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

# Cystic Fibrosis in Adults
## In the Era of Highly Effective Modulators

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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- Medicine-Pediatric Residency at Cleveland Clinic
- Pulmonary Medicine Fellowship
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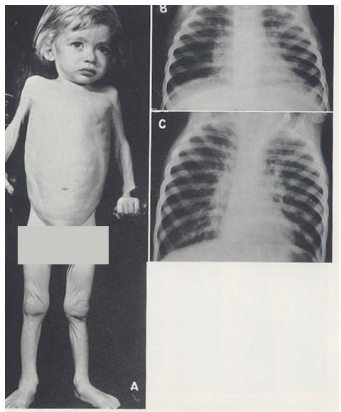
## Disclosures

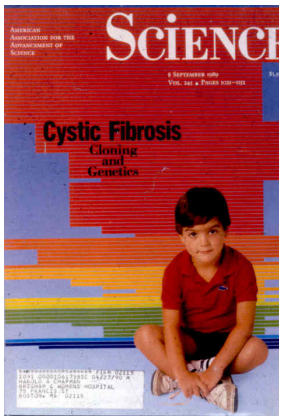
- Cystic Fibrosis Foundation Adult CF Center Grant
- Chair, Cystic Fibrosis Foundation Therapeutic Development Network Protocol Review Committee (FTE support)
- Adult CF Program Principal Investigator, Therapeutic Development Network Grant
- North American Lead Principal Investigator
    - Vertex VX121-101 (manuscript pending)
    - Eloxx-012 (clinical trial ended September 2022)

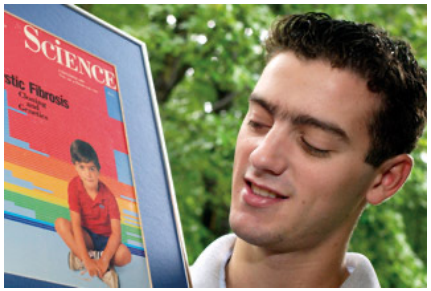
# A Story of Progress



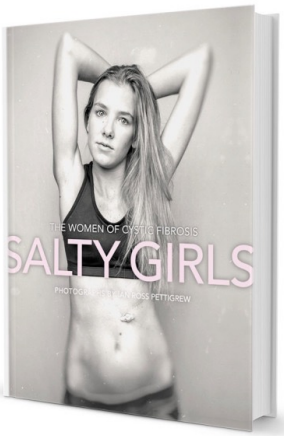
igure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, ve months. B. Lungs at one year, two months. C. Lungs at two years, ve months. When infection becomes established in the viscid secretion the bronchioles at an early age, and persists, the lungs show progres- ve development of peribronchial infiltration and emphysema. The atritional state deteriorates with advance of the infection. (Repro- uced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the ancreas in Infants and Children, *J. Pediat., 34*:663 (1949) with per- mission of C. V. Mosby, St. Louis.)

1950




1989



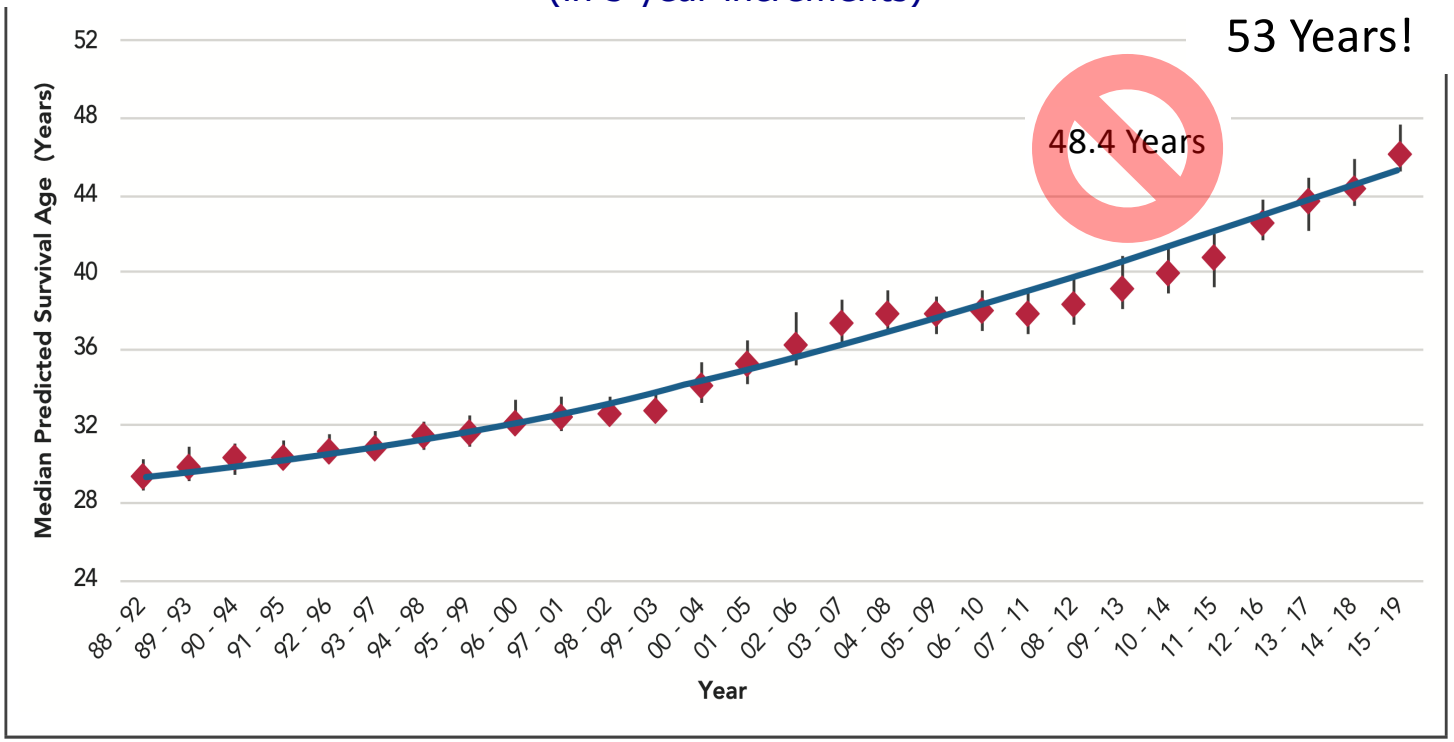

2015

2021

# Improving Survival

## Median Predicted Survival Age, 1988-2020

(in 5 year increments)




CFF 2019 and 2020 Registry Report

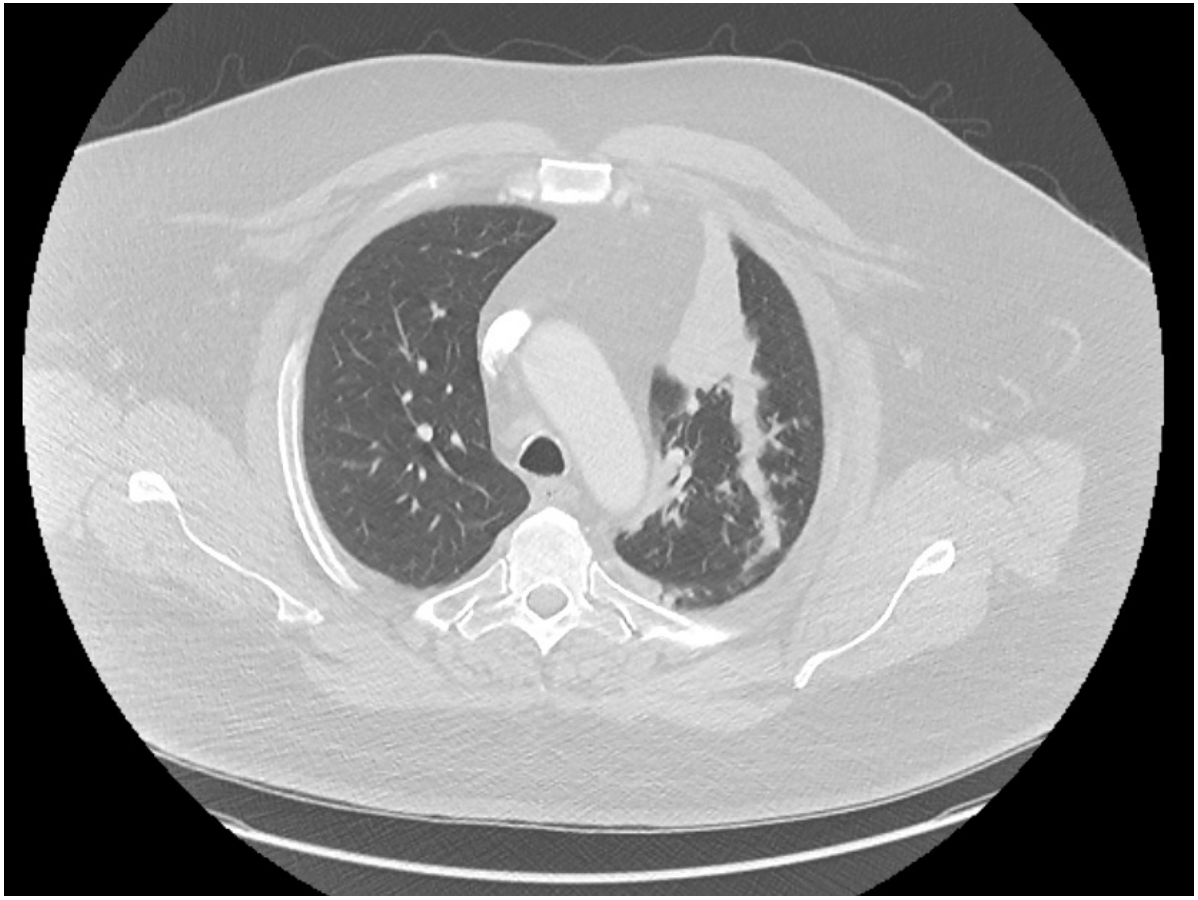
# Patient Case

| 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)<br>Exacerbations increased to 3-4x/year and chronic cough<br><br>**Chest CT in 2016 with diffuse nodular opacities and bronchiectasis**<br><br>**TB testing negative** | |

| **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<br>No Children<br>Family History of Colon cancer |

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

# Patient Case



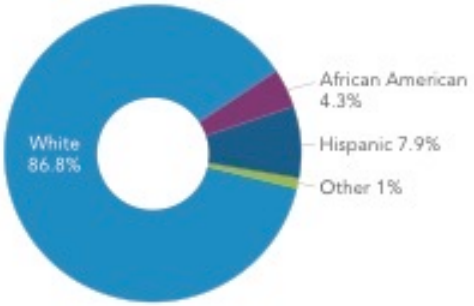
# Quick CF Refresher!

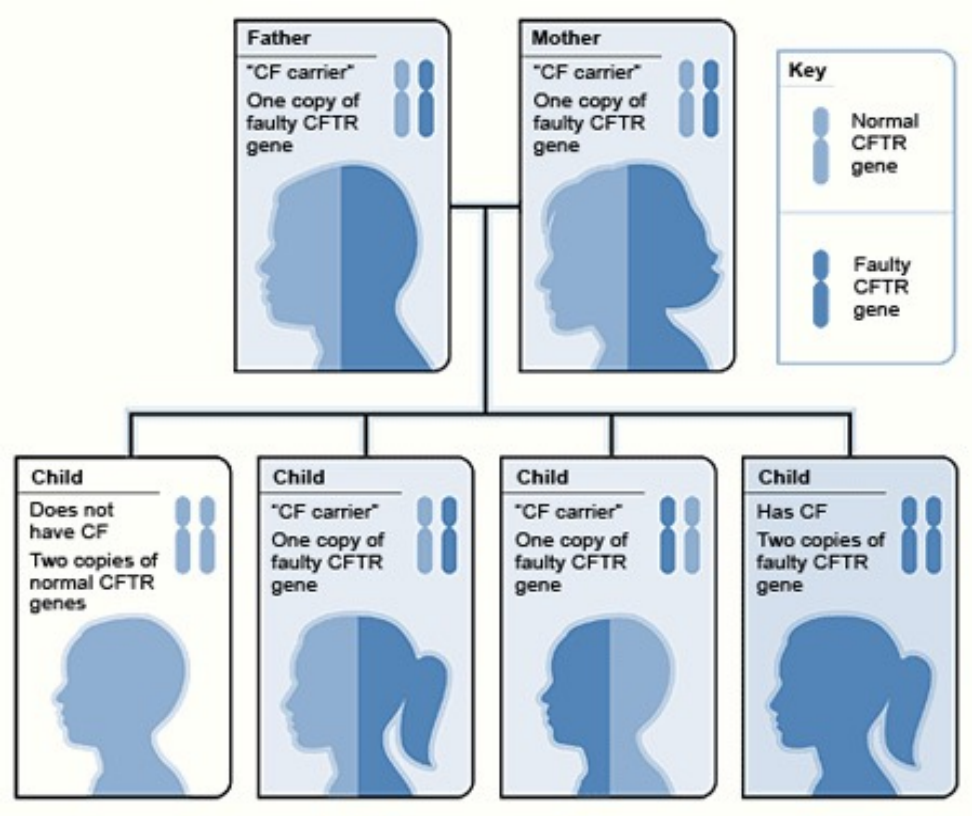
- What is not on your differential?
  - Non-tuberculous mycobacteria (NTM) infection
  - Cystic fibrosis
  - Non-CF bronchiectasis
  - Primary ciliary dyskinesia
  - Metastatic thyroid cancer

# Quick CF Refresher!

# CF: Inheritance Pattern

- Most common lethal inherited disease in Caucasians
- Autosomal recessive inheritance
- Approximately 30,000 patients in the U.S.



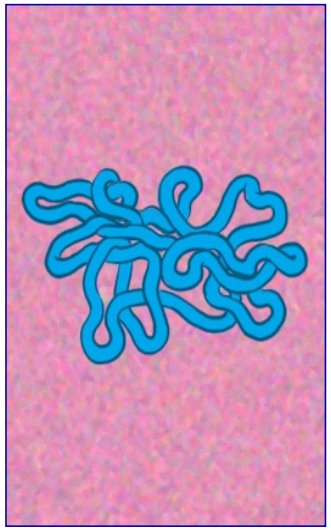




http://www.medicinenet.com/cystic_fibrosis/page3.htm

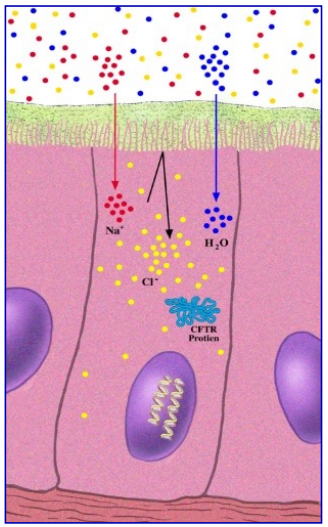
# CF Pathophysiology

Abnormal Gene

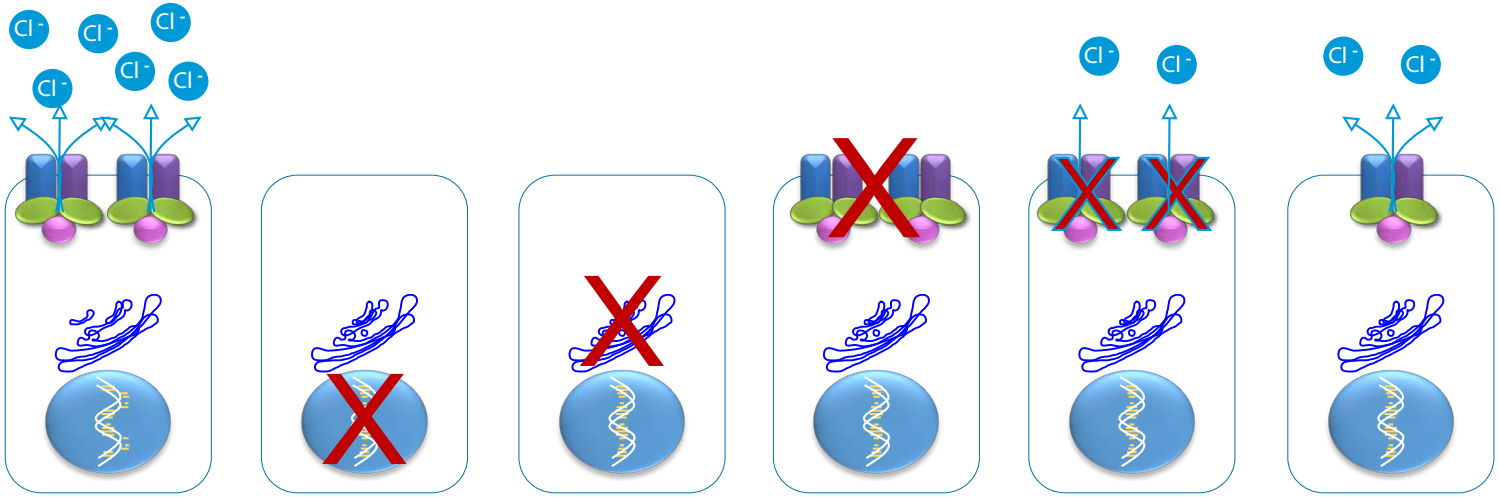
Abnormal Protein



Altered Ion Transport ($Cl^-$ and $HC0^-_3$) & Abnormal Mucus



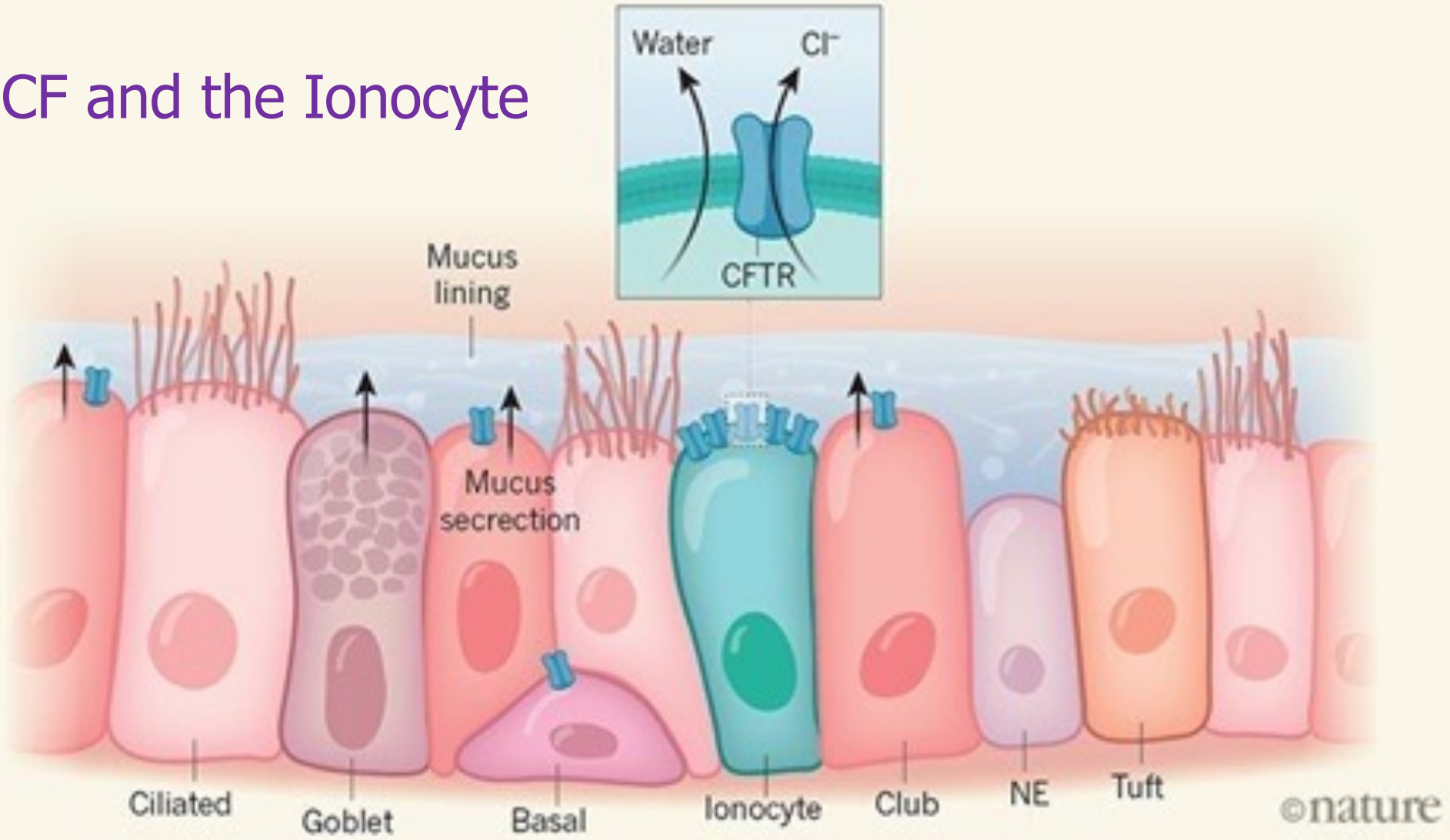
# 5 (or 6) Classes of CFTR Mutations




| | Normal | Class I | Class II | Class III | Class IV | Class V |
|---|---|---|---|---|---|---|
| DESCRIPTION | CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water. | No functional CFTR created. | CFTR protein is created, but misfolded, keeping it from reaching the cell surface. | CFTR protein is created and reaches cell surface, but does not function properly. | The opening in the CFTR protein ion channel is faulty. | CFTR is created in insufficient quantities. |
| EXAMPLES | | G542X<br>W1282X<br>R553X | F508del<br>N1303K<br>I507del | G551D<br>S549N<br>V520F | R117H<br>D1152H<br>R347P | 3849+10kbC->T<br>2789+5G->A<br>A455E |

Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

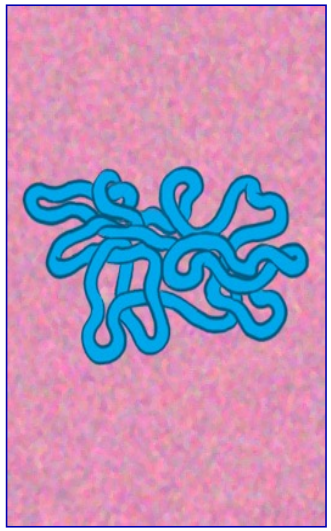
# CF and the Ionocyte



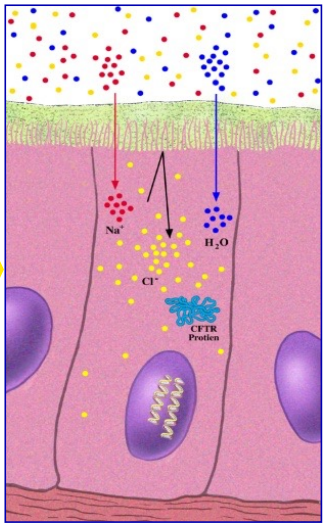
# CF Pathophysiology

Abnormal Gene

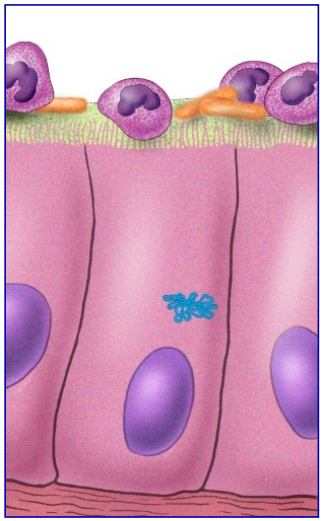
Abnormal Protein



A Altered Ion Transport ($Cl^-$ and $HC0^-_3$) & Abnormal Mucus

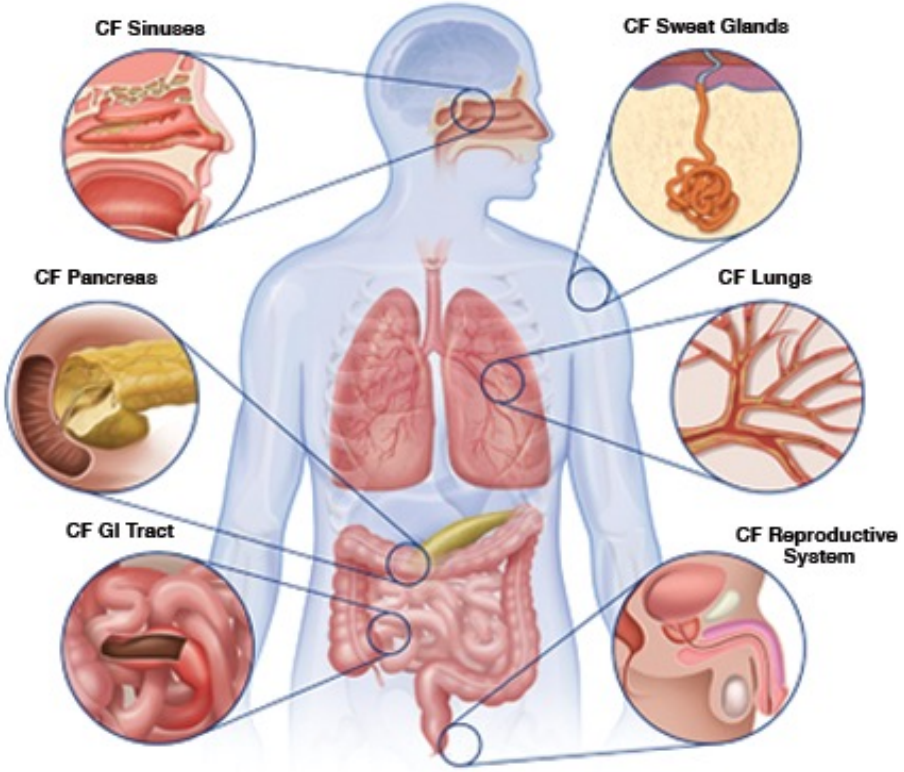



Infection & Inflammation

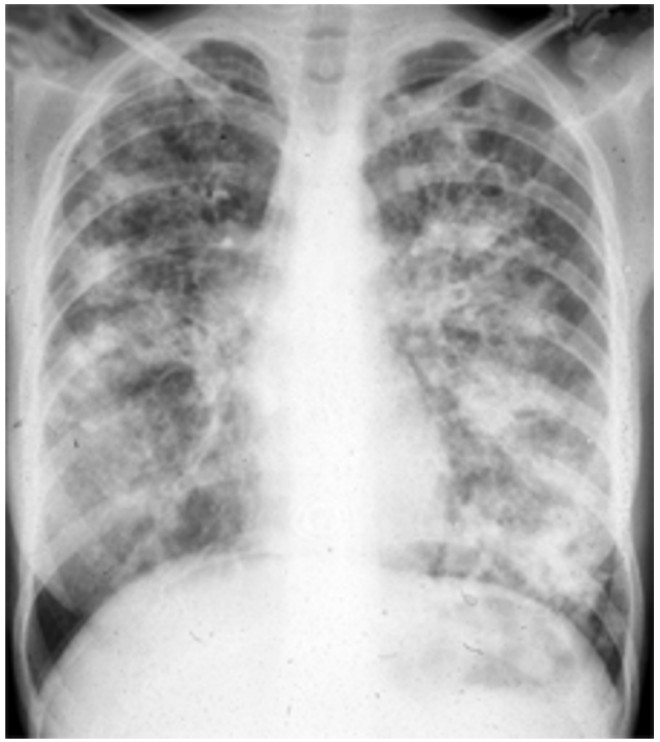


Organ Destruction & Respiratory Failure

# CF - Multi-Organ Involvement

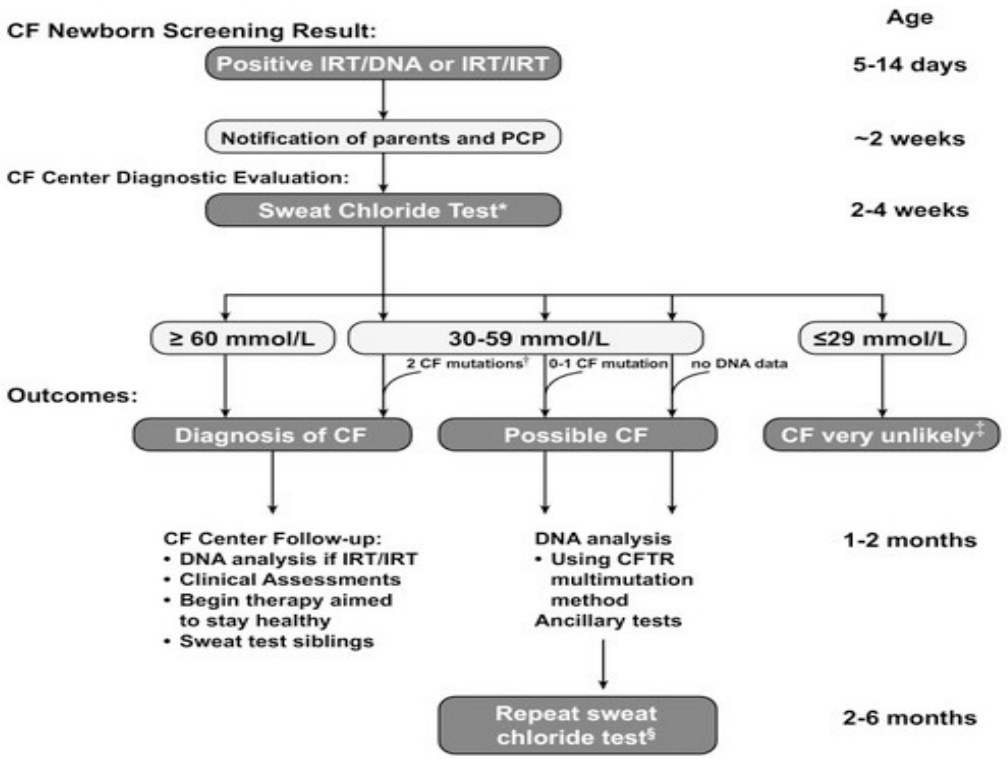



https://www.cftrscience.com/?q=CF-morbidity



Pulmonary Disease is major cause of morbidity and mortality

# 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.

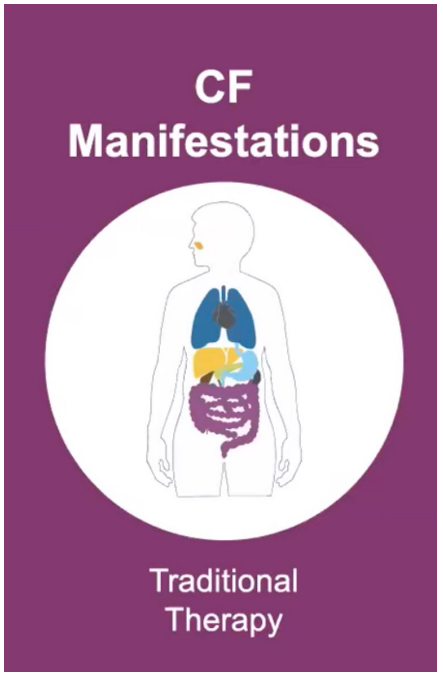
# Patient Case

| General information | |
|---|---|
| Age at diagnosis: | 62 years |
| Current age: | 62 years |
| Sex (M/F): | M |
| Genotype: | **F508Del/R117H** |
| Sweat chloride: | **68 mmol/L** |
| Lung function: | 71% (initial) |
| **Medical background (e.g. exacerbations/infection history):** | |
| Last 2 years<br><br>Hemoptysis 1-2 teaspoon with exacerbations | |

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

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

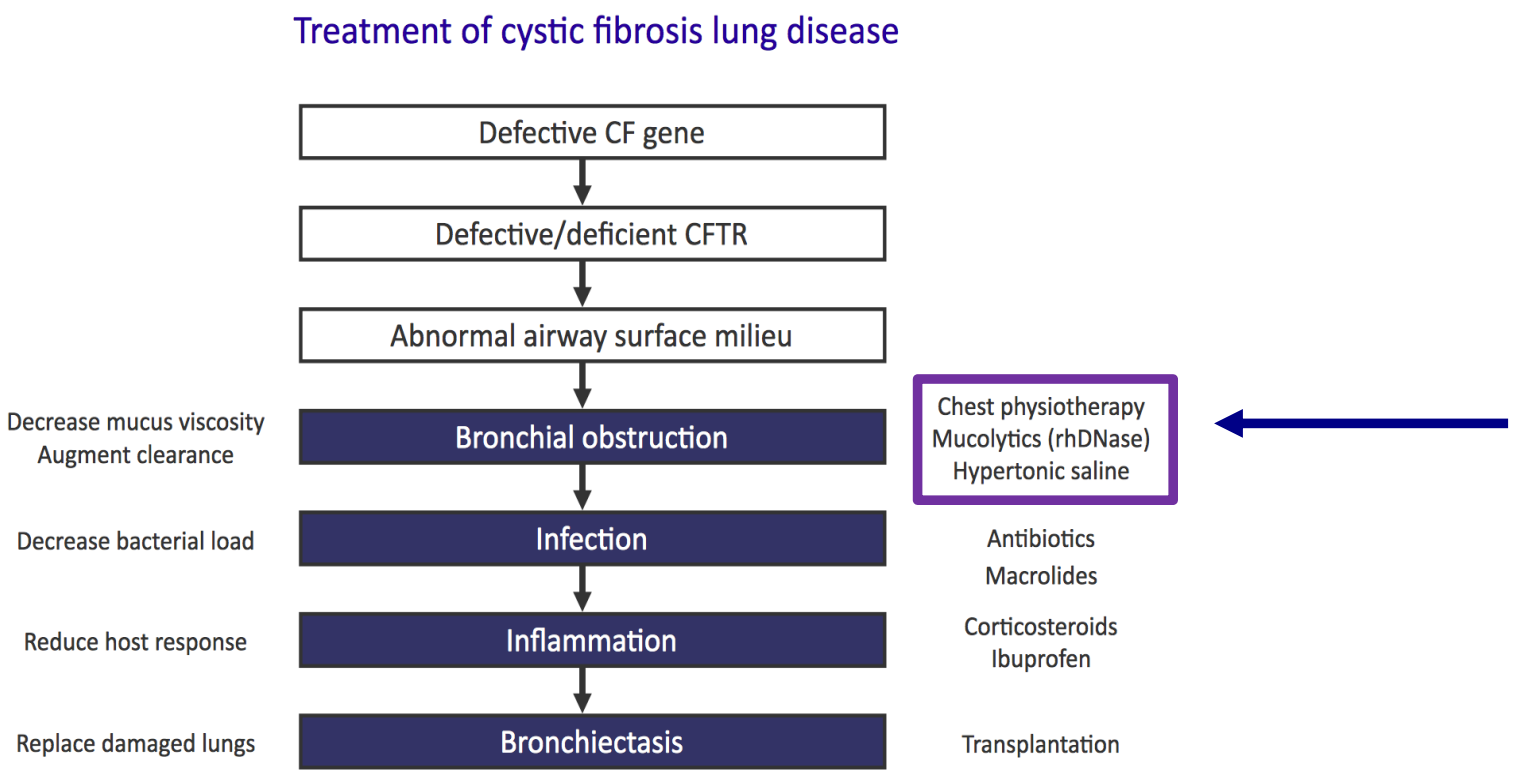
# Pre-Modulator Era
# Therapeutic Approach to CF




Courtesy of CFF

# Traditional Therapeutic Approaches for CF Lung Disease

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



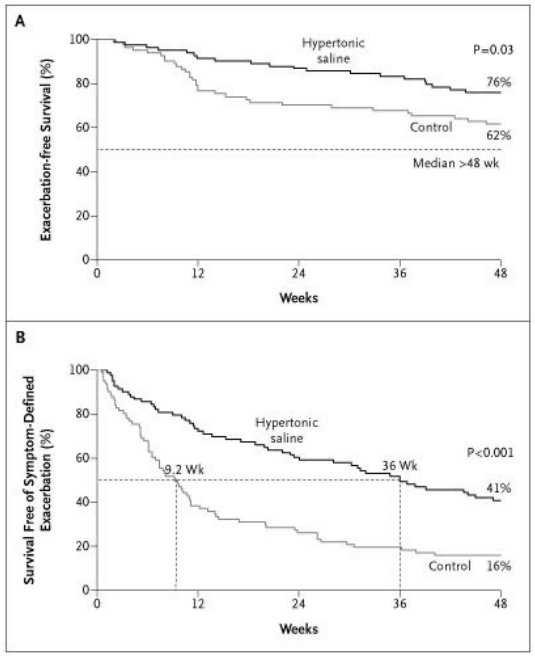
# Therapeutic Approaches for CF Lung Disease

**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

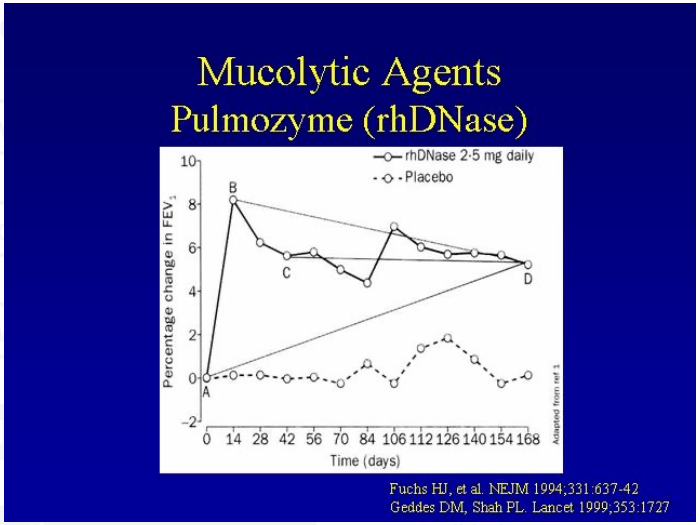
# Therapeutic Approaches for CF Lung Disease

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




- Hypertonic Saline (7%)
- Twice daily

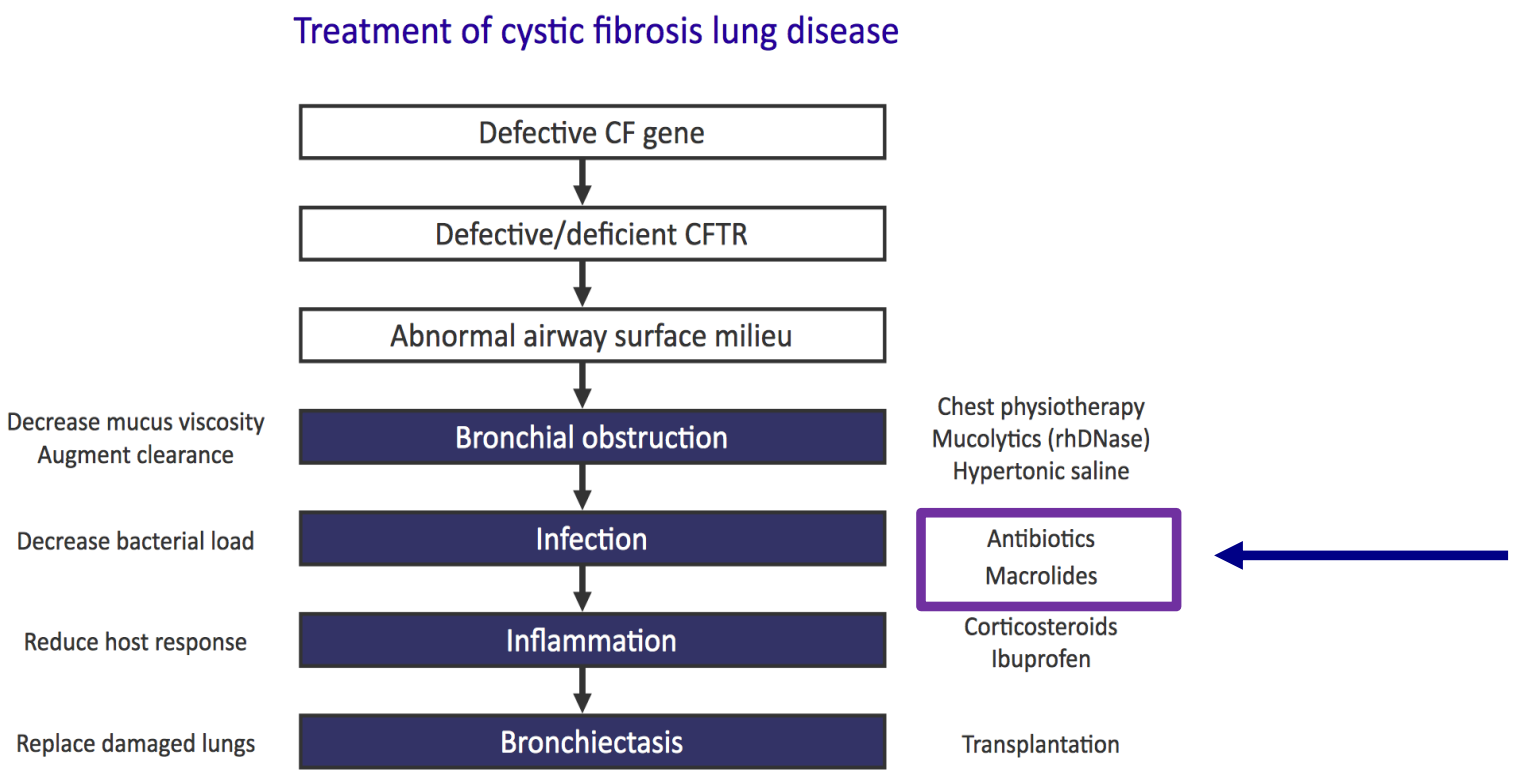
Donaldson SH, et al. N Eng J Med 2006;354:241-250




- Dornase alpha
- Once daily

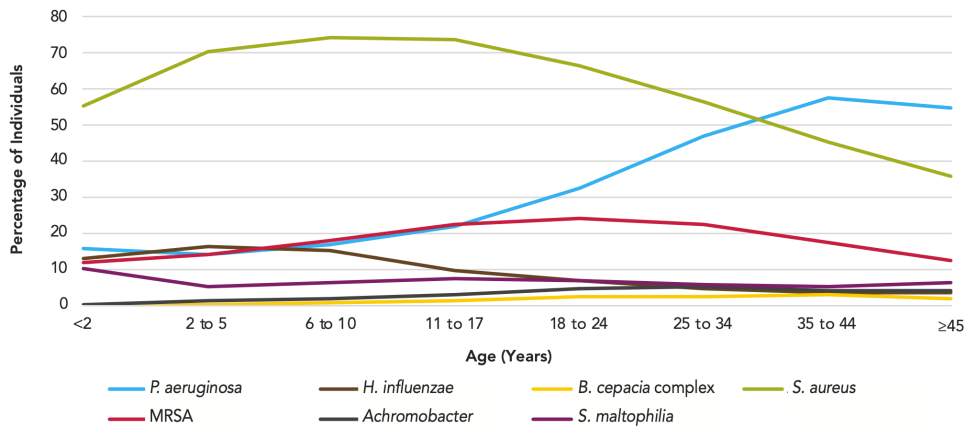
# Traditional Therapeutic Approaches for CF Lung Disease

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

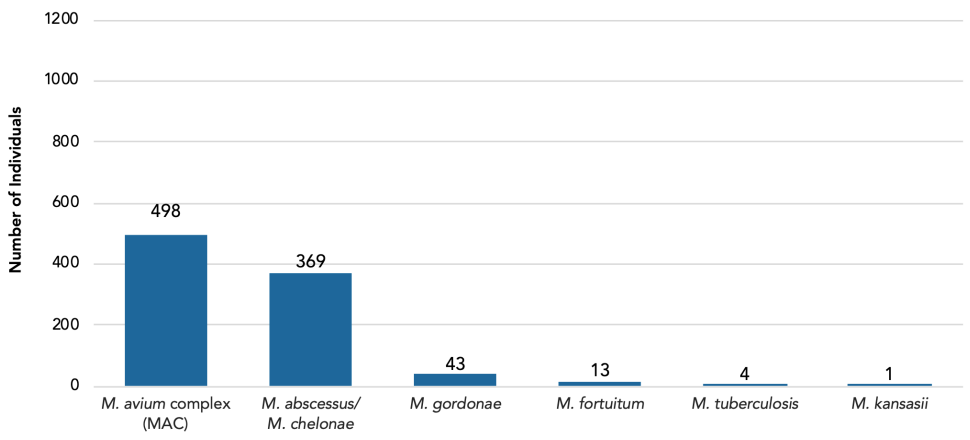


# Bacterial Epidemiology in CF

**Prevalence of Respiratory Microorganisms by Age Cohort, 2020**



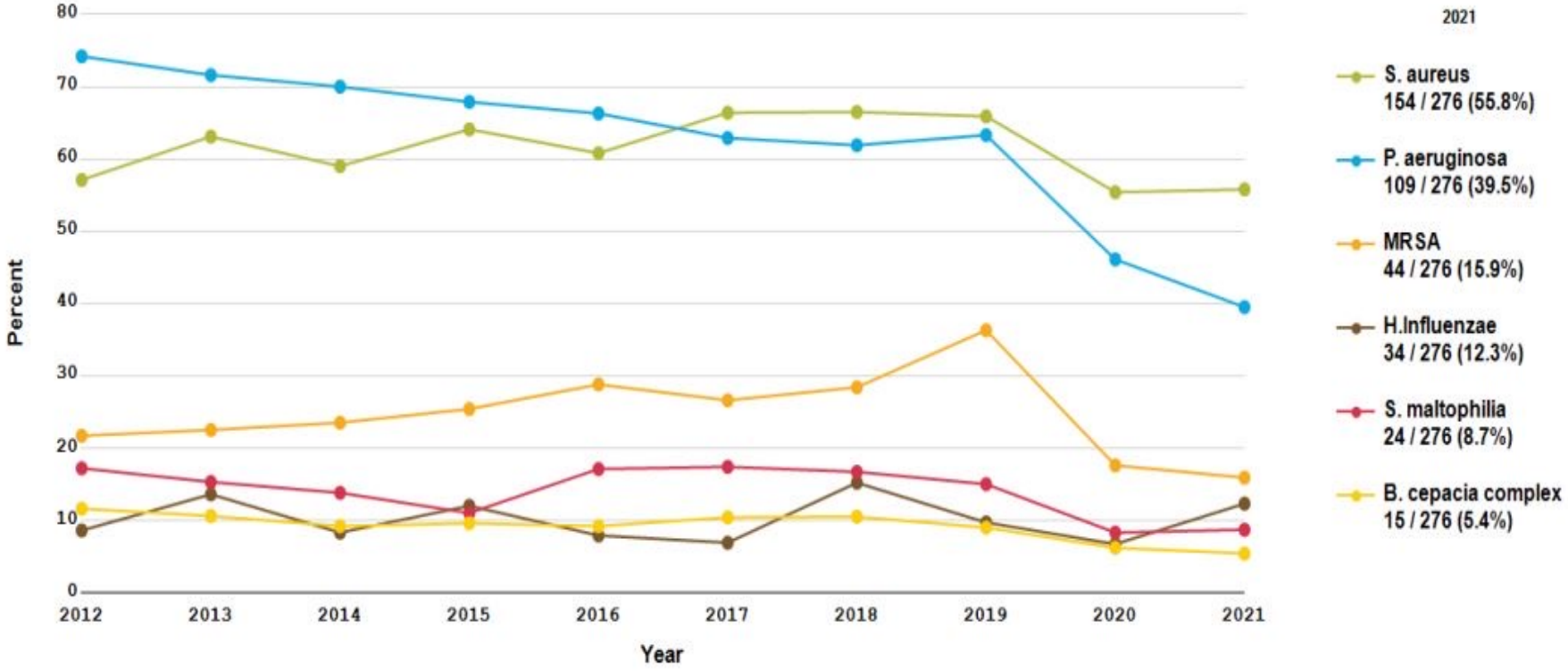

**Mycobacterial Species Isolated in 2020**



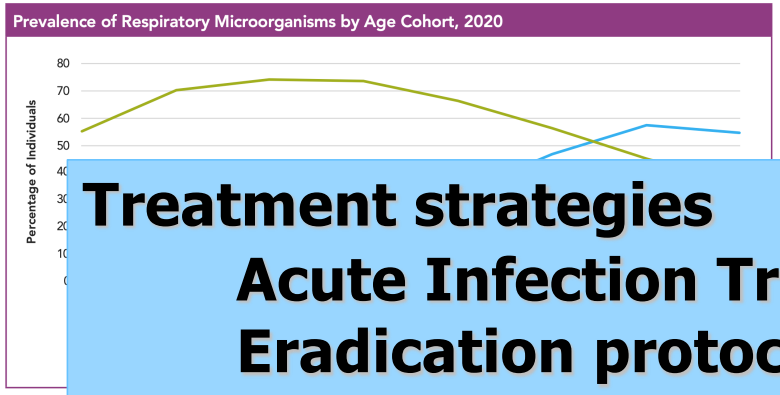

CFF 2019 and 2020 Annual Registry Report

# Aggressive Treatment to Treat and Prevent Airway Infections

BWH/BCH 2021 Annual Registry Report

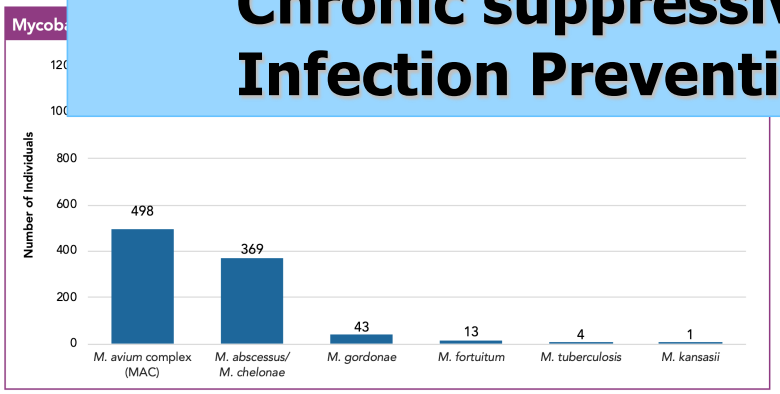


# Management of Acute Infectious Exacerbations




**Treatment strategies**

- **Acute Infection Treatment**
- **Eradication protocols**
- **Chronic suppressive antibiotics**
- **Infection Prevention and Control**




**Pre- Modulator Era**

- 10-15 more at home on IV antibiotics

Pulmonary Disease is major cause of morbidity and mortality

# Transmission of CF Pathogens

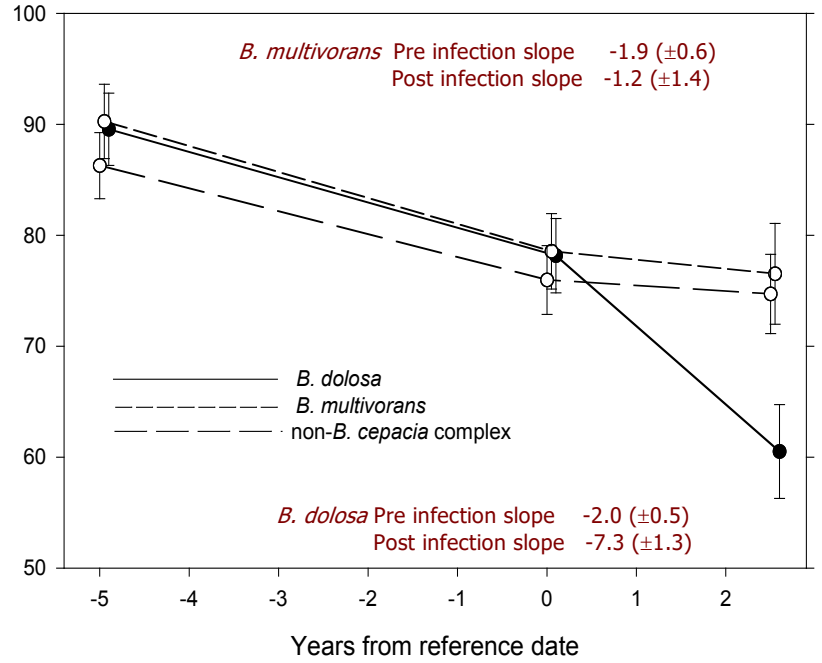
| Non-healthcare Settings | Healthcare Settings |
|---|---|
| ✓Siblings<br>✓Socializing<br>✓Sharing a toothbrush<br>✓Kissing<br>✓Exercise class<br>✓Long car rides | ✓Same hospitalization<br>✓Contaminated environment<br>✓Same clinic session<br>✓Droplets<br>✓Contaminated respiratory equipment<br>✓Handshaking<br>✓Poor hand hygiene |

Saiman L, et al. *Infect Control Hosp Epid* 2003, 2014

# Infection Control?!?

# 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

# The Human Face of the Epidemic - 1992

**First positive *B. dolosa* culture and Alive**

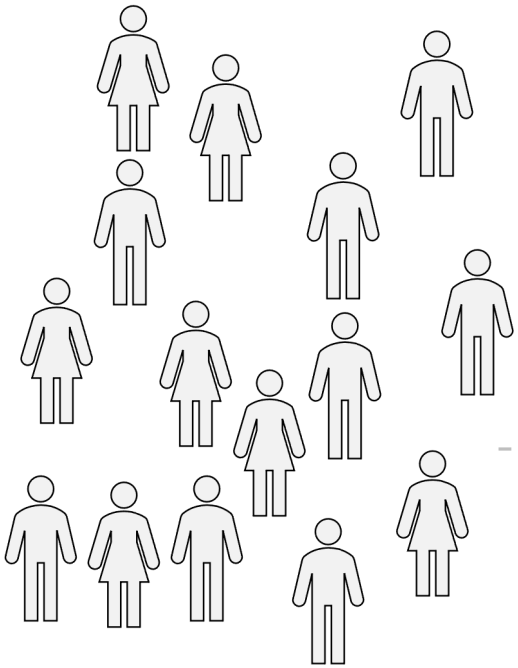
**Passed Away**

**Transplanted and Alive**

# 2001

(not yet aware this is B.dolosa or the coming epidemic)

**First positive B.dolosa culture and Alive**



Patient zero transplanted at BWH

**Transplanted and Alive**

**Passed Away**

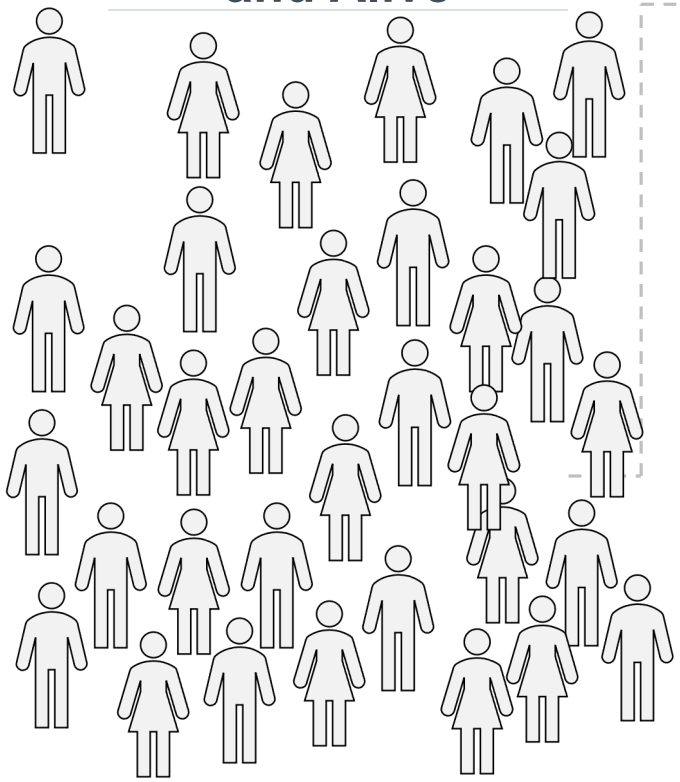
# "*Cepacia* Syndrome"

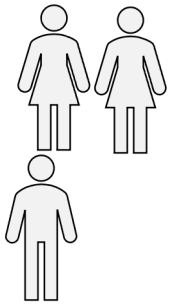
- Fatal combination of necrotizing pneumonia, worsening respiratory failure, and bacteremia
- Previously associated with genomovar III (B.cenocepacia) but documented with other BCC organisms as well
- Bacteremia typically irreversible
- Rapid pulmonary deterioration
  - Pleural effusion
  - Necrotizing pneumonia and Lung abscess
- Death
  - 62-100% of patients

  - Clin Microbiol. 2015 May;53(5):1515-22. doi: 10.1128/JCM.03605-14. Epub 2015 Feb 18.

# 2003

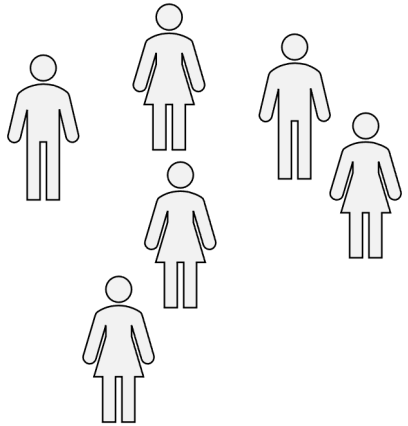
**First positive B.dolosa culture and Alive**





**Transplanted and Alive**

**Passed Away**



# Approach since 2005:

## Enhanced Contact Precautions for all Patients with CF

STOP

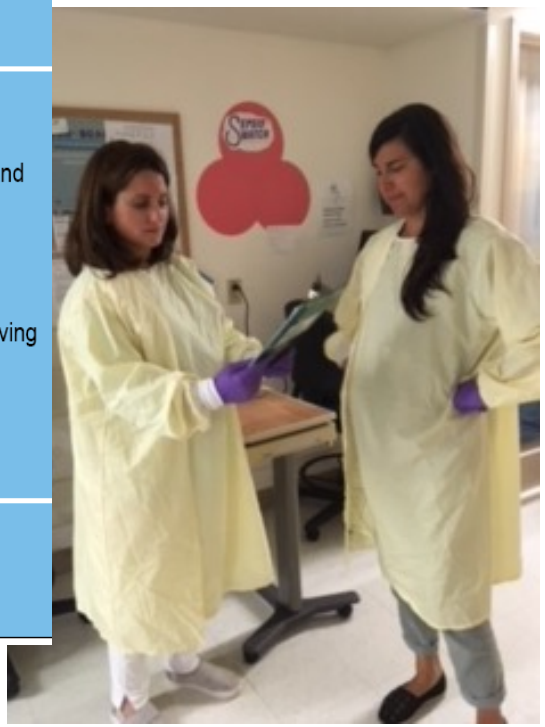
### Enhanced Contact Precautions

*In addition to Standard Precautions*

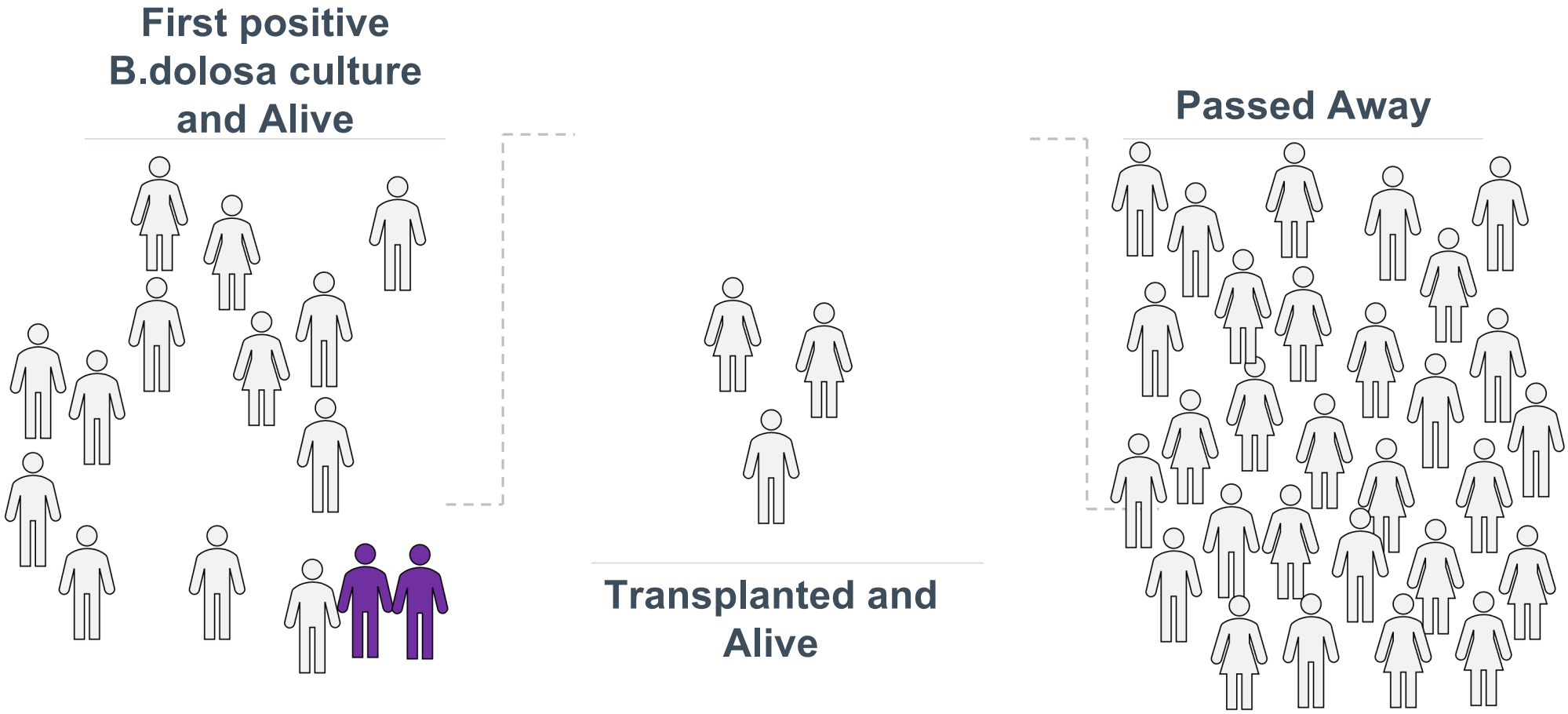
| | |
|---|---|
| **Gloves** | To enter room |
| **Gown** | To enter room and for contact with patient and patient's environment |
| **Equipment** | Dedicate equipment or disinfect prior to use on another patient |
| **Hand Hygiene** | Before entering and immediately after removing protective attire, prior to leaving room |
| **Transport** | Transport for essential purposes only ***Notify receiving department of need for Enhanced Contact Precautions*** |

**Visitors:** Please speak with nurse before entering room
**Visitantes:** Por favor, hable con la enfermera antes de entrar a la sala

For detailed information see reverse side



# No new cases until 2014



# Transmission Outside of the Hospital

- Two Brothers with CF were joined by a third person with CF (B.dolosa) at work site
- Met at a party and didn't know the other had CF
  - Sharing a drink?
  - Double dipping?
- Trevino, et al. **EFFECT OF BITING BEFORE DIPPING (DOUBLE-DIPPING) CHIPS ON THE BACTERIAL POPULATION OF THE DIPPING SOLUTION**. Journal of Food Safety. 2009.

# "The Fist Bump: A More Hygienic Alternative to Handshake"

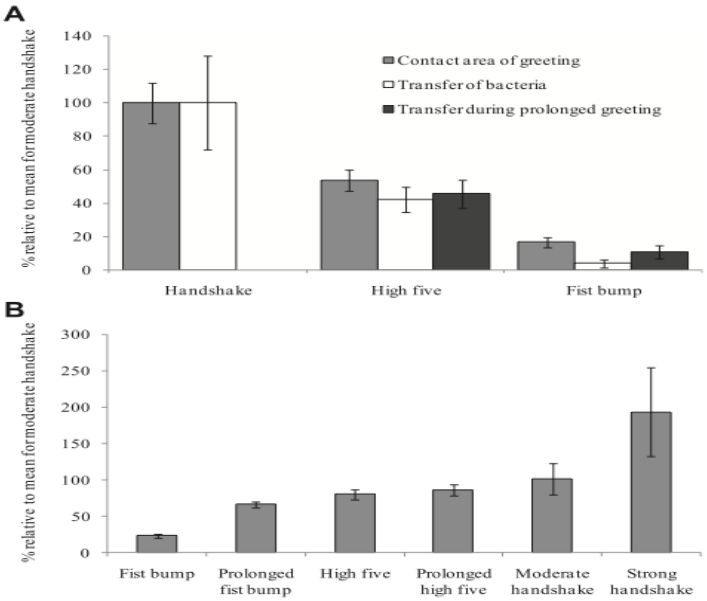
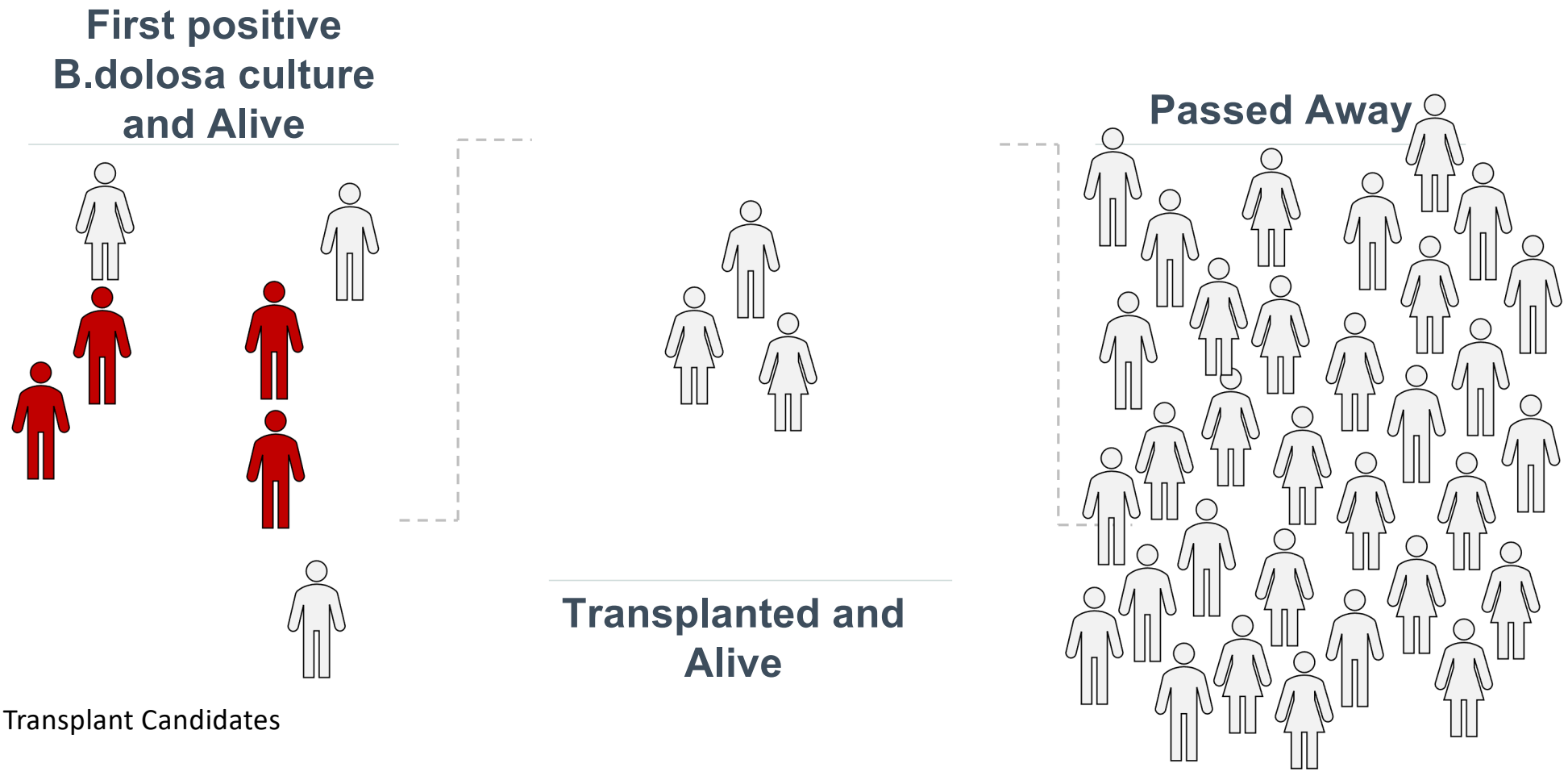



**Fig 1.** Transfer of bacteria in 3 greetings. (A) Area of contact (pale grey), transfer of bacteria during natural greetings (white), and prolonged greetings (dark grey) are all expressed as a percentage of values obtained for the handshake. (B) Transfer per area of contact in the 3 greetings (prolonged and natural duration), and for strong and moderate-strength handshakes (as a percentage relative to the moderate-strength handshake). Error bars denote ± 1 standard deviation (n = 5 in all cases).

Mela S, Whitworth DE. AJIC. August 2014:42(8). 916-917.

# 2022 – Present Day



Assume that ALL CF patients have possible pathogens in their respiratory tract secretions

Educate staff, people with CF and their families about infection control regularly

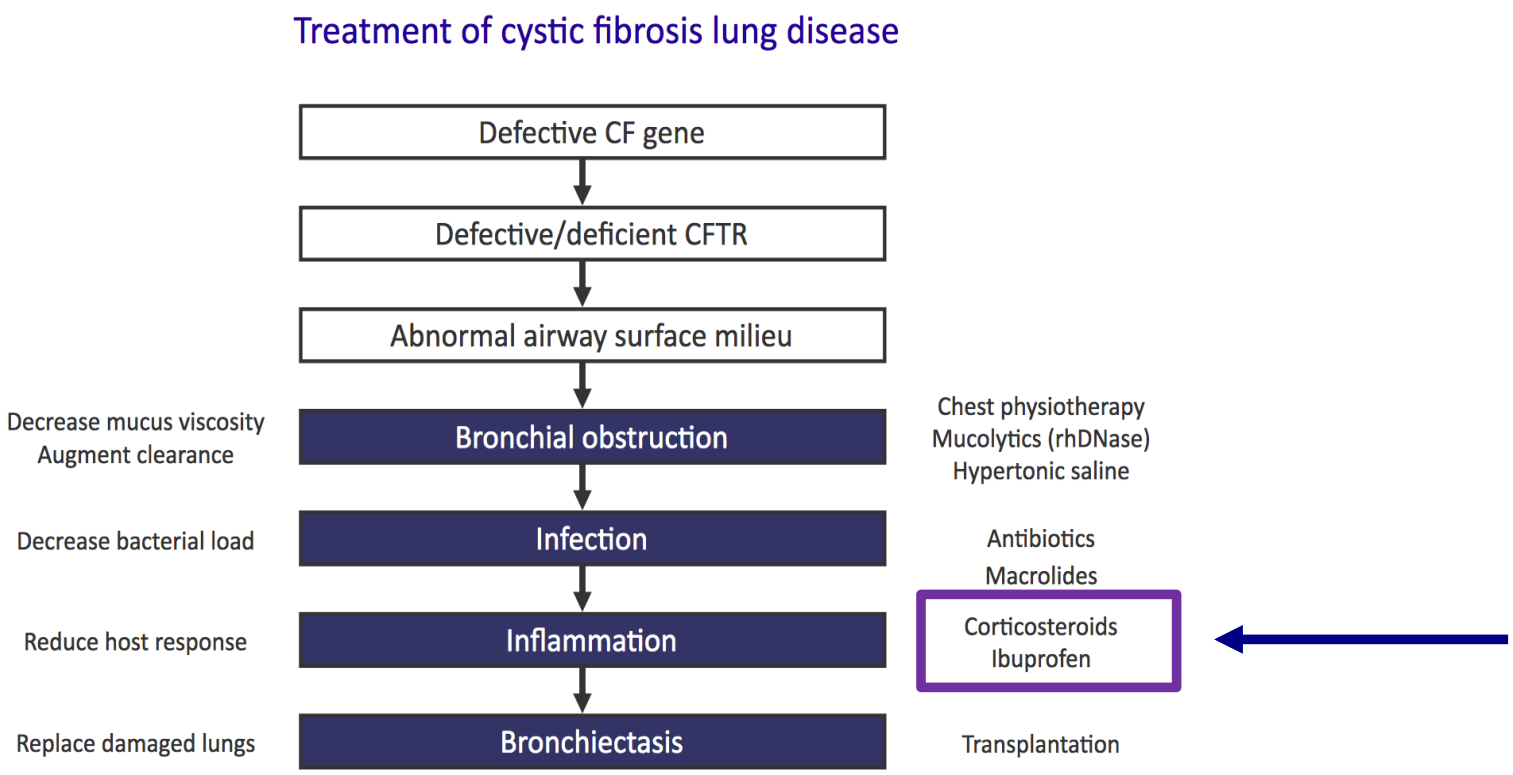
Minimize potential for people with CF to contact each other's secretions via contact or droplets in the CF clinic, in the hospital, and in sponsored ***non-healthcare settings***

Separate people with CF from others with CF by at least **6 feet, recommend masks in hospital and clinic when not in hospital room or clinic room.**

Infection Prevention and Control Committee
Published in 2014
CFF

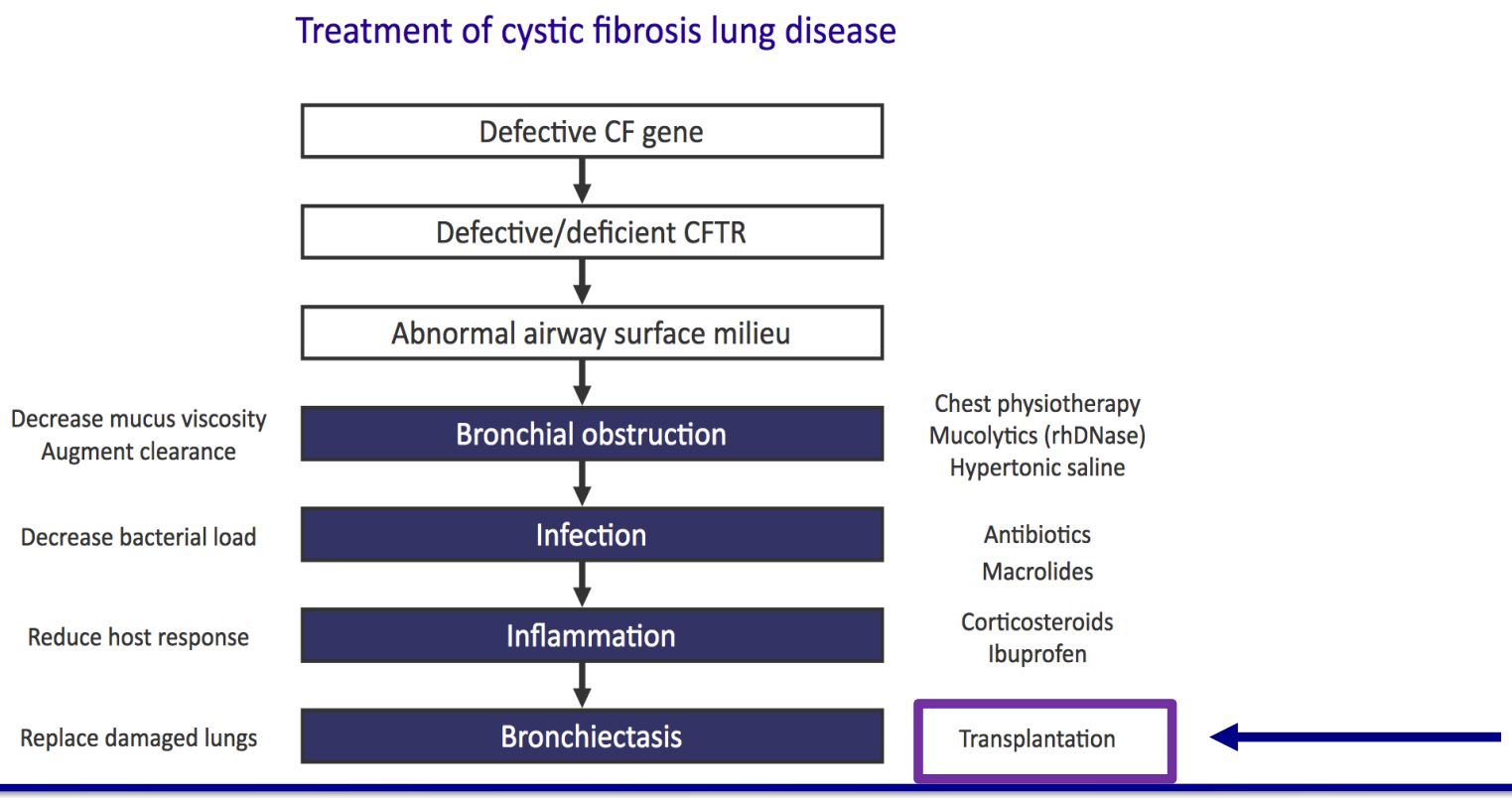
# Traditional Therapeutic Approaches for CF Lung Disease

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



# Traditional Therapeutic Approaches for CF Lung Disease

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

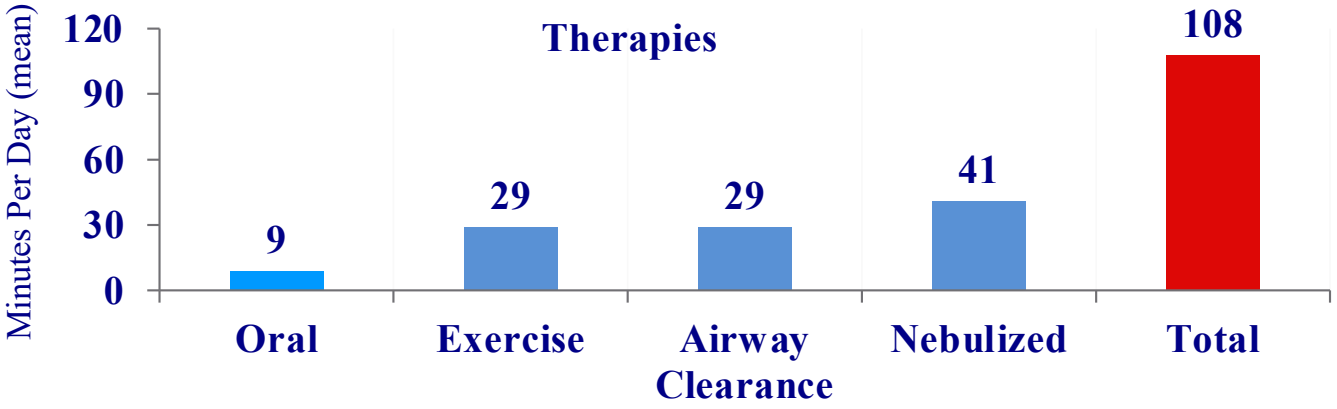


# Chronic Therapies for Maintenance of Lung Health

| **Grade A Recommendation (High Benefit/Substantial)** | **Grade B Recommendation (Mod Benefit/Substantial)** | **No Recommendation (Insufficient Evidence)** |
|---|---|---|
| • Inhaled Tobramycin<br>  • Mod-severe disease<br>• Dornase Alfa<br>  • Mod-severe disease<br>• Inhaled aztreonam<br>  • Mod-severe disease<br>• CFTR Modulators *(modified)*<br>  • (F508del and other eligible mutations) | • Inhaled Tobramycin<br>  • Mild disease<br>• Dornase Alfa<br>  • Mild disease<br>• Inhaled aztreonam<br>  • Mild disease<br>• Hypertonic Saline<br>• Macrolides (PsA)<br>• Ibuprofen (<18 yrs) | • Other aerosalized abx<br>• N-acetyl cysteine<br>• Cromolyn<br>• Inhaled cholinergics<br>• Leukotrienes<br>• Oral Steroids<br>• Inhaled beta-agonist<br>• Macrolides (no PsA)<br>• Chronic oral Anti-Staph |

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



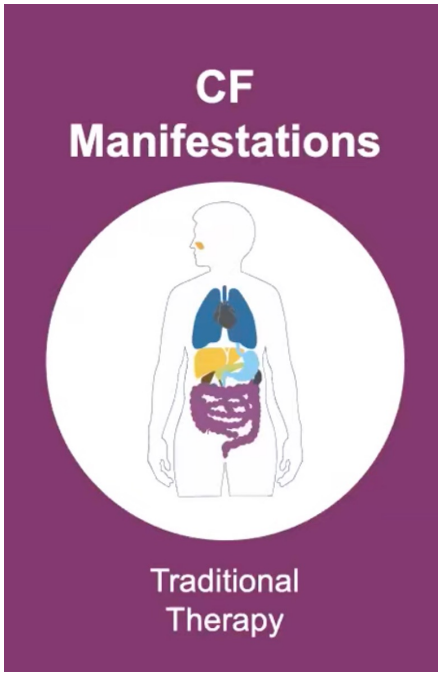

| Medications | Median (Range) |
|---|---|
| # of Oral Medications | 3 (0-7) |
| # of Nebulized Medications | 2 (0-5) |
| # of Inhaled Medications (MDI) | 1 (0-4) |
| **# of Total Medications** | **7 (0-20)** |

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

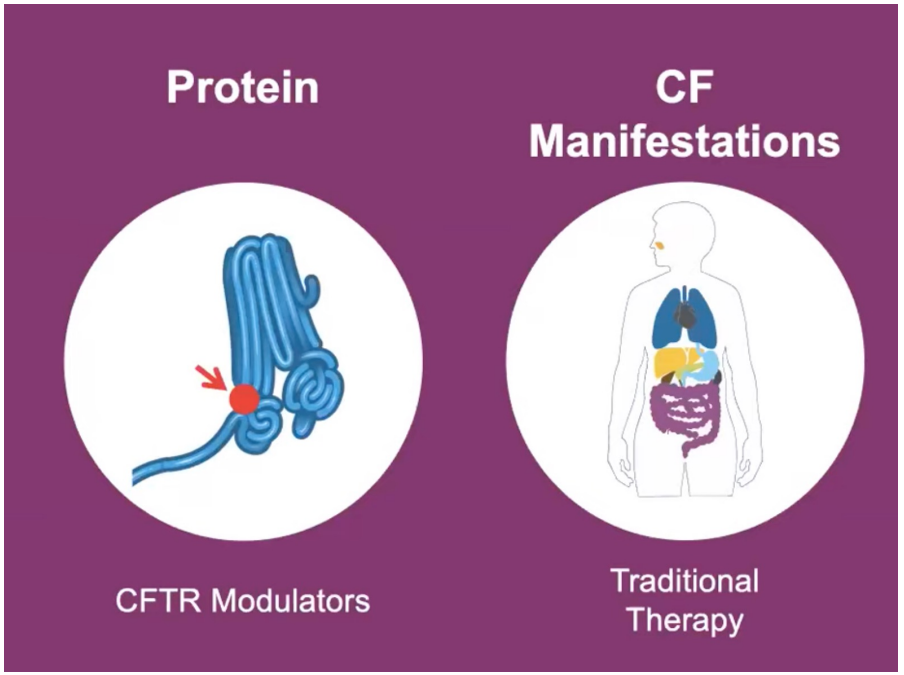
Sawicki GS. *J Cyst Fibros.* 2009;8(2):91-96.

# New Therapeutic Approach to CF



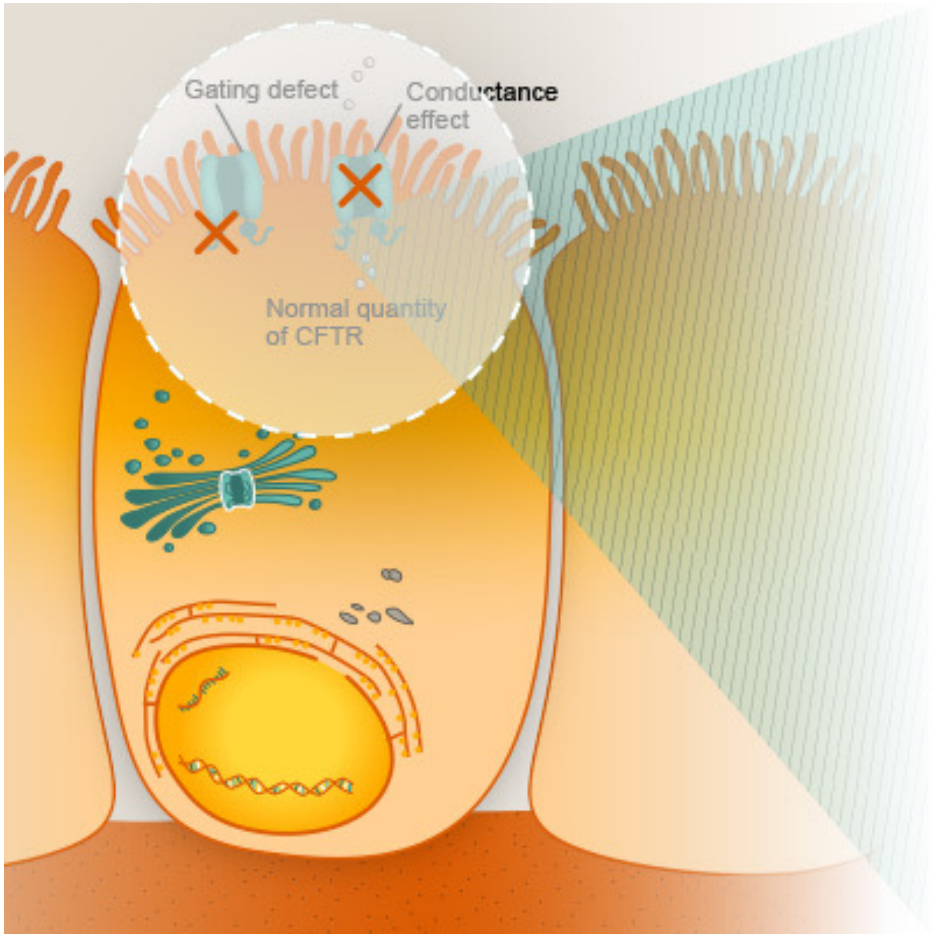

Courtesy of CFF

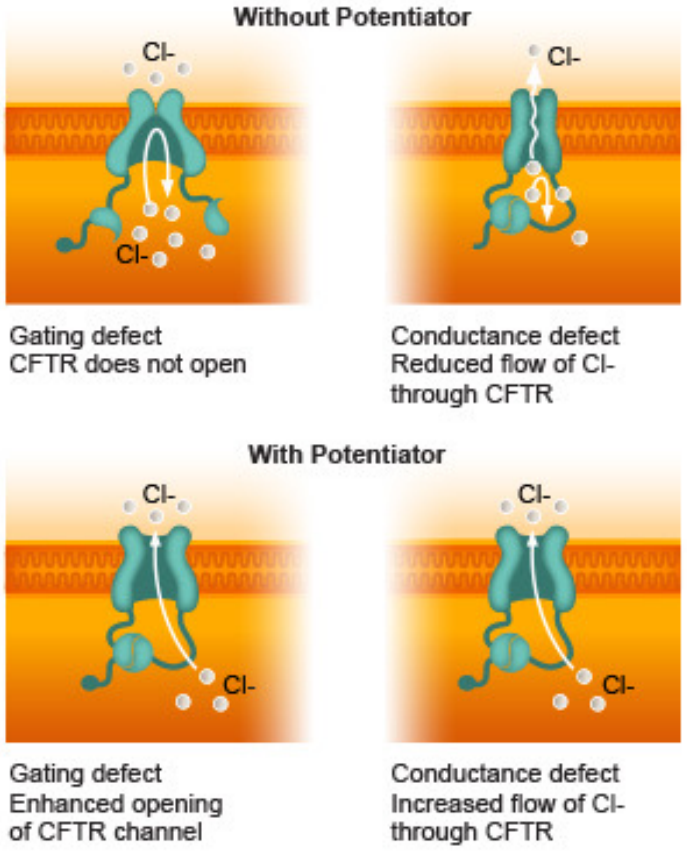
# New Therapeutic Approach to CF




Courtesy of CFF

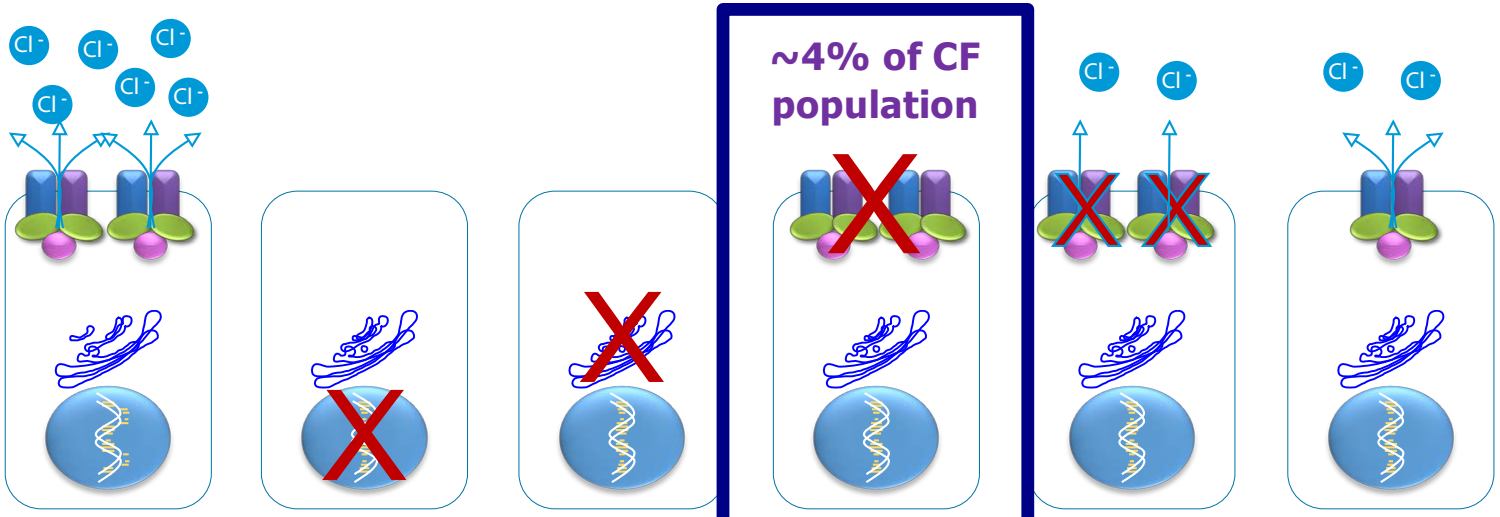
# Precision Medicine – Small Molecule Potentiators




Courtesy of Vertex

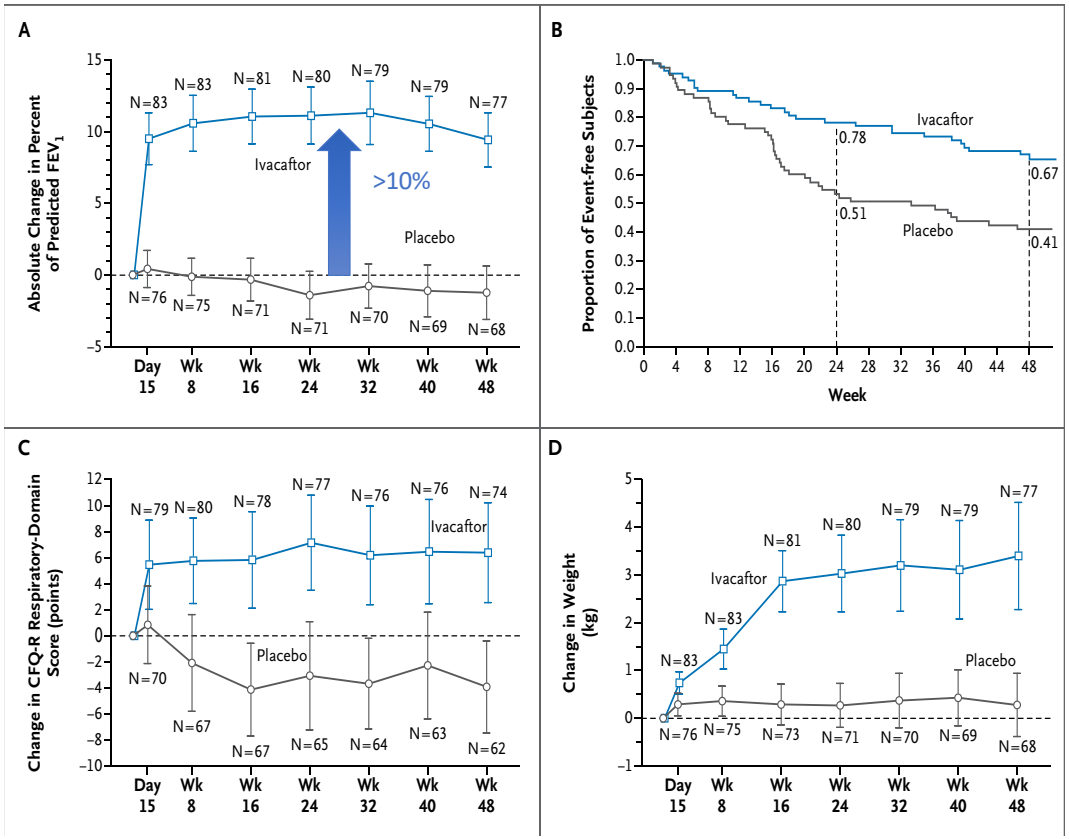
# 5 (or 6) Classes of CFTR Mutations



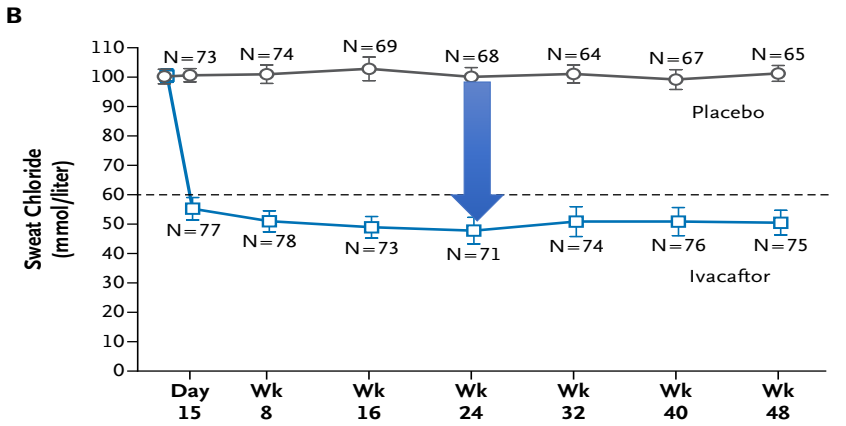

| | Normal | Class I | Class II | Class III | Class IV | Class V |
|---|---|---|---|---|---|---|
| DESCRIPTION | CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water. | No functional CFTR created. | CFTR protein is created, but misfolded, keeping it from reaching the cell surface. | CFTR protein is created and reaches cell surface, but does not function properly. | The opening in the CFTR protein ion channel is faulty. | CFTR is created in insufficient quantities. |
| EXAMPLES | | G542X<br>W1282X<br>R553X | F508del<br>N1303K<br>I507del | G551D<br>S549N<br>V520F | R117H<br>D1152H<br>R347P | 3849+10kbC->T<br>2789+5G->A<br>A455E |

Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

# Ivacaftor (Kalydeco) and health outcomes

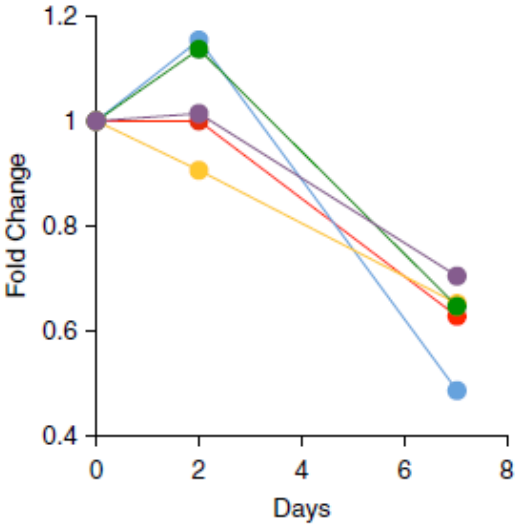



| | Ivacaftor | Placebo |
|---|---|---|
| Absolute change from baseline through Week 24 in the ppFEV$_1$ (percentage points) | 10.4 | -0.2 |
| Treatment difference (percentage points) | 10.6<br>P<0.001 | |



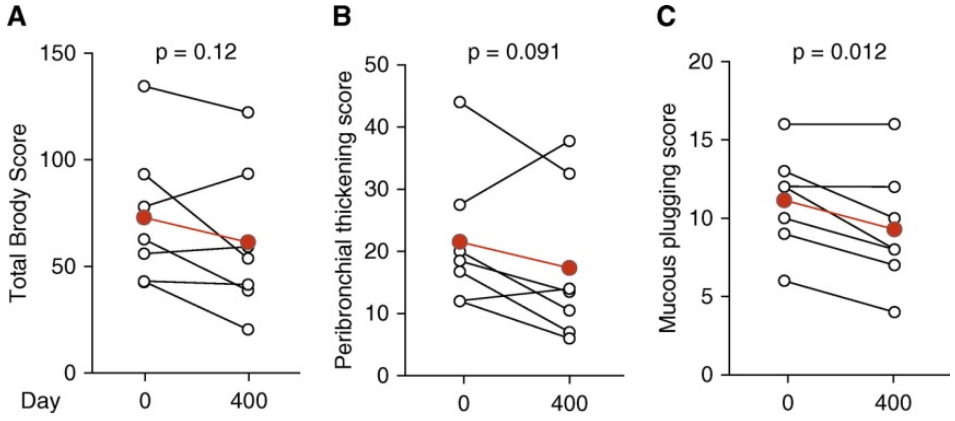

CFQ-R, cystic fibrosis questionnaire respiratory; FEV, forced expiratory volume.
Ramsey BW et al. *N Engl J Med* 2011;365:1663–1672.

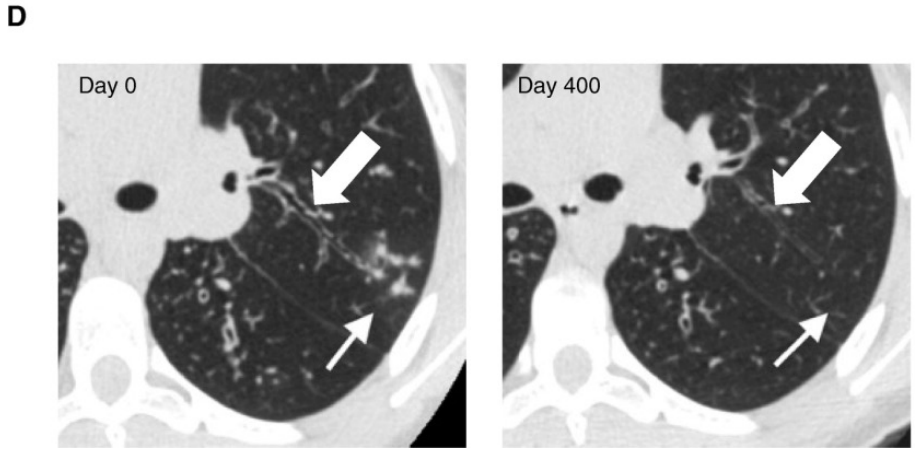
# Single-center data on ivacaftor: Changes in sputum inflammation and CT scans




Neutrophil elastase
Myeloperoxidase
Arginase-1
S100A8
S100A9

p<0.05 for all inflammatory markers at day 7



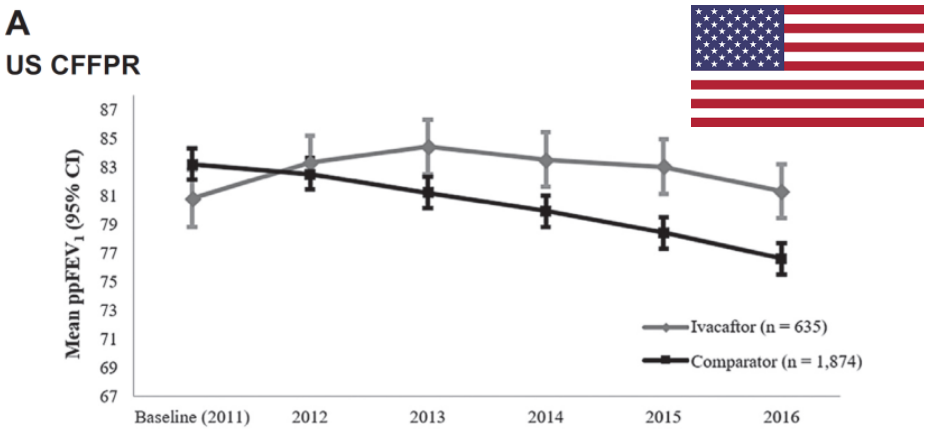

Hisert KB et al. *Am J Respir Crit Care Med* 2017;195(12):1617–1628.

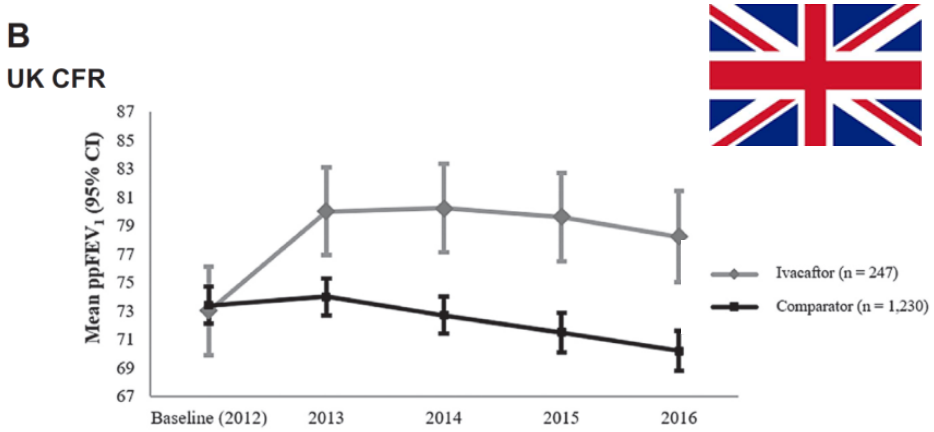
# Lung Health in the Longer Term: $FEV_1$ DECLINE

Contents lists available at ScienceDirect
Journal of Cystic Fibrosis
journal homepage: www.elsevier.com/locate/jcf

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

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




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

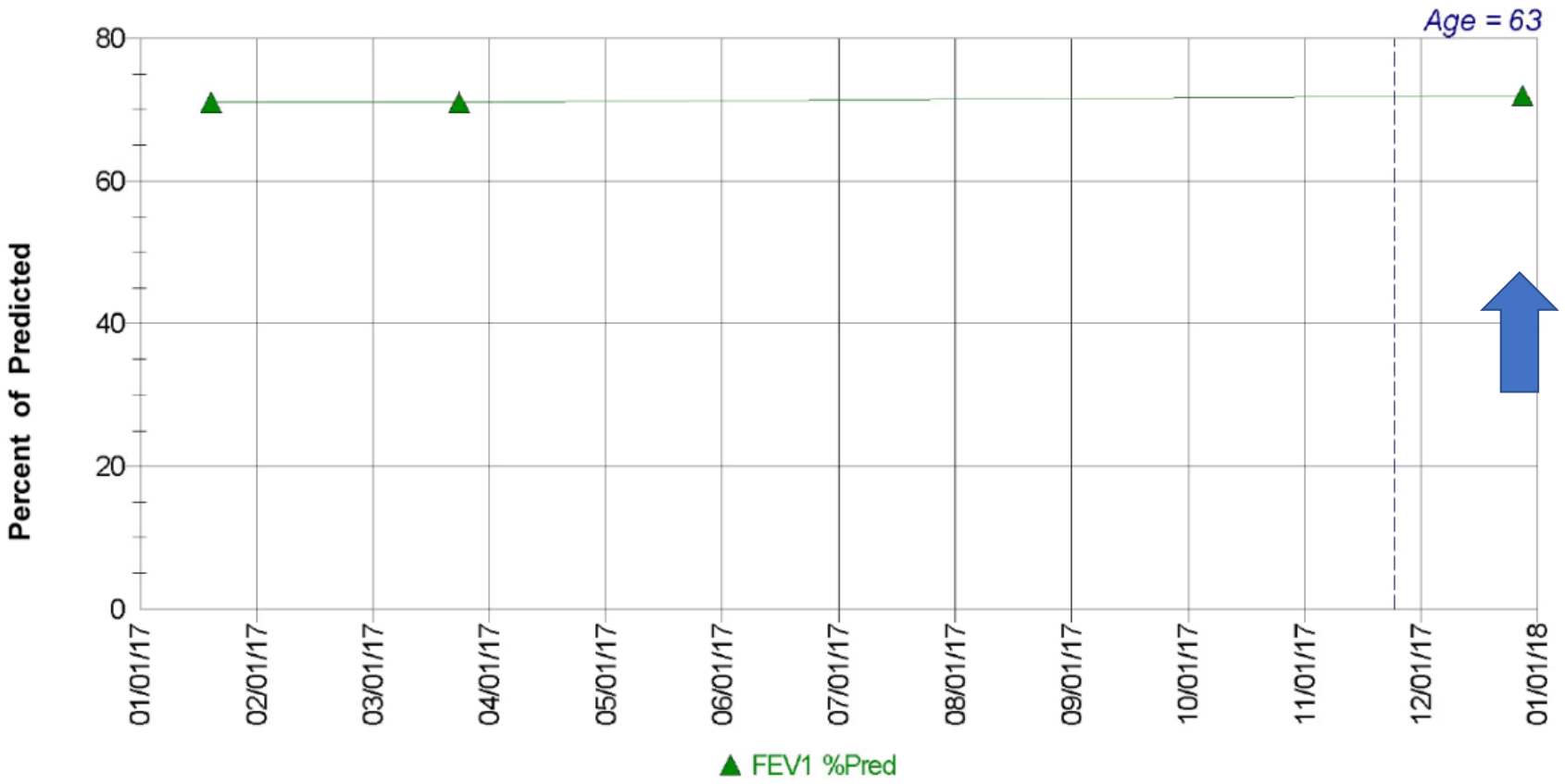
# Patient Case

| General information | |
|---|---|
| Age at diagnosis: | 62 years |
| Current age: | 62 years |
| Sex (M/F): | M |
| Genotype: | **F508Del/R117H** |
| Sweat chloride: | **68 mmol/L** |
| Lung function: | 71% (initial) |
| **Medical background (e.g. exacerbations/infection history):** | |
| Last 2 years<br>Hemoptysis 1-2 teaspoon with exacerbations | |

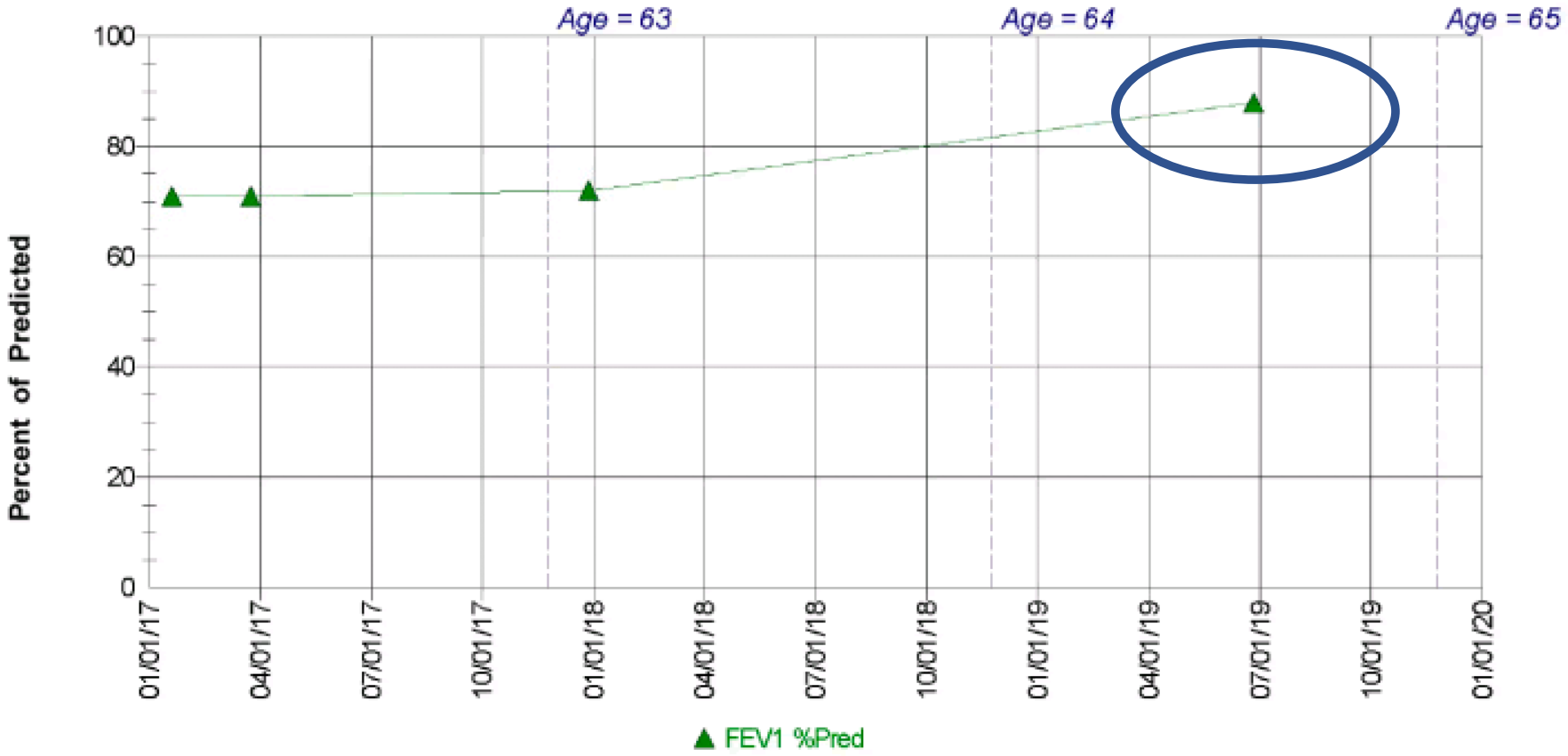
| Comorbidities: |
|---|
| Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity |
| **Lifestyle/circumstance:** |
| Decreased activity, desk job |
| **CFTR Treatment:** |
| **Eligible for ivacaftor** |
|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

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

# Patient Case



# Patient Case



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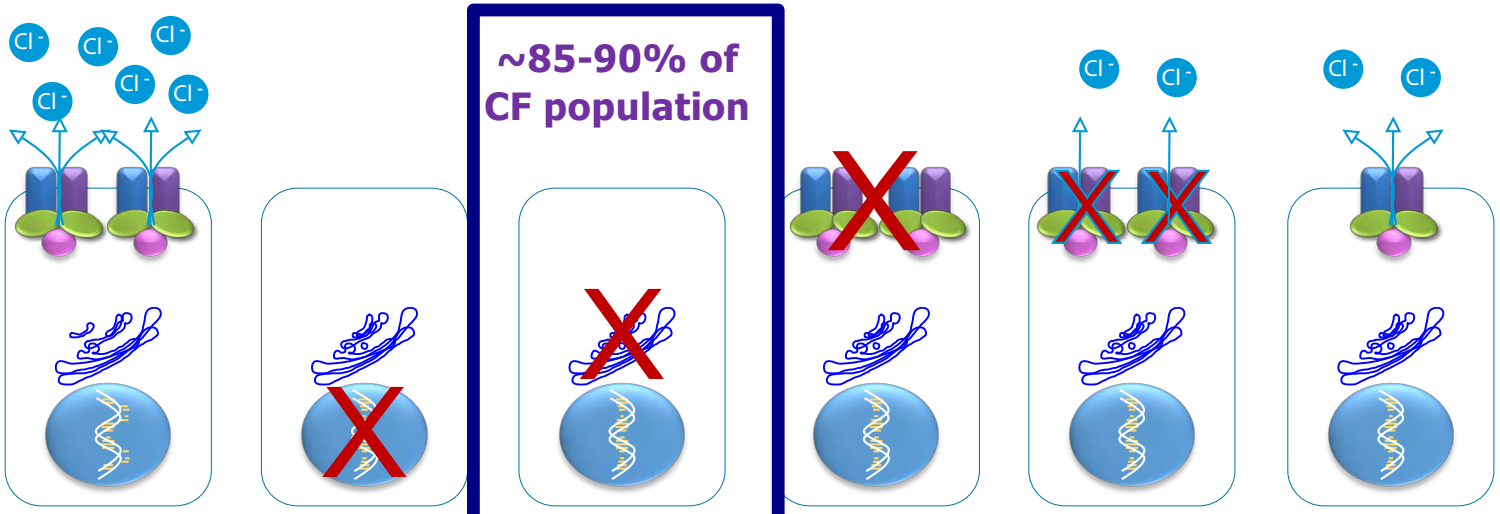


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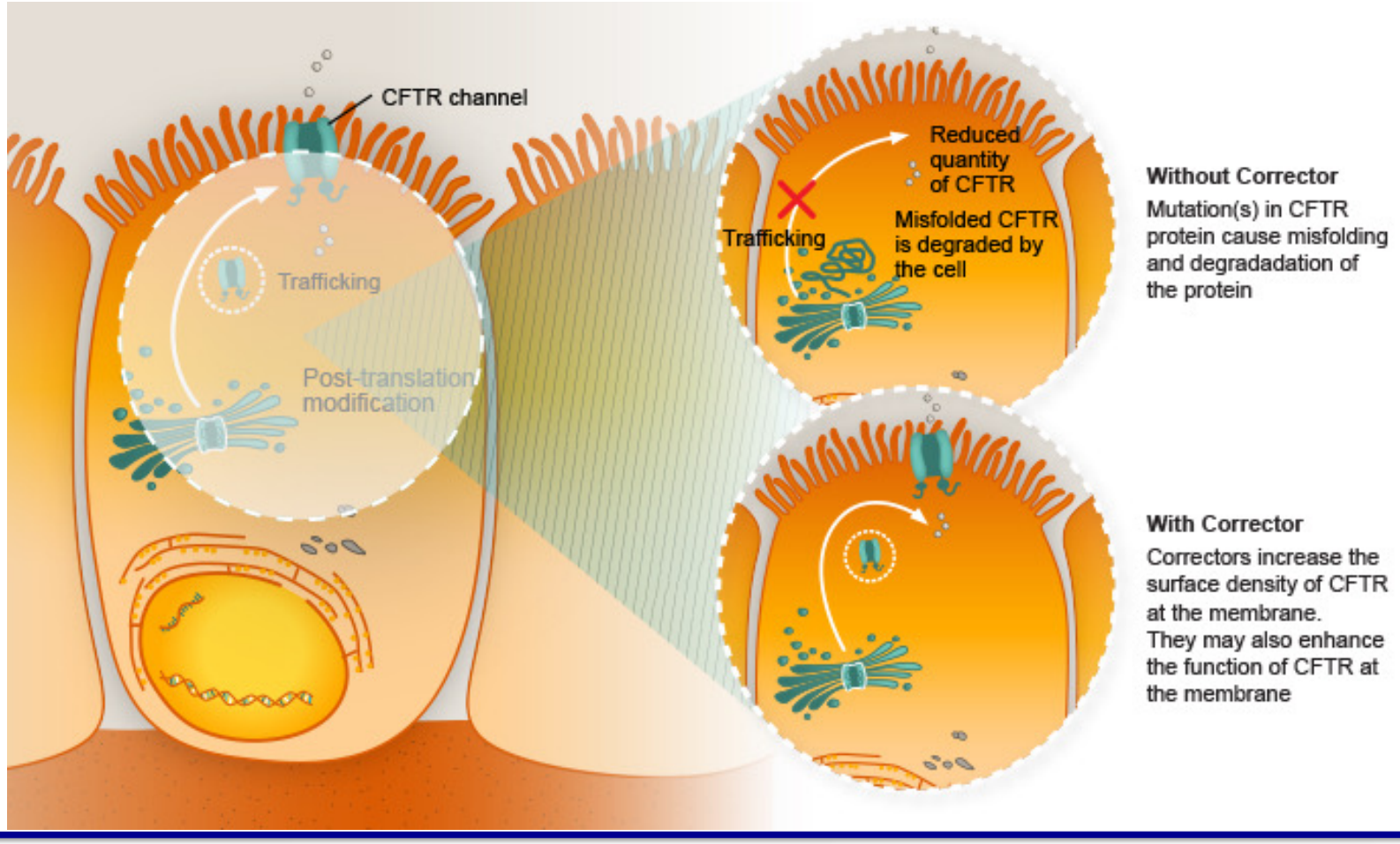
Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

# Small Molecule Potentiator + Corrector



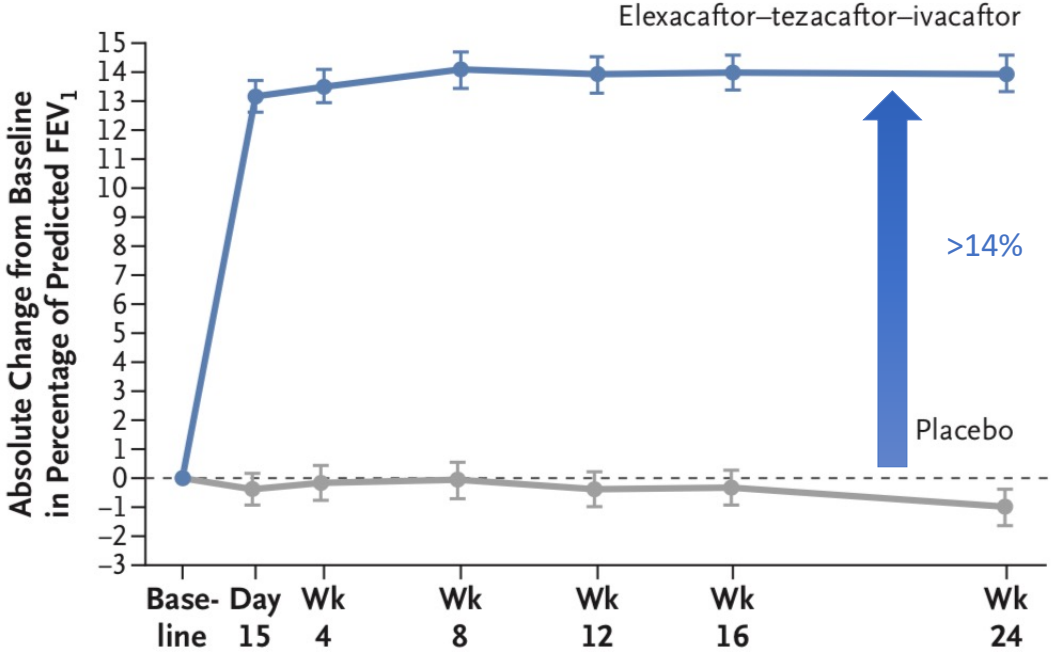
October 21, 2019

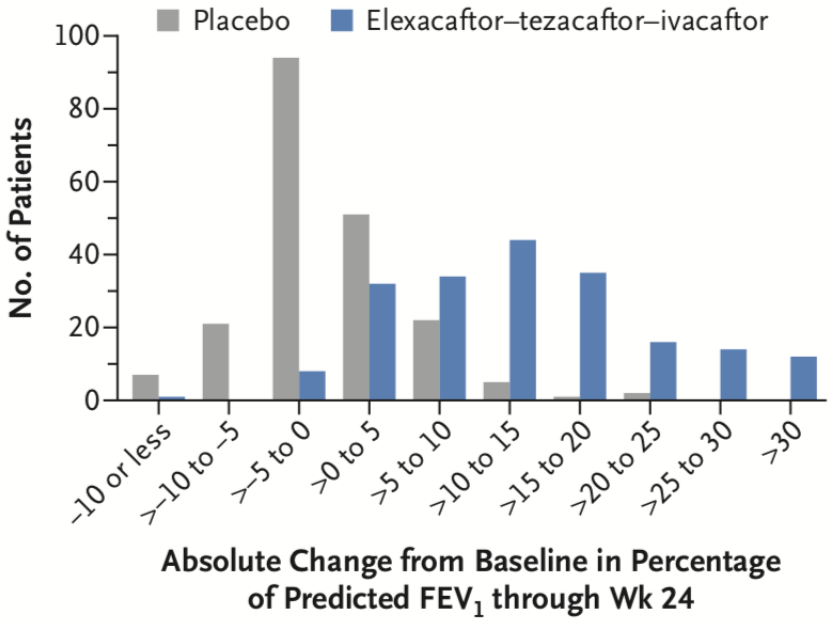
# FDA Approved elexacaftor/tezacaftor/ivacaftor (Trikafta) for those with at least **one copy F508Del**

(preceded by Orkambi 2016 and Symdeko 2018)

# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

## Lung Function Response (FEV1)

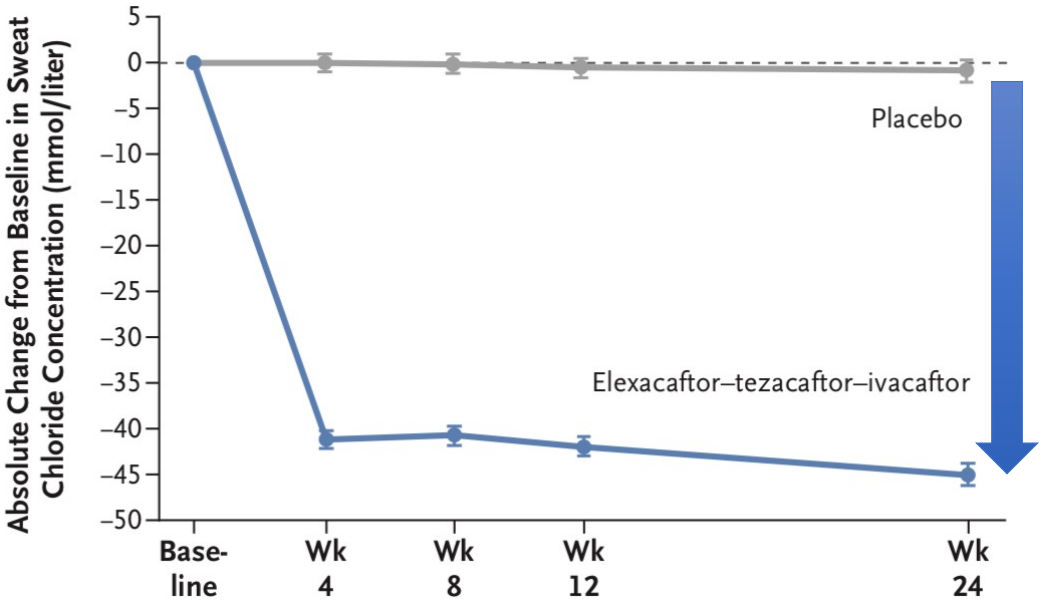


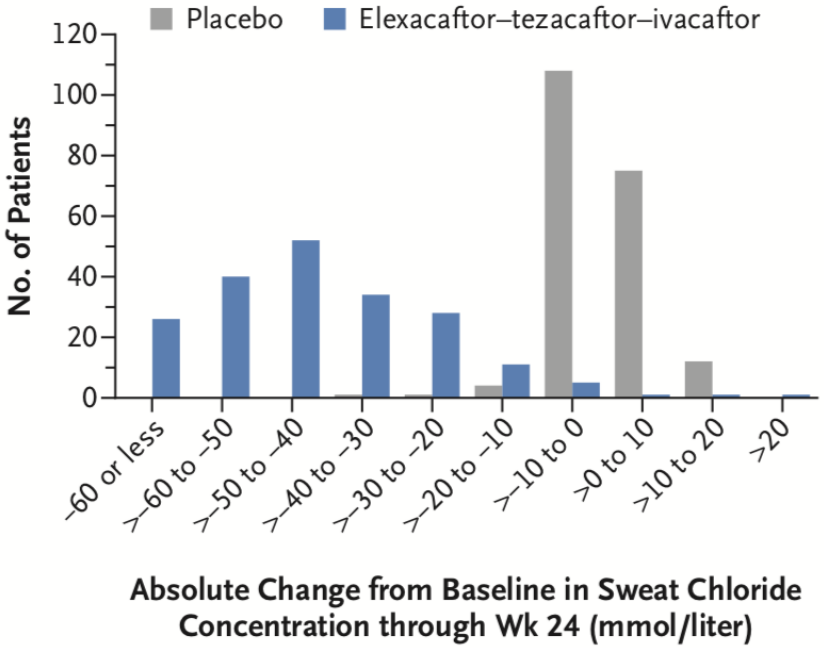




Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

## Sweat Chloride Response (mmol/liter)

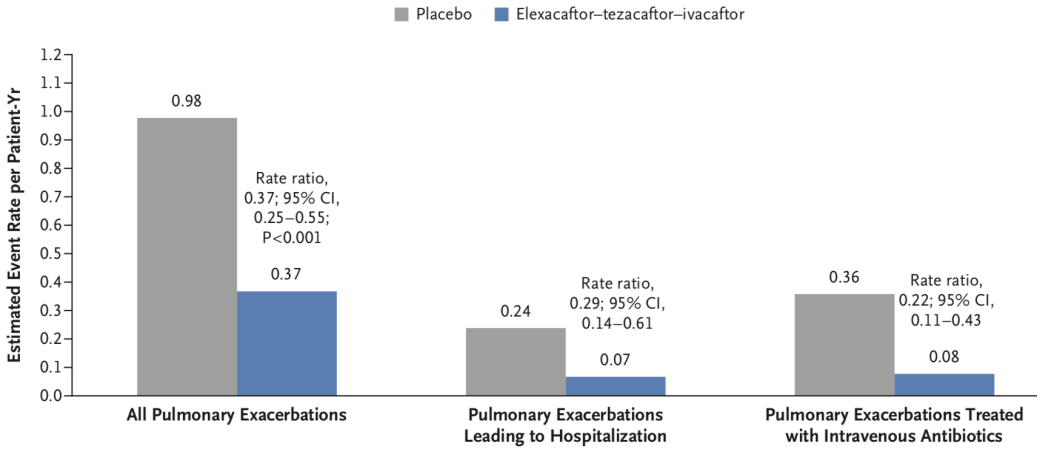


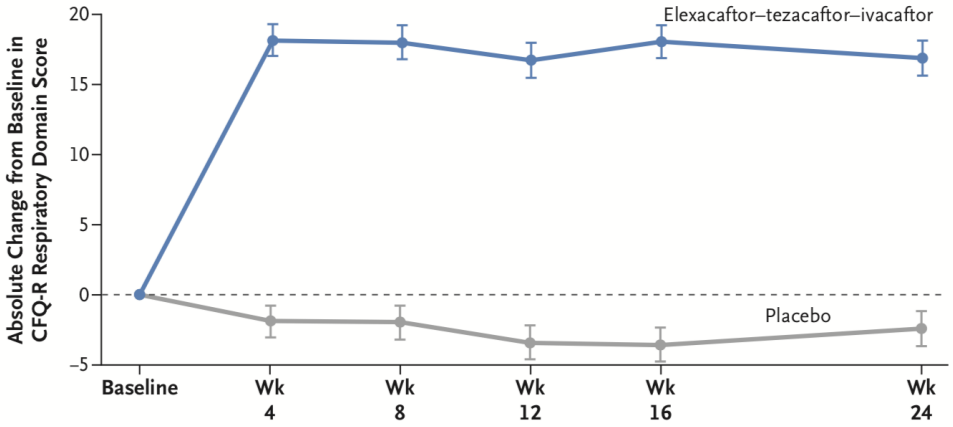




Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

# Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

## Exacerbations and CFQ-R




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

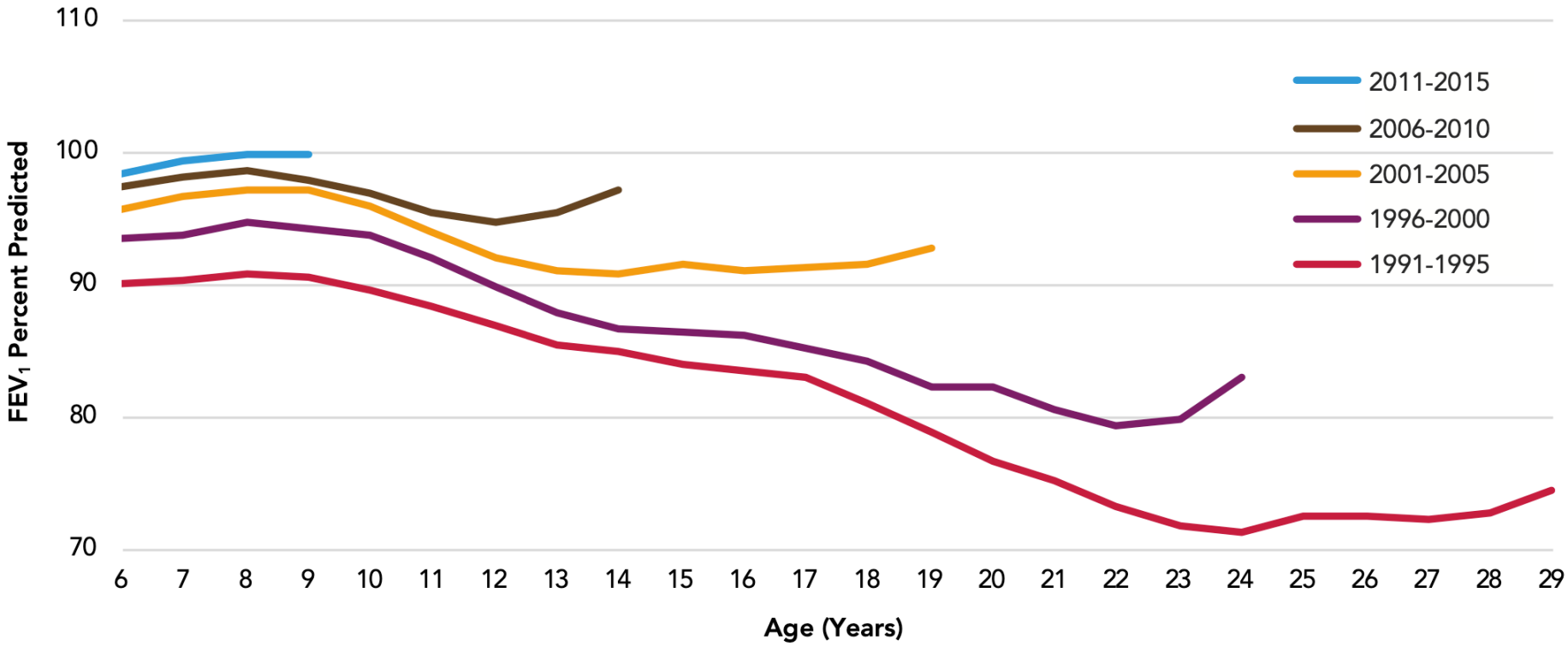
# CF - Multi-Organ Involvement



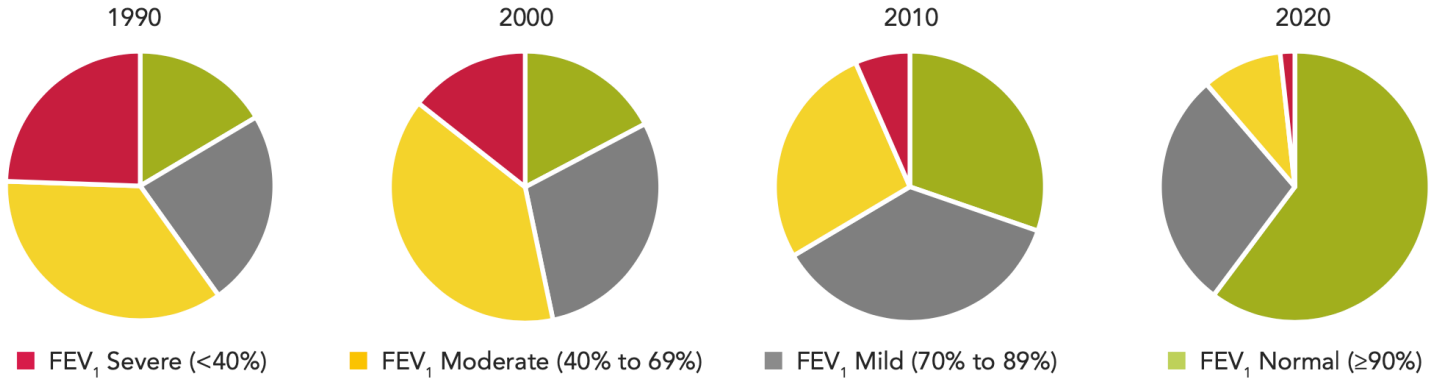

Pulmonary Disease is major cause of morbidity and mortality

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

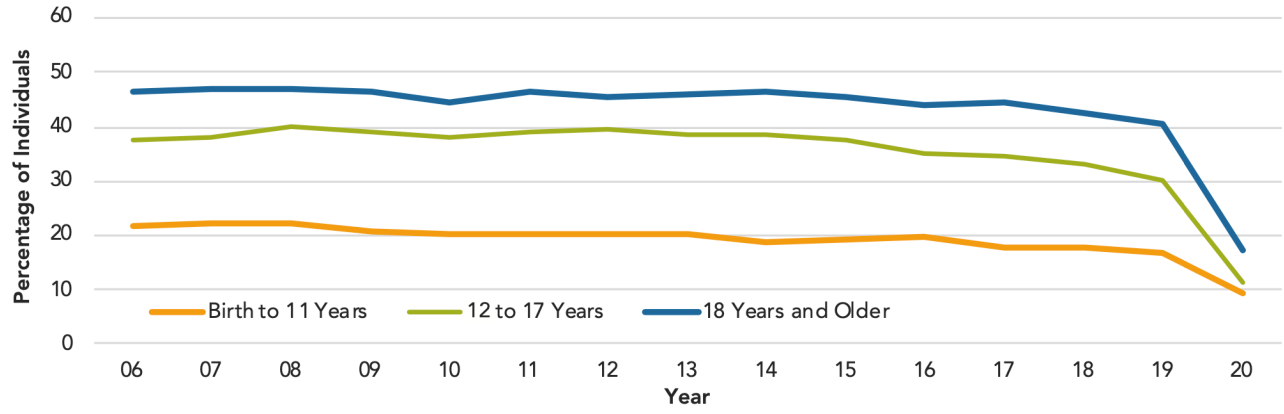
# Median FEV1 Percent Predicted, by Age and Birth Cohort



## Median $FEV_1$ Percent Predicted in 18-Year-Olds, 1990–2020

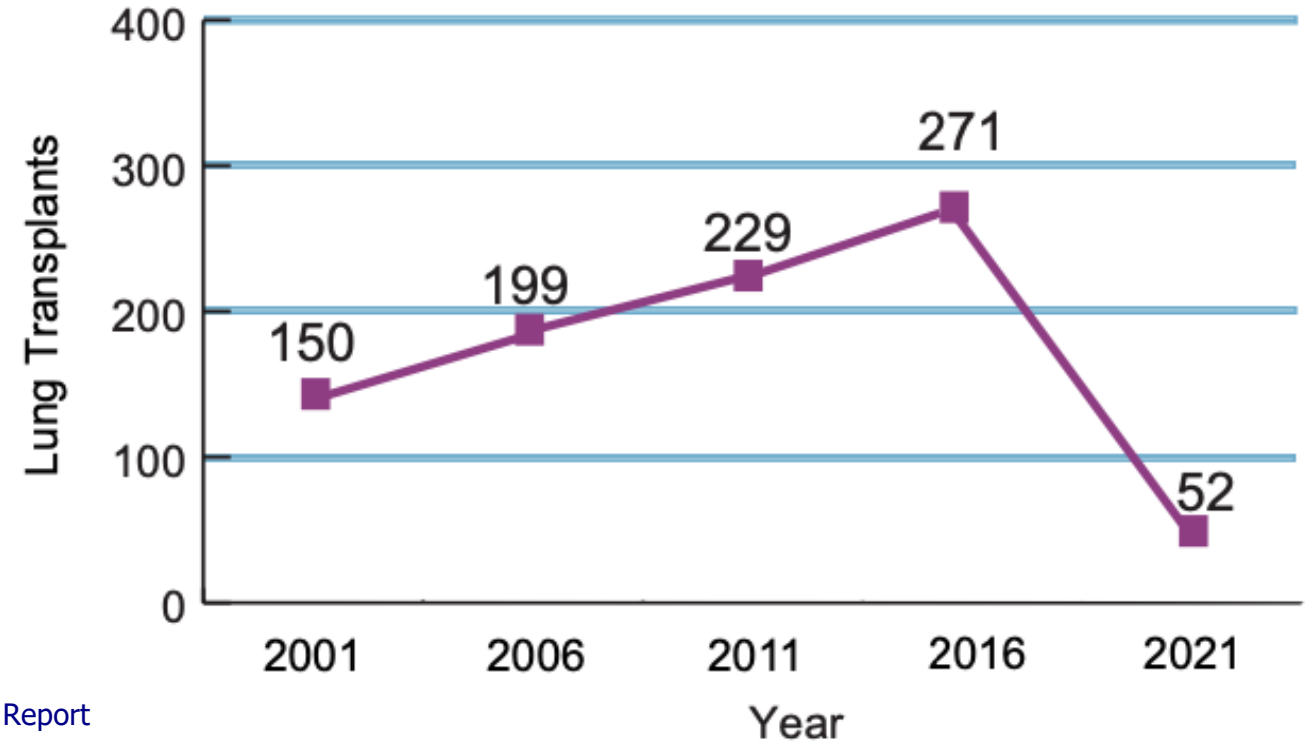



## Individuals Treated with IV Antibiotics for a Pulmonary Exacerbation, 2006–2020




CFF 2020 Registry Report

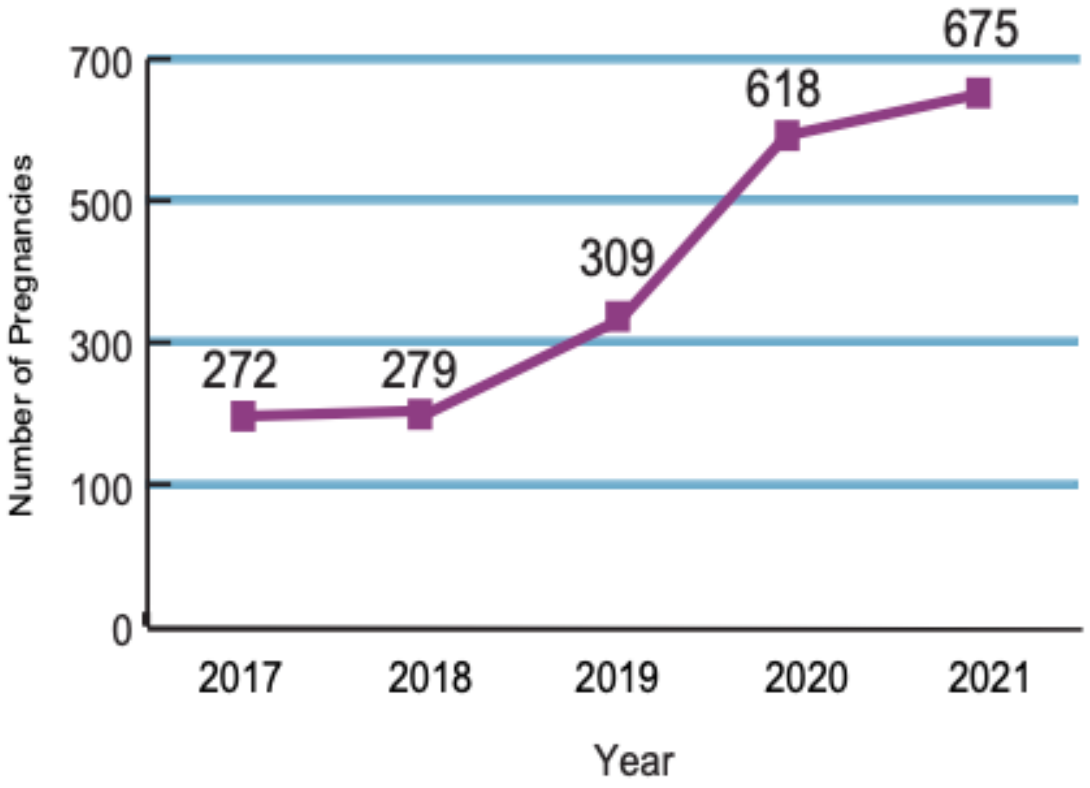
# Lung Transplants by Year




CFF 2021 Registry Report

# Number of CF Pregnancies by Year

(does not include fathers with CF)




- 35% infertility prior to modulators
  - Thick cervical mucus
  - Abnormal cervical and uterine pH
  - Nutritional deficiency
  - Delayed puberty and anovulation

CFF 2021 Registry Report
Taylor-Cousar. J Clin Med. 2020
Kazmerski et al. Ped Pulm. 2021

# In utero impact of CFTR modulators

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Case report

## Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Christopher N. Fortner[a,*], Julie M. Seguin[a], Denise M. Kay[b]

# In utero impact of CFTR modulators

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

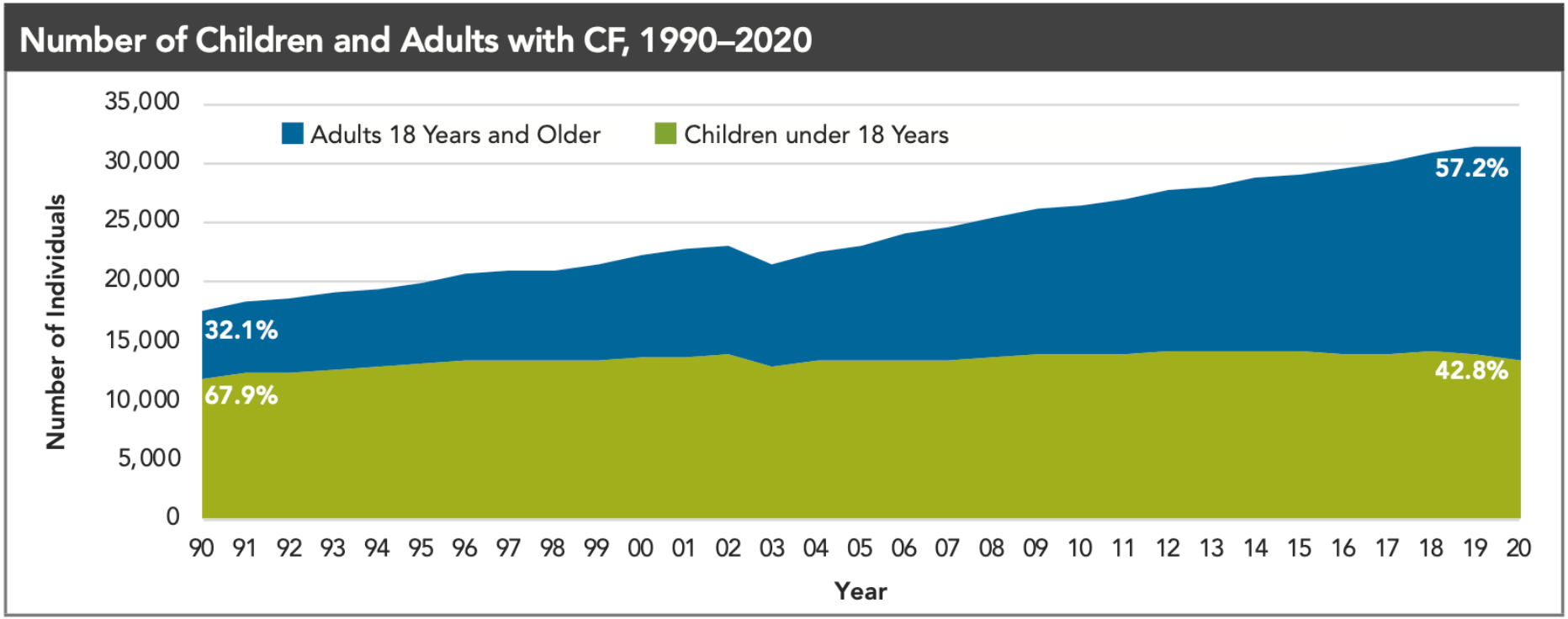
Case Report

## A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus

Sylvia Szentpetery*, Kimberly Foil, Sara Hendrix, Sue Gray, Christina Mingora, Barbara Head, Donna Johnson, Patrick A. Flume

*Medical University of South Carolina, Charleston, SC 29424, USA*

# More Adults than Children with CF



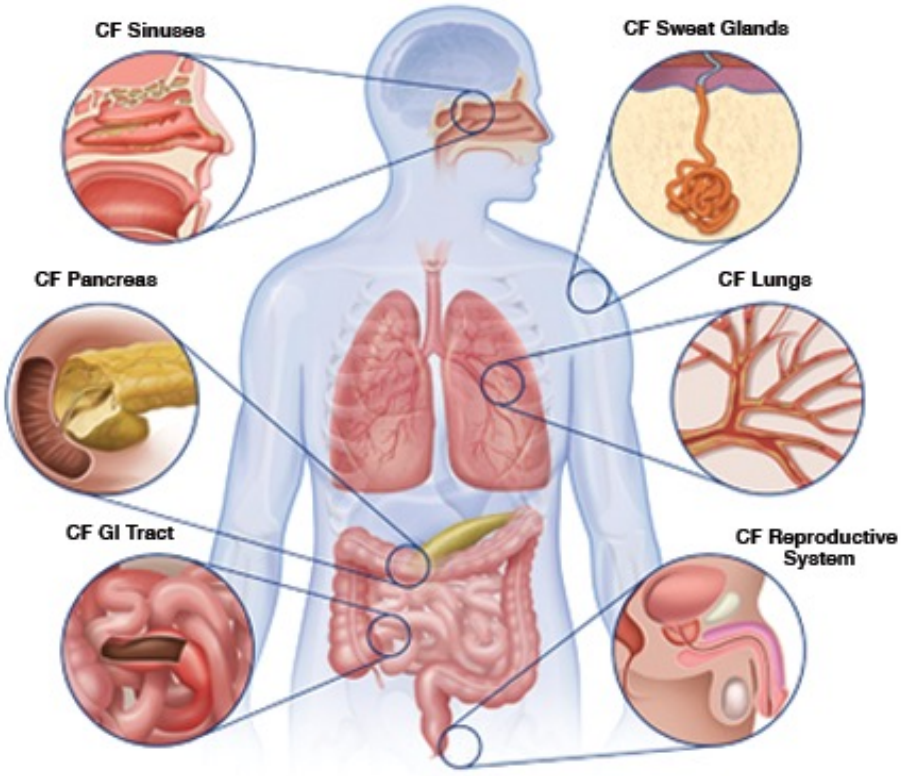

CFF 2020 Annual Registry Report



BRIGHAM AND WOMEN'S HOSPITAL | The Lung Center |

Boston Children's Hospital

# CF - Multi-Organ Involvement




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



Pulmonary Disease is major cause of morbidity and mortality

# 2021 Registry Data - Primary Cause of Death

| Cause | Number of Individuals | Percentage |
|---|---|---|
| Respiratory/cardiorespiratory | 103 | 44.4 |
| Transplant-related | 47 | 20.3 |
| Other | 40 | 17.2 |
| Unknown | 29 | 12.5 |
| Liver Disease/Liver Failure | 6 | 2.6 |
| Suicide or Drug Overdose | 7 | 3.0 |

CFF 2021 Registry Report

- COVID-19 contributing factor for 8 deaths
- Colon Cancer increasing cause of death

# Increased Risk of GI Tract Cancer in CF

Preventable
Screening available

- Colorectal Cancer
  - 5-7 fold increased risk
  - 25-31 fold increased risk after lung transplant
  - 50% with adenomas compared to 11% in general population
- Esophageal Cancer
  - 3.7 fold

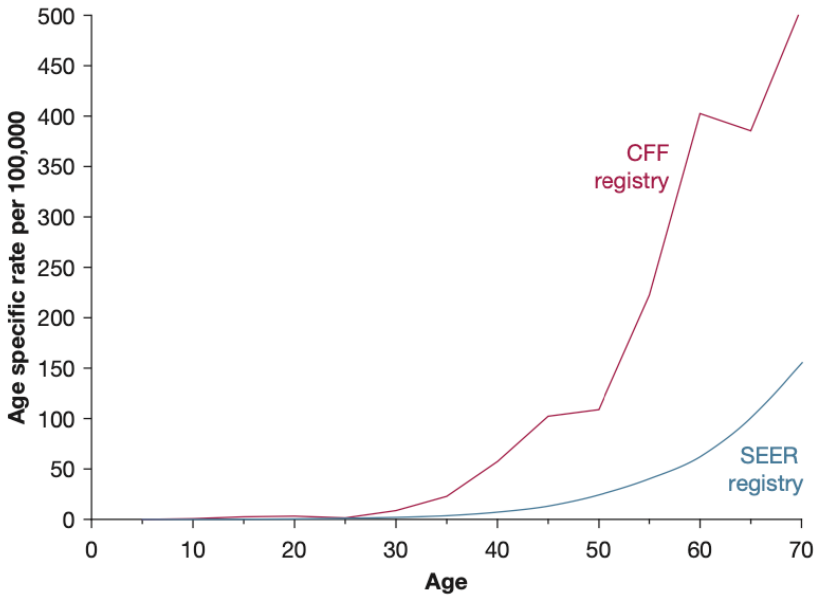
Very Rare
Screening not available

- Pancreatic Cancer
  - Perhaps up to 2.5 fold
- Gallbladder cancer
  - Perhaps up to 4.3 fold

Hadjiliadis D et al. Gastroenterology. 2018;154:736–745
Maisonneuve P et al. J Natl Cancer Inst. 2013;105: 122–129
Niccum DE et al. J Cyst Fibros. 2016;15:548-53

Courtesy of Steve Freedman

# Increased Risk of GI Tract Cancer in CF




- Higher incidence of GERD, inflammatory bowel disease, diabetes
- Impaired mucosal barrier function, bowel microbiome alteration, inflammation (bowel obstruction), abnormal immune response
- Nutrition
  - High fat and low fiber diet
  - Vitamin D deficiency
- CFTR related
  - Associated with Class I-III mutations
  - Risk associated with higher sweat $Cl^-$
  - CF carriers at higher risk for CRC, stomach and other GI related cancers
- CFTR gene acts as a tumor suppressor gene
  - Does GI cancer in CF behave differently than non-CF?

Maisonneuve at al. Chest. 2022
Than et al. Oncogene. 2016
Liu et al. Cancer Manag Res. 2020

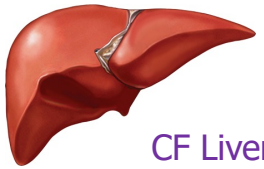
# Screening

- Colonoscopy and Endoscopy are screening methods of choice
- Screening begins at age 40 for CF patients prior to transplant with rescreening at 5 years, or 3 years if adenomatous polyps are discovered
- Screening begins at age 30 or within 2 years of transplant with rescreening at 5 years, or shortened to 2 years if adenomatous polyps are discovered

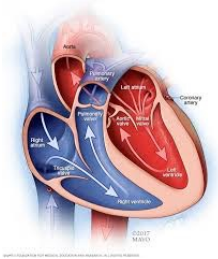
- No screening recommendations for gastric cancer
- No screening recommendations for biliary and pancreatic cancer

Maisonneuve at al. Chest. 2022
Than et al. Oncogene. 2016
Liu et al. Cancer Manag Res. 2020

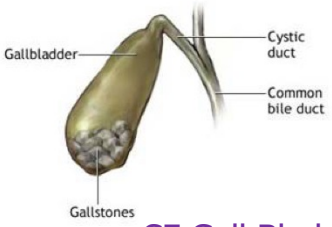
# CF - Multi-Organ Involvement (Cont'd)



CF Liver Disease

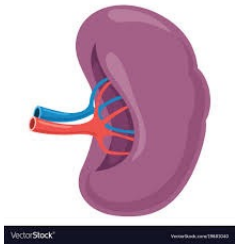


Pulmonary HTN and Cor pulmonale




CF Gall Bladder

Splenomegaly and splenic infarcts

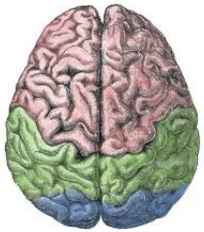


Nephrotoxic Meds (immune complex deposition)

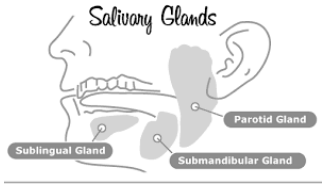
Ototoxic Meds (CFTR in cochlea)

Indirect

CF Bone Health



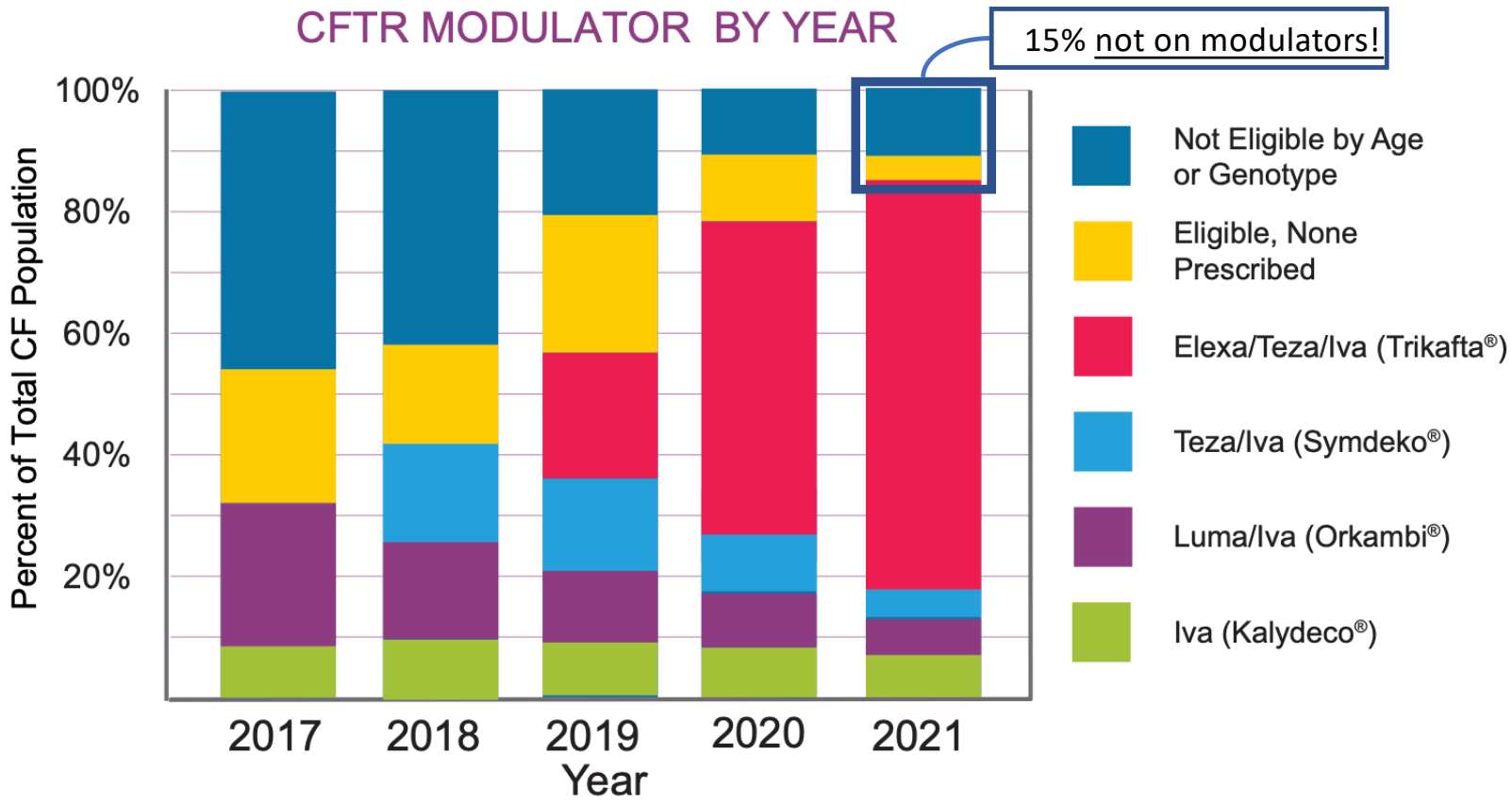
Arnold-Chiari Malformation



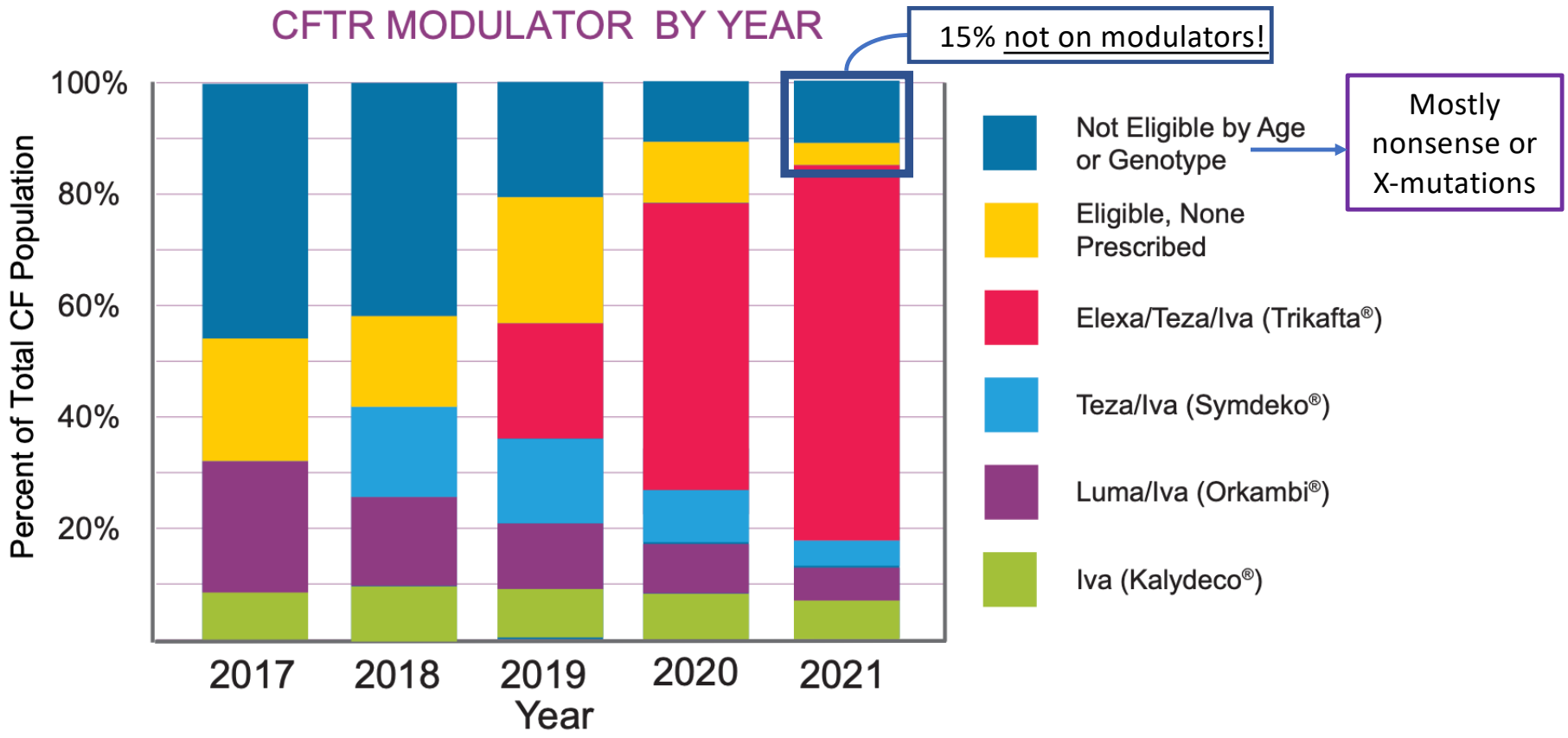

Salivary duct plugging and stones


CF Mental Health

# Not all CF patients eligible for modulators



# Not all CF patients eligible for modulators



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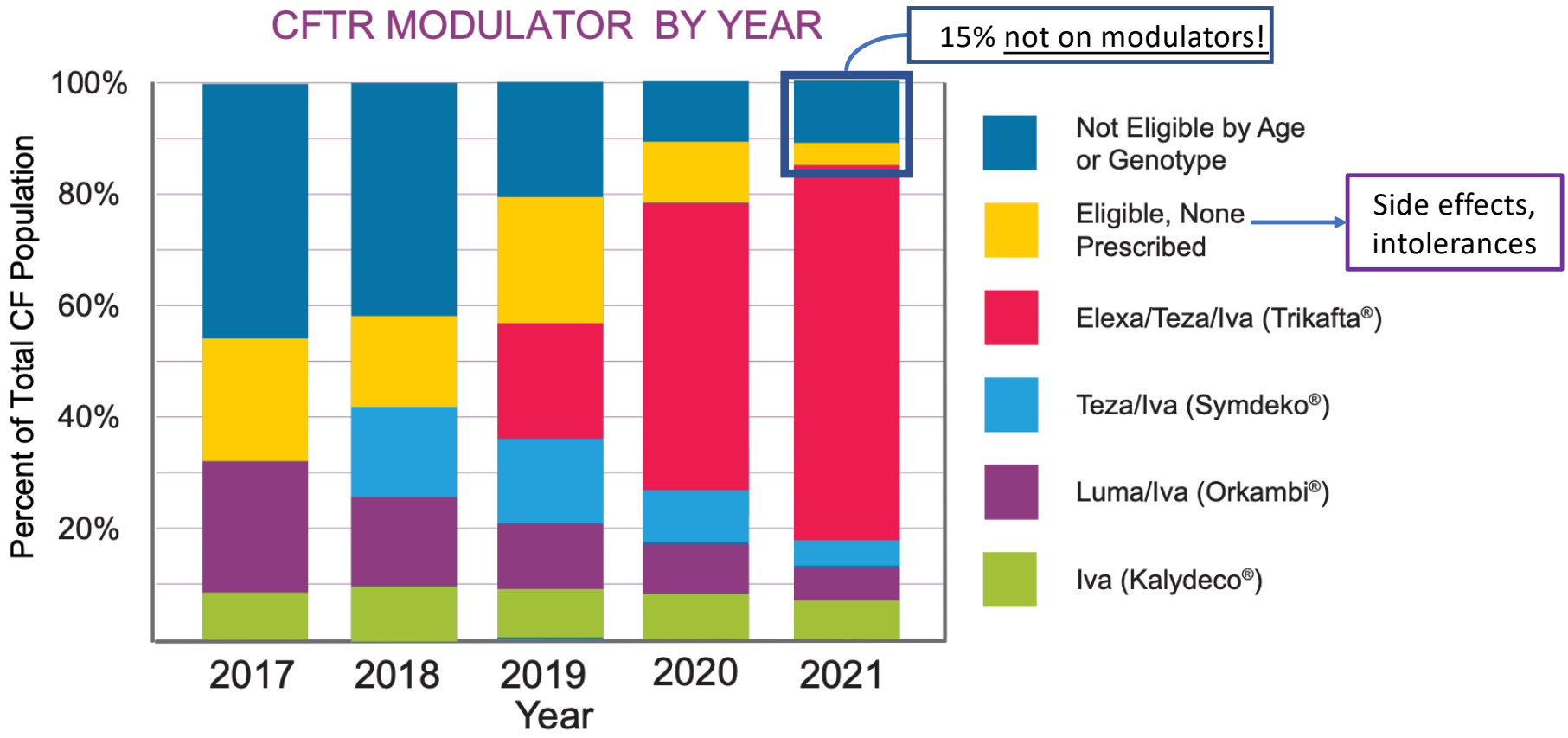
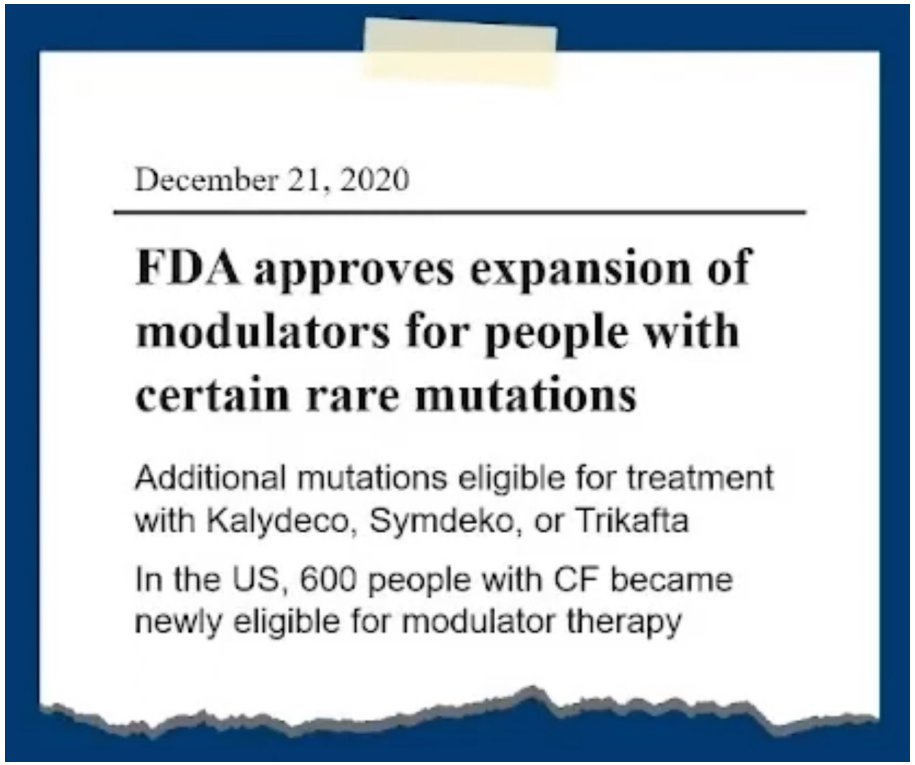


# Expanding indication through Theratyping



December 21, 2020

**FDA approves expansion of modulators for people with certain rare mutations**

Additional mutations eligible for treatment with Kalydeco, Symdeko, or Trikafta

In the US, 600 people with CF became newly eligible for modulator therapy

- testing CFTR modulators on cell lines expressing rare CFTR mutations to see if the proteins they produce show improved function
  - Ion transport using nasal epithelial cells
  - Forskolin-induced swelling of intestinal organoids

Courtesy of CFF

# Expanding indication through Theratyping and clinical trials



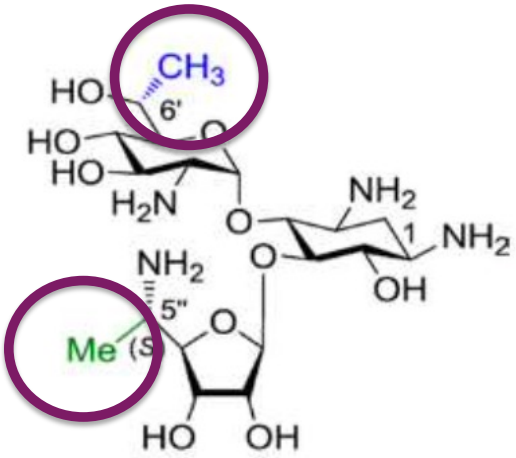
Courtesy of CFF

# We are still not done!

- 10-15% without an effective treatment
  - CFTR not eligible
  - Unable to tolerate current modulators
  - Sweat chloride not fully normalized
- Established disease:
  - Advanced Lung Disease remains (some improvement noted)
  - Pulmonary exacerbations:
    - On CFTR modulators significantly reduced, not prevented
    - 10-15% still experiencing rapid progression
- Cost and regional differences in availability
  - LMIC do not have access
  - Part of Global Health Advisory Board Initiative

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

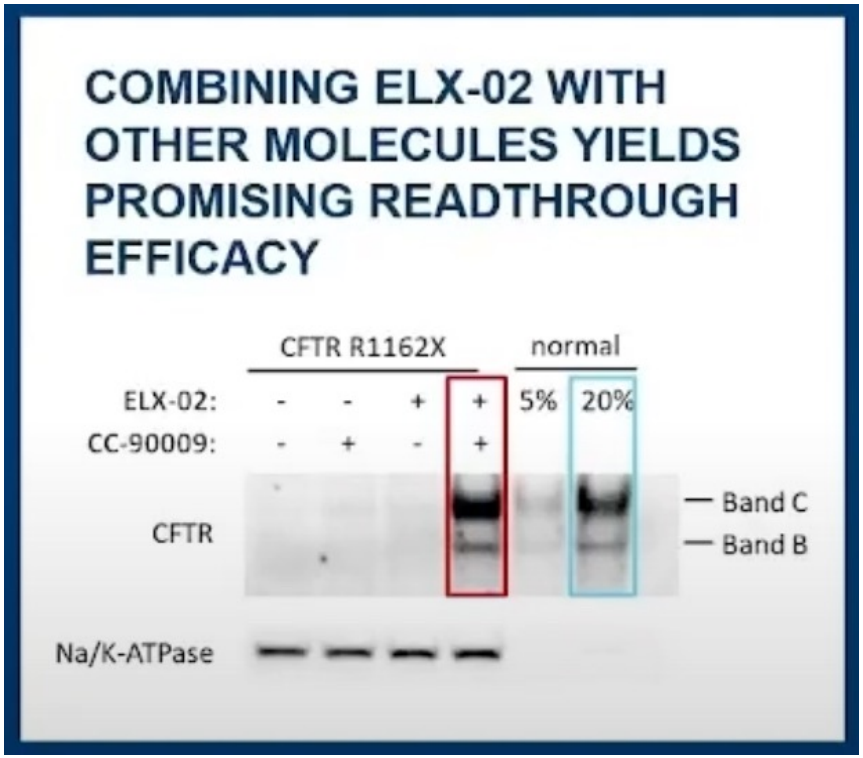
- Aminoglycosides bind to the decoding site in the small subunit of the ribosomal RNA (rRNA) and is capable of inducing translation read-through
- Reducing the accuracy of rRNA codon-anticodon recognition increases the probability of translational read-through of stop codons
- However, aminoglycosides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



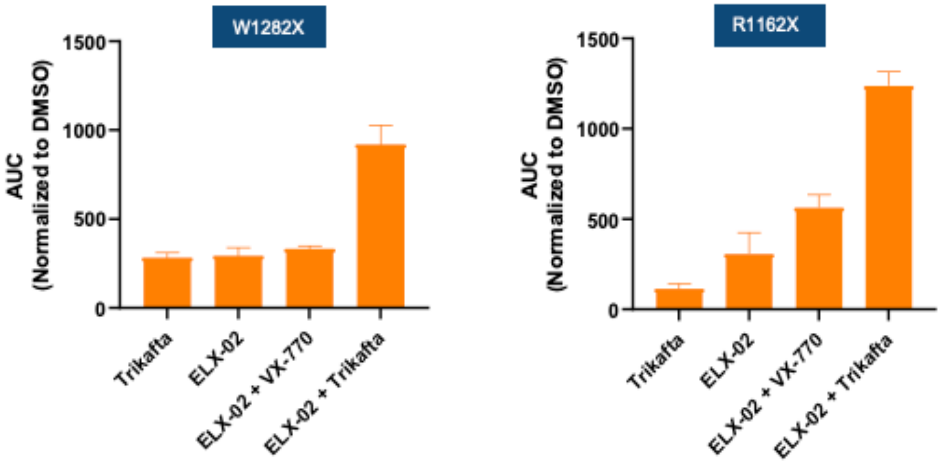

J Med Chem. 2012 Dec 13;55(23):10630-43.

Adapted from data provided by Eloxx

# Promise of Readthrough Efficacy

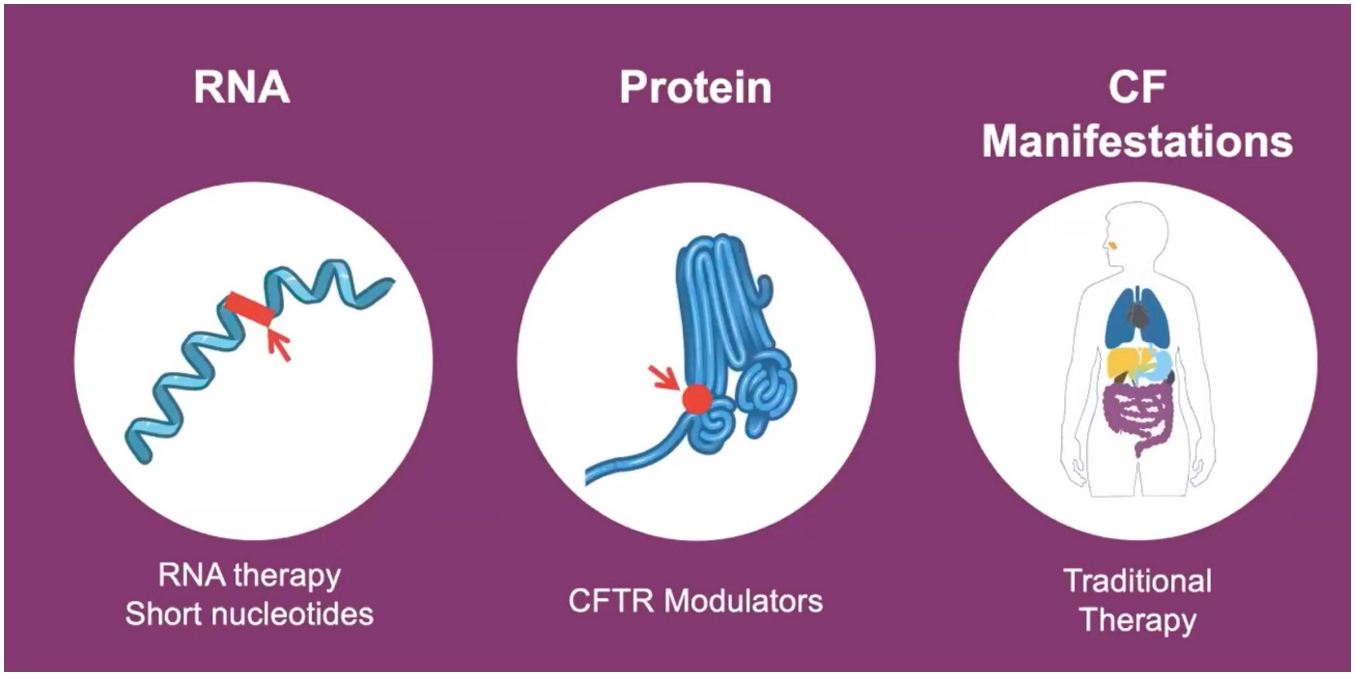



## ELX-02 and Trikafta on Swelling in W1282X Homozygous or R1162X Homozygous Patient Organoids



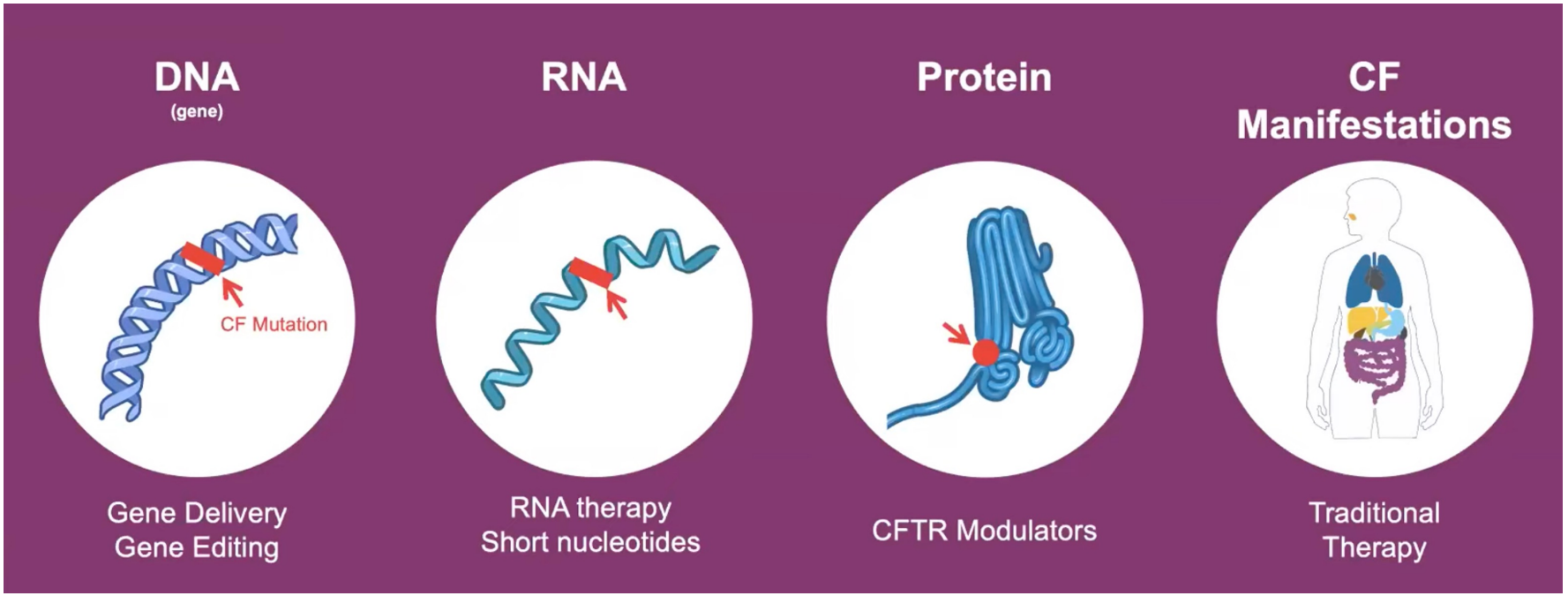

- Data generated by CFFT Lab, Lexington, MA

# Therapeutic Approach to CF




Courtesy of CFF

# Therapeutic Approach to CF




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

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  - 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

# Thank you!


Boston Children's Hospital


Brigham and Women's Hospital

## Adult Cystic Fibrosis Center