PsA)</li> <li>• Ibuprofen (&lt;18 yrs)</li> </ul>	<ul style="list-style-type: none"> <li>• Other aerosolized abx</li> <li>• N-acetyl cysteine</li> <li>• Cromolyn</li> <li>• Inhaled cholinergics</li> <li>• Leukotrienes</li> <li>• Oral Steroids</li> <li>• Inhaled beta-agonist</li> <li>• Macrolides (no PsA)</li> <li>• Chronic oral Anti-Staph</li> </ul>

Flume et al. Am J Respir Crit Care Med 2007;176:957-969

Mogayzel et al. Am J Respir Crit Care Med 2013; 187:680-689

# High Treatment Burden in CF



Medications	Median (Range)
# of Oral Medications	3 (0-7)
# of Nebulized Medications	2 (0-5)
# of Inhaled Medications (MDI)	1 (0-4)
<b># of Total Medications</b>	<b>7 (0-20)</b>

## CF Related Observational and Interventional Studies

- PROMISE
  - Observational study looking at impact of triple combination CFTR modulator
- SIMPLIFY
  - Interventional study of discontinuing either Hypertonic Saline or Dornase Alfa while on triple combination CFTR modulator

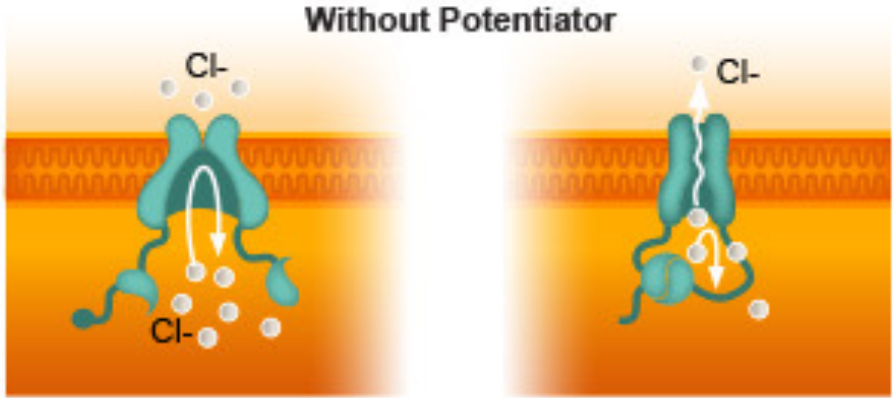
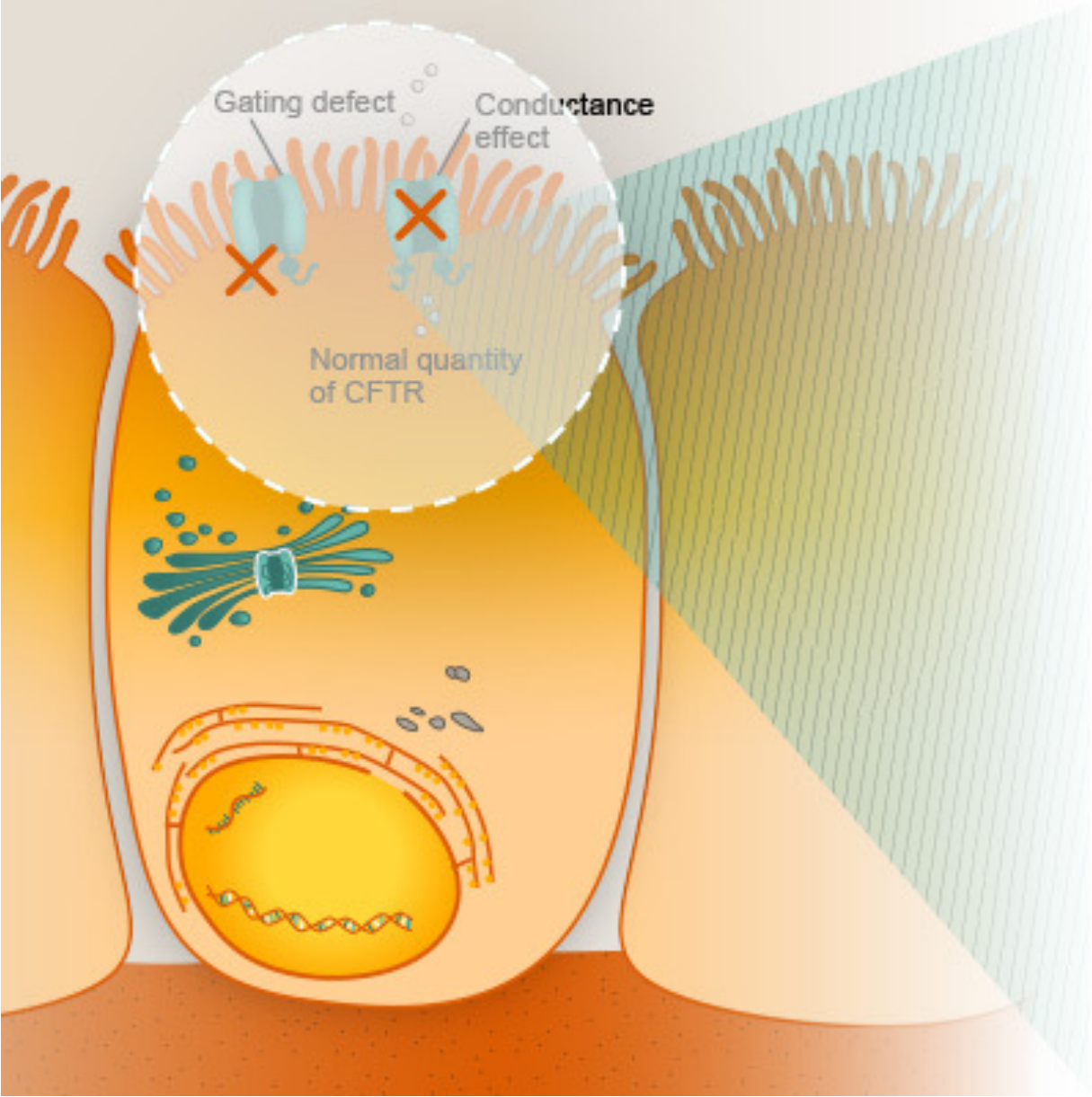
Sawicki GS. *J Cyst Fibros.* 2009;8(2):91-96.



# CF Care: At the Dawn of Precision Medicine

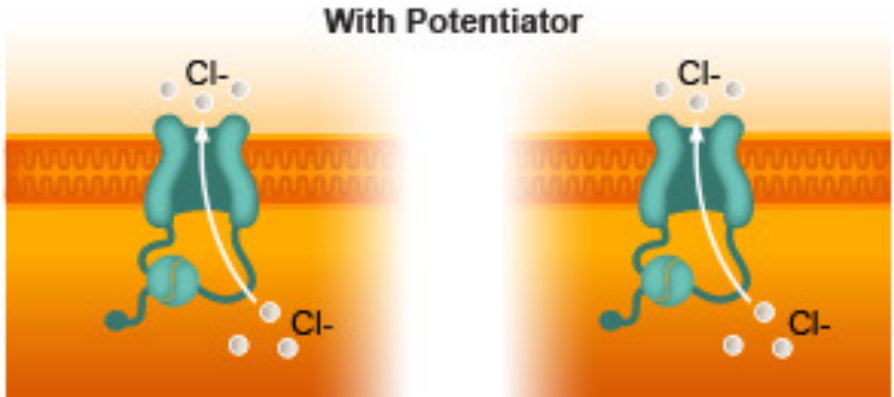


# Precision Medicine - Potentiators



Gating defect  
CFTR does not open

Conductance defect  
Reduced flow of Cl-  
through CFTR

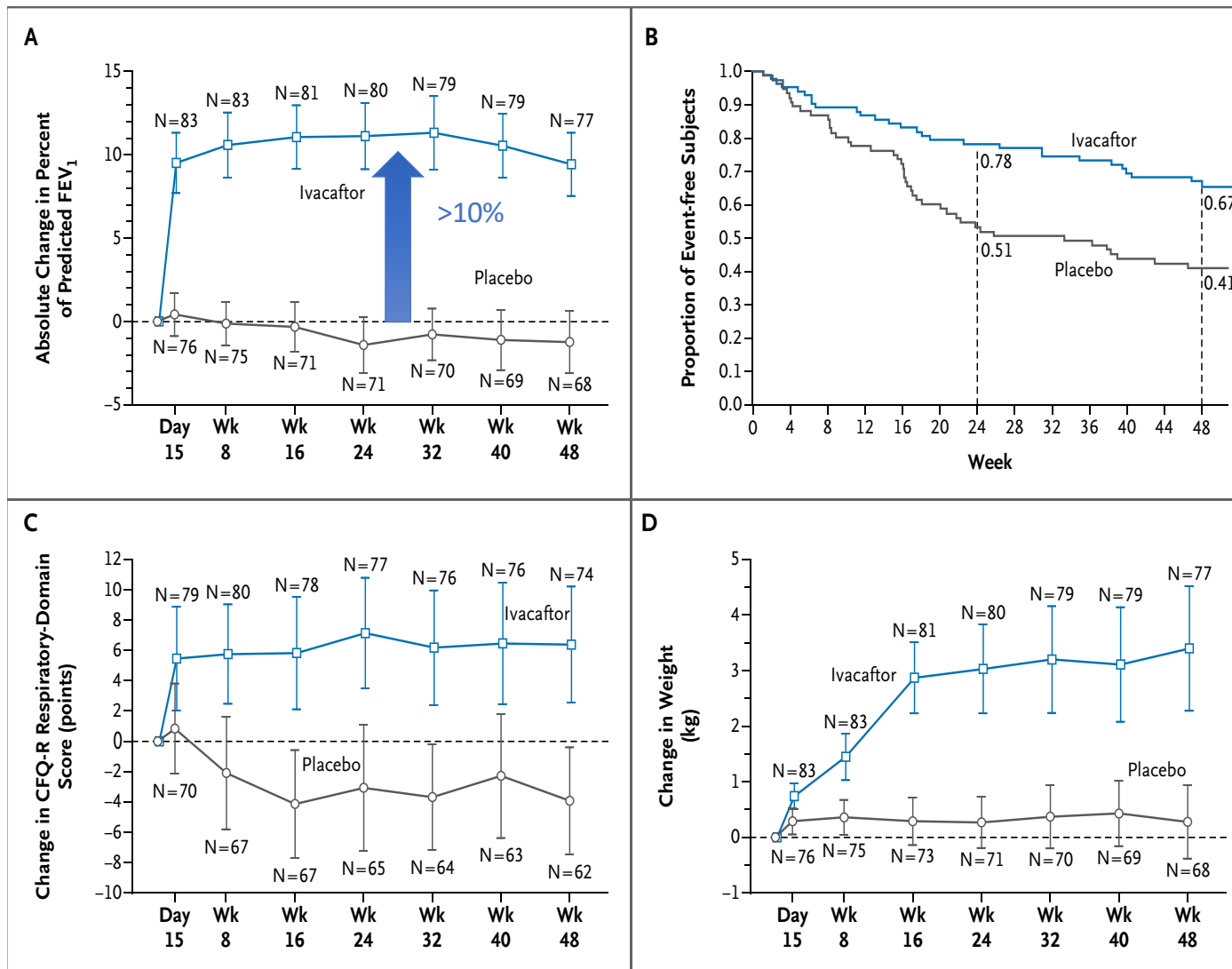


Gating defect  
Enhanced opening  
of CFTR channel

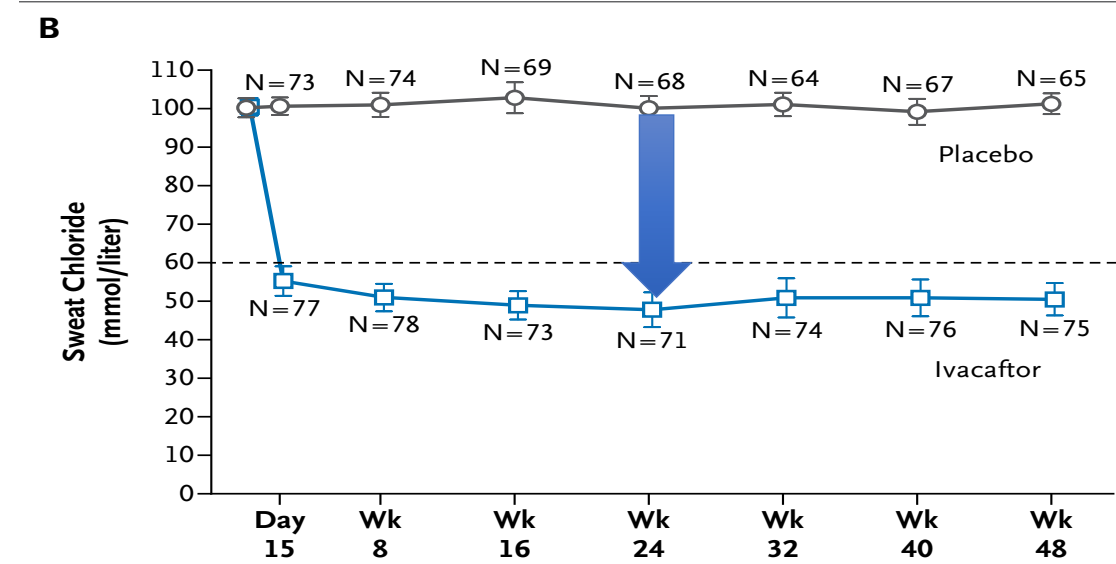
Conductance defect  
Increased flow of Cl-  
through CFTR

Courtesy of Vertex

# Ivacaftor (Kalydeco) and health outcomes

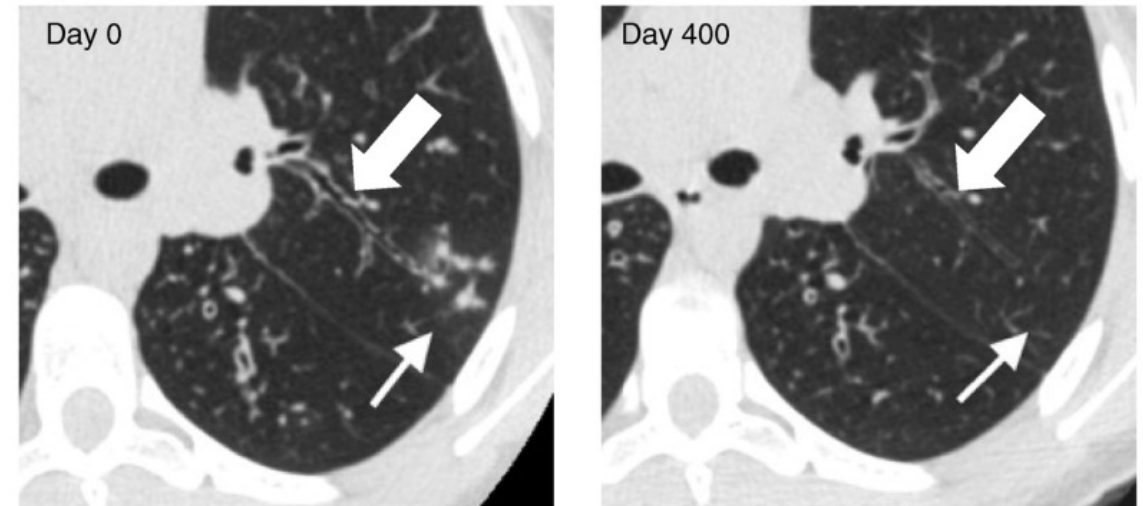
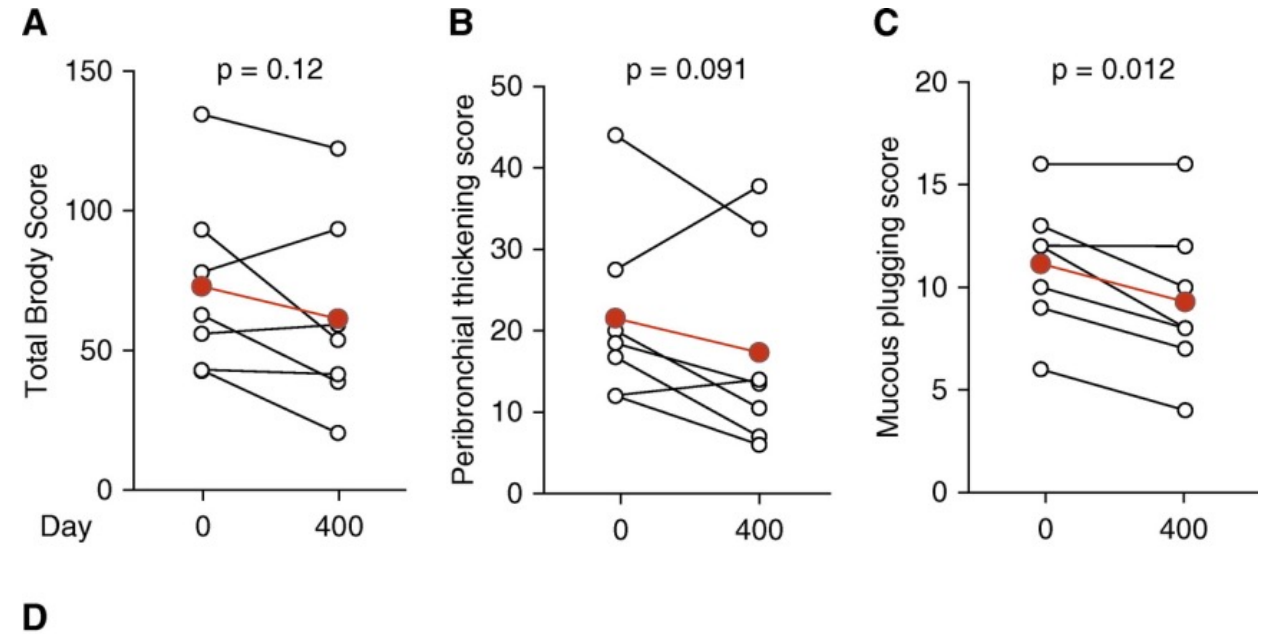
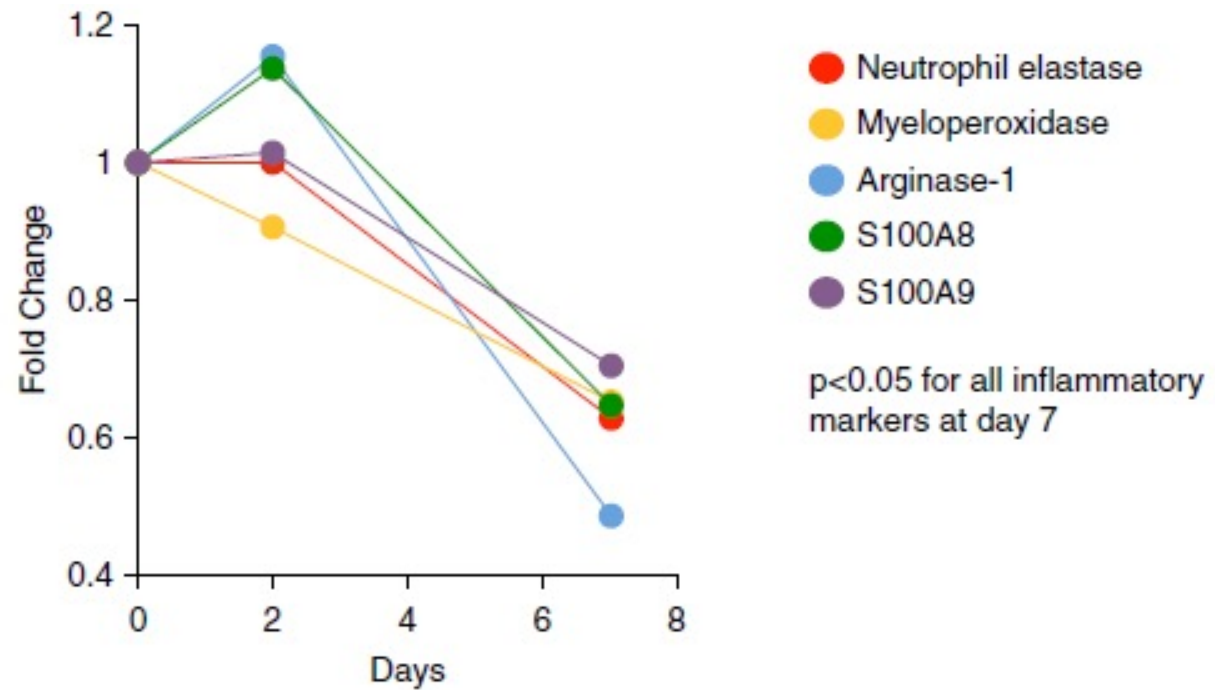


	Ivacaftor	Placebo
Absolute change from baseline through Week 24 in the ppFEV <sub>1</sub> (percentage points)	10.4	-0.2
Treatment difference (percentage points)	10.6 P<0.001	



CFQ-R, cystic fibrosis questionnaire respiratory; FEV, forced expiratory volume.  
 Ramsey BW et al. *N Engl J Med* 2011;365:1663–1672.

# Single-center data on ivacaftor: Changes in sputum inflammation and CT scans



Hisert KB et al. *Am J Respir Crit Care Med* 2017;195(12):1617–1628.

# Lung Health in the Longer Term: FEV<sub>1</sub> DECLINE



Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

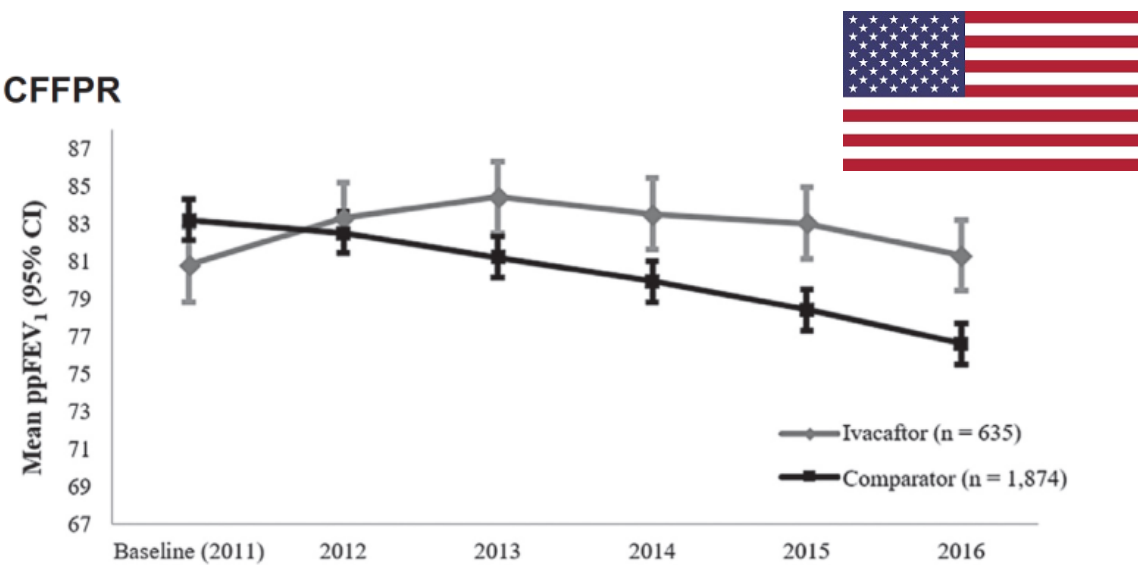
journal homepage: [www.elsevier.com/locate/jcf](http://www.elsevier.com/locate/jcf)

Journal of  
**Cystic  
Fibrosis**

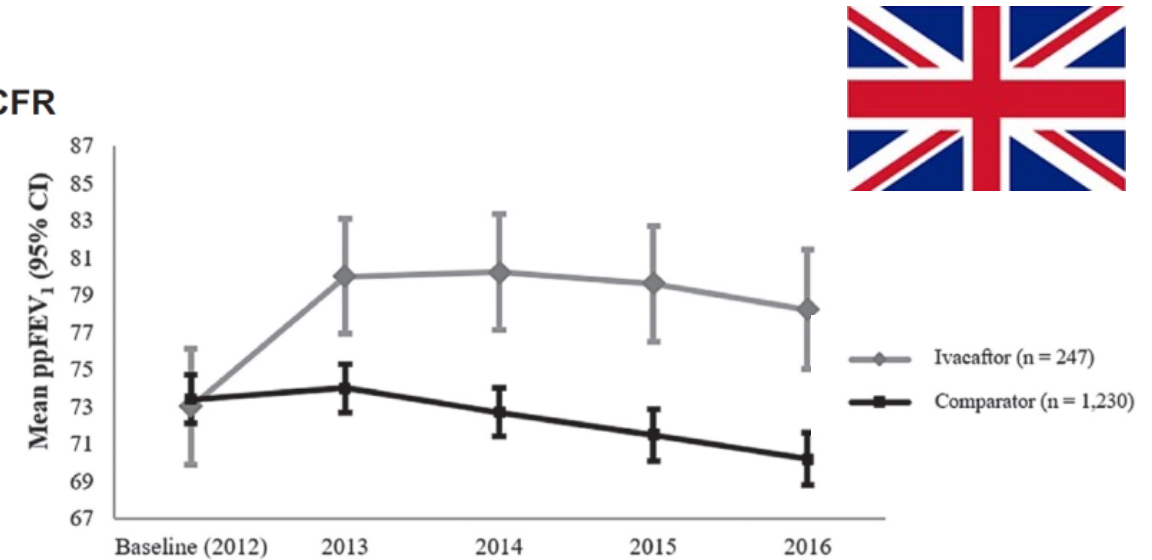
Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries

Nataliya Volkova<sup>a,\*</sup>, Kristin Moy<sup>a</sup>, Jennifer Evans<sup>b</sup>, Daniel Campbell<sup>a</sup>, Simon Tian<sup>a</sup>, Christopher Simard<sup>a</sup>, Mark Higgins<sup>c</sup>, Michael W. Konstan<sup>d</sup>, Gregory S. Sawicki<sup>e</sup>, Alexander Elbert<sup>f</sup>, Susan C. Charman<sup>g</sup>, Bruce C. Marshall<sup>f</sup>, Diana Bilton<sup>g,h</sup>

**A**  
US CFFPR



**B**  
UK CFR



**Significant improvements in survival  
and need for transplantation**

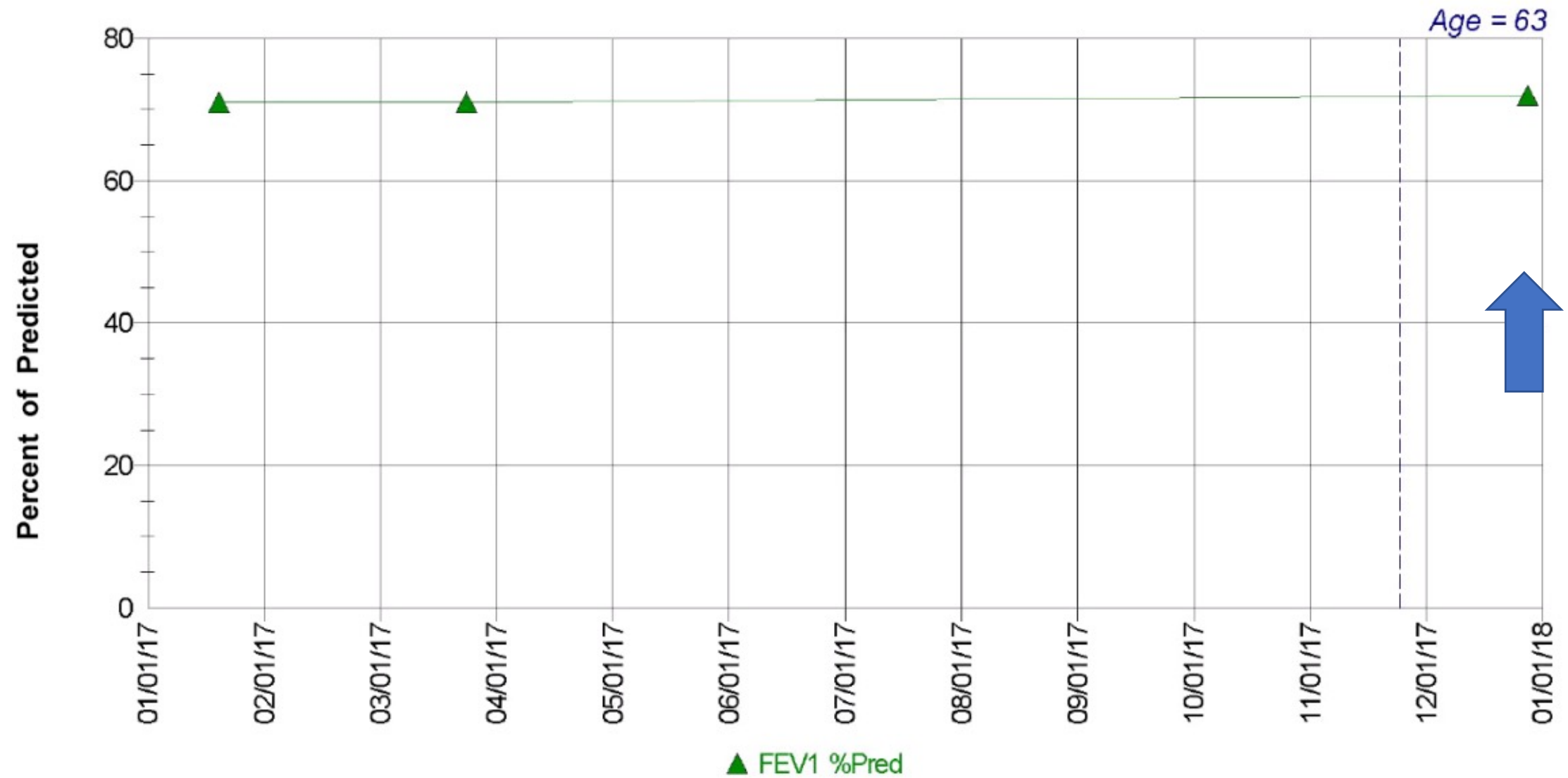
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Lung function:	71% (initial)
Medical background (e.g. exacerbations/infection history):	
Last 2 years	
Hemoptysis 1-2 teaspoon with exacerbations	

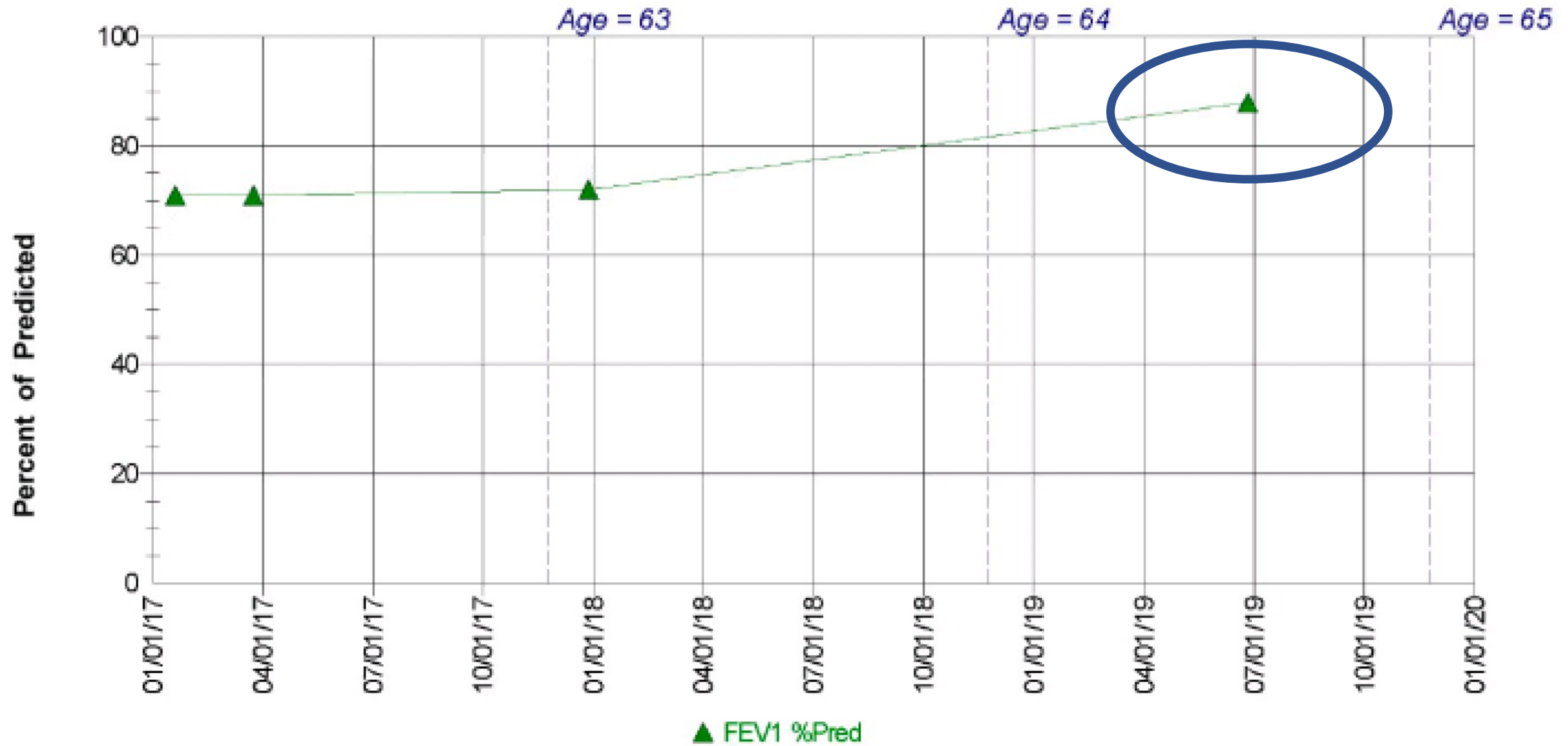
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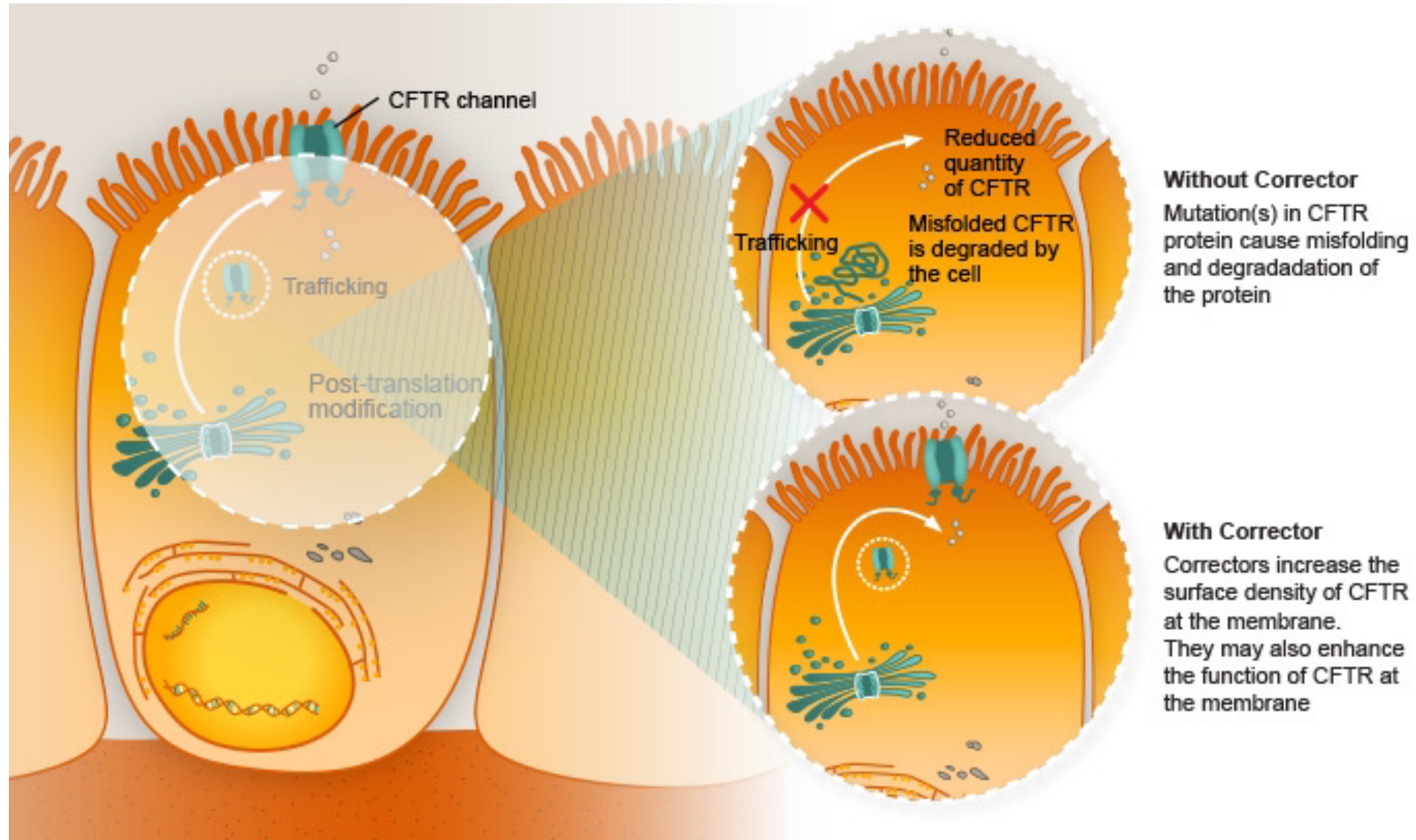
# Patient Case



# Patient Case



# Precision Medicine - Correctors + Potentiator



**Without Corrector**  
Mutation(s) in CFTR protein cause misfolding and degradation of the protein

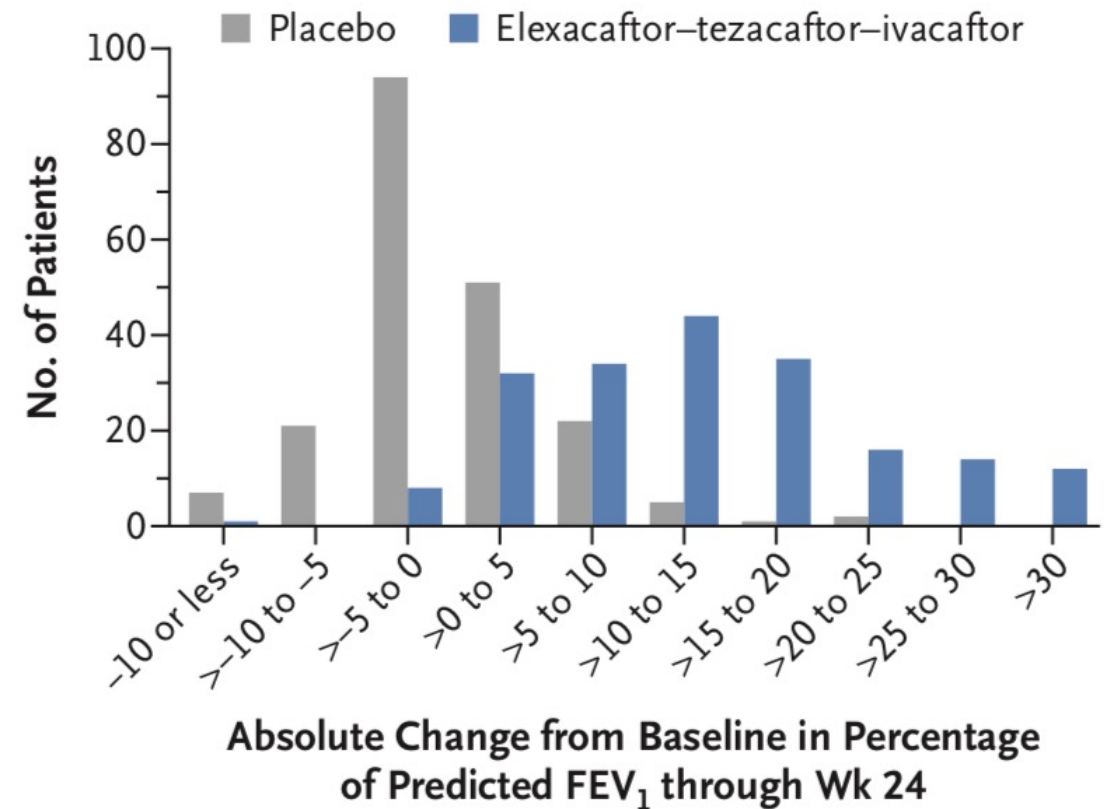
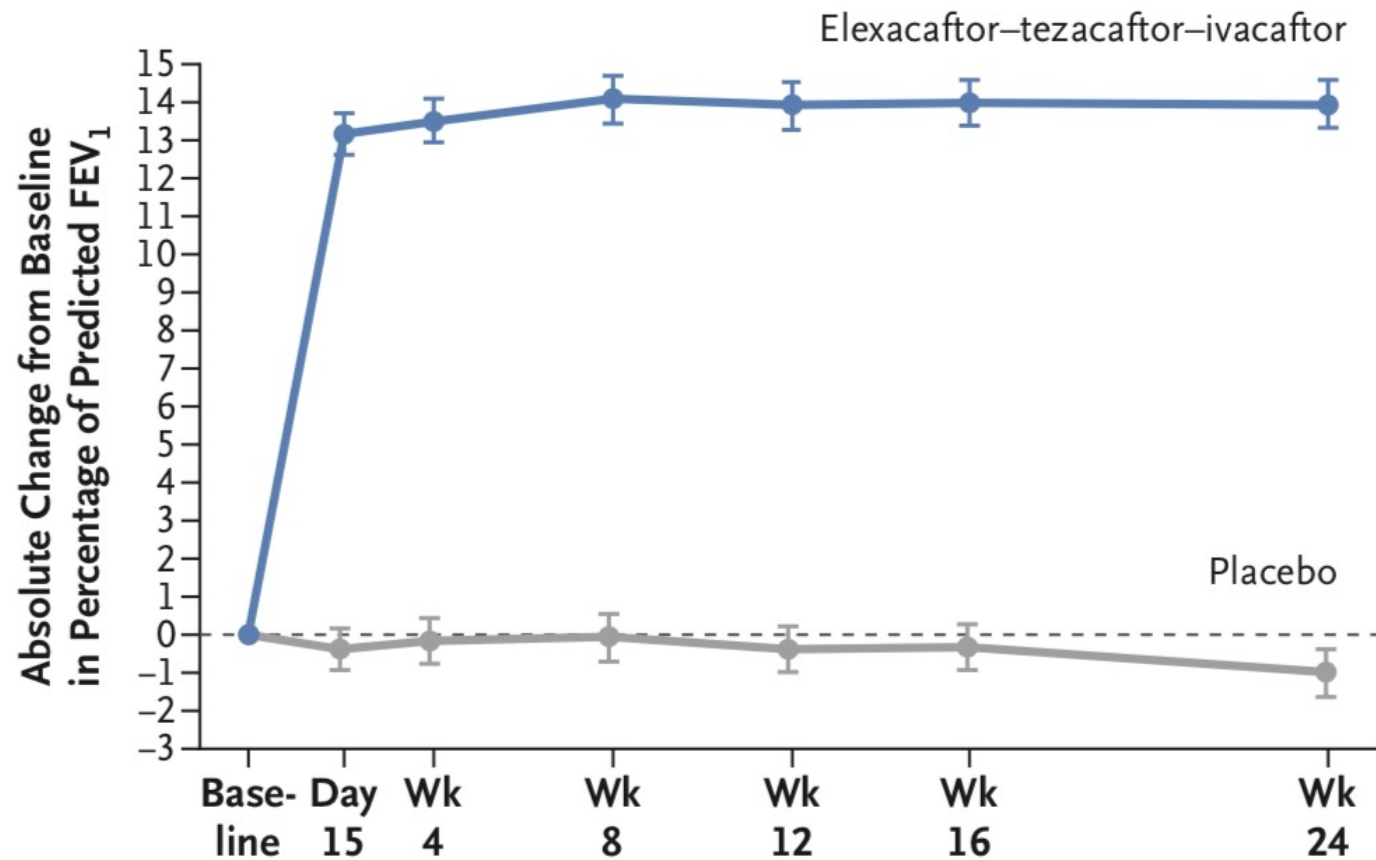
**With Corrector**  
Correctors increase the surface density of CFTR at the membrane. They may also enhance the function of CFTR at the membrane

October 21, 2019

FDA Approved Trikafta  
(elexacaftor/tezacaftor/ivacaftor)  
for those with at least **one copy F508Del**

# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

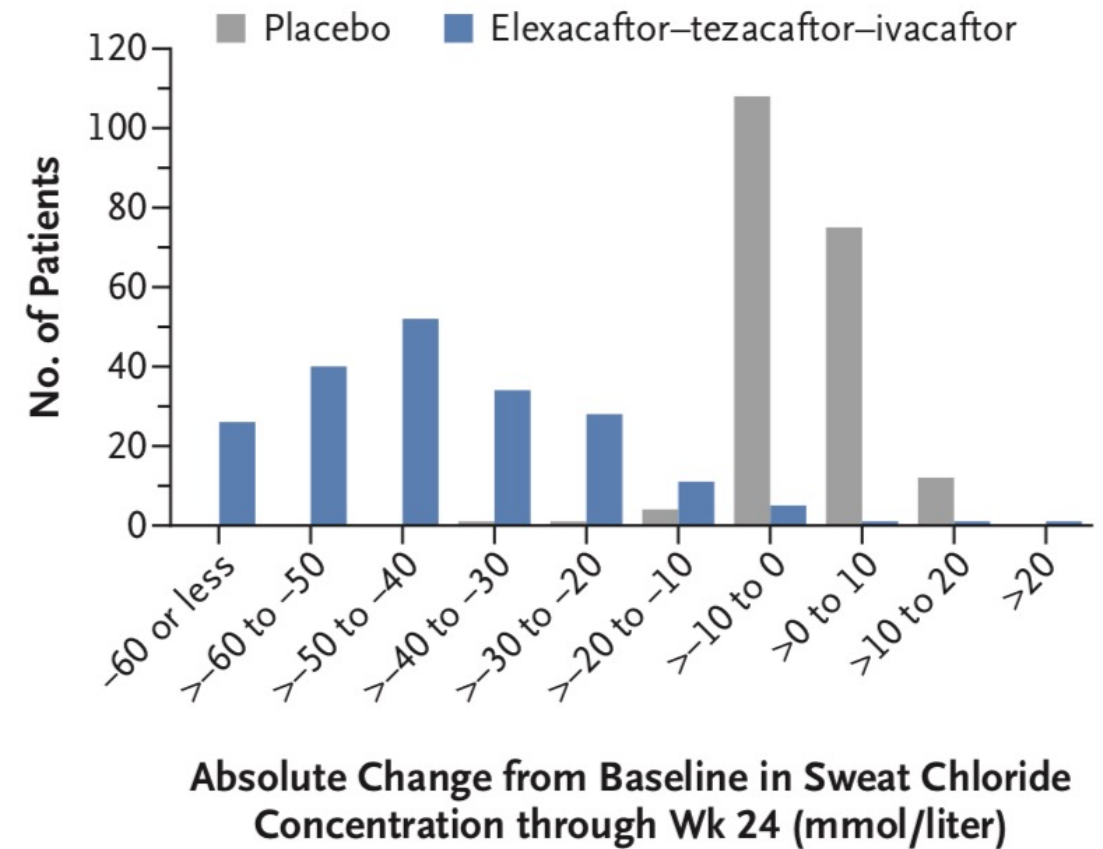
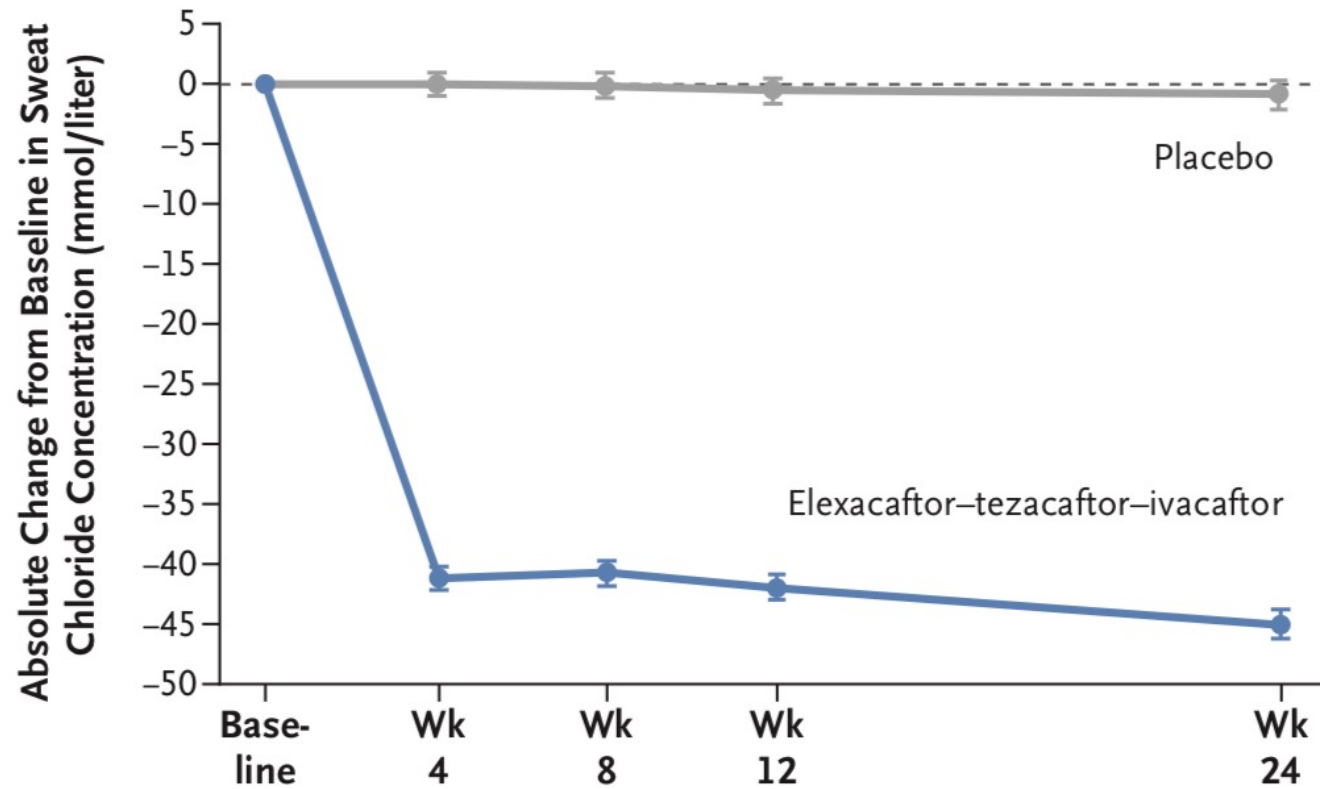
## Lung Function Response (FEV<sub>1</sub>)



Middleton, PG et al. *N Engl J Med* 2019;1-10.DOI 10.1056

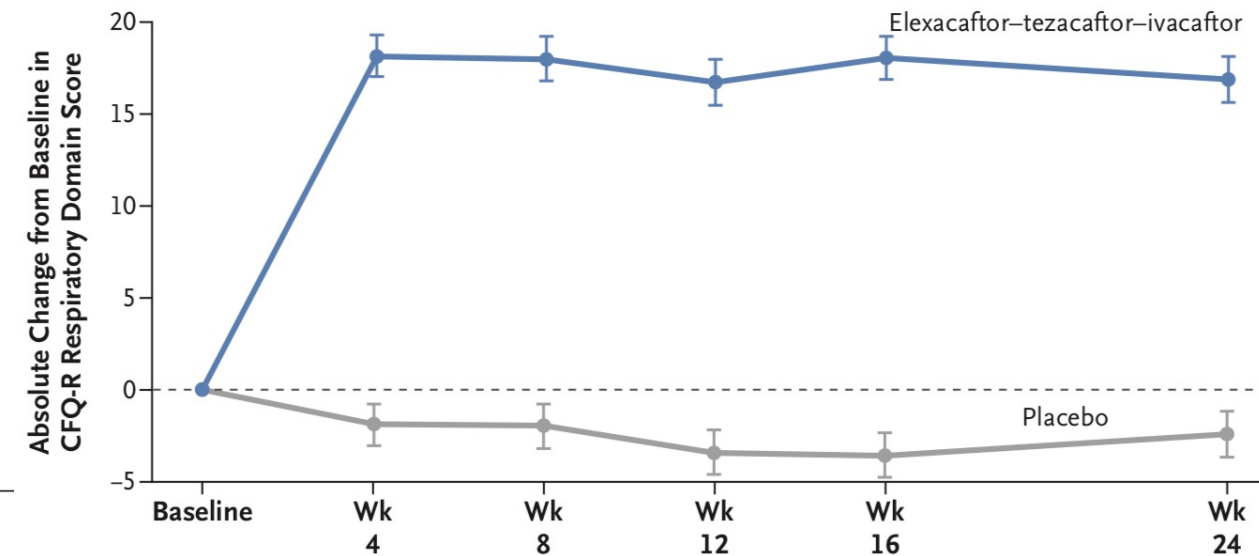
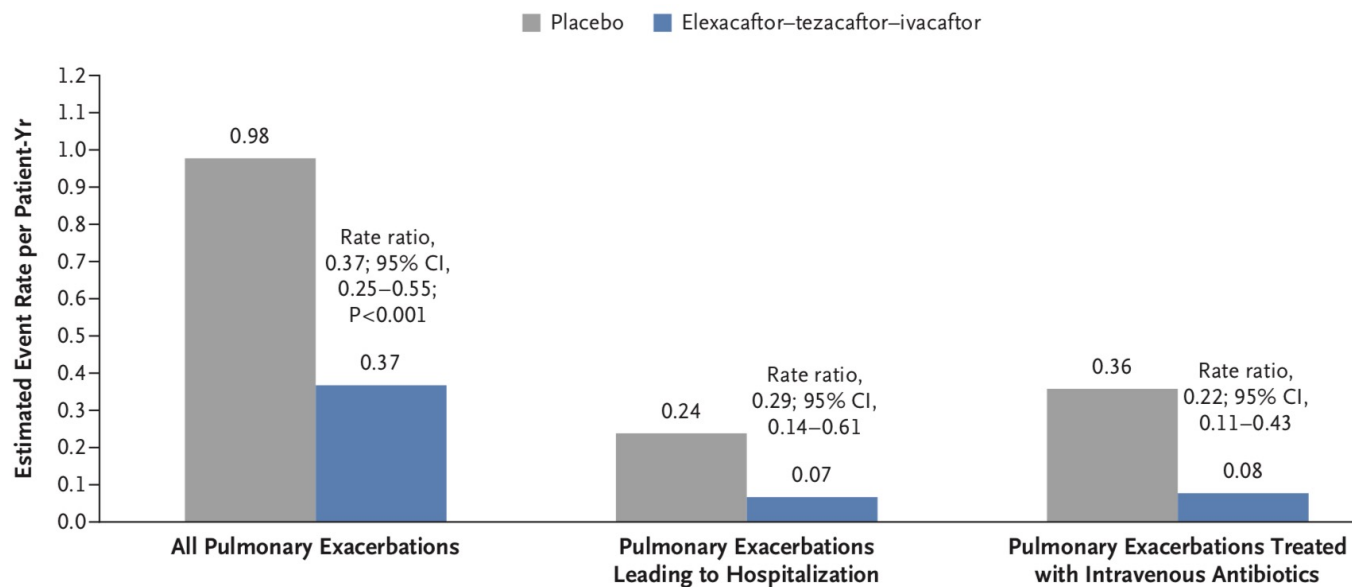
# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

## Sweat Chloride Response (mmol/liter)



Middleton, PG et al. *N Engl J Med* 2019;1-10.DOI 10.1056

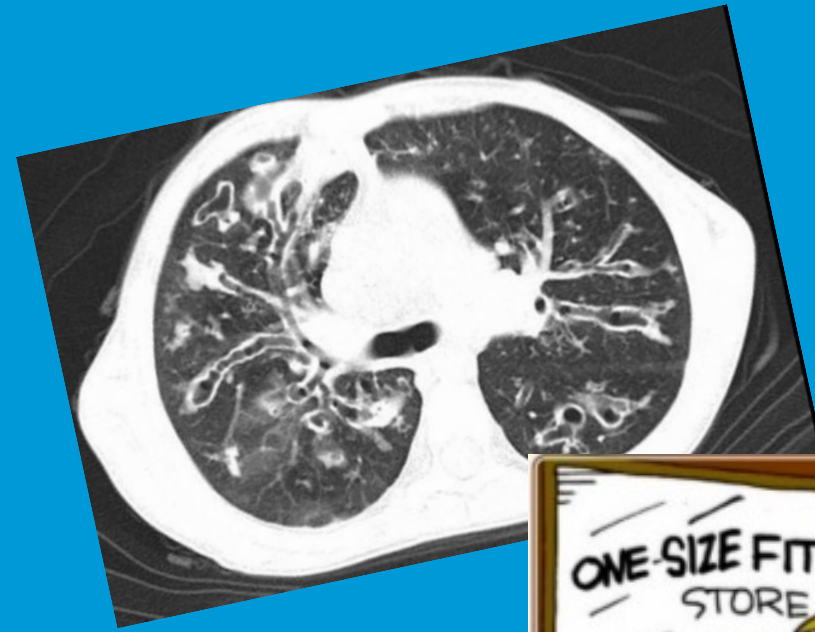
# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta) Exacerbations and CFQ-R



Middleton, PG et al. *N Engl J Med* 2019;1-10.DOI 10.1056

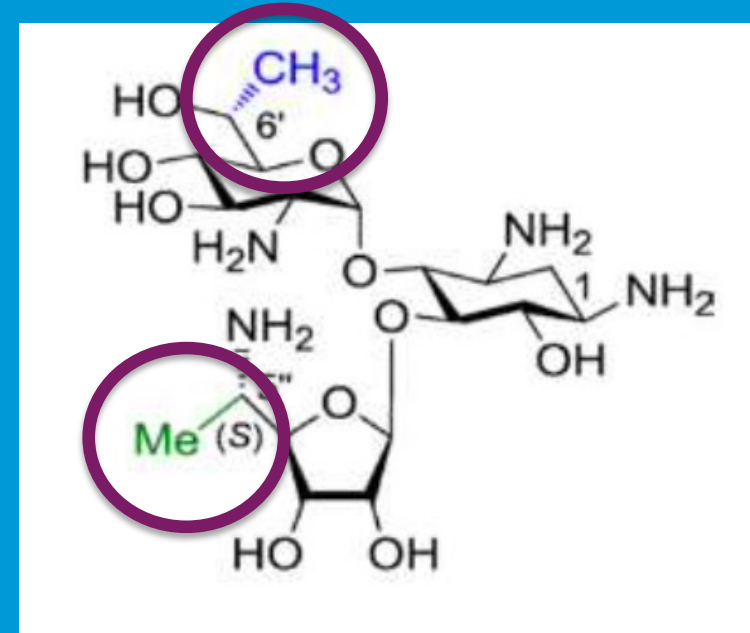
# So, Are We Done?

- No, more work to do:
  - Established disease:
    - ALD remains but observing some reversal
  - Pulmonary exacerbations:
    - Significantly reduced, not prevented
  - Chronic infection:
    - Some change but chronic infection model remains
  - Extrapulmonary effects
  - Extending use to younger patients
  - Sweat chloride still not fully normalized
  - 10% without a drug
  - Some unable to tolerate
  - Working on non-pulmonary complications
- Cost and regional differences in availability



# Rationale for development of ELX-02 to treat CFTR nonsense mutations

- Aminoglycosides bind to the decoding site in the small subunit of the ribosomal RNA (rRNA) and is capable of inducing translation read-through
- Reducing the accuracy of rRNA codon-anticodon recognition increases the probability of translational read-through of stop codons
- However, aminoglycosides limited by hearing and kidney toxicity and not optimized for read-through



J Med Chem. 2012 Dec 13;55(23):10630-43.

Adapted from data provided by Eloxx



**Boston Children's Hospital**  
Where the world comes for answers

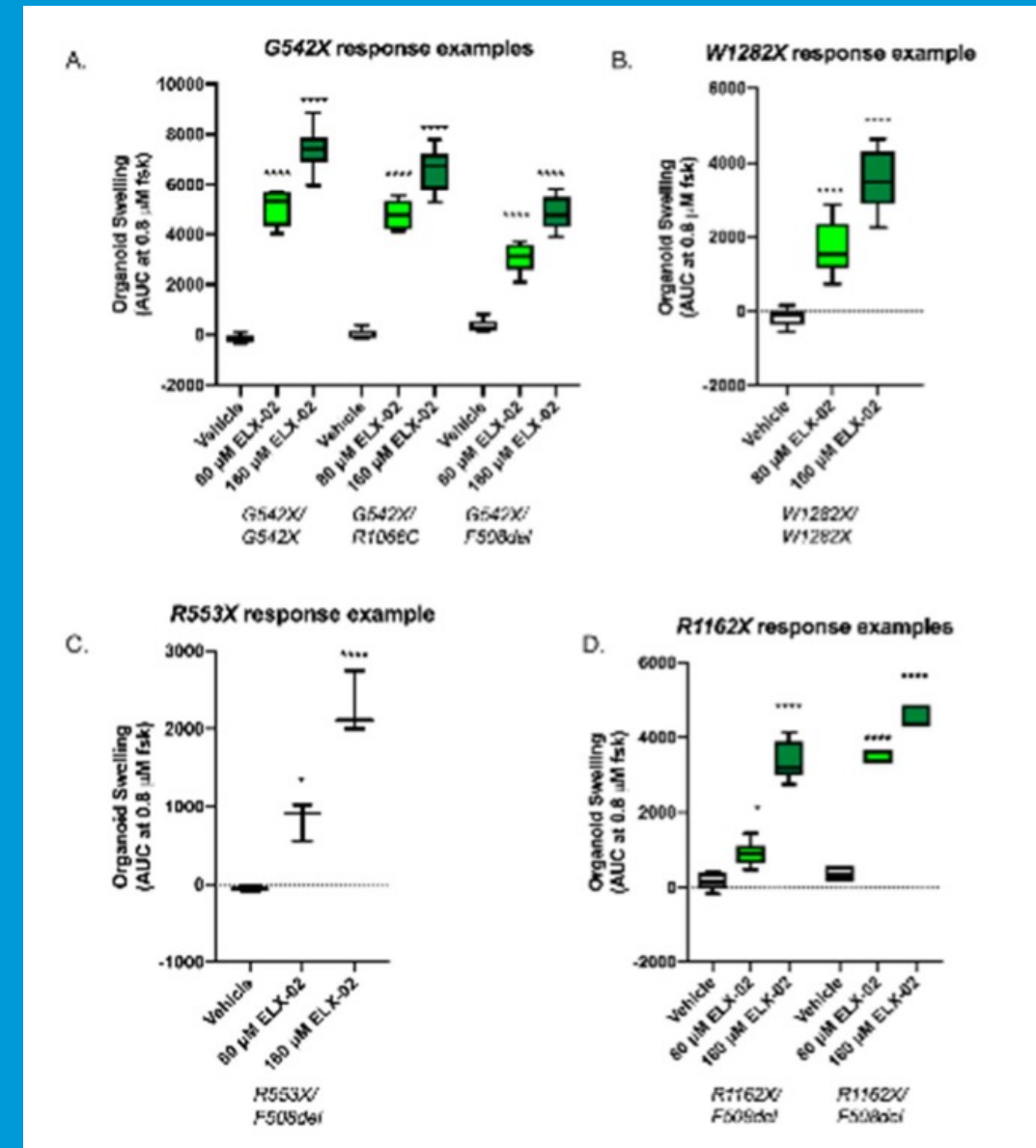
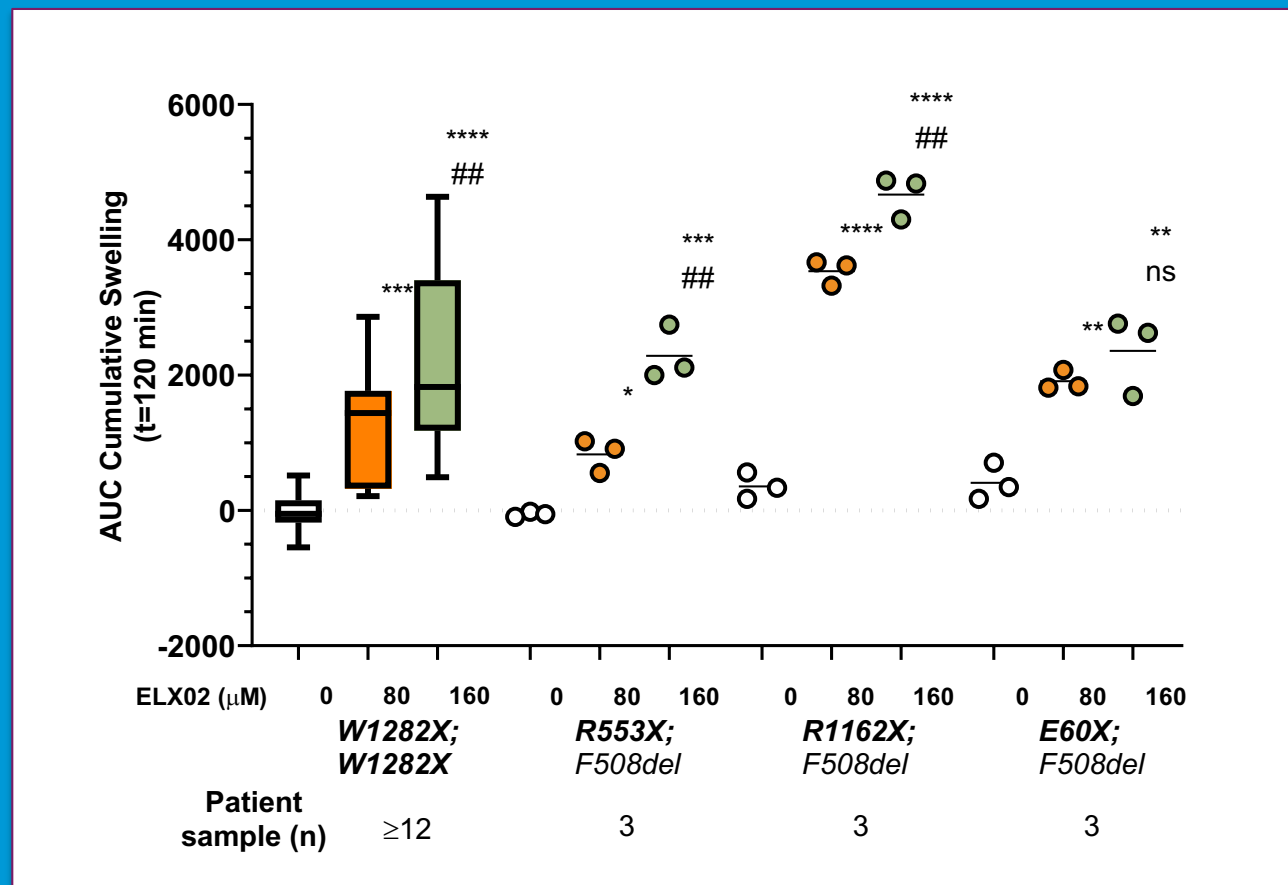


**Harvard**  
Medical School



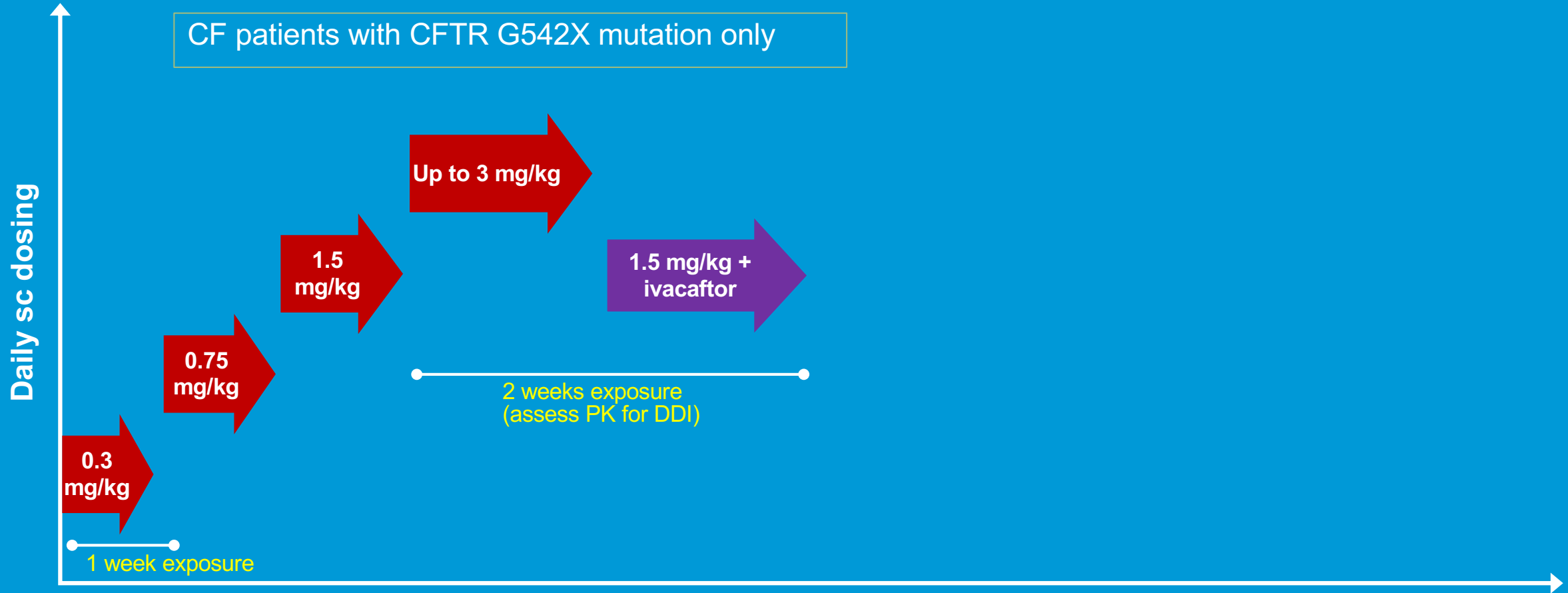
**Brigham and Women's Hospital**  
Founding Member, Mass General Brigham

# CFTR-dependent Forskolin Induced Swelling in Organoids from Nonsense Bearing CF Patients exposed to ELX-02

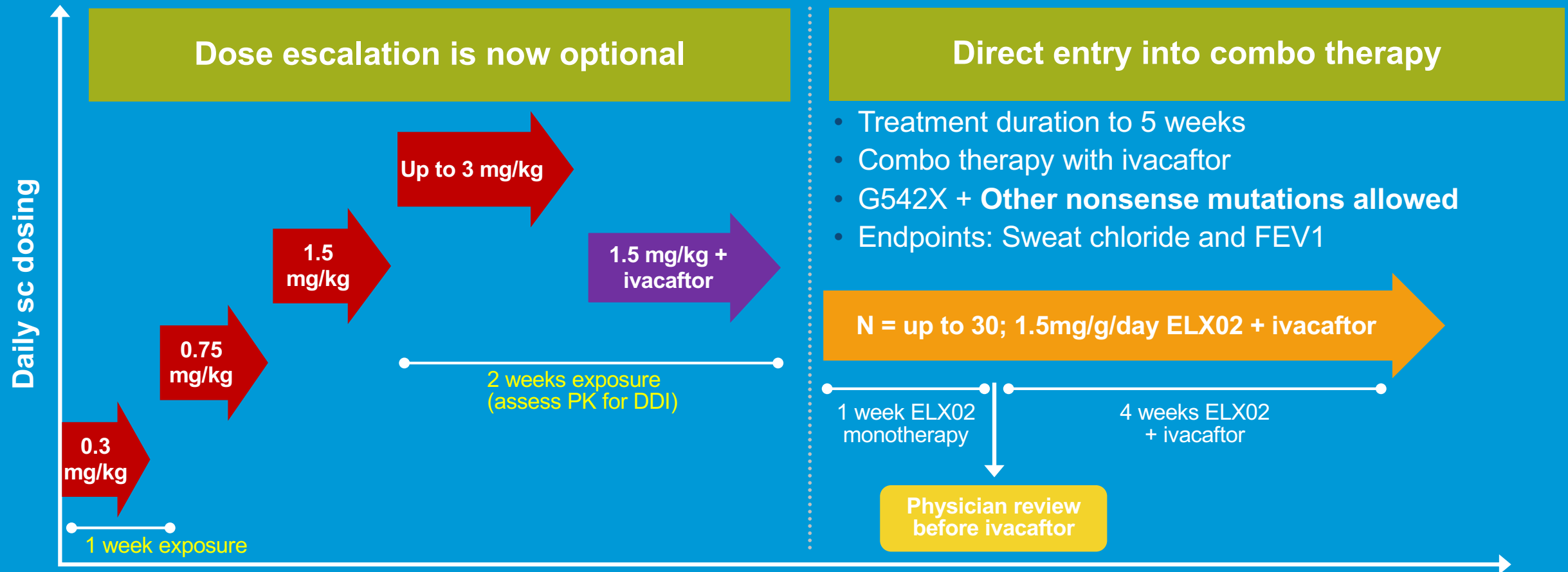


\* All exposures for 48 hours. Data generated by HUB and courtesy of Eloxx

# ELX-02 Dose Escalation Study



# Trial amendment – Longer Treatment With Ivacaftor Combo Therapy



Courtesy of Eloxx

# CFF 2018 Commitment

- \$100 Million Infection Research Initiative
- Industry and Academic Researches
  - Detection
  - Diagnosis
  - Prevention
  - Treatment
- Addressing the need to treat acute/chronic infections in era of increased risk of antibiotic resistance

Courtesy of CFF



**REPAIR  
CFTR PROTEIN**



**RESTORE  
CFTR PROTEIN**



**FIX OR REPLACE  
CFTR GENE**

# Future of CF Therapeutics

Courtesy of CFF

# Summary Points

- CF is autosomal recessive disease that has a highly variable phenotypic expression among patients of all ages, particularly adults, with improved survival overall
- Diagnosis of CF is made by a combination of clinical manifestations, sweat chloride levels, CFTR mutation analysis
- Chronic airway infection with any number of organisms, but most typically *P.aeruginosa*, leads to progression of obstructive lung disease. NTM an increasing concern not discussed
- Precision medicine with new therapies involving small molecule potentiators and correctors, including a highly effective triple combination potentiator/correctors currently available to nearly 90% of patients
- Future CF therapeutics include gene editing and gene replacement, as well as focus on anti-microbials, anti-inflammatories, attention to nutrition and anticipating complications in a multi-disciplinary care team setting

## Board Questions 1-4 based on Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #1 of hospitalization
  - Tachypnea, chest pain and worsening SOB

## Question #1

- What is LEAST likely complication associated with this patient's presentation:
  - A) Pulmonary Embolism
  - B) Mucus plugging
  - C) Non-ST elevation MI
  - D) Pneumothorax

## Question #1

- What is LEAST likely complication associated with this patient's presentation:
  - A) Pulmonary Embolism
  - B) Mucus plugging
  - C) Non-ST elevation MI
  - D) Pneumothorax
- Changing demographic with increasing age, long standing CFRD, increased BMI with h/o high fat high salt diet, changing our differential

## Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #2
  - You are called to patient bedside due to 250cc of bright red blood.
  - Bleeding stopped on its own, VSS and patient describes chest discomfort on right side

## Question #2

- What is LEAST helpful intervention:
  - A) Perform a bronchoscopy to determine whether bleeding coming from right or left lung
  - B) Ask patient to lie down with right side of chest down
  - C) Give Vitamin K while in process of checking PT/INR
  - D) Call interventional radiology for potential Bronchial artery embolization (BAE)
  - E) Oral tranexamic acid or aminocaproic acid

## Question #2

- What is LEAST helpful intervention:
  - A) Perform a bronchoscopy to determine whether bleeding coming from right or left lung
  - B) Ask patient to lie down with right side of chest down
  - C) Give Vitamin K while in process of checking PT/INR
  - D) Call interventional radiology for potential Bronchial artery embolization (BAE)
  - E) Oral tranexamic acid or aminocaproic acid
- Increased use of TXA and aminocaproic acid leading to decreased urgent BAE's (more elective) and improved outcomes

## Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #4
  - Bleeding subsides and chest pain improves with oxycodone since NSAIDs have led to her bleeding in the past
  - She develops worsening RLQ pain and vomiting. She also has diarrhea

## Question #3

- What is the MOST LIKELY diagnosis for this patient:
  - A) appendicitis
  - B) distal intestinal obstruction syndrome (DIOS)
  - C) exacerbation of inflammatory bowel disease (IBD)
  - D) chronic pancreatitis
  - E) adenocarcinoma of the colon

## Question #3

- What is the MOST LIKELY diagnosis for this patient:
  - A) appendicitis
  - B) distal intestinal obstruction syndrome (DIOS)
  - C) exacerbation of inflammatory bowel disease (IBD)
  - D) chronic pancreatitis
  - E) adenocarcinoma of the colon
- Increased risk of adenocarcinoma of bowels, particularly post-transplant. Screening starts at age 35

## Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #16
  - She is feeling better after BAE with bleeding stabilized, bowel movements are normal and ready to go home after 16 days of antibiotics

## Question #4

- Based on her CFTR mutation profile, what new CFTR small molecule modulator medication is she eligible for:
  - A) ivacaftor (Kalydeco)
  - B) lumacaftor/ivacaftor (Orkambi)
  - C) tezacaftor/ivacaftor (Symdeko)
  - D) none of the above

## Question #4

- Based on her CFTR mutation profile, what new CFTR small molecule modulator medication is she eligible for:
  - A) ivacaftor (Kalydeco)
  - B) lumacaftor/ivacaftor (Orkambi)
  - C) tezacaftor/ivacaftor (Symdeko)
  - D) none of the above
- The answer is elexacaftor/tezacaftor/ivacaftor (Trikafta)

## Question #5

- Which statement is true regarding our patient and their CFTR mutations?
  - A) At least two grandparents are carriers of the CFTR gene mutation
  - B) They have a sibling who does not share either of their CFTR gene mutations
  - C) Both parents are carriers of the CFTR gene mutation
  - D) All of the above

## Question #5

- Which statement is true regarding our patient and their CFTR mutations?
  - A) At least two grandparents are carriers of the CFTR gene mutation
  - B) They have a sibling who does not share either of their CFTR gene mutations
  - C) Both parents are carriers of the CFTR gene mutation
  - D) All of the above

# Thank you!



Boston Children's Hospital



Brigham and Women's Hospital

## Cystic Fibrosis Center