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

Cystic Fibrosis in Adults

In Era of CFTR Modulators

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Ahmet Uluer, DO MPH

- University of Michigan
- Kansas City University School of Medicine and Biosciences
- Medicine-Pediatric Residency at Cleveland Clinic
- Pulmonary Medicine Fellowship
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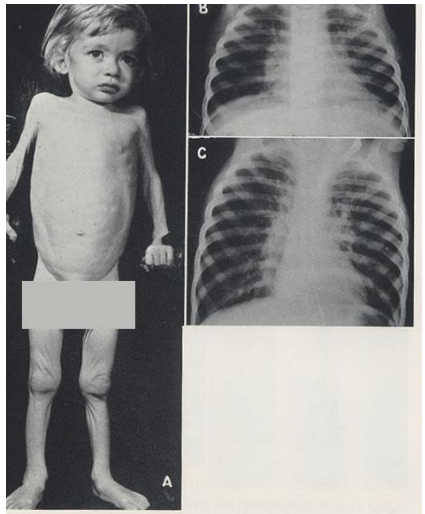
- Assistant Professor, Harvard Medical School
- Director, Adult CF Program at Brigham and Women's Hospital and Boston Children's Hospital
- Director, Bridges Adult Transition Program at Boston Children's Hospital

Disclosures

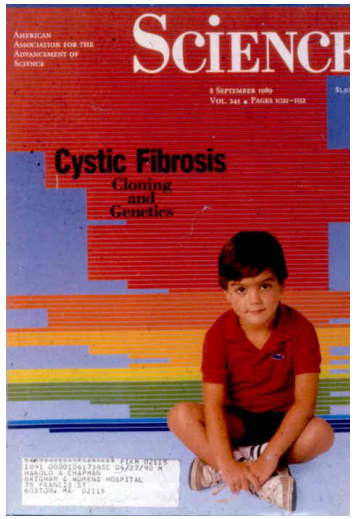
- Cystic Fibrosis Foundation Adult CF Center Grant
- Chair, Cystic Fibrosis Foundation Therapeutic Development Network Protocol Review Committee (FTE support)
- Adult CF Program Principal Investigator, Therapeutic Development Network Grant

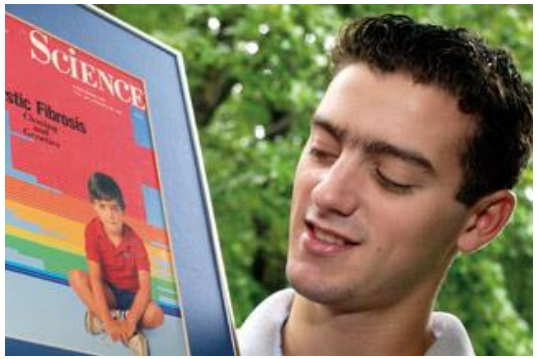
A Story of Progress



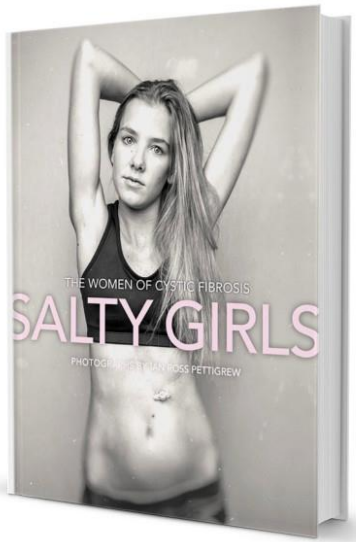
igure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, ve months. B. Lungs at one year, two months. C. Lungs at two years, ve months. When infection becomes established in the viscid secretion the bronchioles at an early age, and persists, the lungs show progres- ve development of peribronchial infiltration and emphysema. The attritional 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

Congratulations to our 10 runners with CF completing the 125th Boston Marathon

The '26.2 Miles Apart' CF Marathon Project

Documentary Premiere September 27th, 2024

CFF Community Blog

I have always been an avid runner, starting when I was 6 years old, eventually running competitively in high school and in college. I had a knack for it and a deep love of the sport. My love for running, however, changed after I graduated from college in 2017. I was mentally and physically exhausted from years of training, and I was repeatedly let down due to debilitating lung infections.

Two years later, I was facing a lot of setbacks because of my cystic fibrosis; my CF was truly becoming a force in my life, and I had little or no control over it. In September 2019, I found myself inside the four walls of a hospital room hooked up to IV antibiotics. This is not somewhere any of us would want to be, but I knew it was time, and I was hopeful the antibiotic cocktail would flush out the infection in my lungs.

Plus: Adult CF Team Members who ran alongside in solidarity: Olivia Killilea, Jillian Ng, Lauren Cardoni, Ahmet Uluer

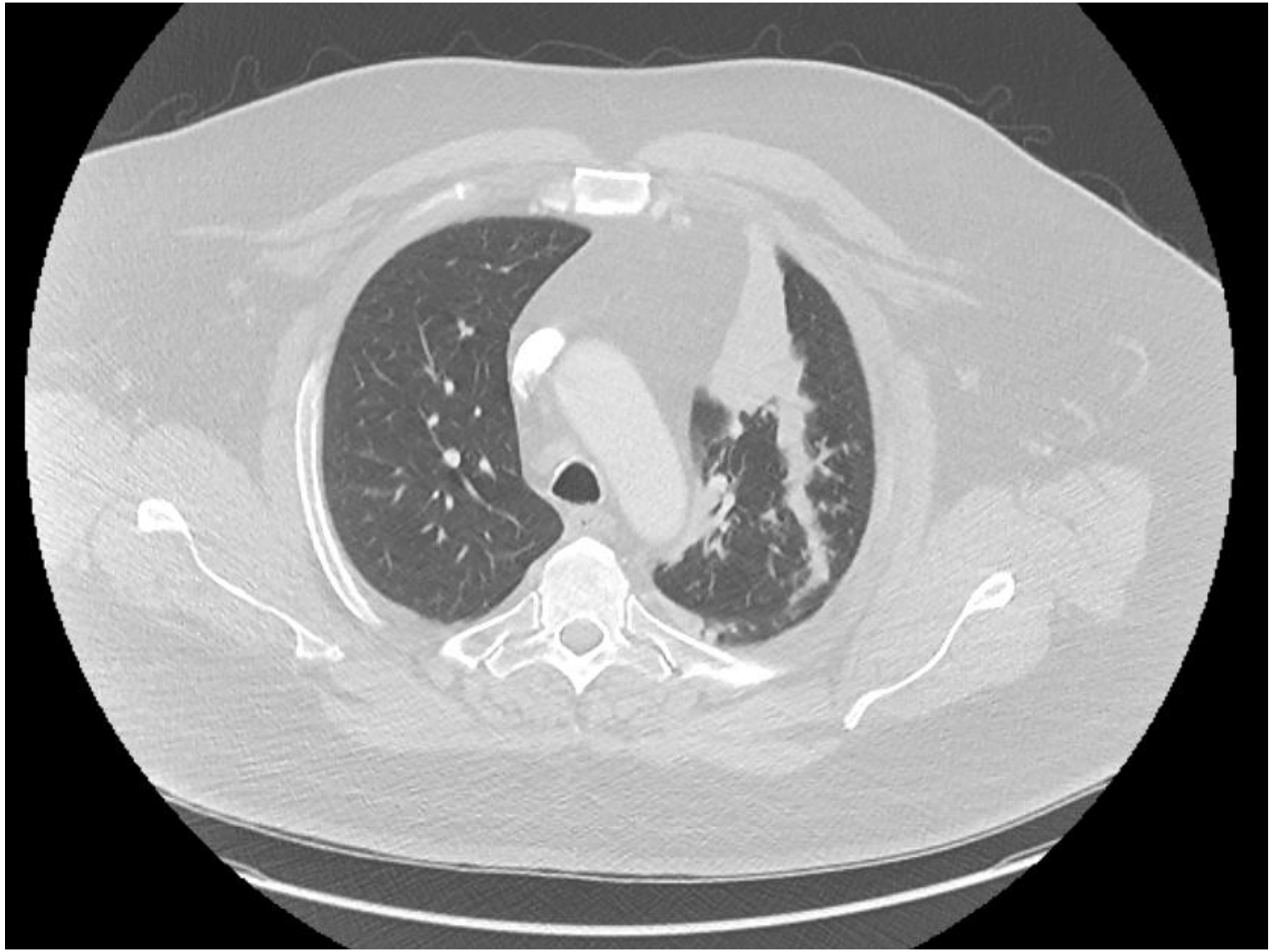
Patient Case

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 **Chest CT in 2016 with diffuse nodular opacities and bronchiectasis** **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 No Children Family History of Colon cancer

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

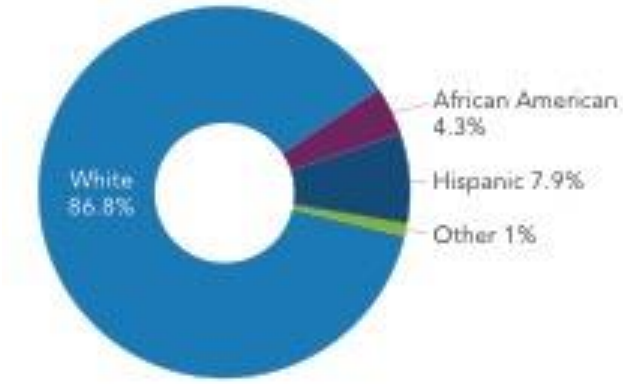
Patient Case

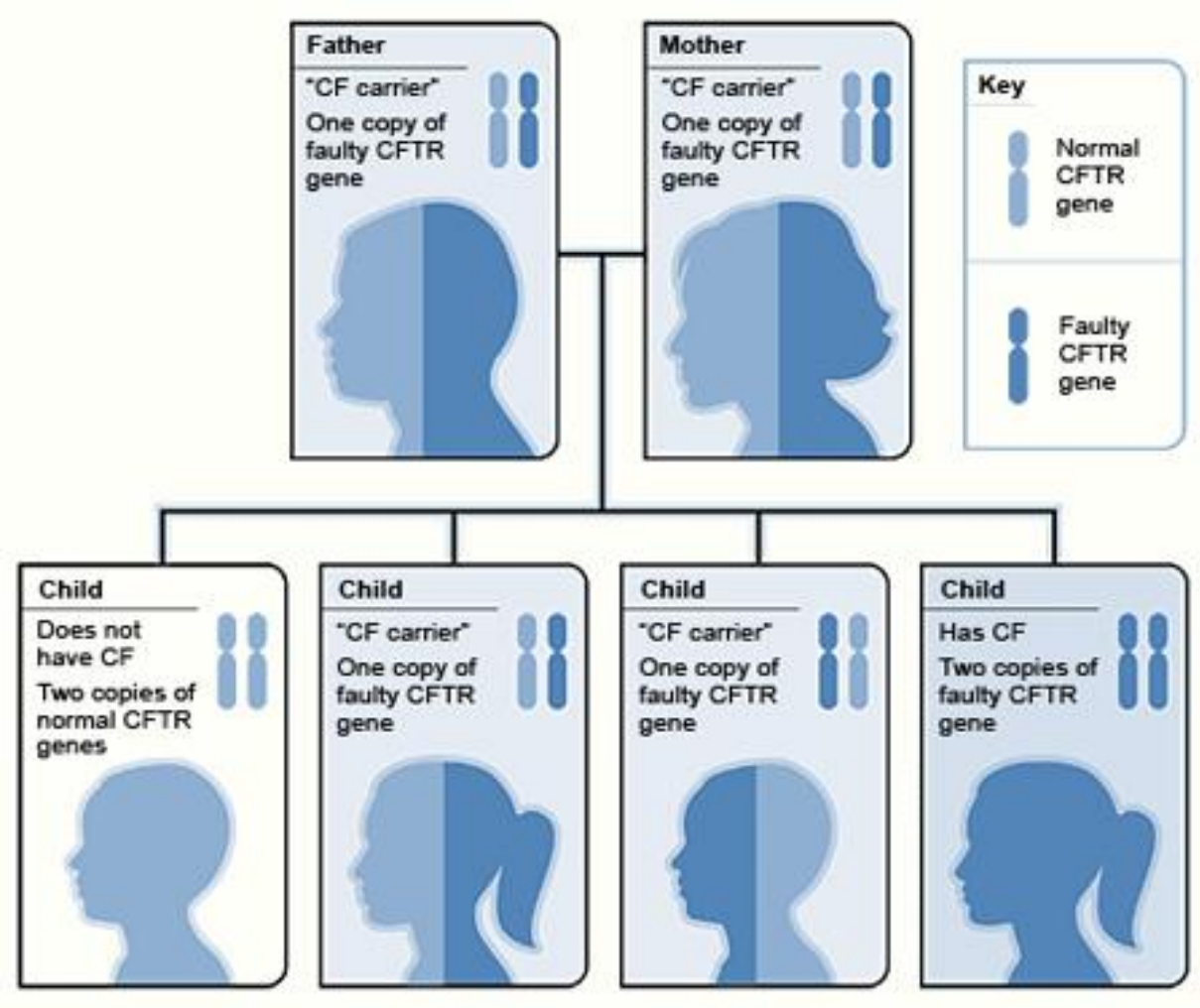


Quick CF Refresher!

CF: Inheritance Pattern

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

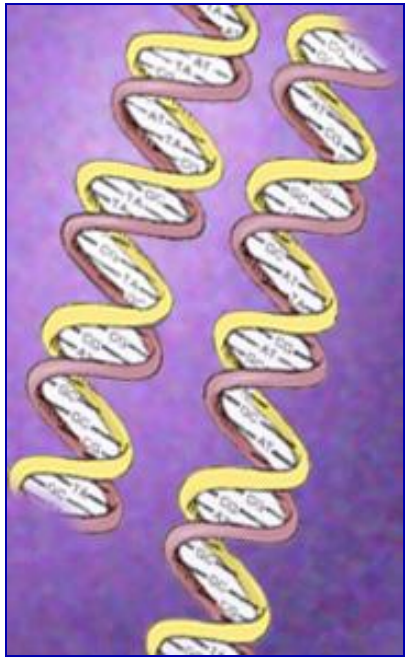




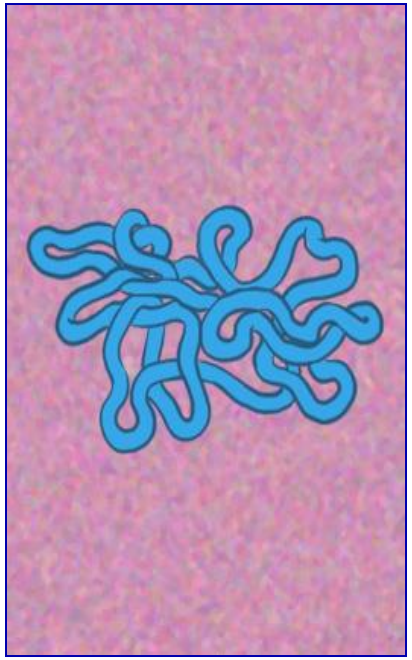
http://www.medicinenet.com/cystic_fibrosis/page3.htm

CF Pathophysiology

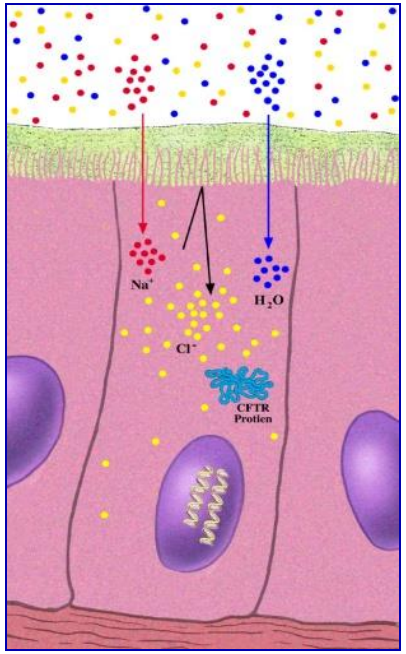
Abnormal Gene



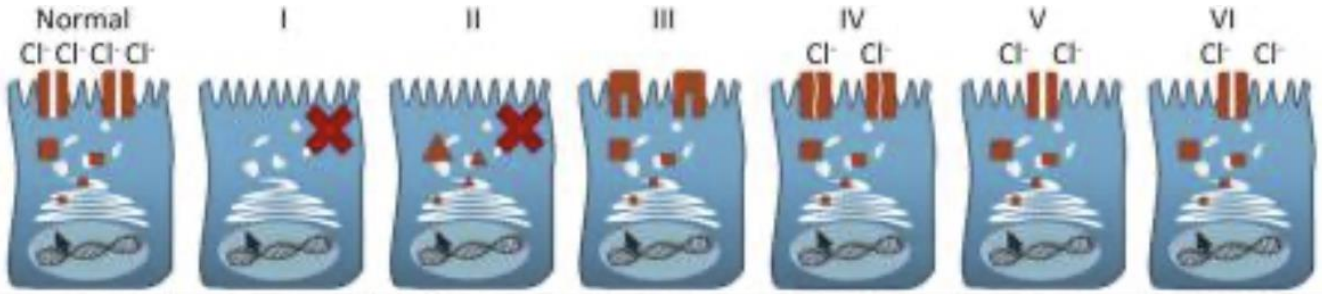
Abnormal Protein



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



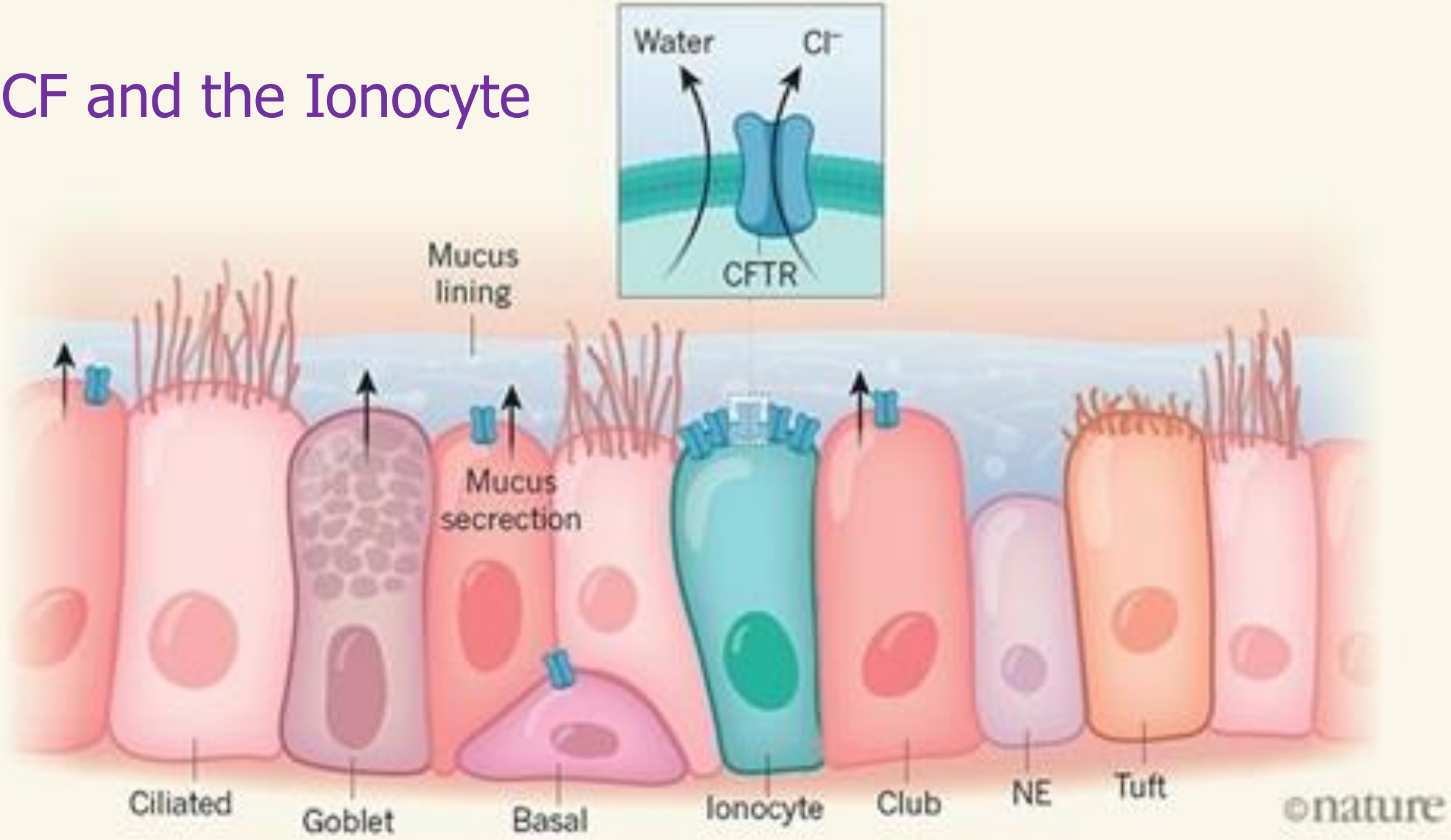
6 Classes of CFTR Mutations



	Normal	I	II	III	IV	V	VI
Molecular defect		No CFTR synthesis (mRNA or protein)	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced CFTR synthesis	Decreased CFTR stability
Prevalence		10%	88%	4%	< 2%	Rare	
Type of mutations		Nonsense Frameshift Canonical splice	Missense Aminoacid deletion	Missense Aminoacid change		Splicing defect Missense	Missense Aminoacid change
Mutation examples		G542X W1282X R553X R1162X	F508del I507del N1303K M1101K	*G551D* G551S S1255P G178R	R117H R347P R334W R1070W	A455E 3272-26A>G 3849+10kb C>T	4326delTC Gln1412X 4279insA
Therapeutic approach		*Read through** compounds, ELX-02; **kalydeco®** (Ivacaftor)	*Correctors** (+potentiators***)* **Orkambi®** (Lumacaftor +Ivacaftor); **Trikafta®**; GLP222 **; AB8V-3067*	*Potentiators (+correctors)* **kalydeco®**; **Trikafta®** (Elexacaftor + tezacaftor + Ivacaftor); **Symdeko®** (tezacaftor-Ivacaftor)		*Splicing modulators* Antisense oligonucleo-tides; **kalydeco®**; **Trikafta®**	*Stabilizers*

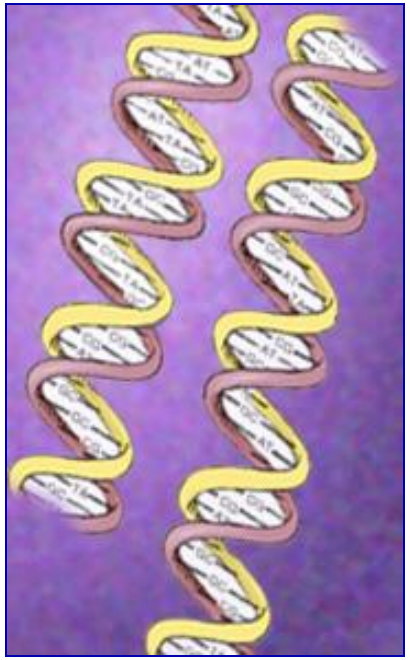
Gene Therapy 2022. June 29;399-406

CF and the Ionocyte

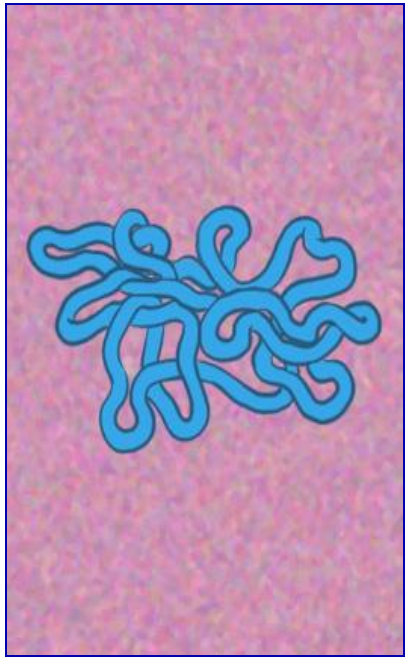


CF Pathophysiology

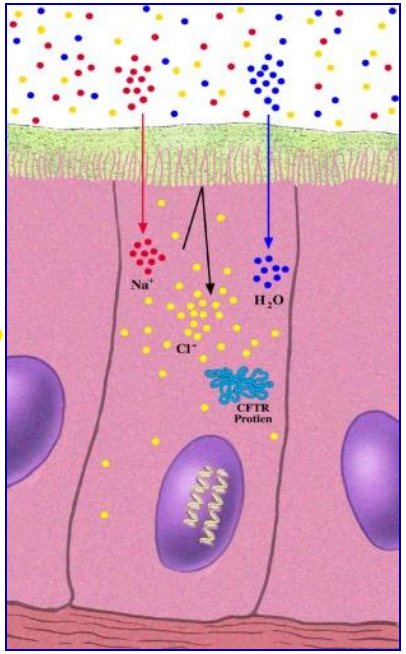
Abnormal Gene



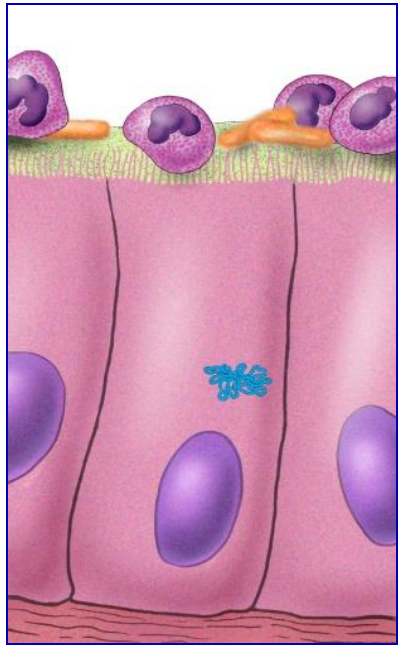
Abnormal Protein



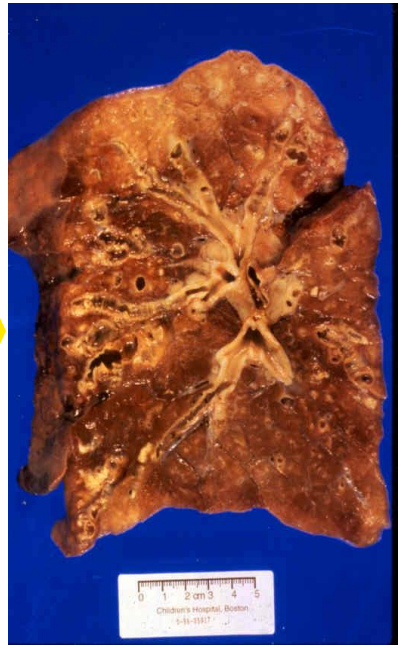
A Altered Ion Transport (Cl^- and $HC0^-_3$) & Abnormal Mucus



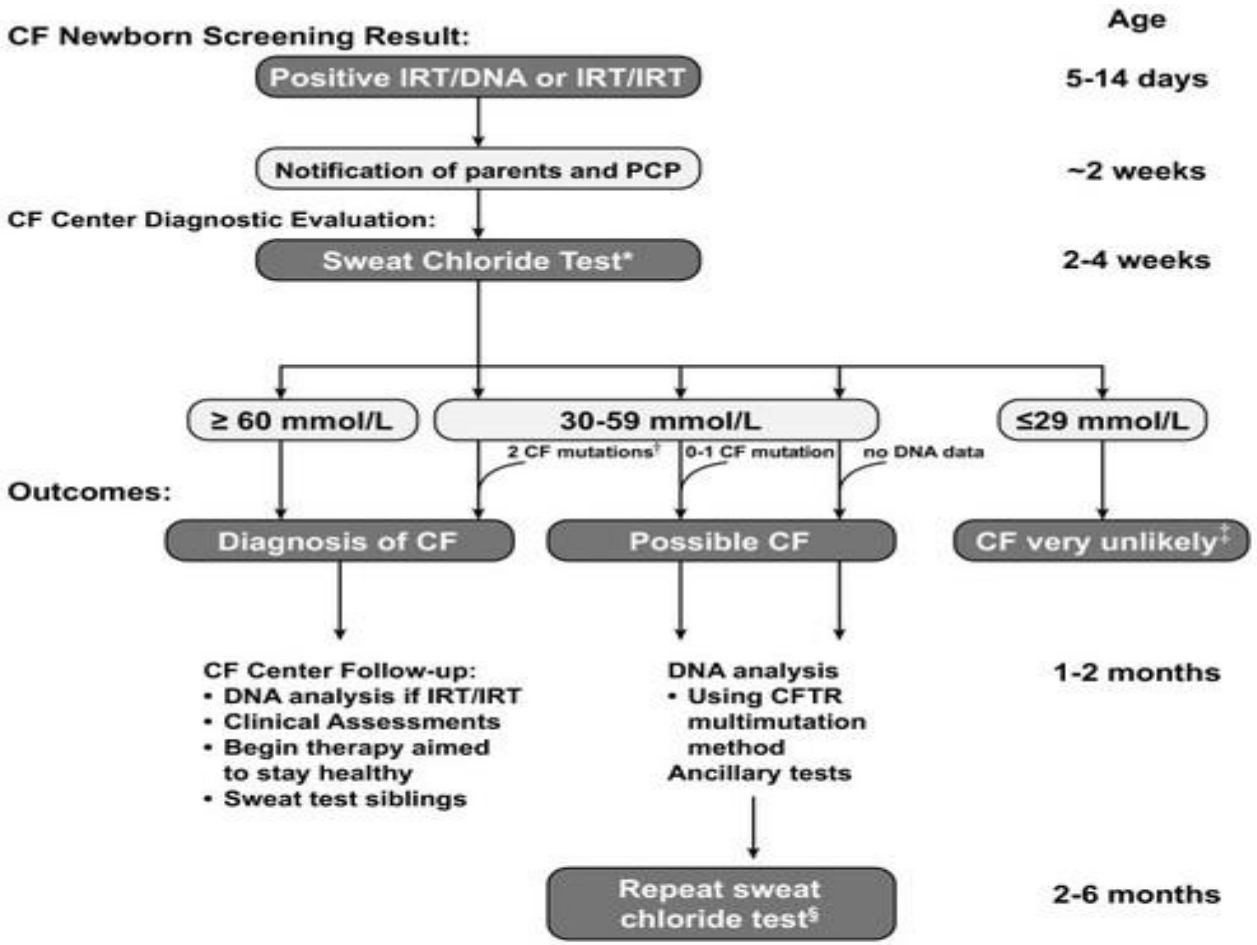
Infection & Inflammation



Organ Destruction & Respiratory Failure



Diagnosis of Cystic Fibrosis



(J Pediatr 2008;153:S4-S14)

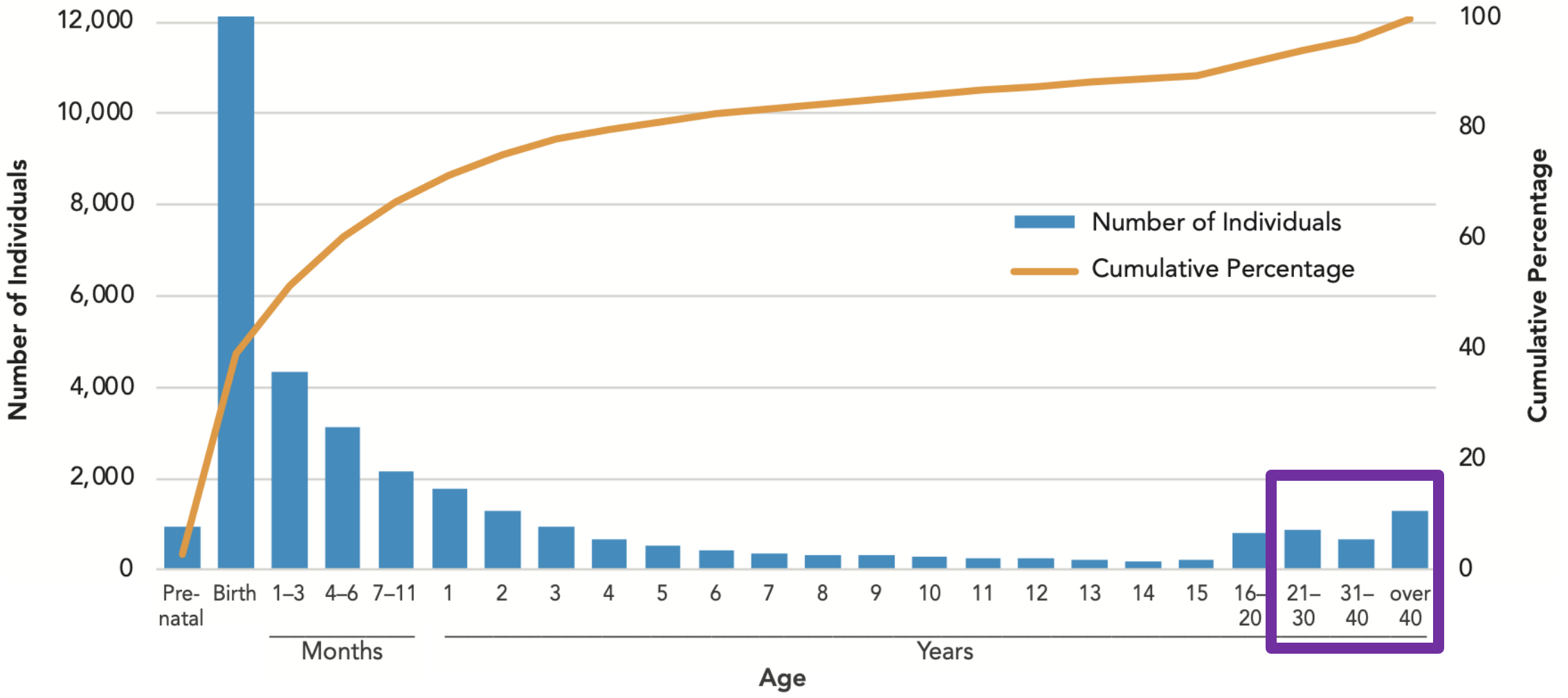
* If the baby is at least 2kg and more than 36 weeks gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 µl, respectively.

† 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.

Age of Diagnosis of all Individuals seen with CF in 2023



CFF 2023 Annual Registry Report

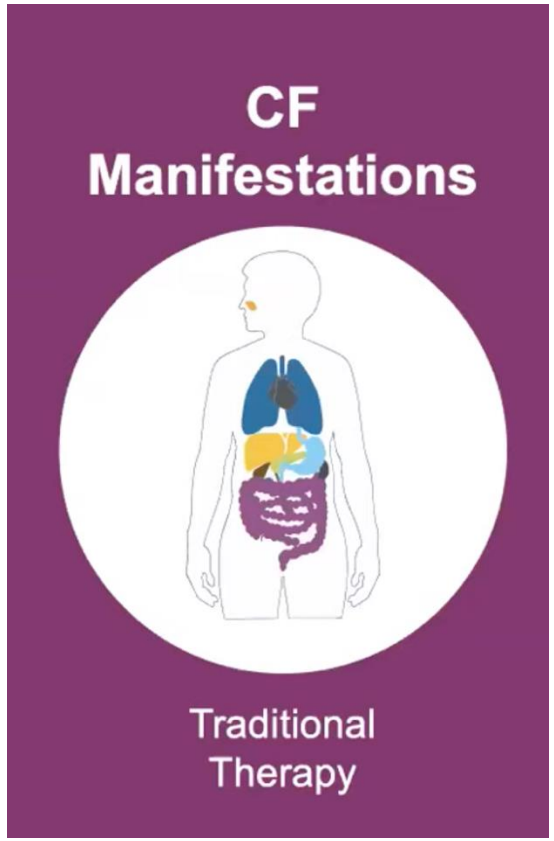
Patient Case

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 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 **(prior to elexacaftor/tezacaftor/ivacaftor approval)**
Other
Never smoked No Children Family History of Colon cancer

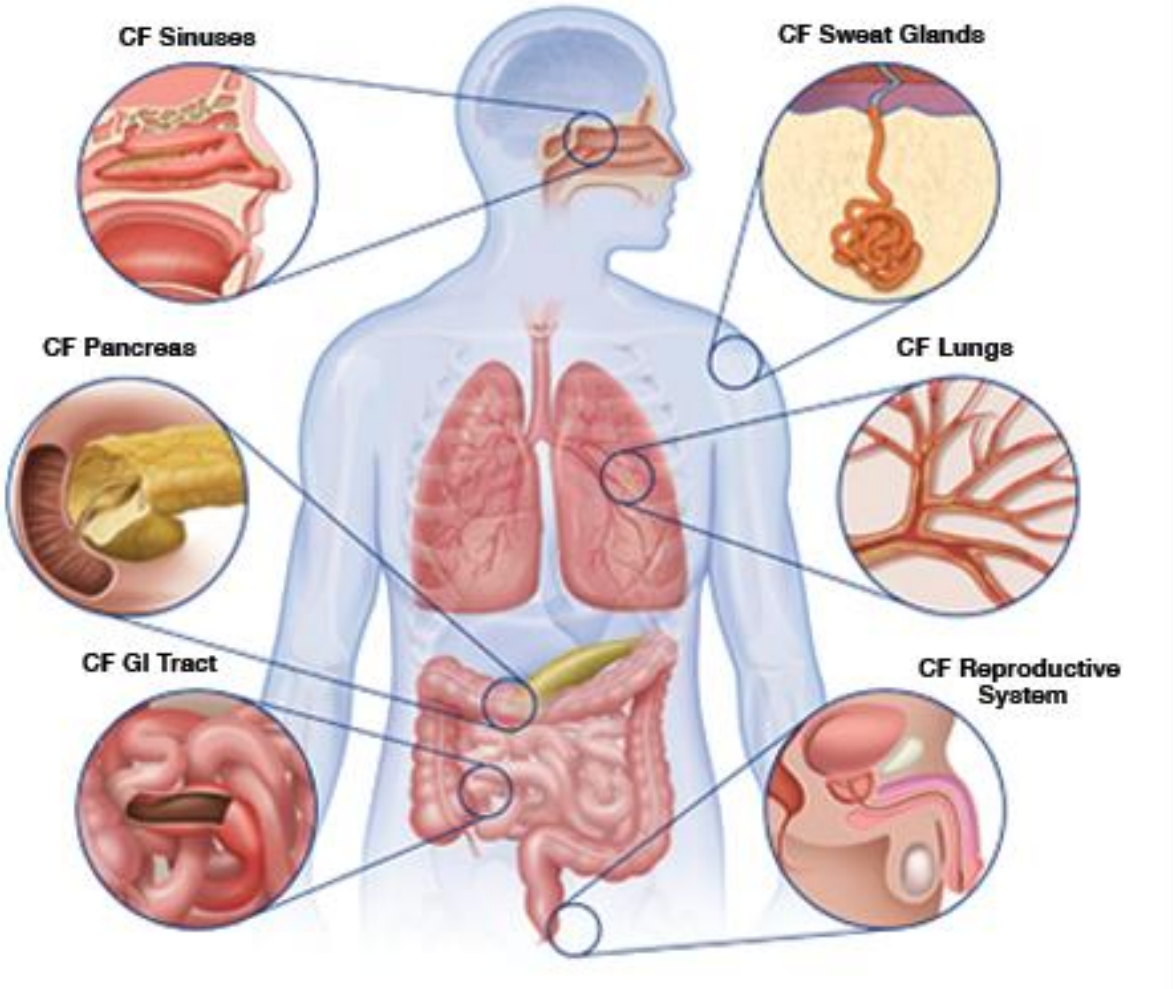
CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

Pre-Modulator Era
Therapeutic Approach to CF (~90%)

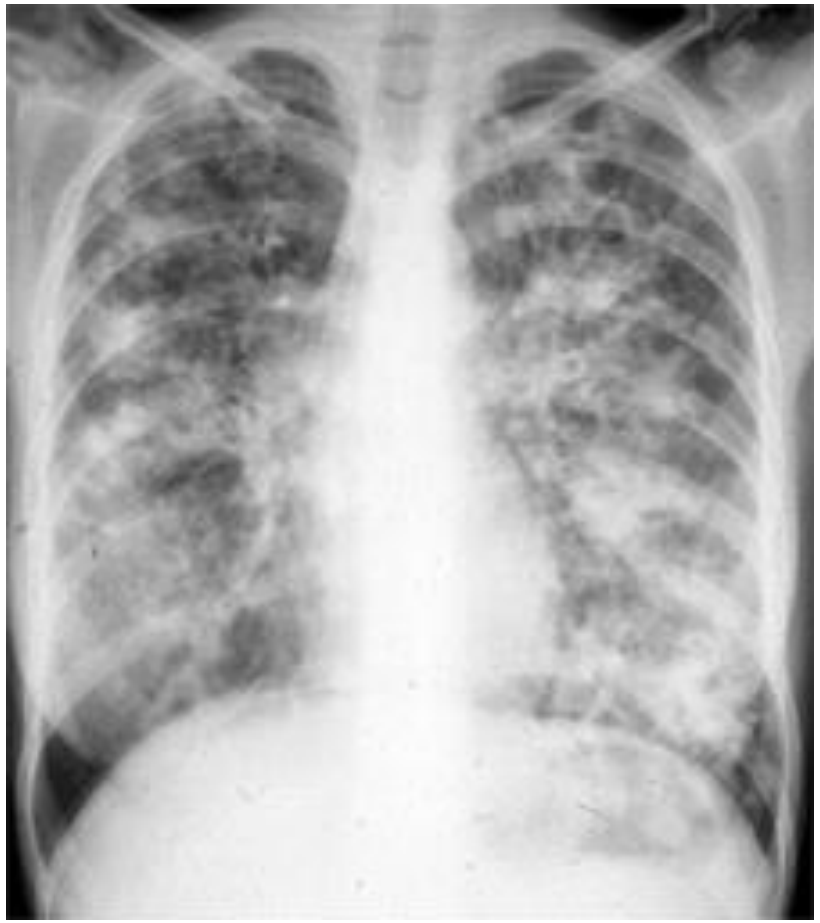


Courtesy of CFF

CF - Multi-Organ Involvement

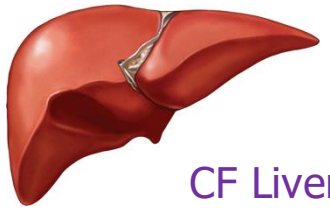


https://www.cftrscience.com/?q=CF-morbidity

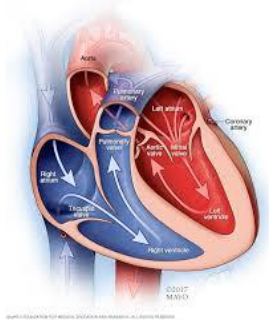


Pulmonary Disease is major cause of morbidity and mortality

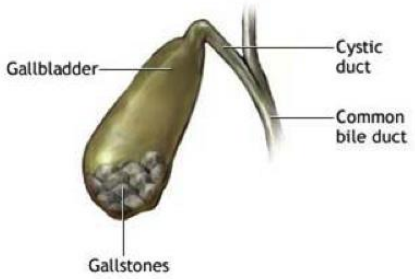
CF - Multi-Organ Involvement (Cont'd)



CF Liver Disease

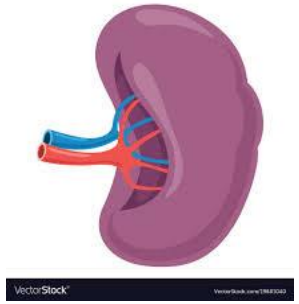


Pulmonary HTN, Cor pulmonale, CVD?

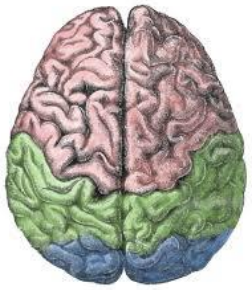


CF Gall Bladder

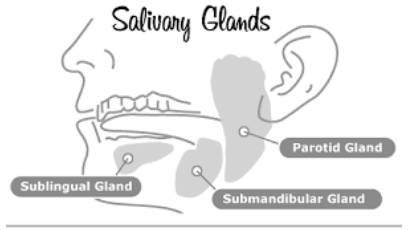
Splenomegaly and splenic infarcts



CF Bone Health



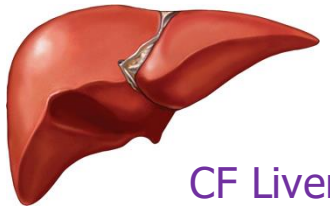
Arnold-Chiari Malformation



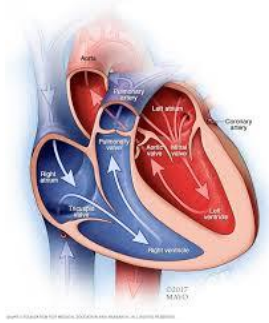
Salivary duct plugging and stones

CF Mental Health

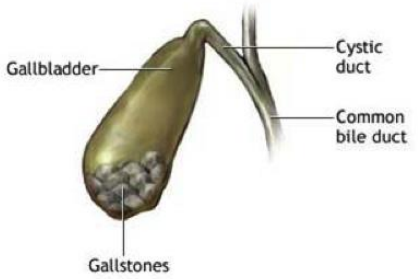
CF - Multi-Organ Involvement (Cont'd)



CF Liver Disease

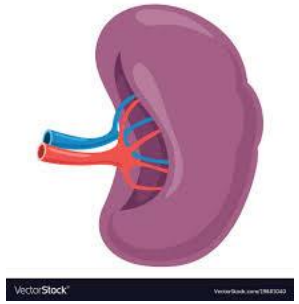


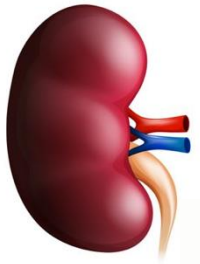
Pulmonary HTN and Cor pulmonale



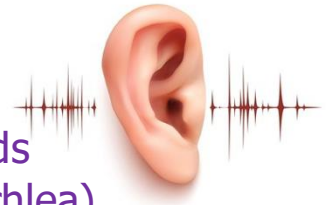
CF Gall Bladder

Splenomegaly and splenic infarcts





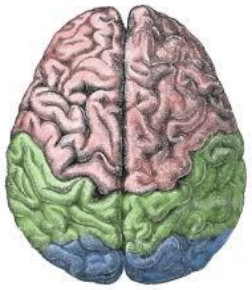
Nephrotoxic Meds (immune complex deposition)



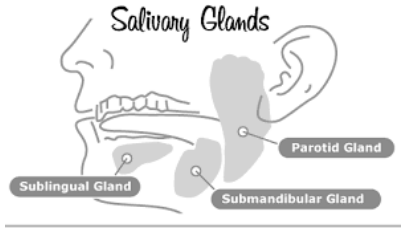
Ototoxic Meds (CFTR in cochlea)

Indirect

CF Bone Health



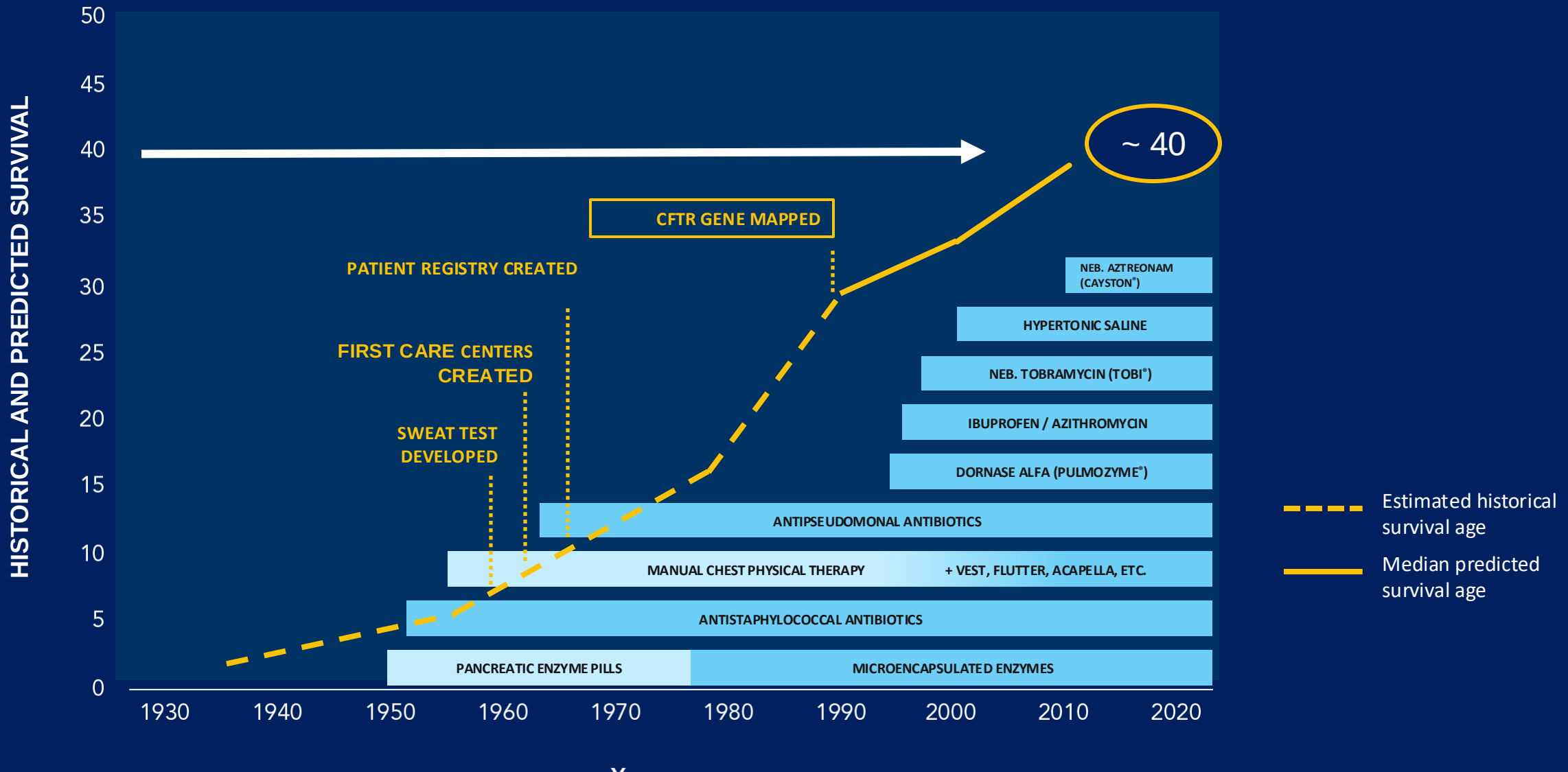
Arnold-Chiari Malformation



Salivary duct plugging and stones

CF Mental Health

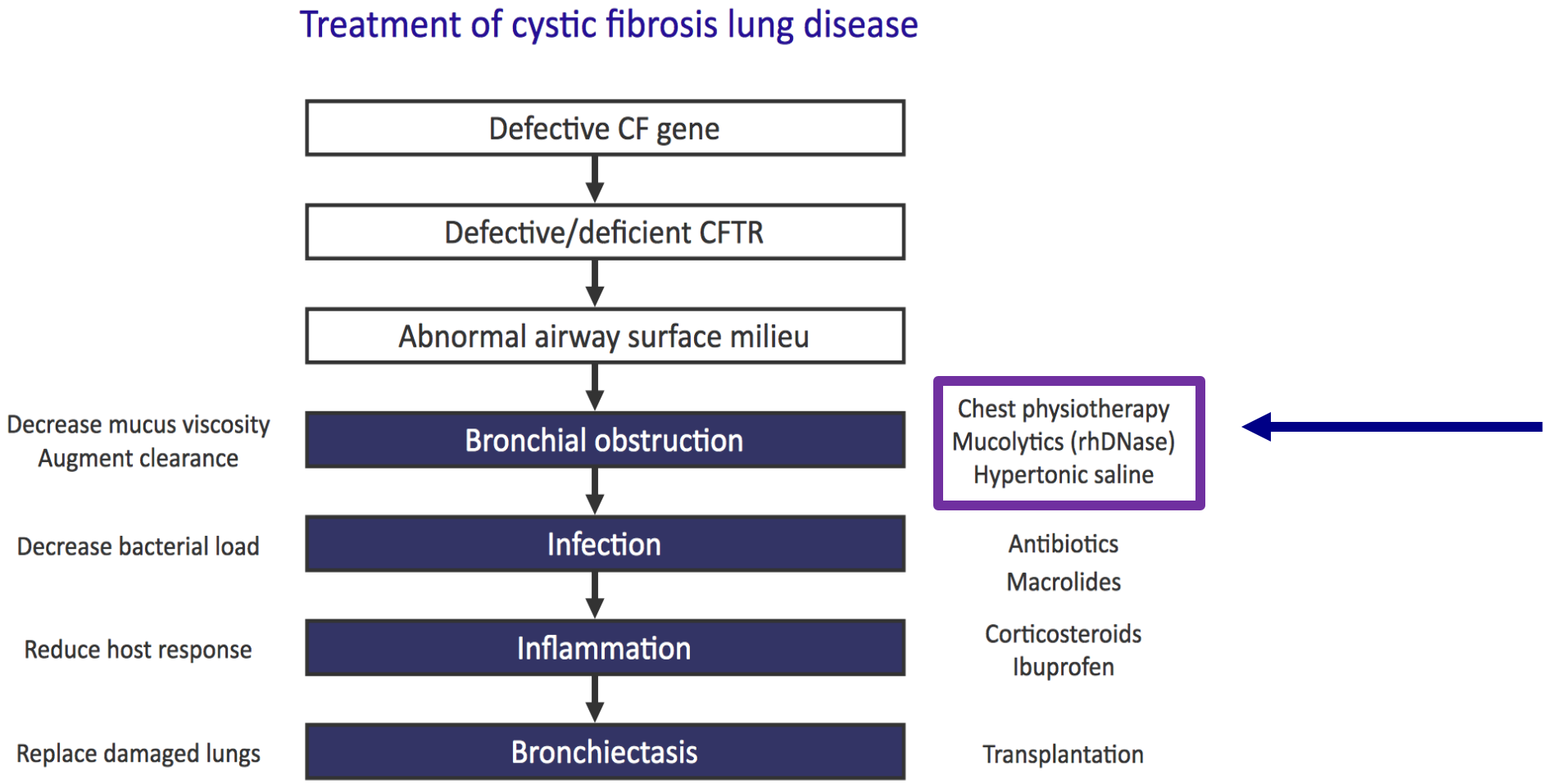
Timeline of advances in CF



Slide courtesy of JP Clancy; 2022 CFFPR

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

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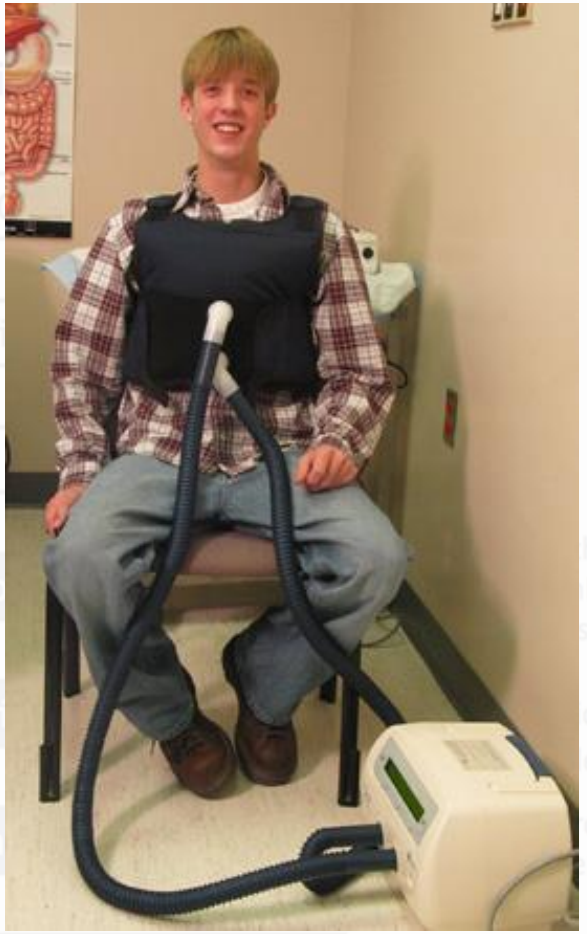
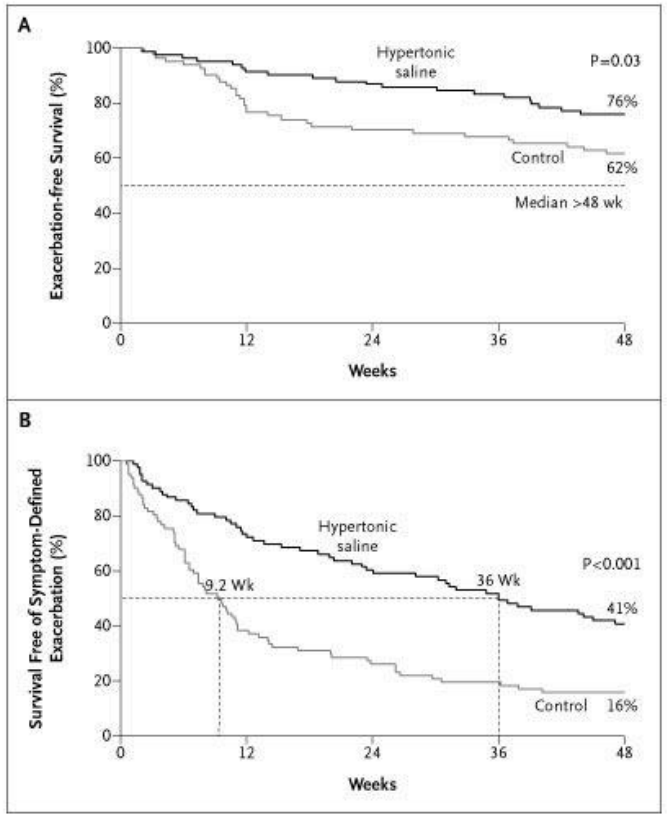


- High Frequency Chest Wall Compression (Vest)
- Manual Percussion and Drainage
- Positive Expiratory Pressure Device (PEP)
- Active Cycle Breathing and Autogenic drainage
- Exercise
- Others

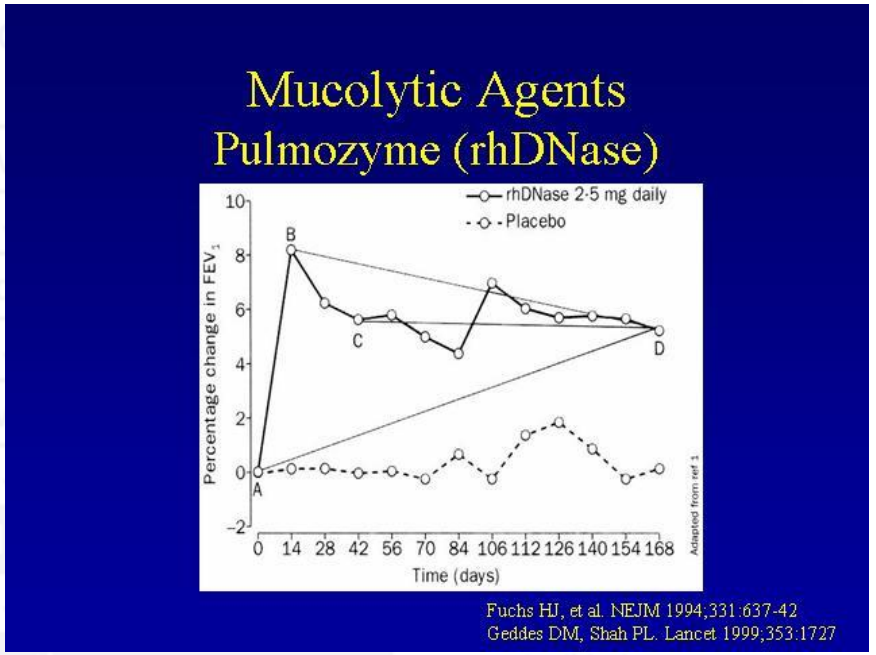
Therapeutic Approaches for CF Lung Disease

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



- Hypertonic Saline (7%)
- Twice daily

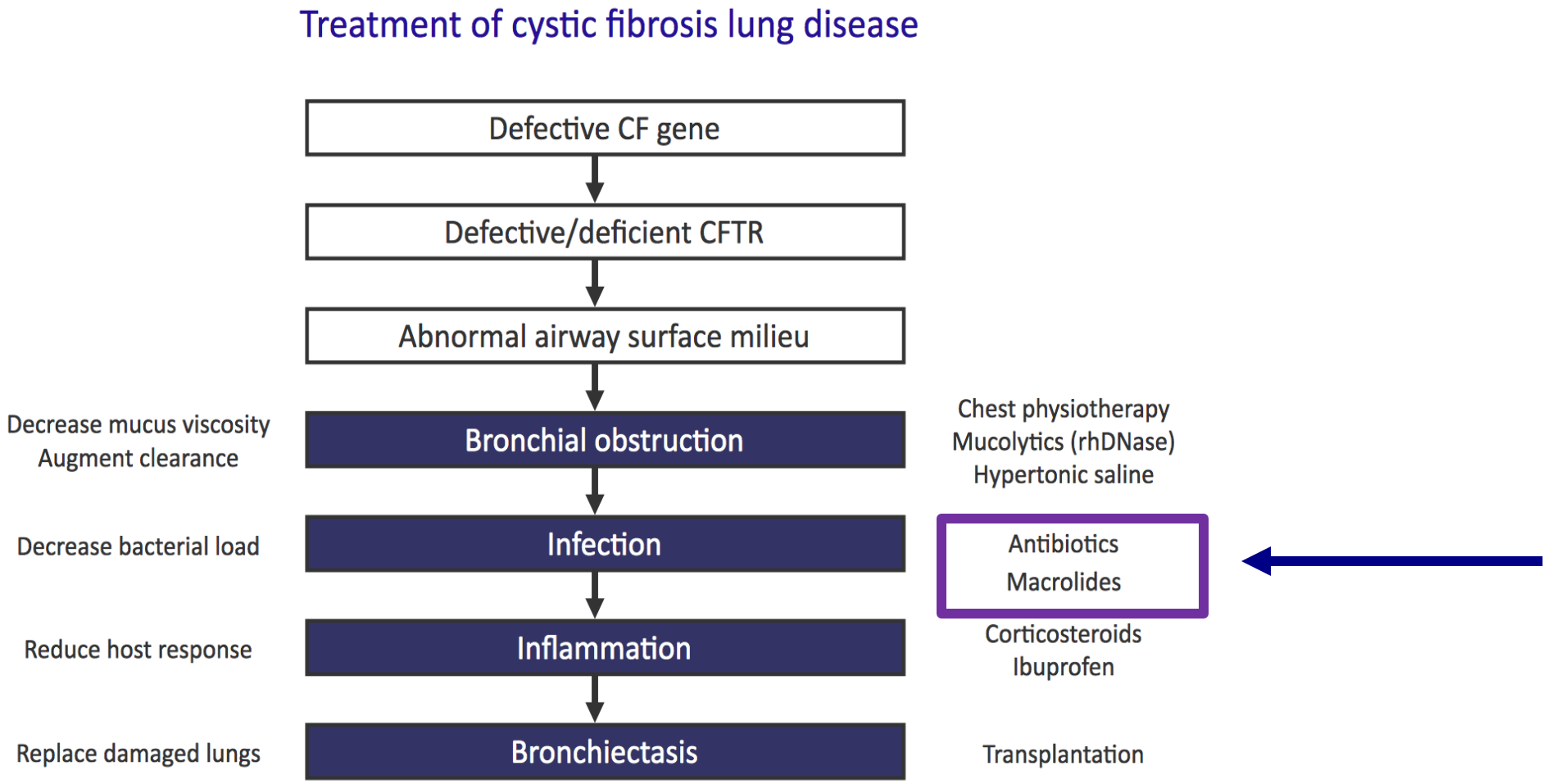
Donaldson SH, et al. N Eng J Med 2006;354:241-250



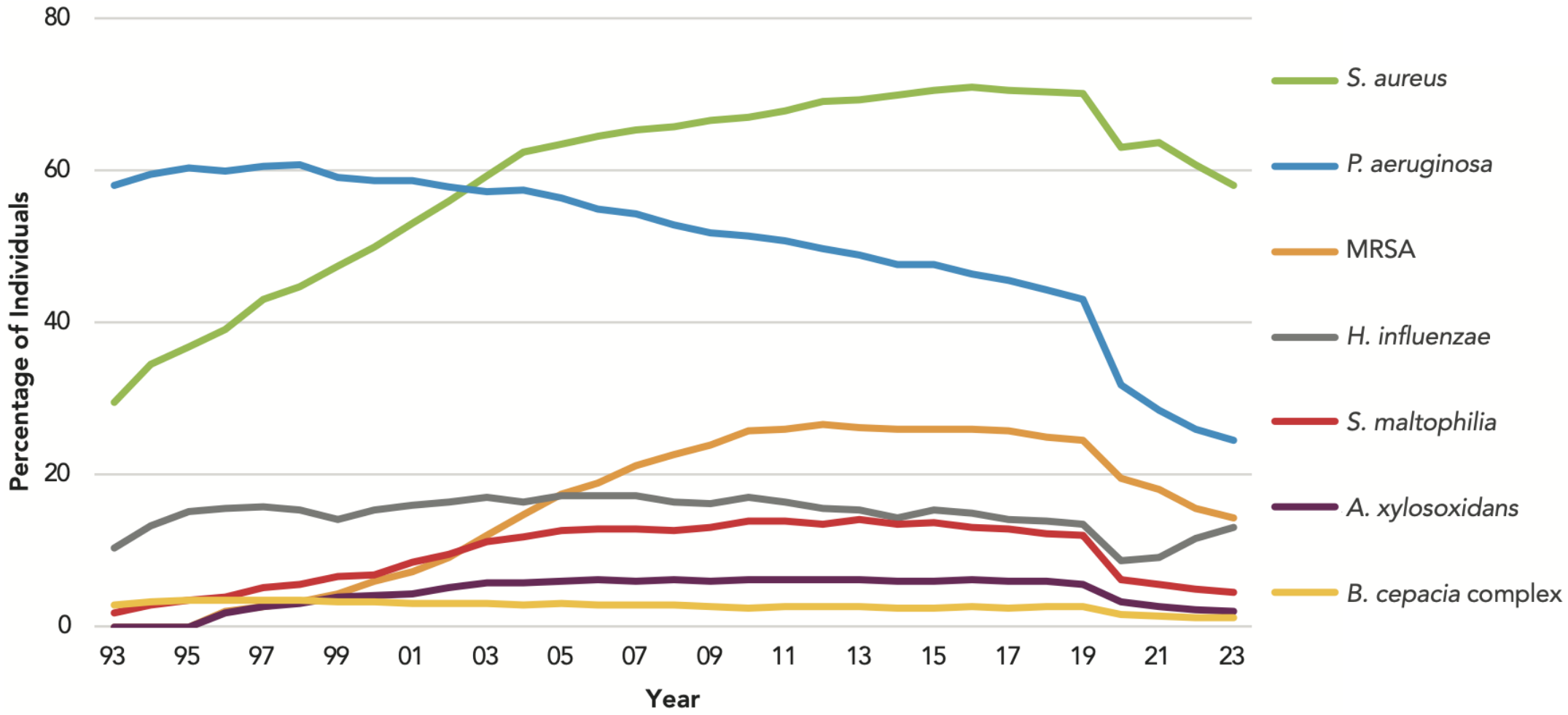
- Dornase alpha
- Once daily

Traditional Therapeutic Approaches for CF Lung Disease

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

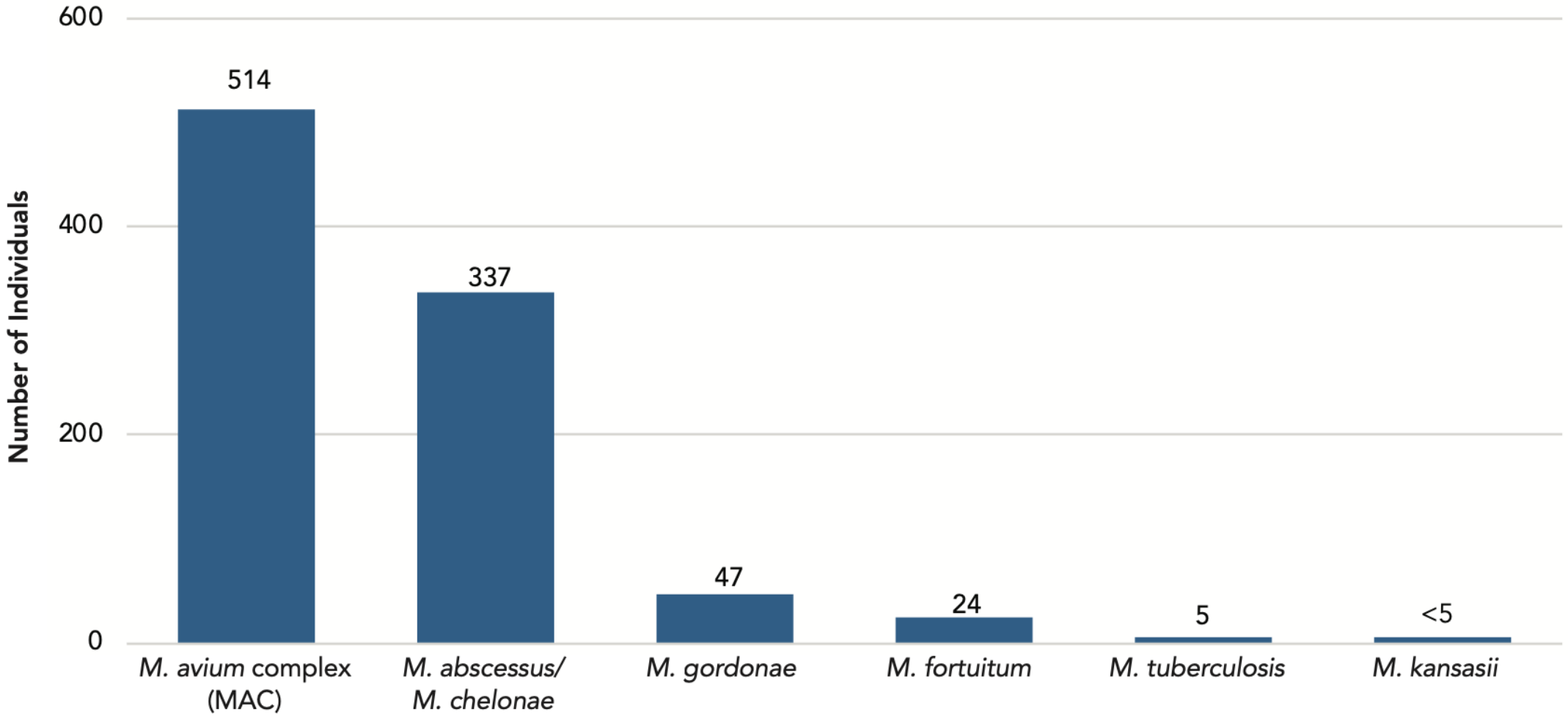


Prevalence of Respiratory Microorganisms in 2023



CFF 2023 Annual Registry Report

Non-Tuberculous Mycobacteria in 2023



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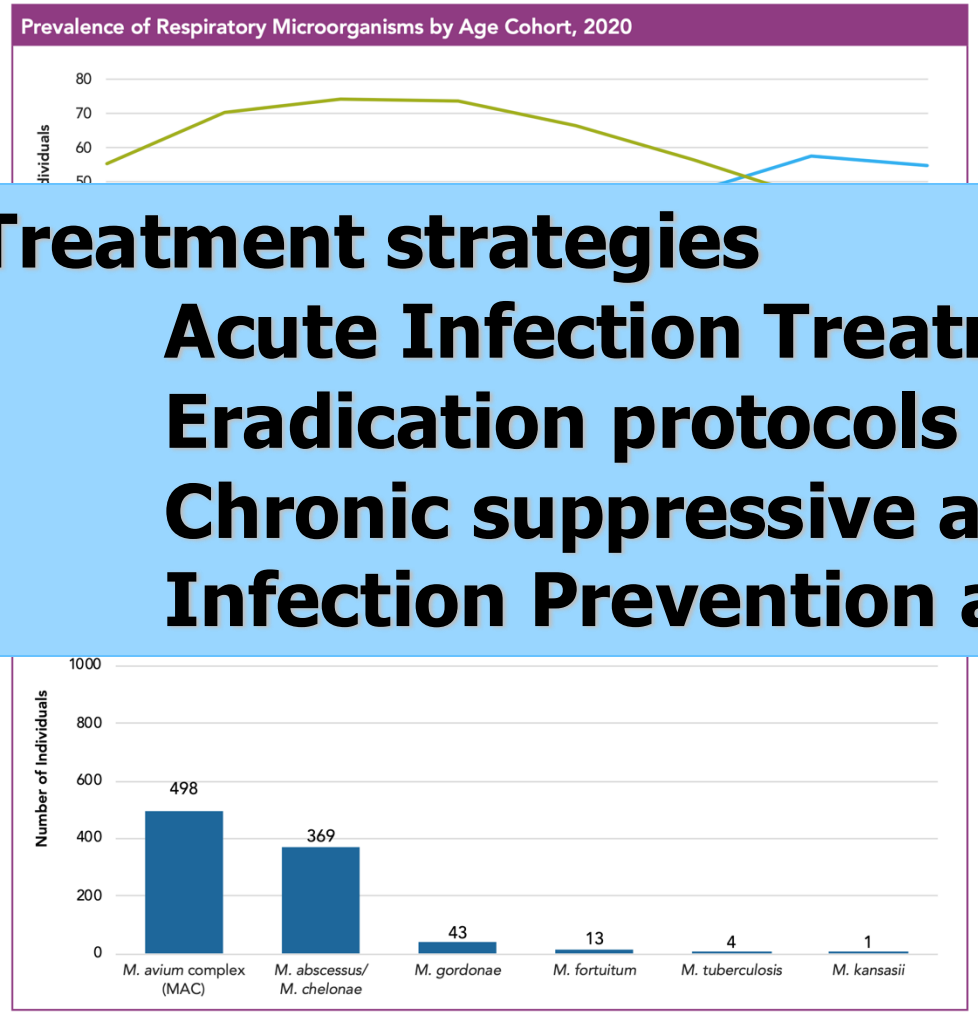
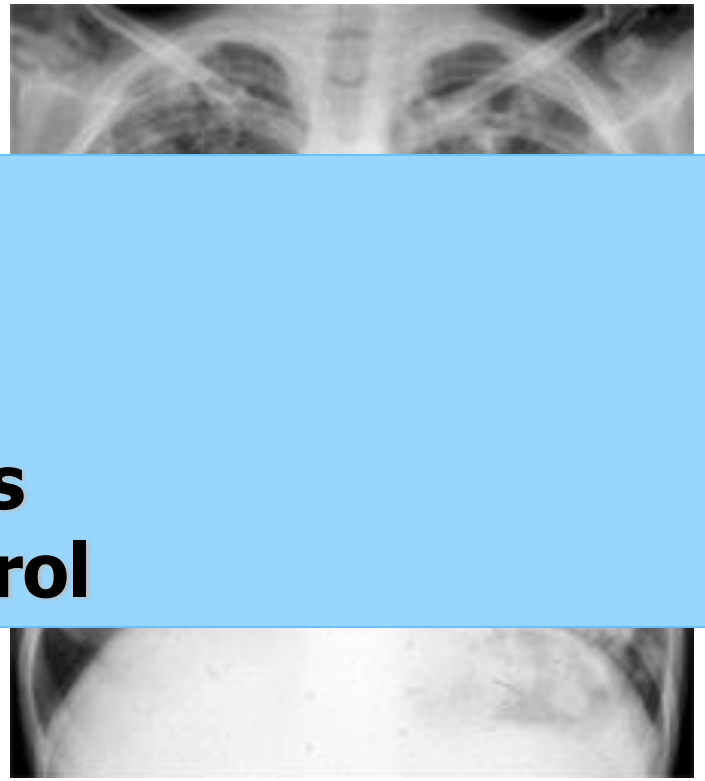
Management of Acute Infectious Exacerbations



Treatment strategies

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



Pulmonary Disease is major cause of morbidity and mortality

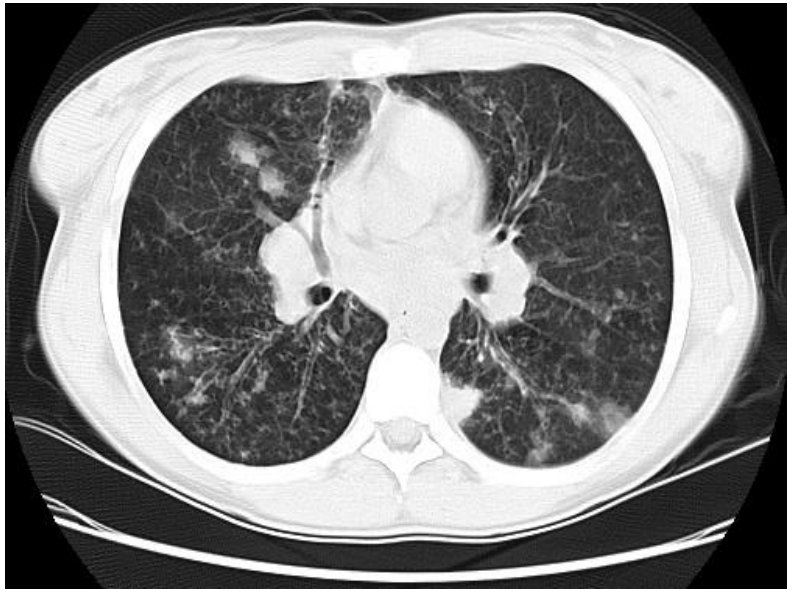
Transmission of CF Pathogens

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

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

"Cepacia Syndrome"

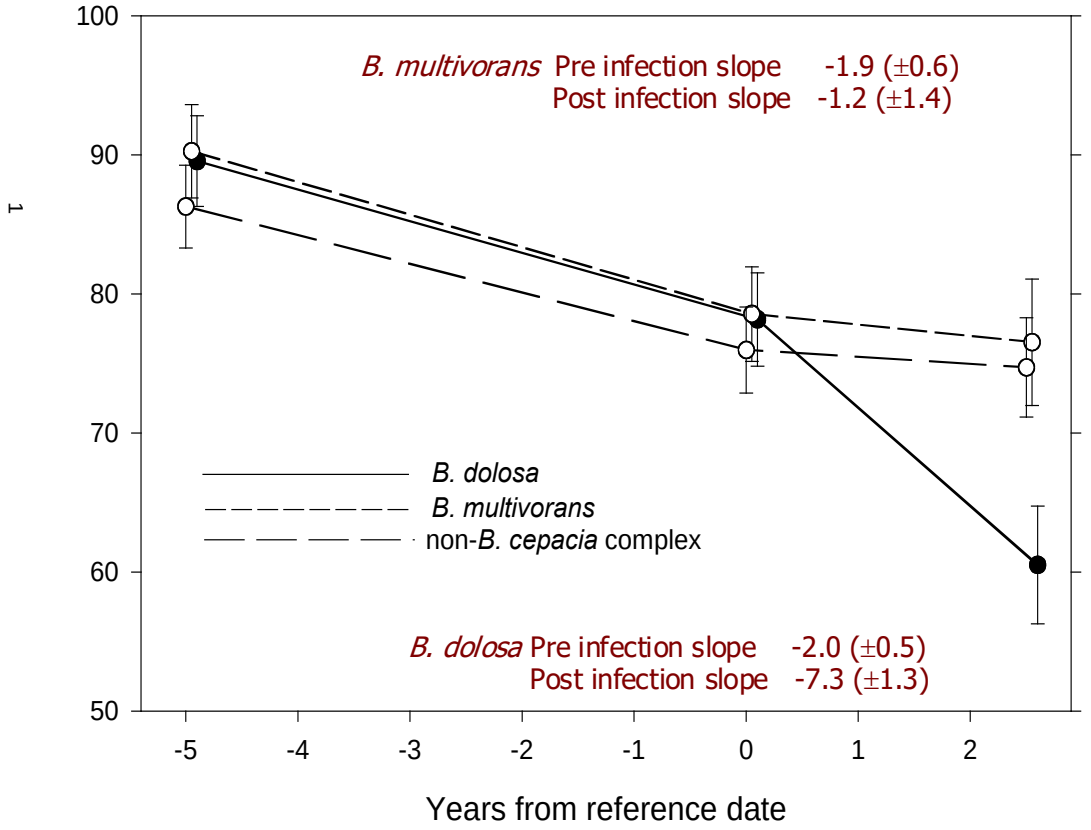
- Fatal combination of necrotizing pneumonia, worsening respiratory failure, and bacteremia
- Previously associated with genomovar III (B.cenocepacia) but documented with other BCC organisms as well
- Bacteremia typically irreversible
- Rapid pulmonary deterioration
  - Pleural effusion
  - Necrotizing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

Preventing Infection and consequences of *B. dolosa* transmission

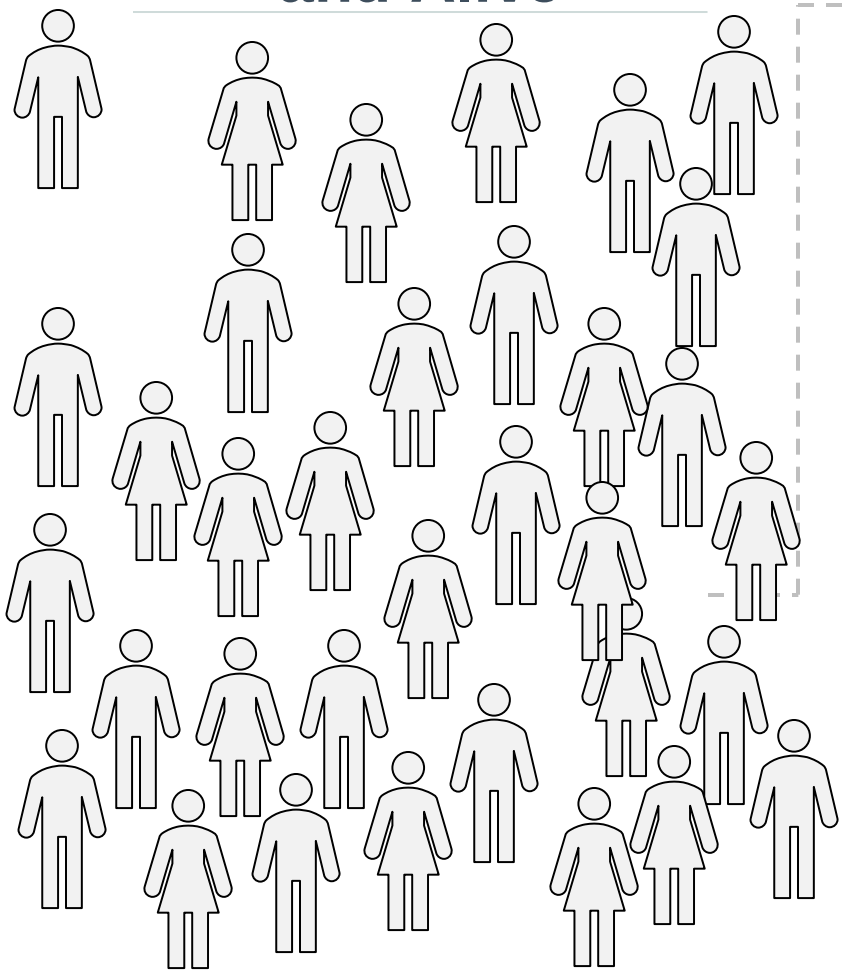
- Infection prevention and control is the most effective way to prevent new infections in CF

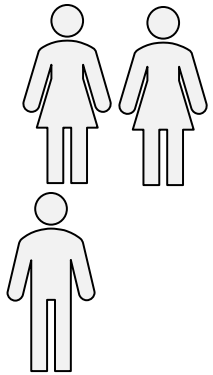


Kalish, Waltz et al. AJRCCM 2006

The Human Face of the Epidemic - 2003

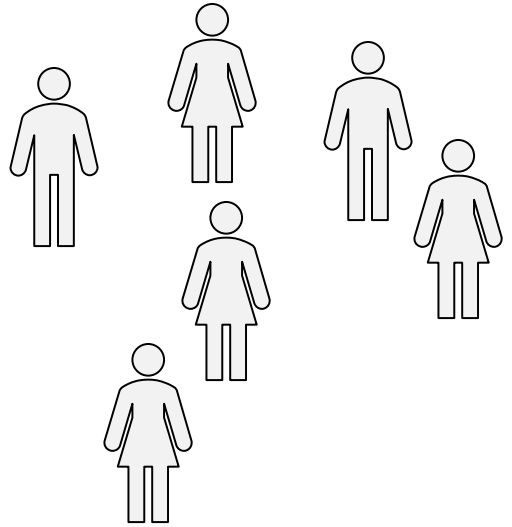
First positive B.dolosa culture and Alive





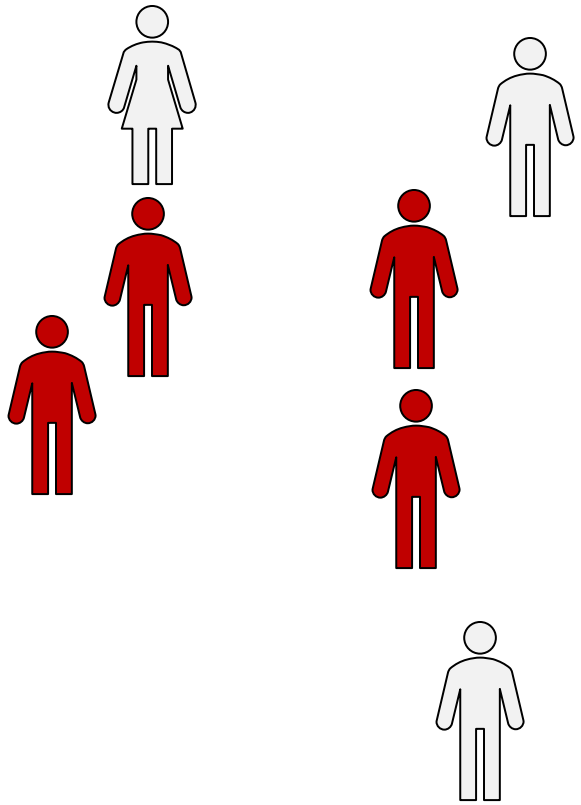
Transplanted and Alive

Passed Away

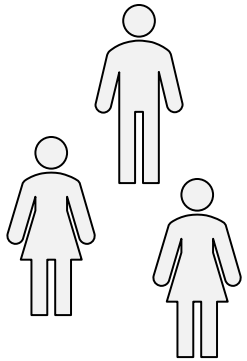


2024 – Present Day

First positive B.dolosa culture and Alive

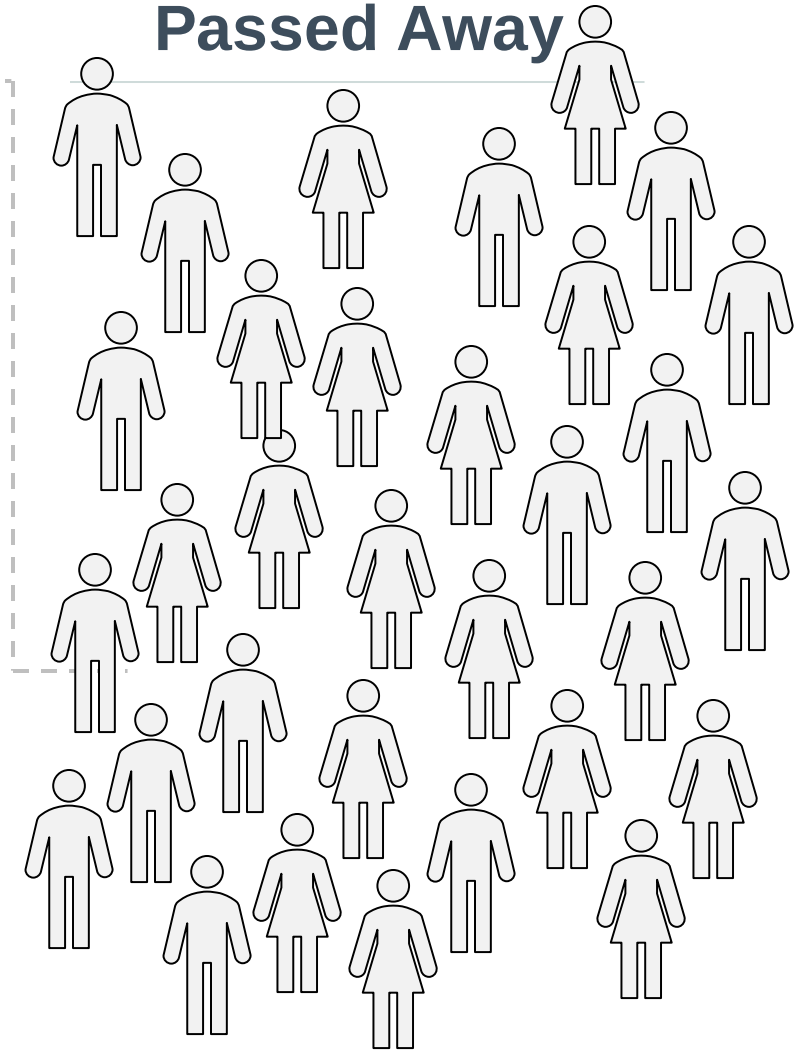


Transplant Candidates



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

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

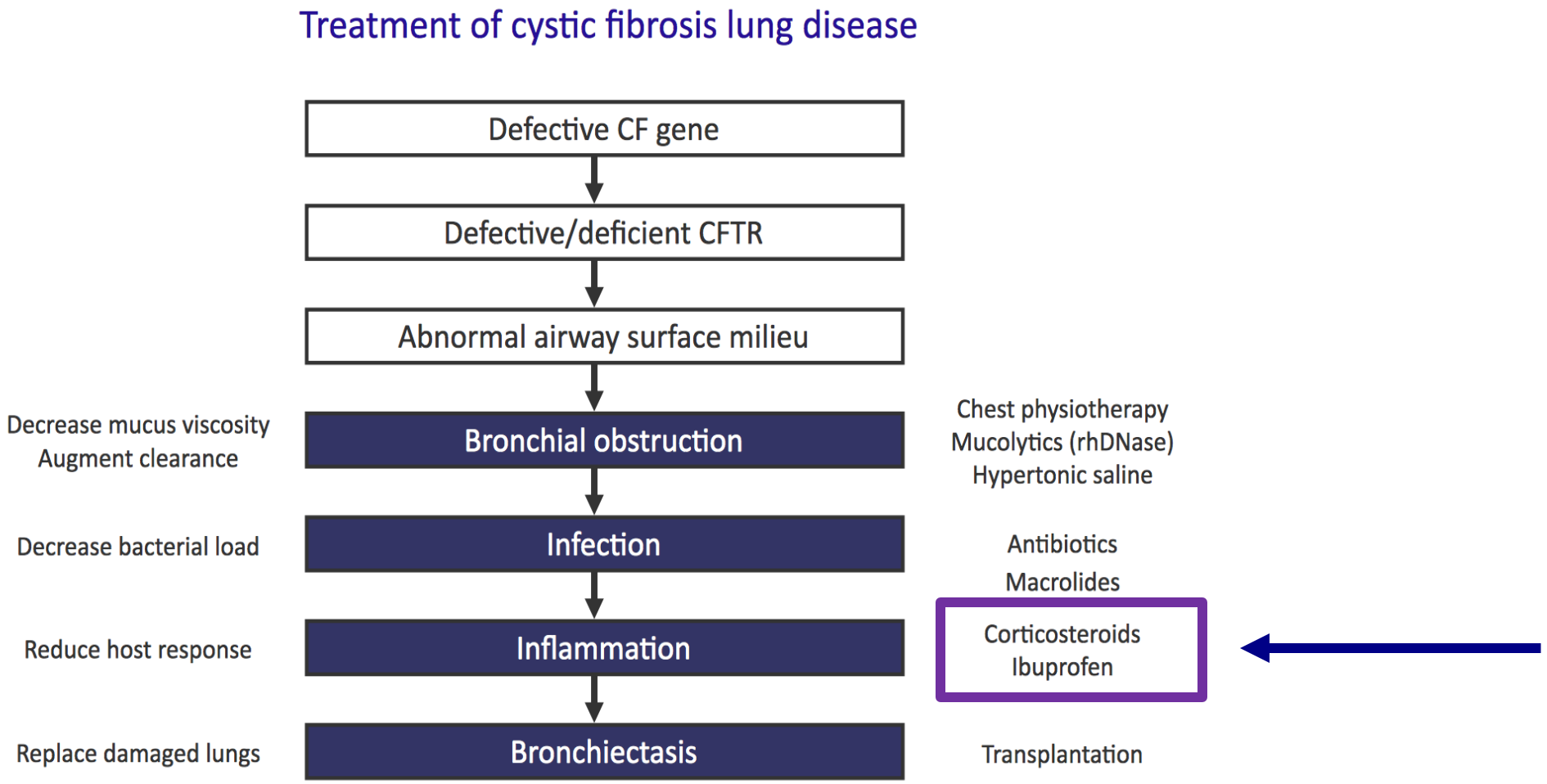
Minimize potential for people with CF to contact each other's secretions via contact or droplets in the CF clinic, in the hospital, and in sponsored ***non-healthcare settings***

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

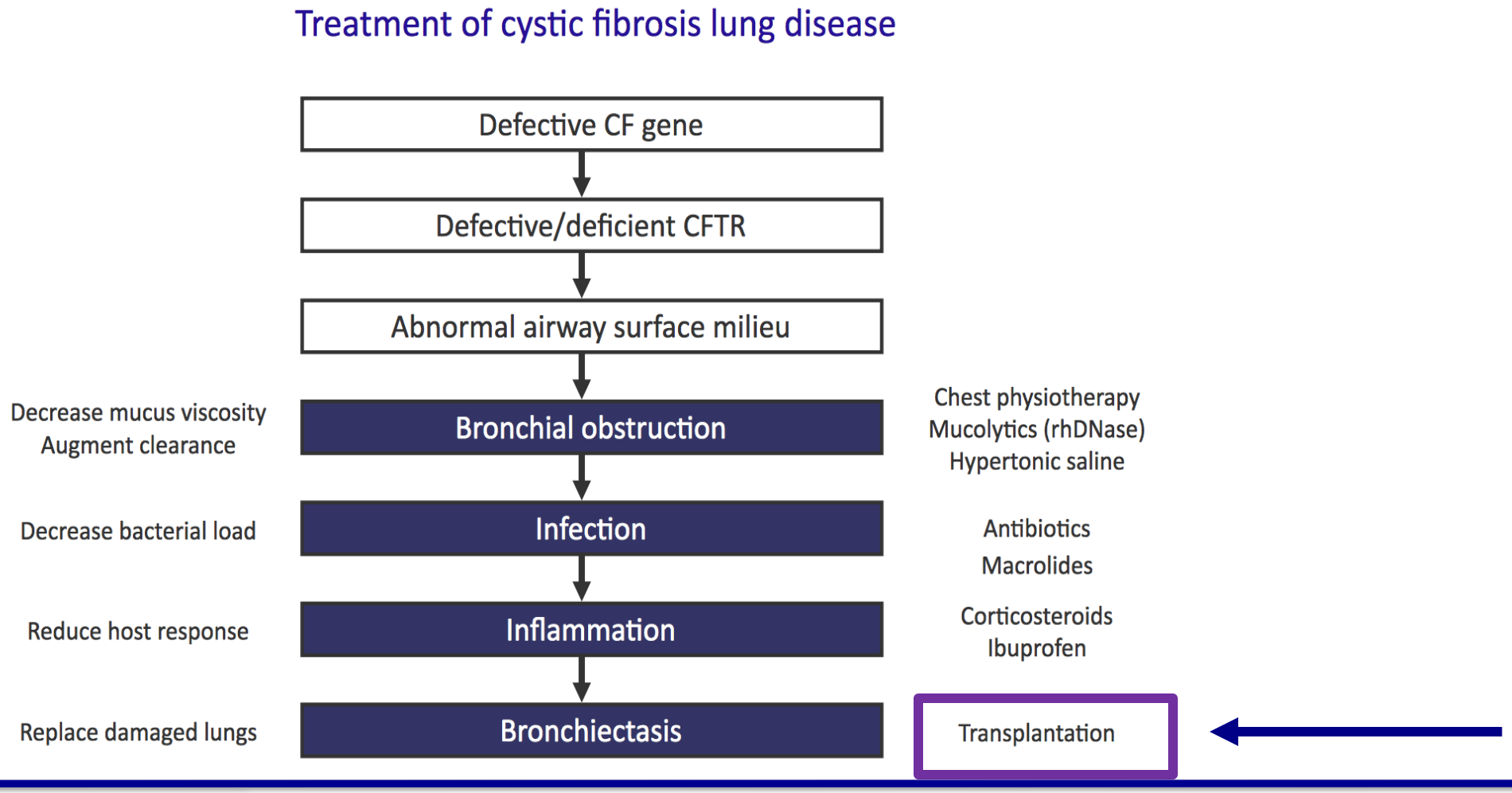
Traditional Therapeutic Approaches for CF Lung Disease

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

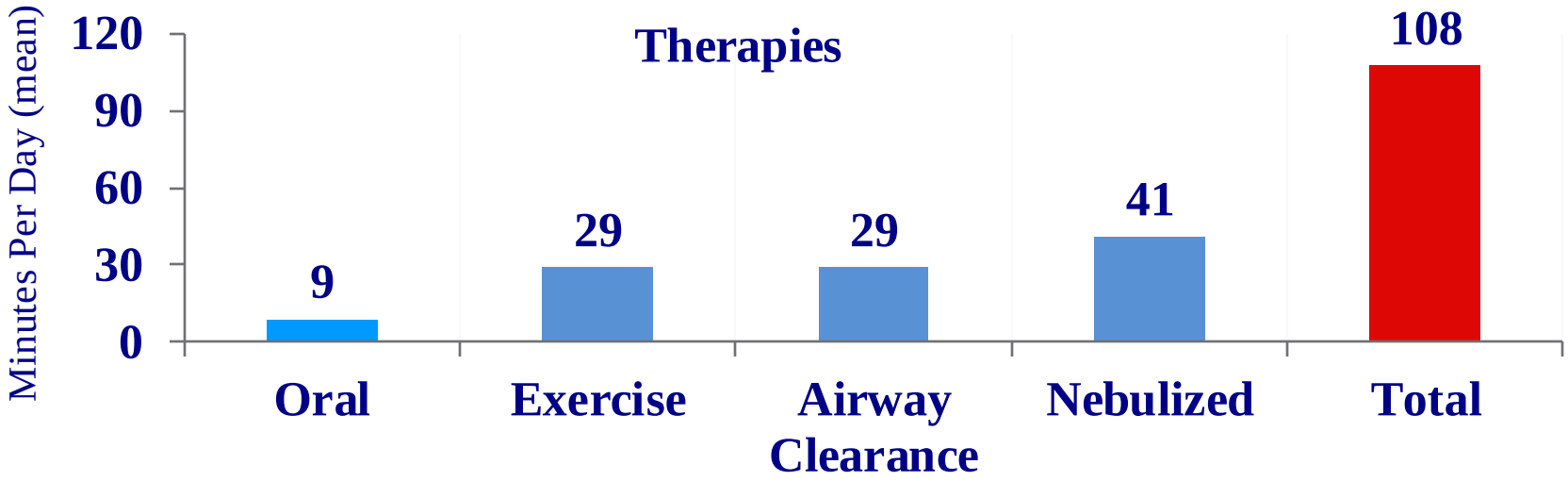


Traditional Therapeutic Approaches for CF Lung Disease

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



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.

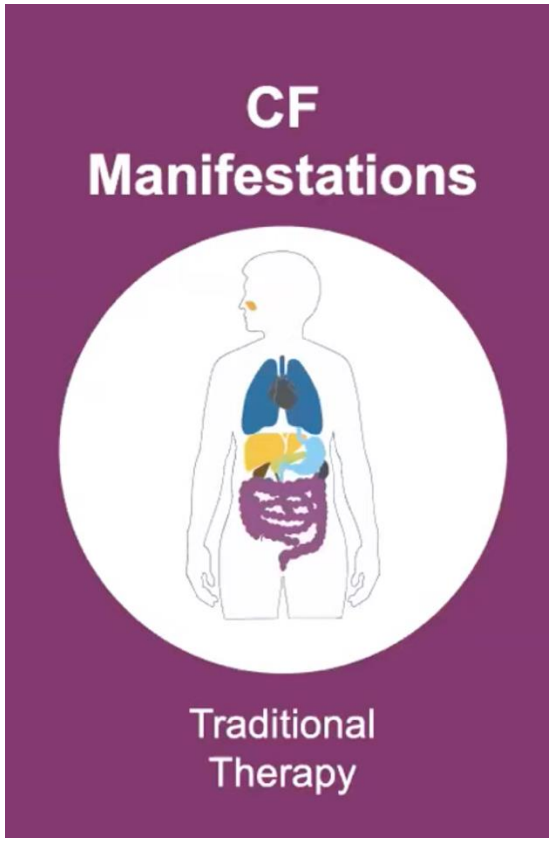
Simplify Study

Grade A Recommendation (High Benefit/Substantial)

- Inhaled Tobramycin
  - Mod-severe disease
- Dornase Alfa
  - Mod-severe disease
- Inhaled aztreonam
  - Mod-severe disease
- CFTR Modulators *(modified)*
  - (F508del and other eligible mutations)

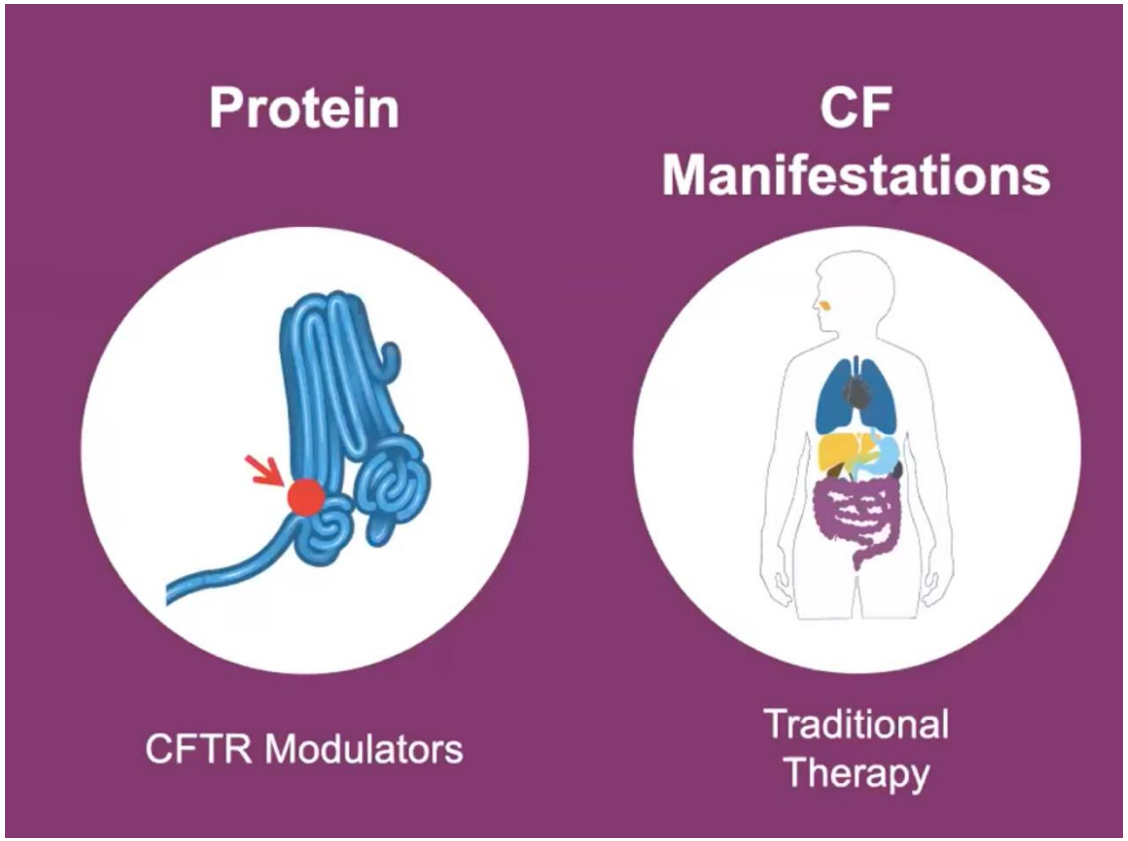
Flume et al. Am J Respir Crit Care Med 2007;176:957-969
Mogayzel et al. Am J Respir Crit Care Med 2013; 187:680-689

New Therapeutic Approach to CF



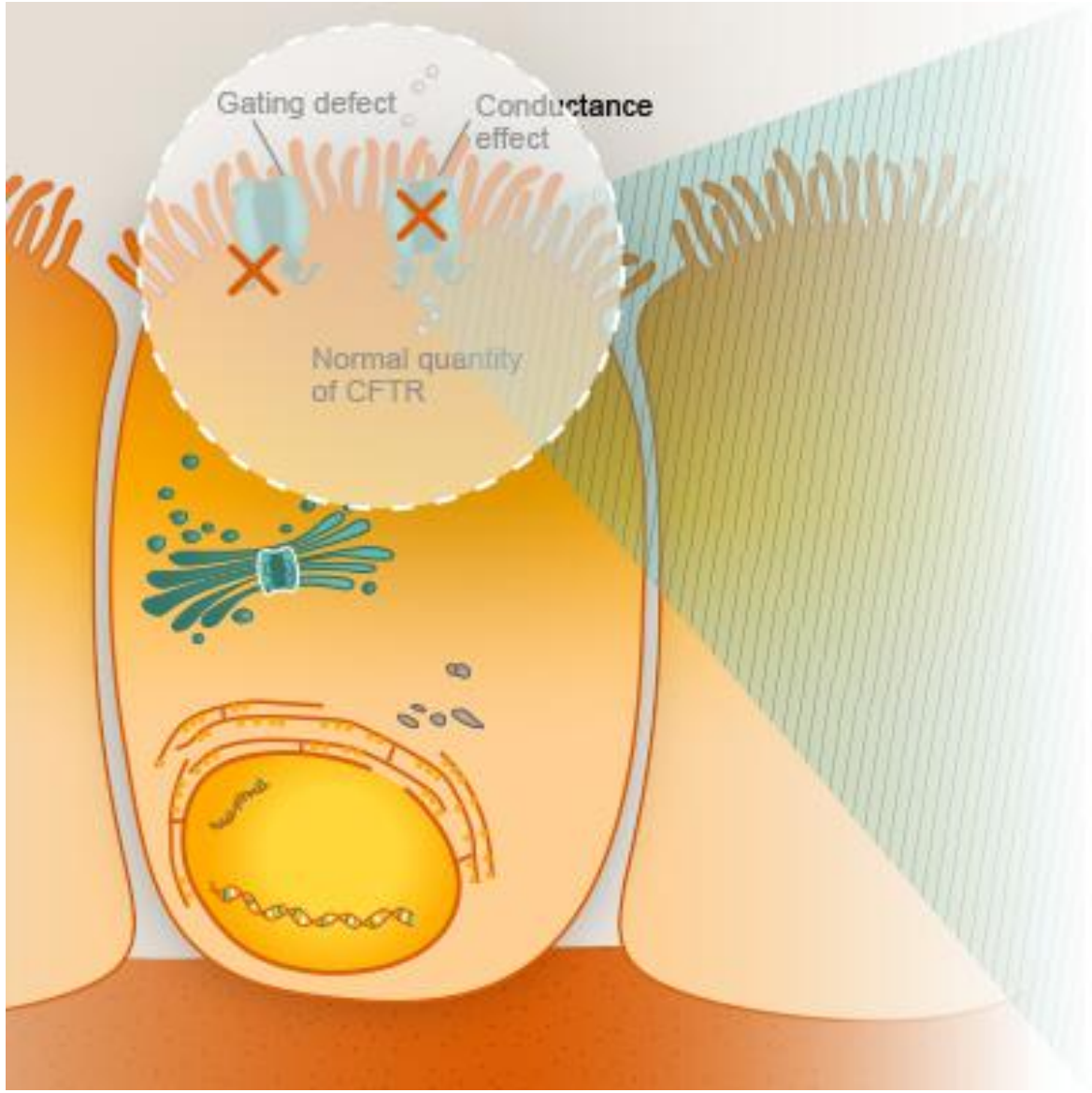
Courtesy of CFF

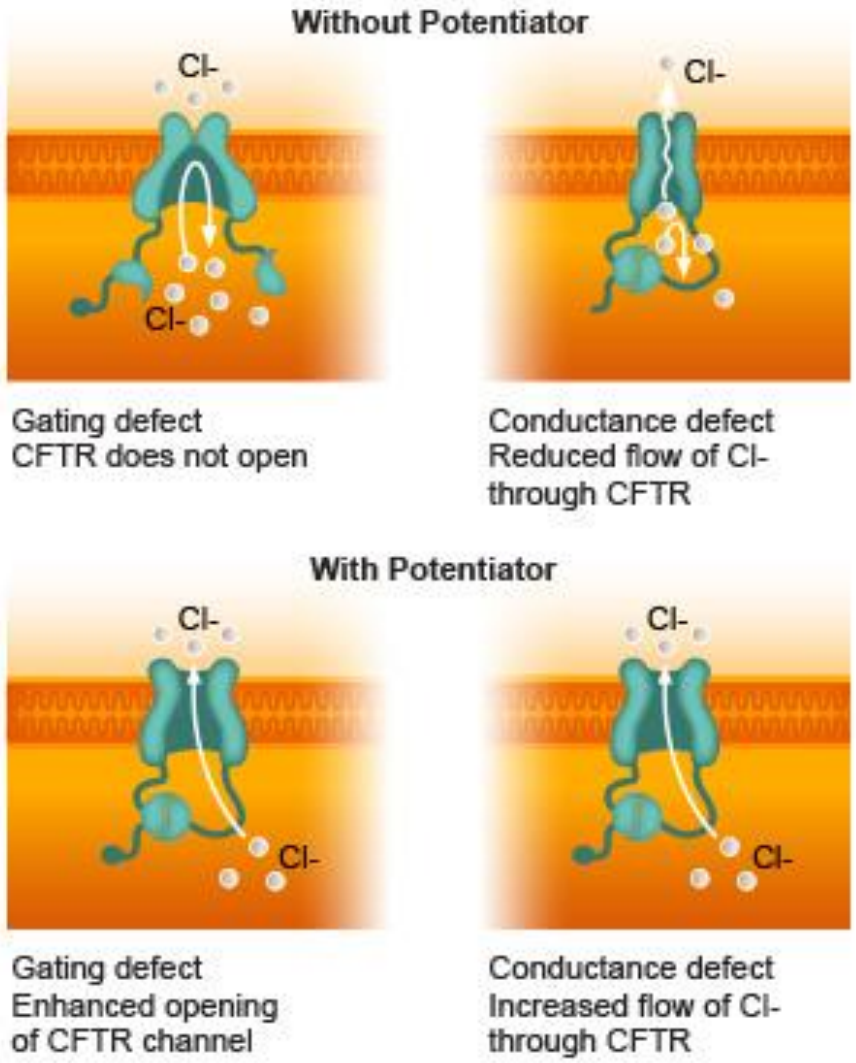
New Therapeutic Approach to CF



Courtesy of CFF

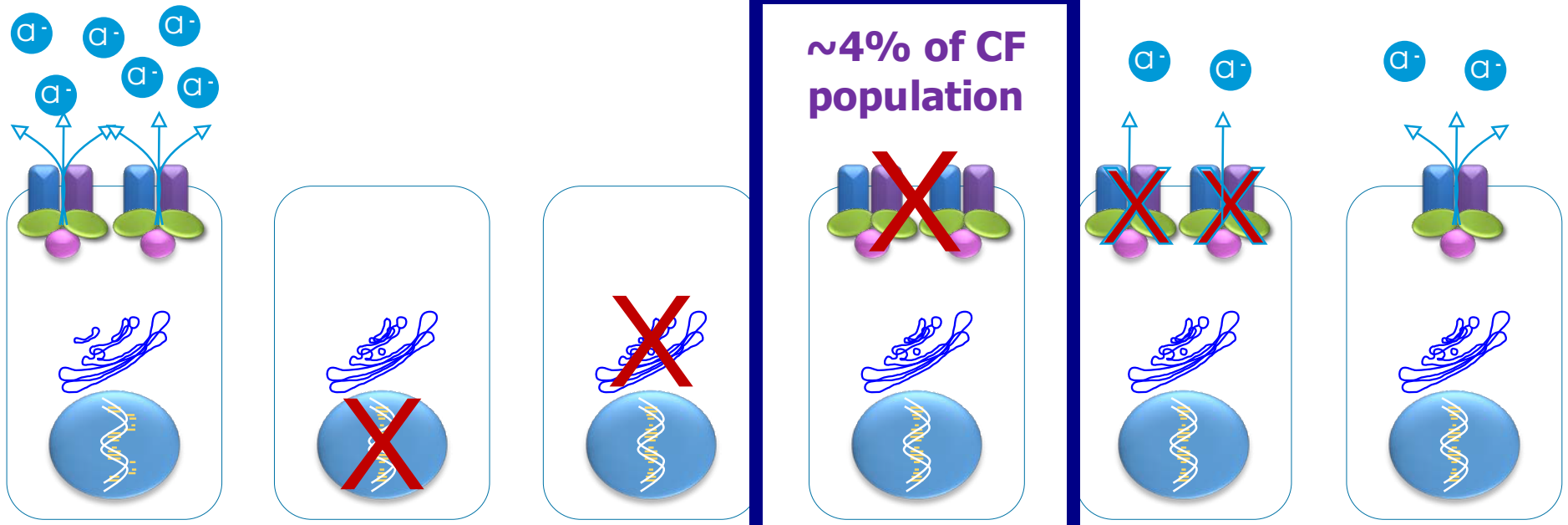
Precision Medicine – Small Molecule Potentiators





Courtesy of Vertex

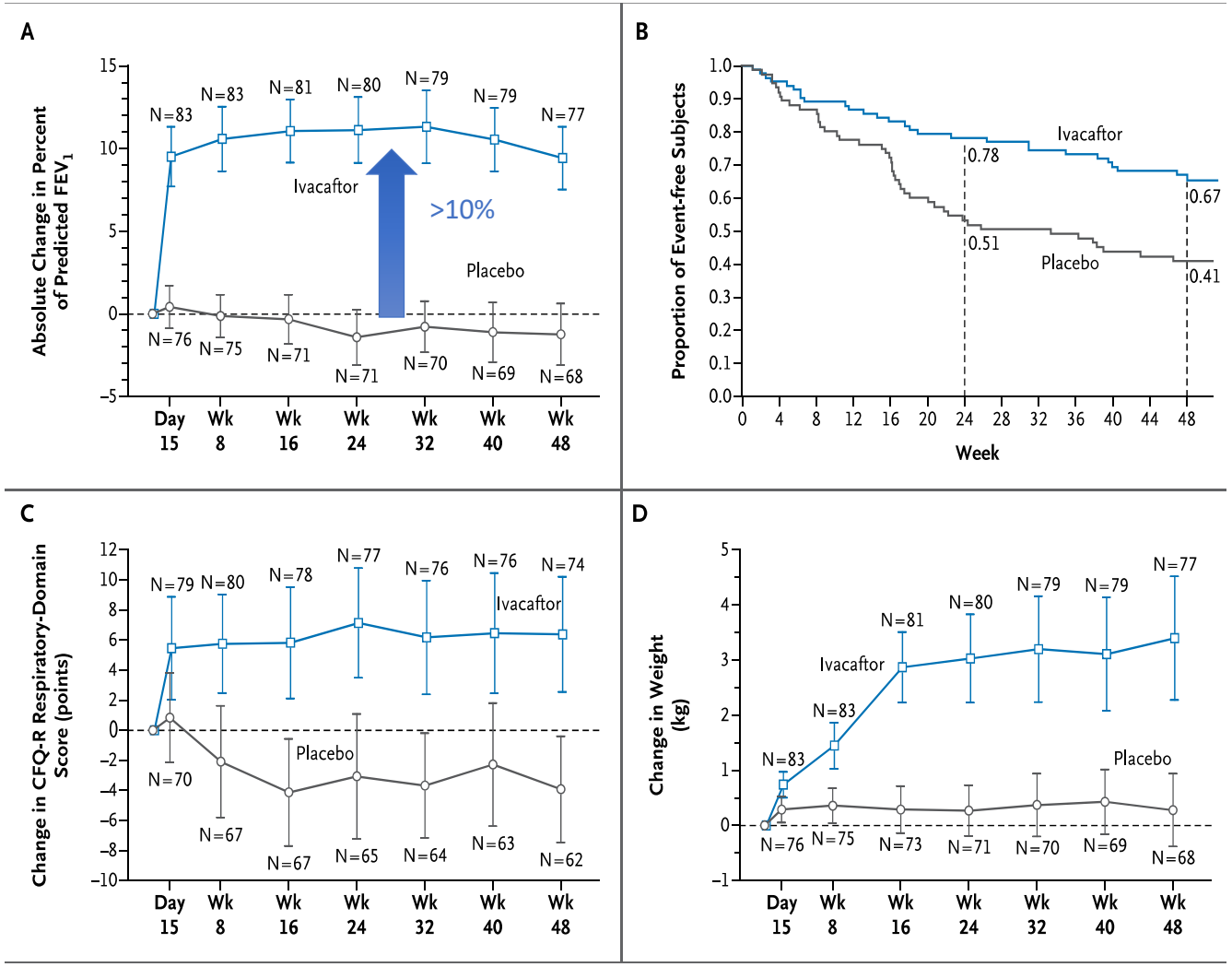
5 (or 6) Classes of CFTR Mutations



	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 W1282X R553X	F508del N1303K I507del	G551D S549N V520F	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

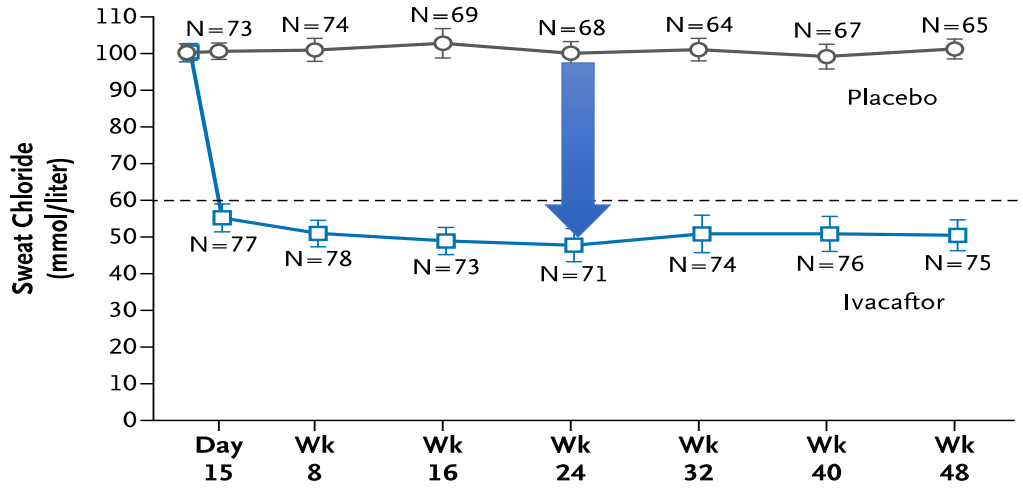
Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

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 P<0.001	

B



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

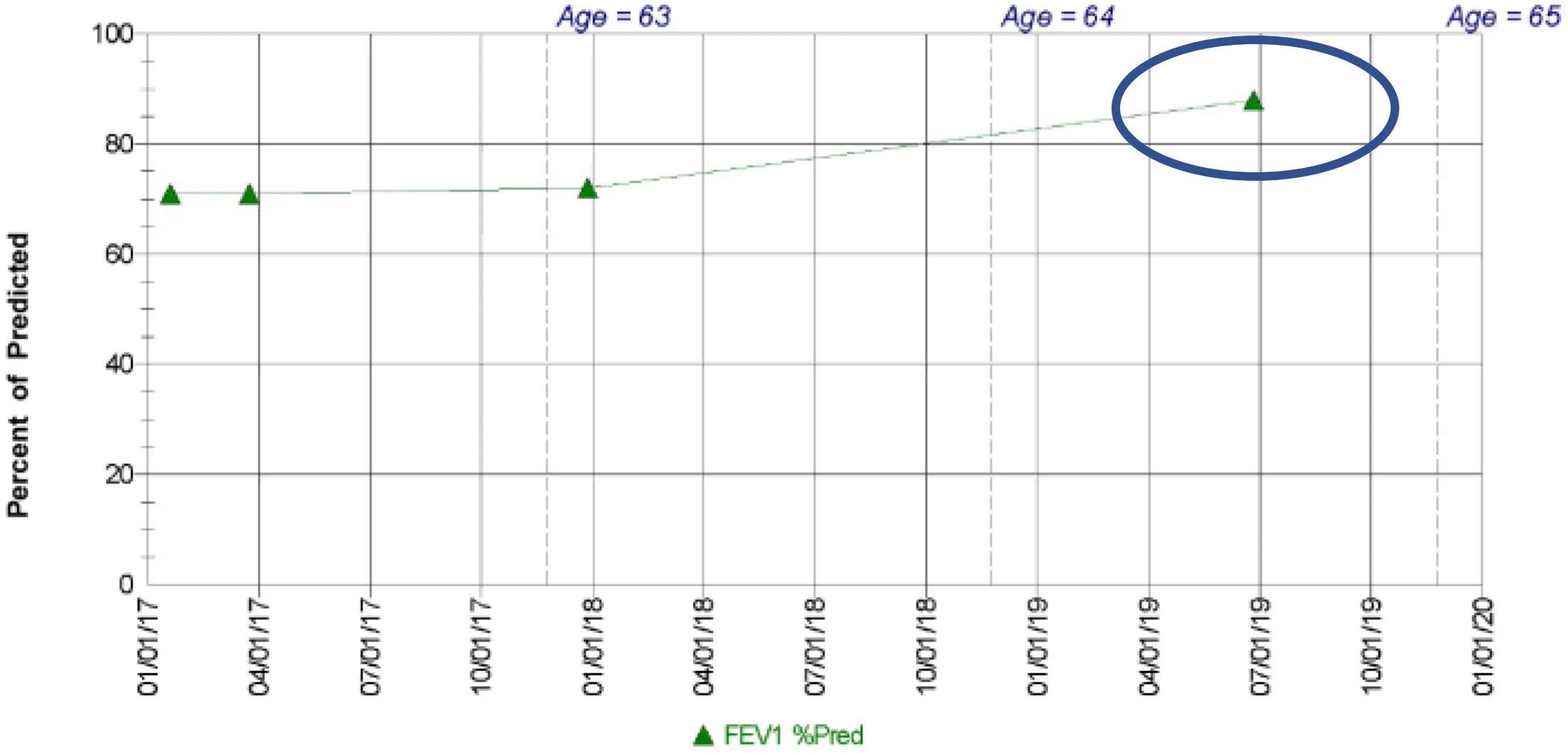
Patient Case

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 Hemoptysis 1-2 teaspoon with exacerbations	

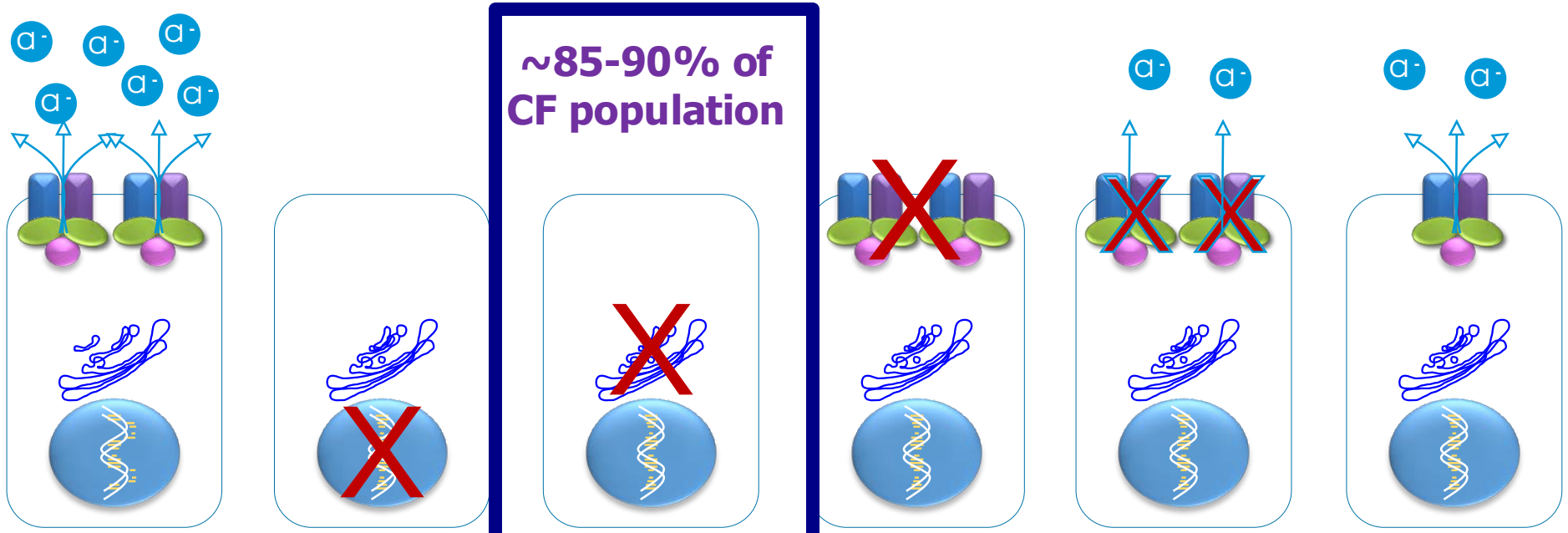
Comorbidities:
Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity
Lifestyle/circumstance:
Decreased activity, desk job
CFTR Treatment:
Eligible for ivacaftor **(prior to elexacaftor/tezacaftor/ivacaftor approval)**
Other
Never smoked No Children Family History of Colon cancer

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

Patient Case



5 (or 6) Classes of CFTR Mutations

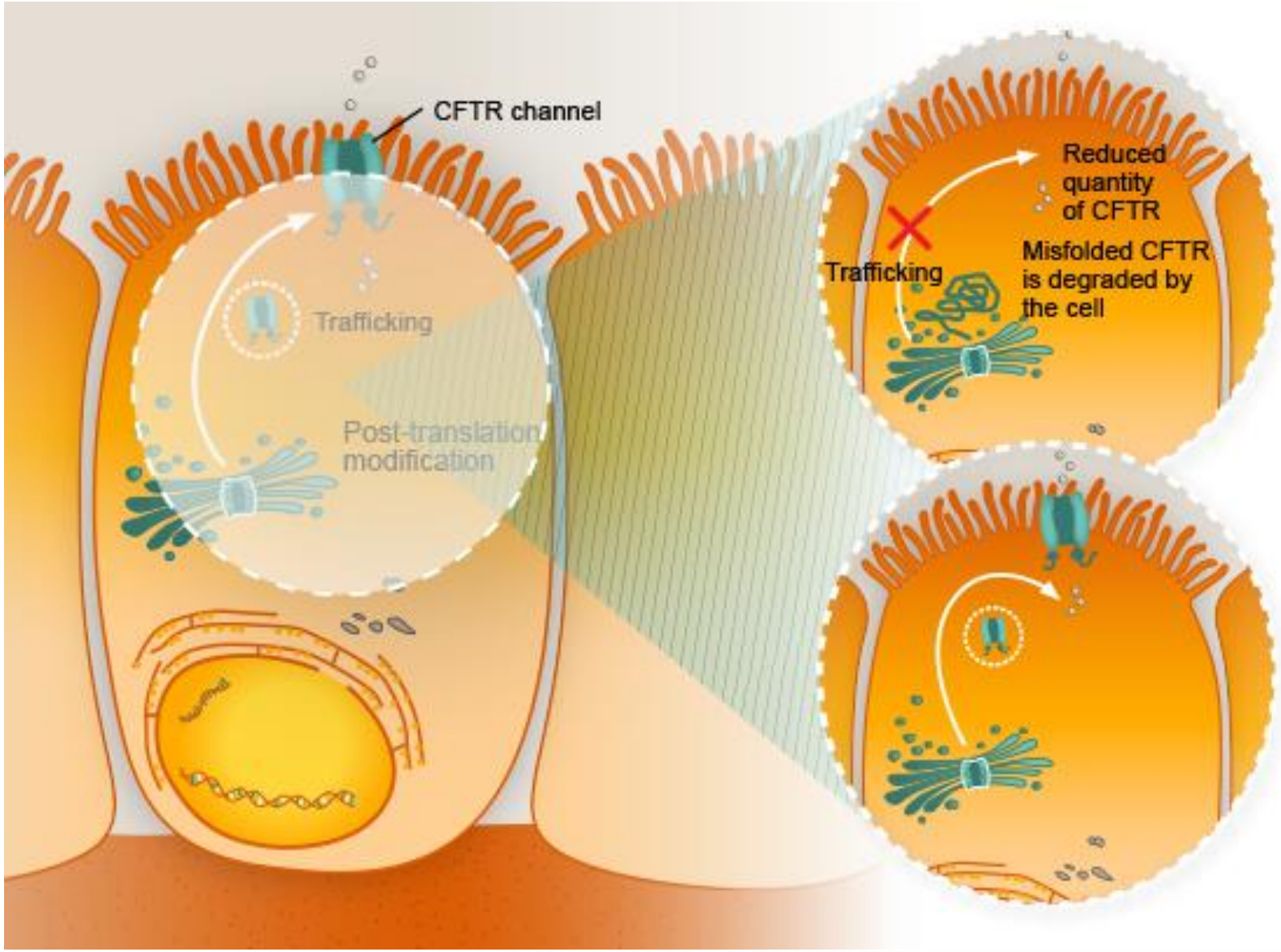


~85-90% of CF population

	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 unction properly.	The opening in the CFTR protein ion channel is faulty.	CFTR is created in insufficient quantities.
EXAMPLES		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

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

Small Molecule Potentiator + Corrector



Without Corrector

Mutation(s) in CFTR protein cause misfolding and degradadation 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

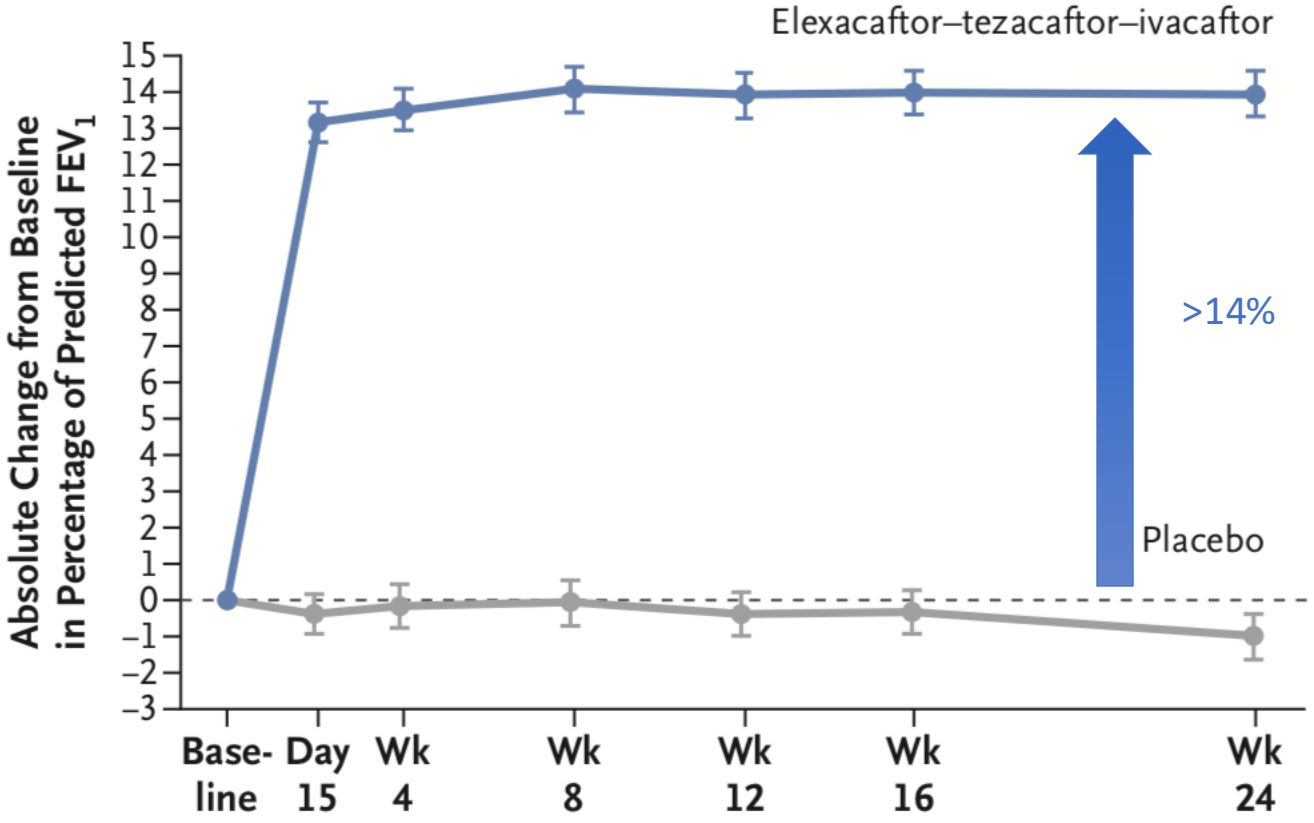
October 21, 2019

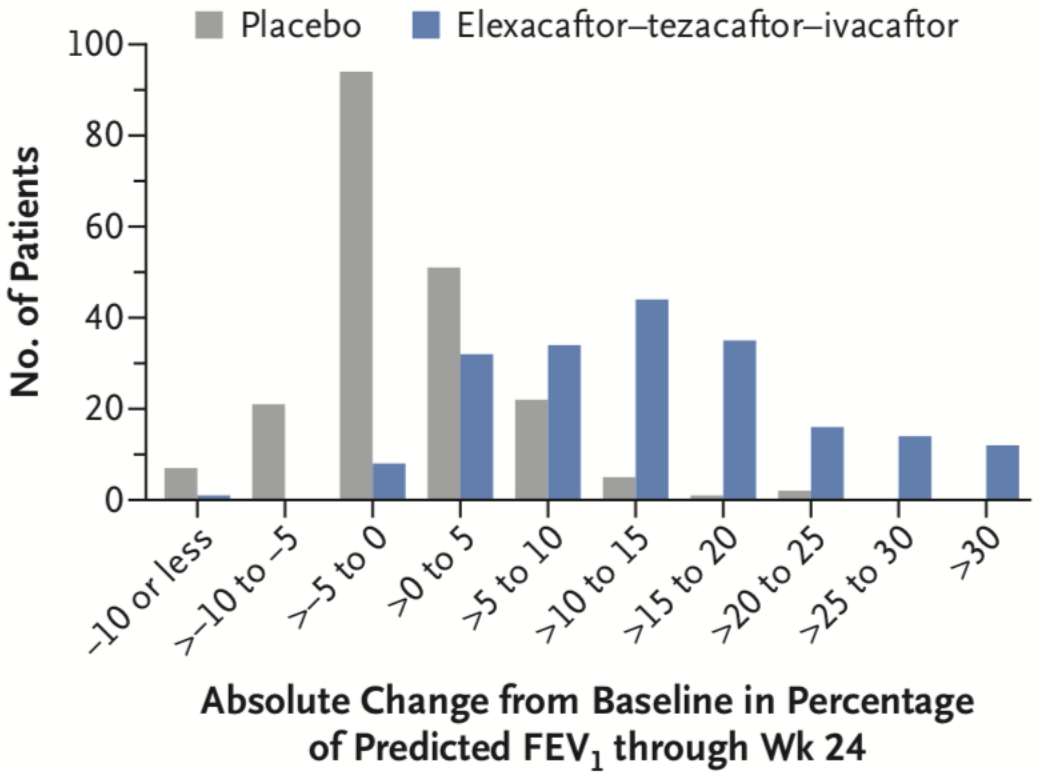
FDA Approved elexacaftor/tezacaftor/ivacaftor (Trikafta) for those with at least **one copy F508Del**

(preceded by Orkambi 2016 and Symdeko 2018)

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

Lung Function Response (FEV1)

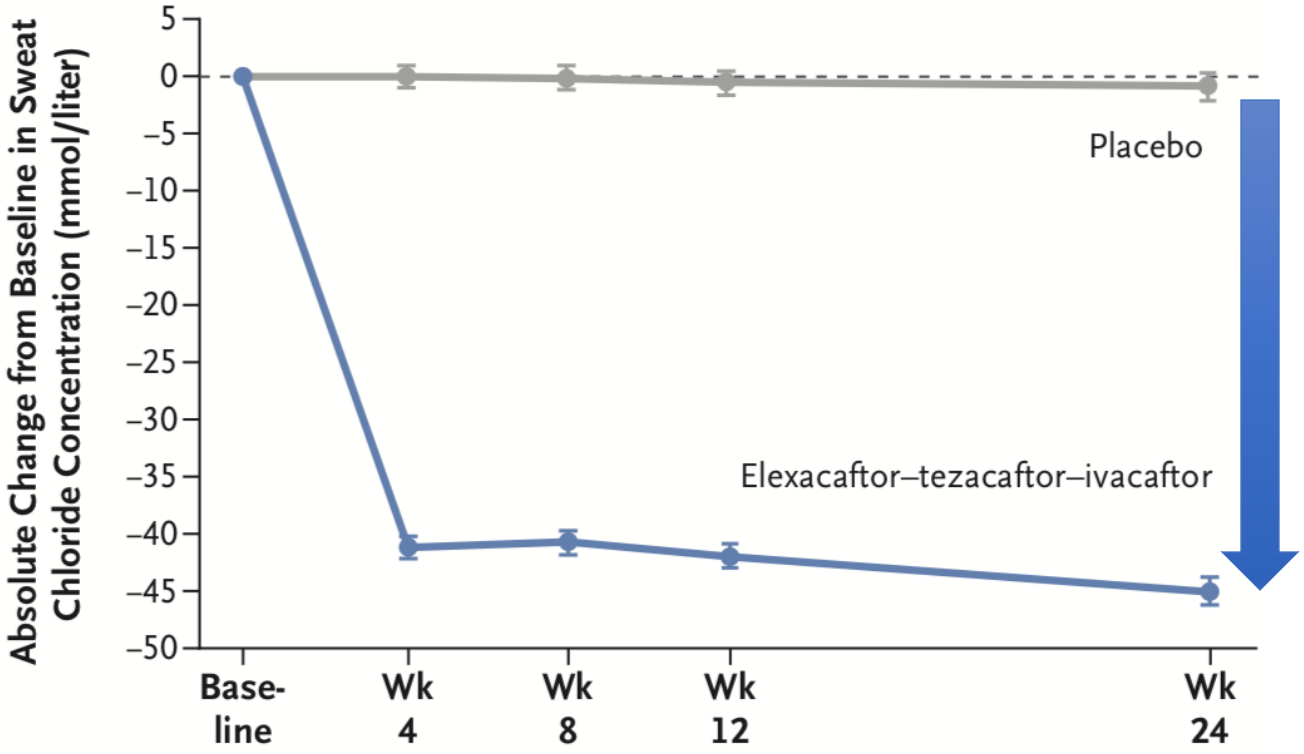


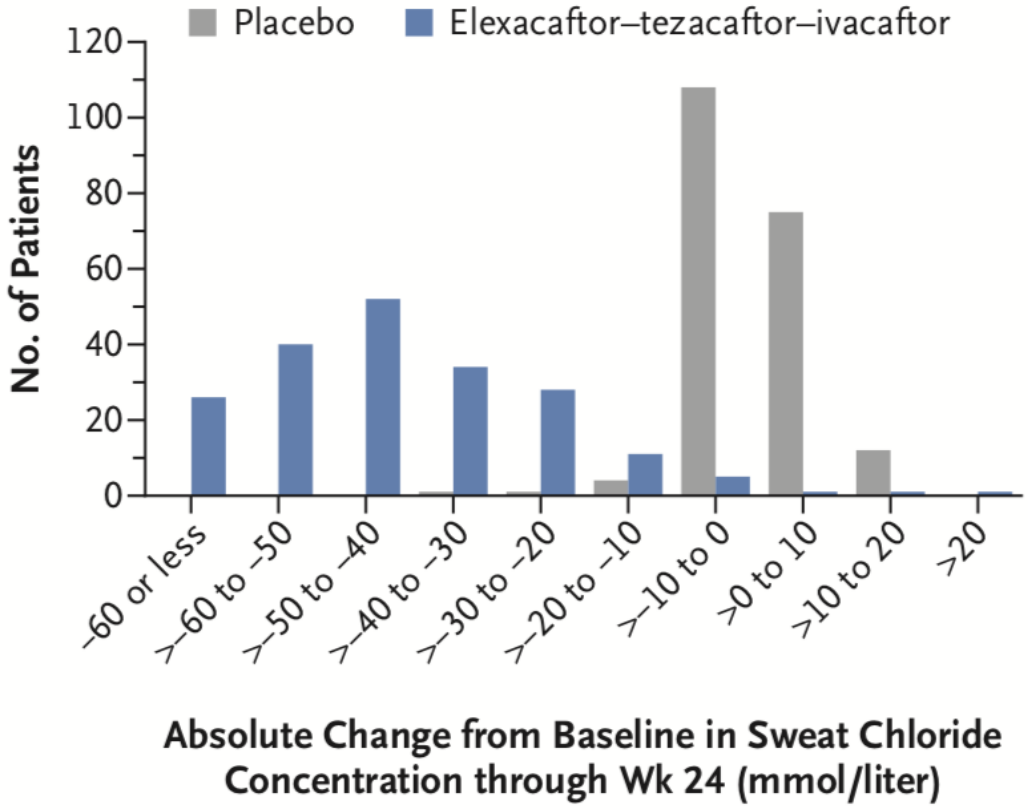


Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

Sweat Chloride Response (mmol/liter)

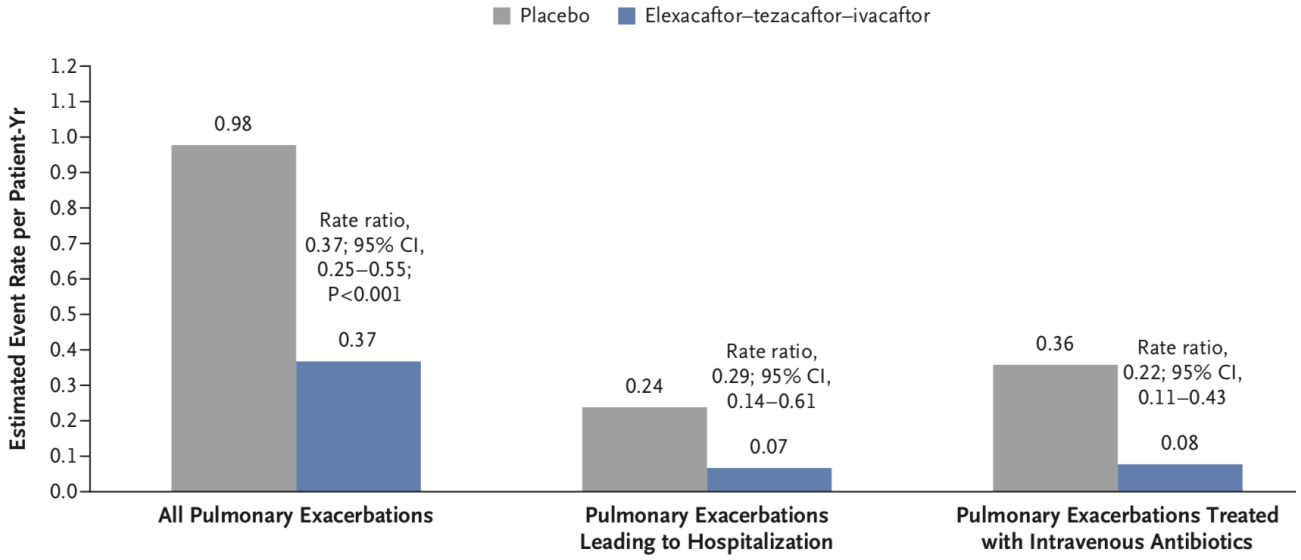


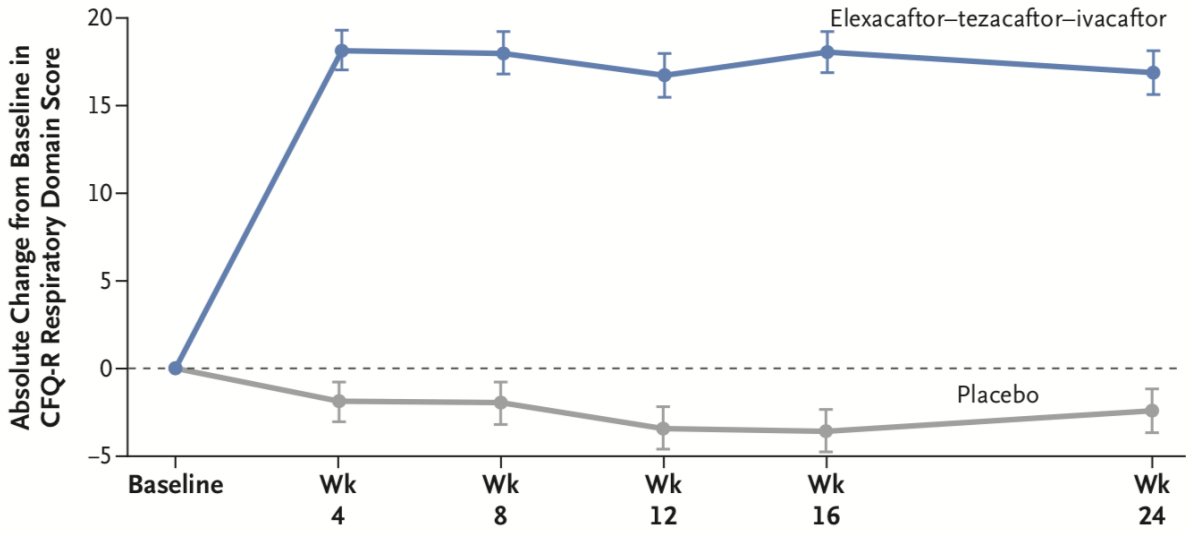


Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

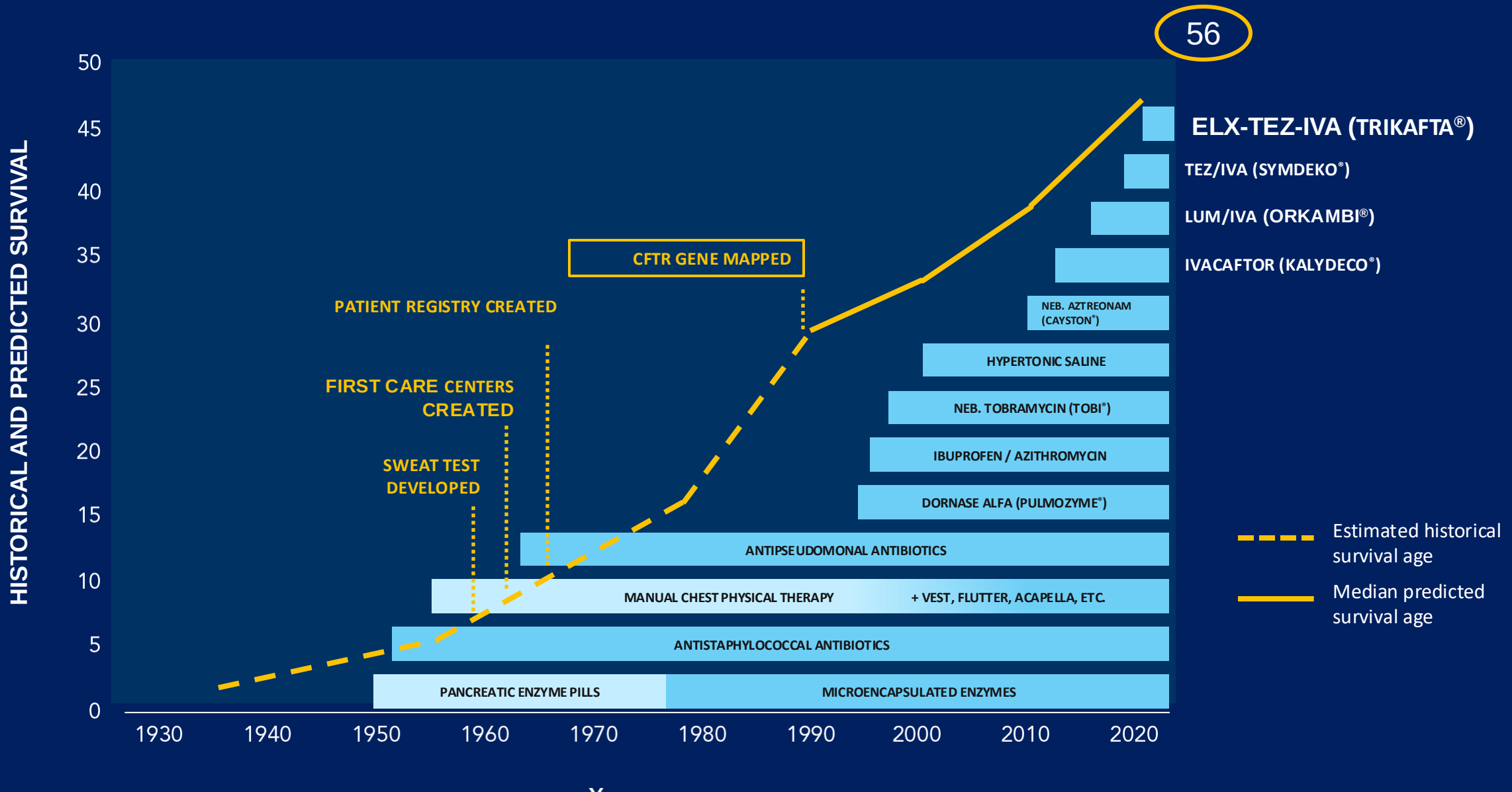
Exacerbations and CFQ-R





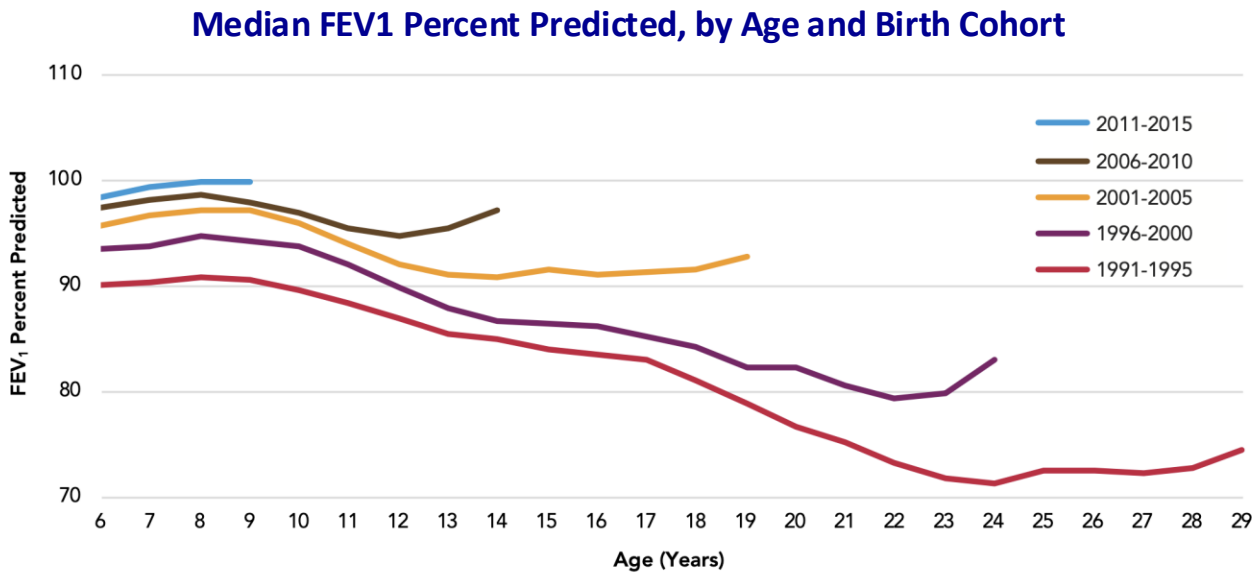
Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

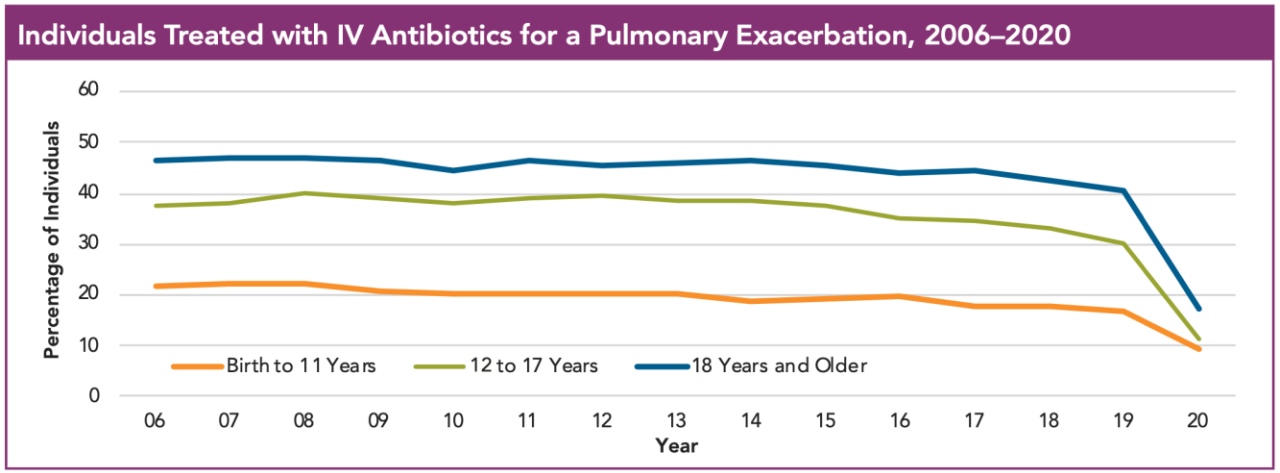
Timeline of advances in CF

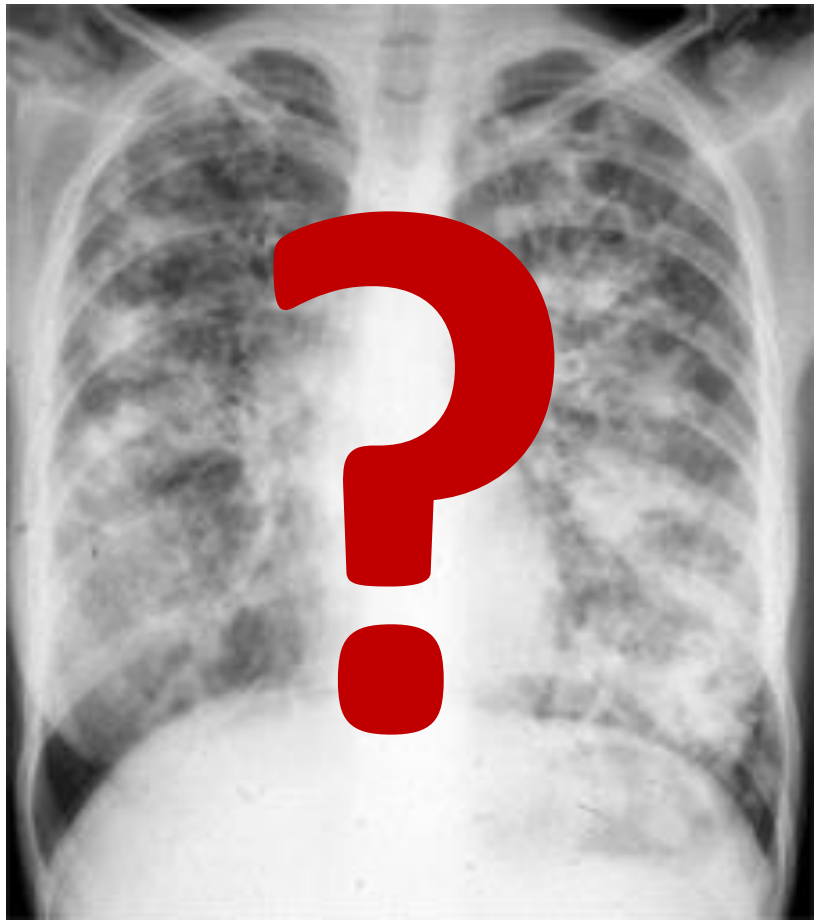


Slide courtesy of JP Clancy; 2022 CFFPR

CF - Multi-Organ Involvement



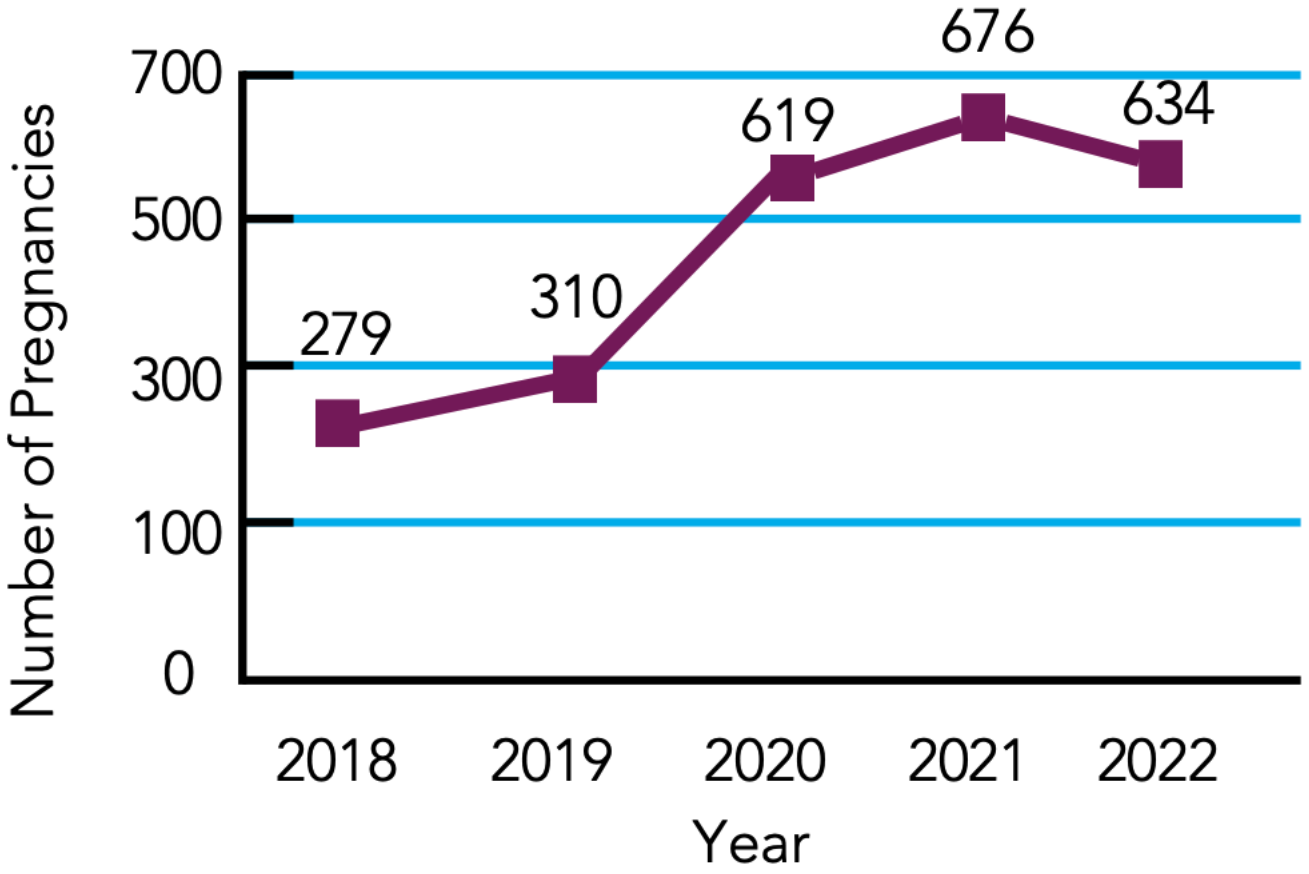




Pulmonary Disease is major cause of morbidity and mortality

Number of CF Pregnancies by Year

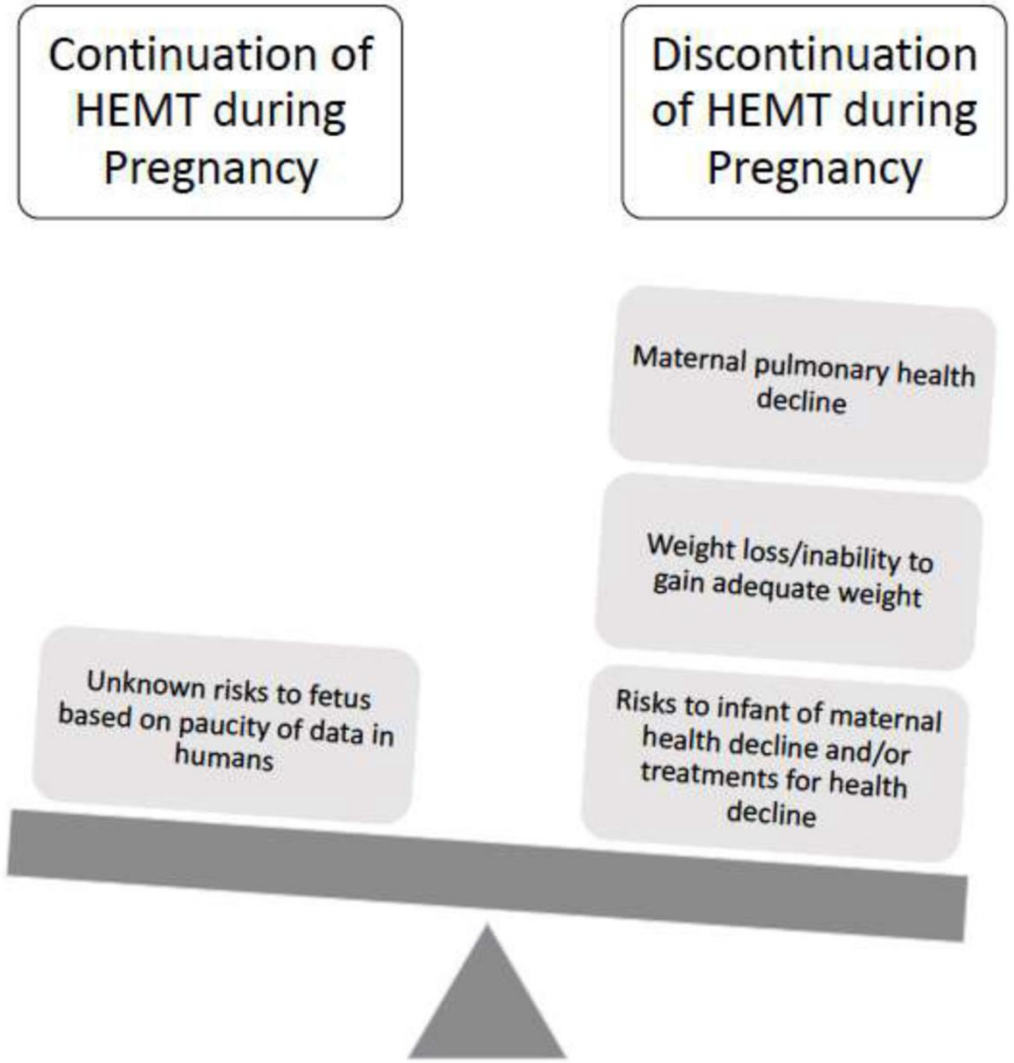
(does not include fathers with CF)



- 35% infertility prior to modulators. Now…
  - Thin cervical mucus
  - Improved cervical and uterine pH
  - Improved BMI
  - Improvement in delay of puberty and anovulation

CFF 2022 Registry Report
Taylor-Cousar. J Clin Med. 2020
Kazmerski et al. Ped Pulm. 2021

CFTR Modulators and CF Pregnancies



Ramos KJ, et al. J of CF. 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

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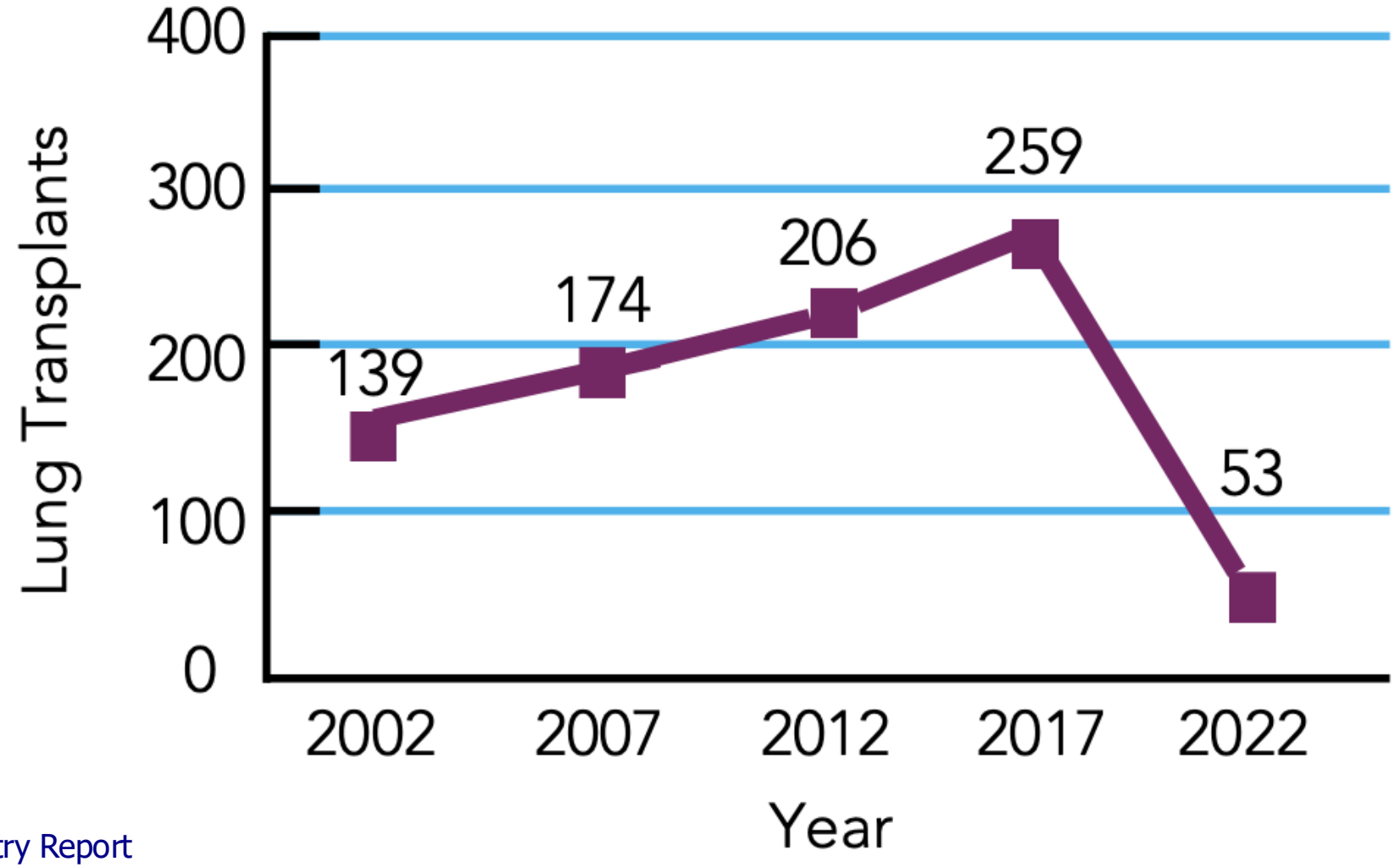
Case Report

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

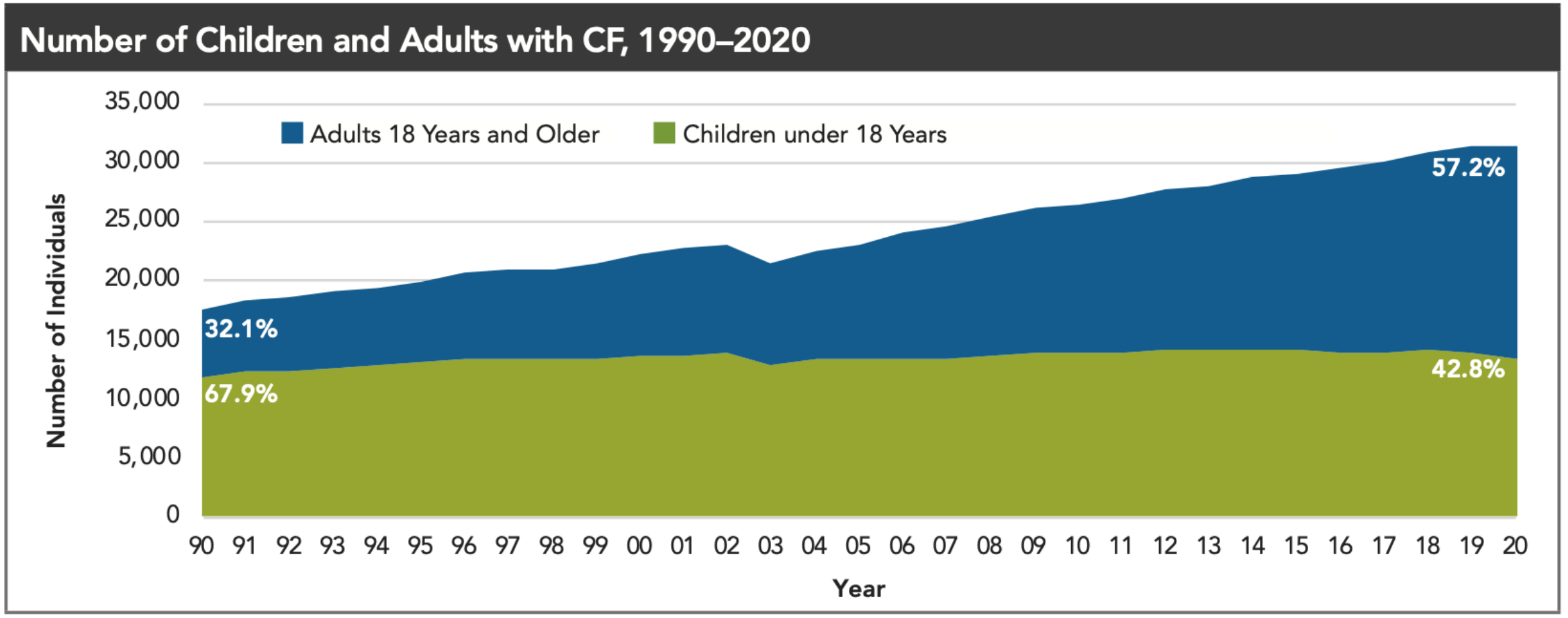
Medical University of South Carolina, Charleston, SC 29424, USA

Lung Transplants by Year



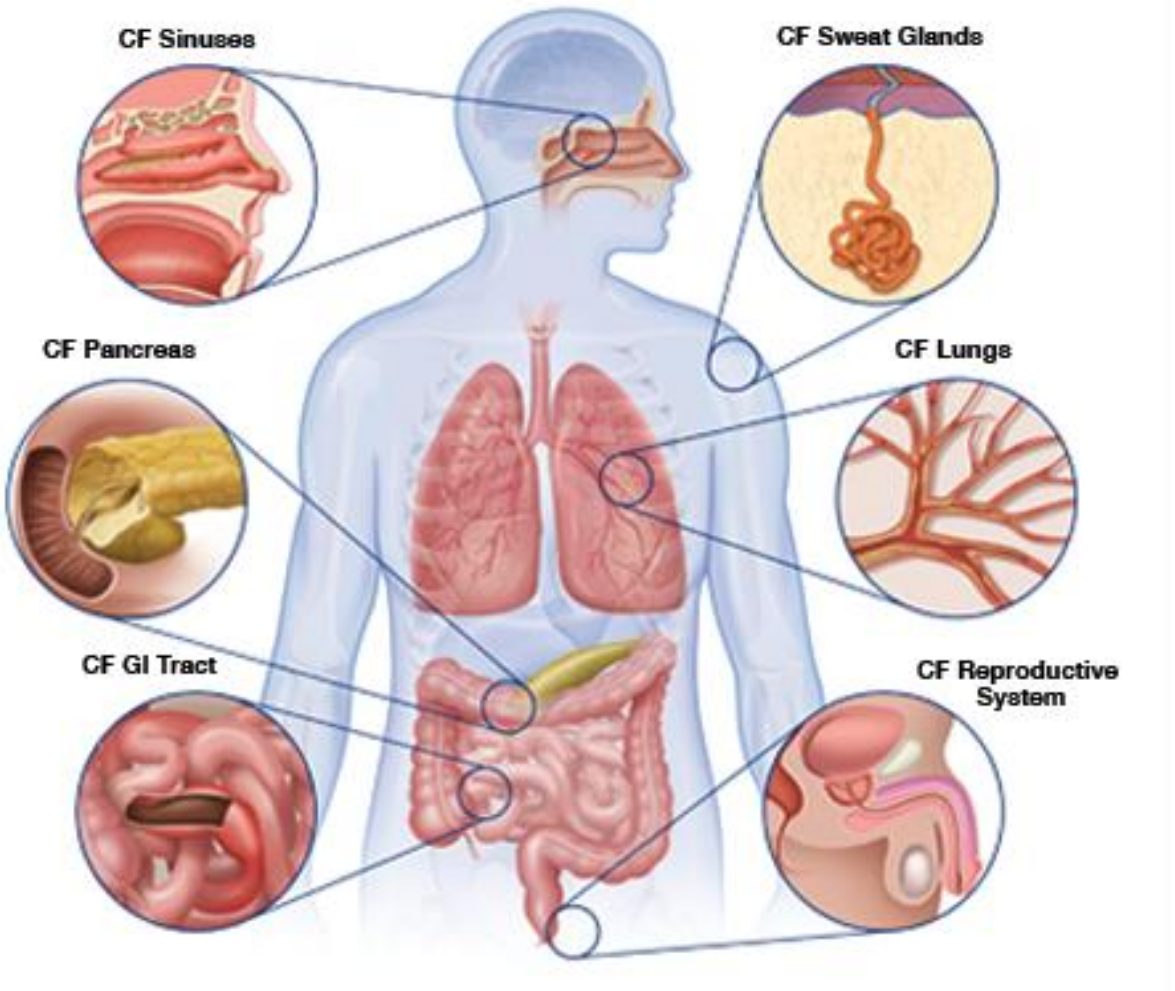
CFF 2022 Registry Report

More Adults than Children with CF

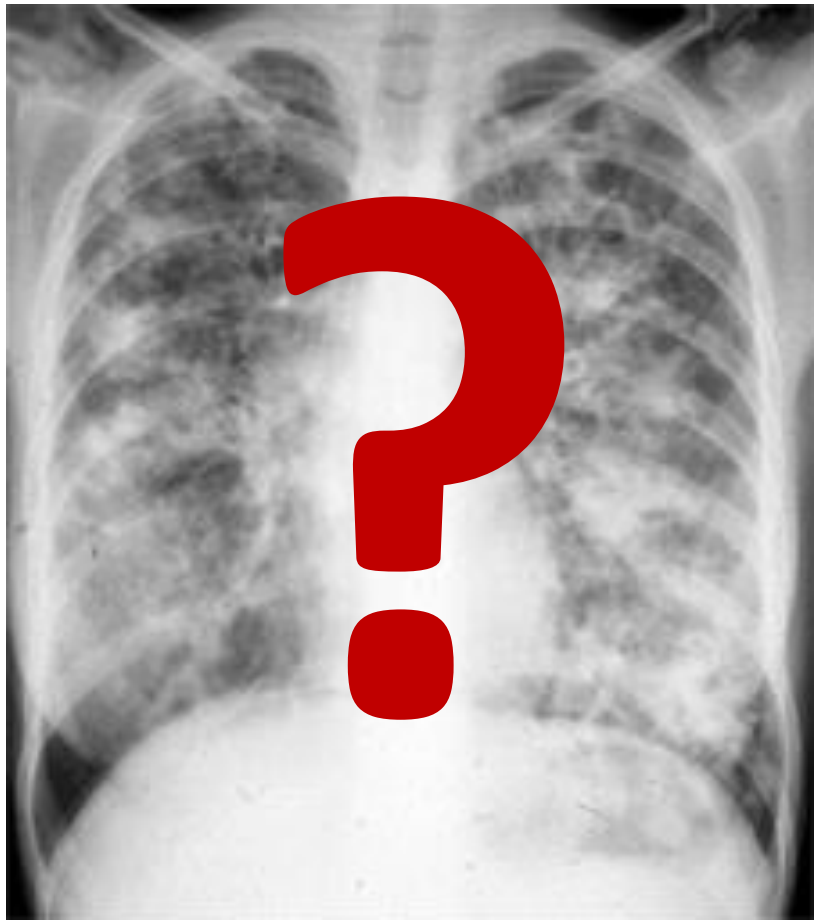


CFF 2020 Annual Registry Report

CF - Multi-Organ Involvement



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



Pulmonary Disease is still a cause of morbidity and mortality

CF Related Diabetes – Impact on CF Community

Complications of CFRD in 2021			
	Age < 18 (%)	Age ≥ 18 (%)	All (%)
Number of Individuals (n)	**665**	**4,996**	**5,661**
Retinopathy	0.0	1.0	0.9
Microalbuminuria	0.0	1.2	1.1
Chronic renal insufficiency	0.0	1.9	1.7
Chronic renal failure requiring dialysis	0.0	0.2	0.1
Peripheral neuropathy	0.2	1.5	1.3
Any episodes of severe hypoglycemia	3.8	4.8	4.7

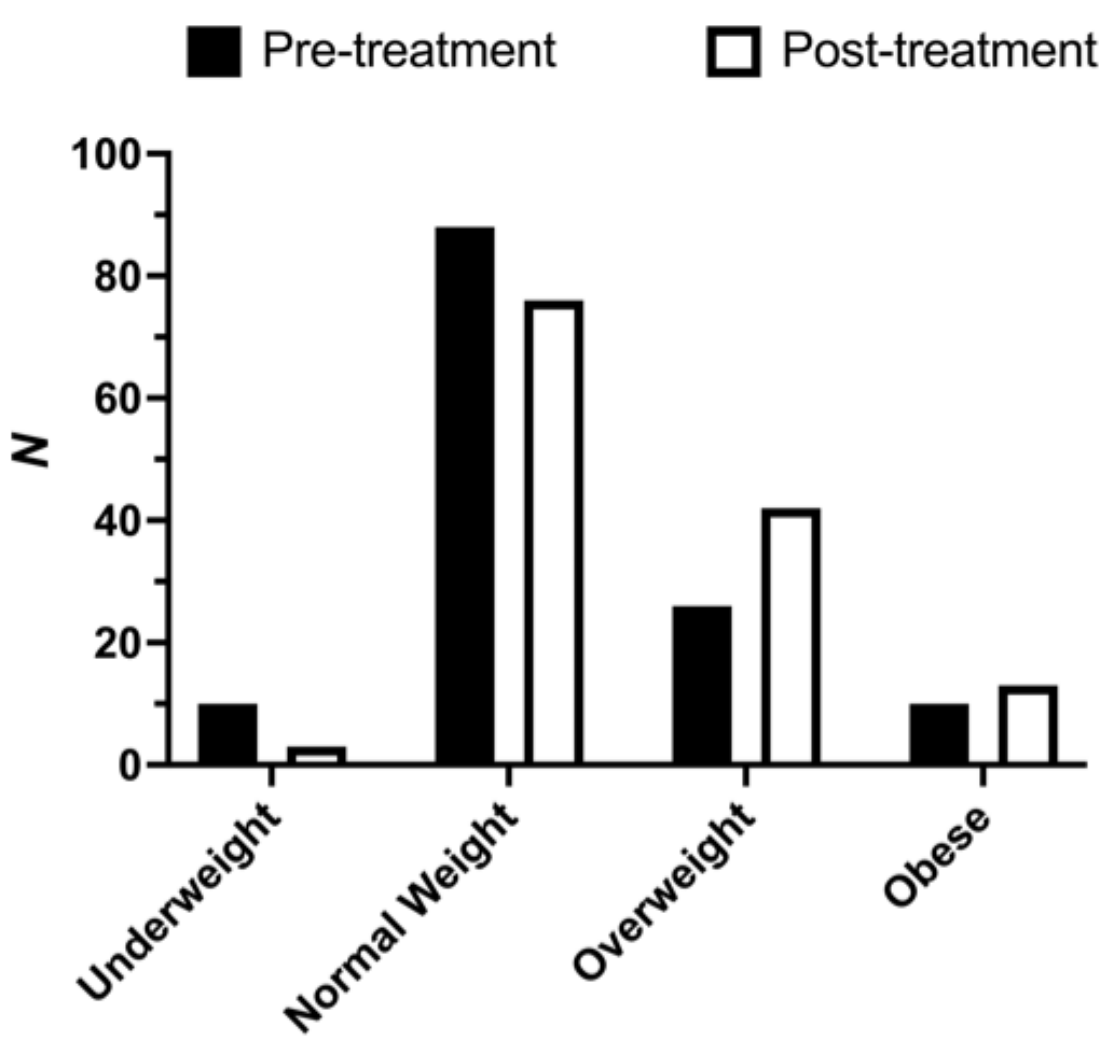
Microvascular Disease

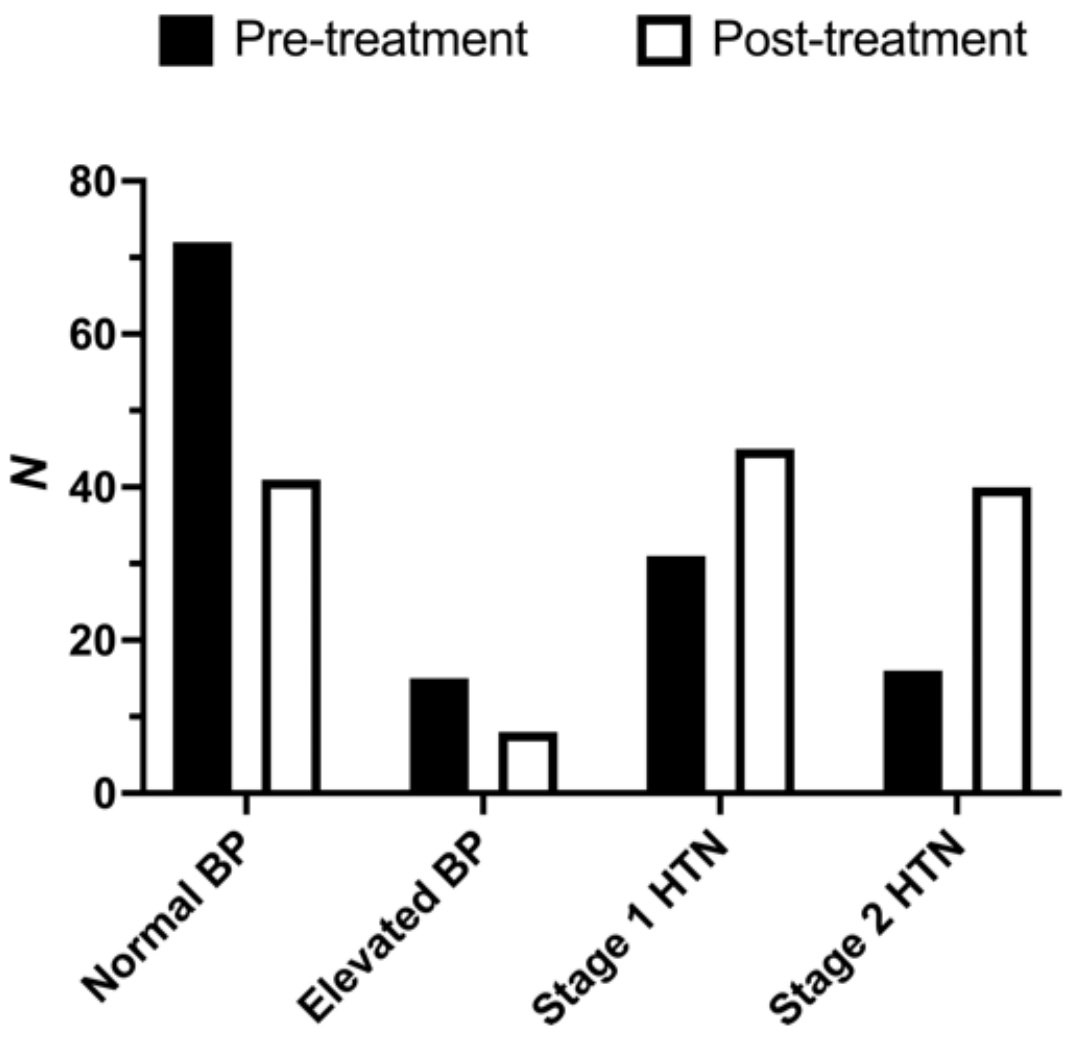
Macrovascular Disease

- Coronary artery disease
- Cerebrovascular accident
- Peripheral vascular disease

CFF 2021 Registry Report

Impact of CFTR Modulators on CVD





Petersen MC, et al. J Cystic Fibros 2022;21:265

Risk of Cardiovascular Disease in CF

- Autopsy of children and adults with CF from the 1950s showed minimal early atherosclerosis, but these data are from another time
- Aging associated obesity, hypertension, cystic-fibrosis-related diabetes, and chronic kidney disease more prevalent now
- Historical CF diet previously more focused on nutrition-poor foods, saturated fats and excessive sugar, including other decisions that impact gut microbiome and dysbiosis (early weaning to solids, lifelong systemic and enteric antibiotics)
- CFTR modulators lead to increasing body mass index, serum lipids, particularly low-density lipoprotein in those with cystic-fibrosis-related diabetes
- Cohort of adults with cystic fibrosis and SARS-CoV-19 infection (*n* ??422) reported that 22.5% had a history of ischemic heart disease, suggesting that CVD might be under-reported in this population

1. Holman, R. L., Blanc, W. A. & Andersen, D. *Pediatrics* **24**, 34–39 (1959)
2. Silverborn, M., Jeppsson, A., Martensson, G. & Nilsson, F. *J. Heart Lung Transplant* **24**, 1536–1543 (2005)
3. Petersen, M. C., Begnel, L., Wallendorf, M. & Litvin, M. *J. Cyst. Fibros.*(2021).
4. Saunders, T., et al. *Nat Cardiovasc Res* **1**, 187–188 (2022).

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

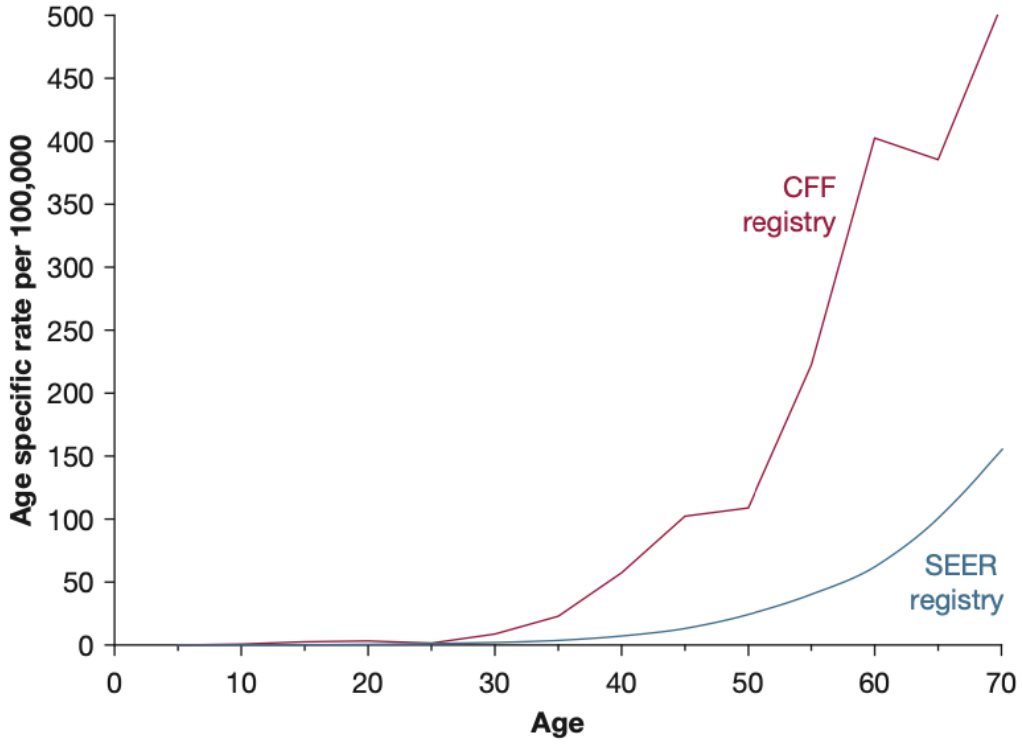
Very Rare
Screening not available

- 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

CFF Colorectal Cancer Screening Recommendations

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

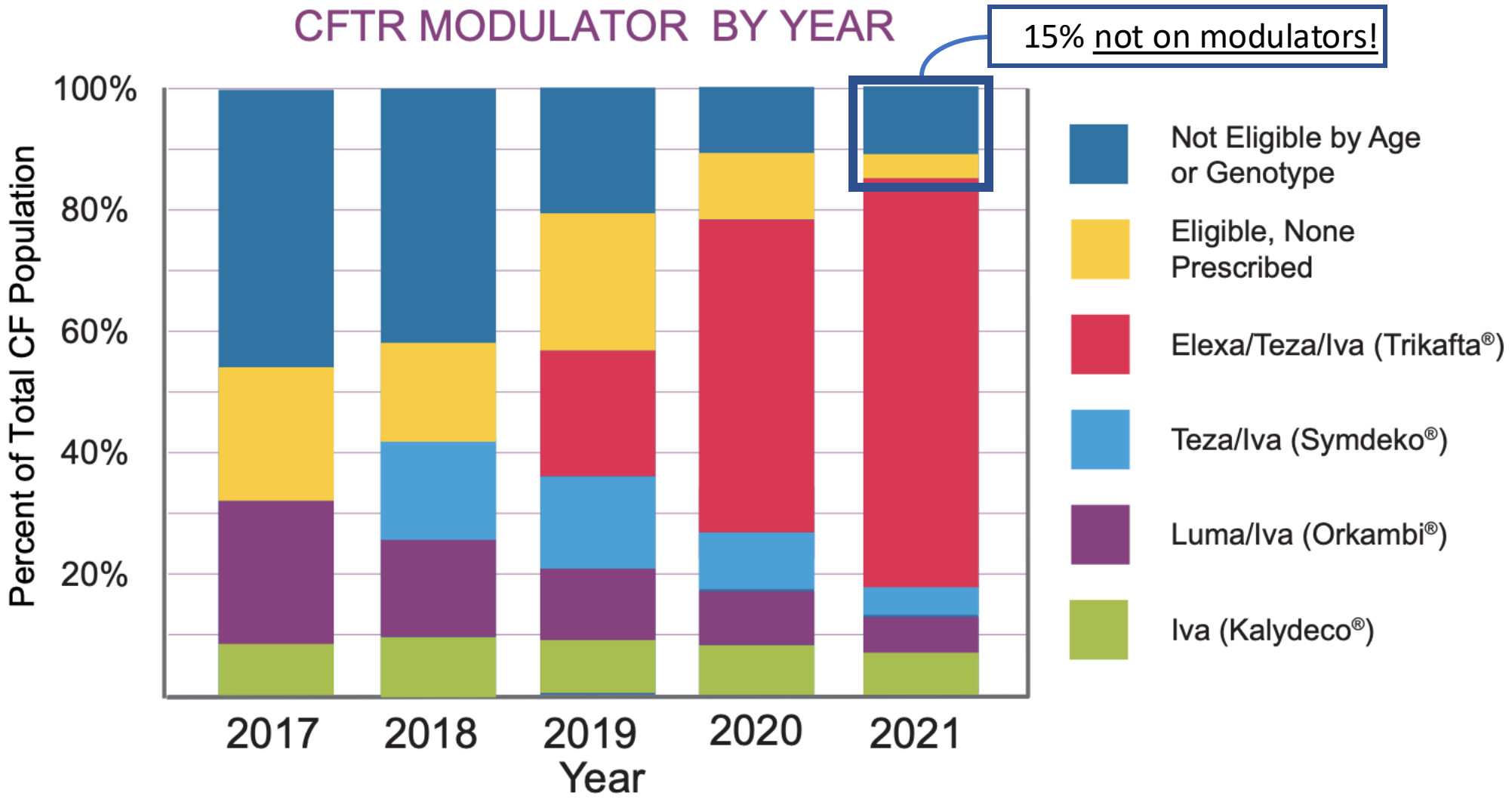
Maisonneuve at al. Chest. 2022
Than et al. Oncogene. 2016
Liu et al. Cancer Manag Res. 2020

CFF Colorectal Cancer Screening Recommendations

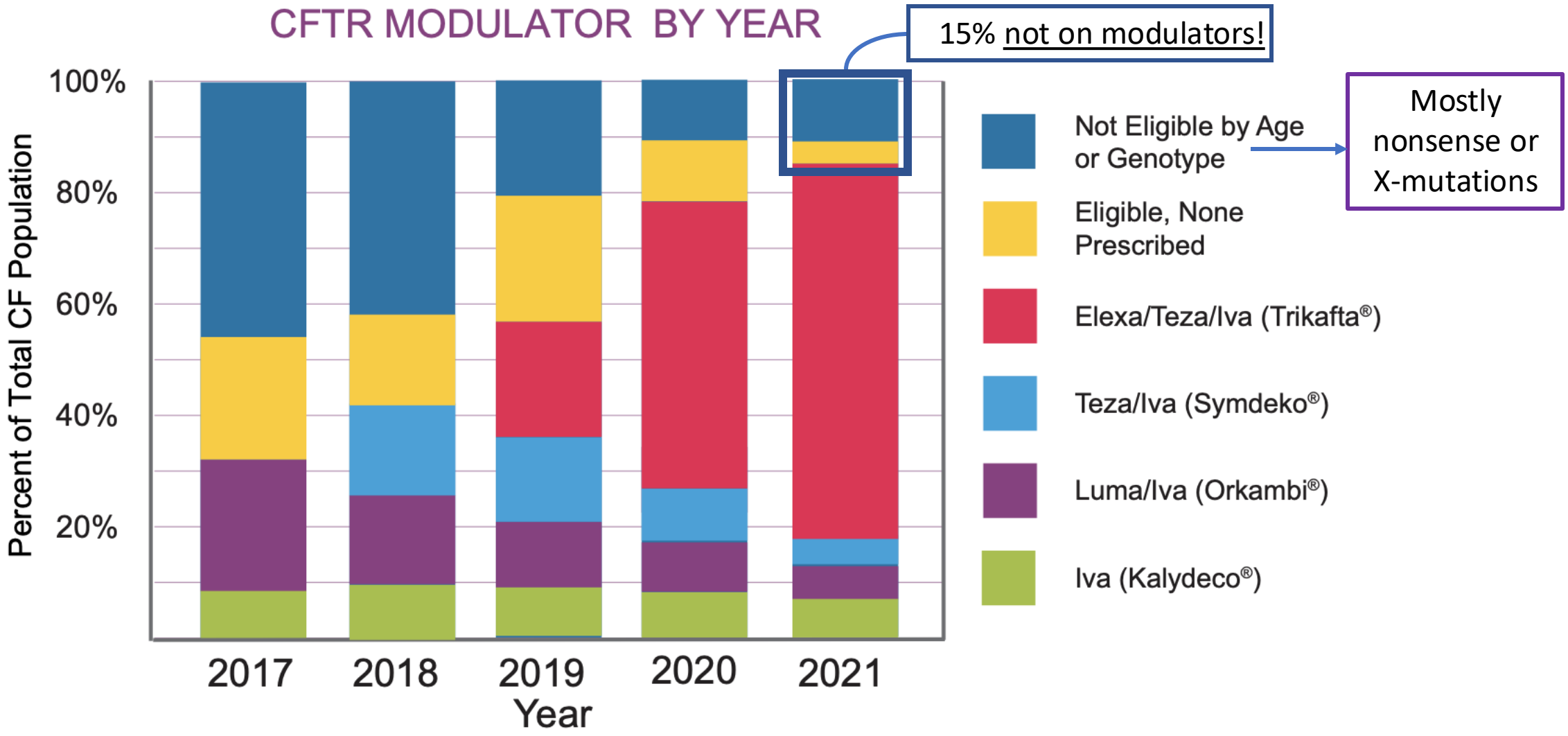
- Colonoscopy and Endoscopy are screening methods of choice
- Screening guidelines begin at age ~~40~~ 35…30? for CF patients prior to transplant with rescreening at 5 years, or 3 years if adenomatous polyps are discovered
- Post-Organ Transplant, screening begins at age 30 or within 2 years of transplant with rescreening at 5 years, or shortened to 2 years if adenomatous polyps are discovered
- Other screening methods being studied (NICE-CF Study)
  - Microscopic blood (FIT test)
  - Colorectal DNA tests (e.g. Cologuard^{R})
  - Study includes people age 40+ or 30+ if post-organ transplant

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

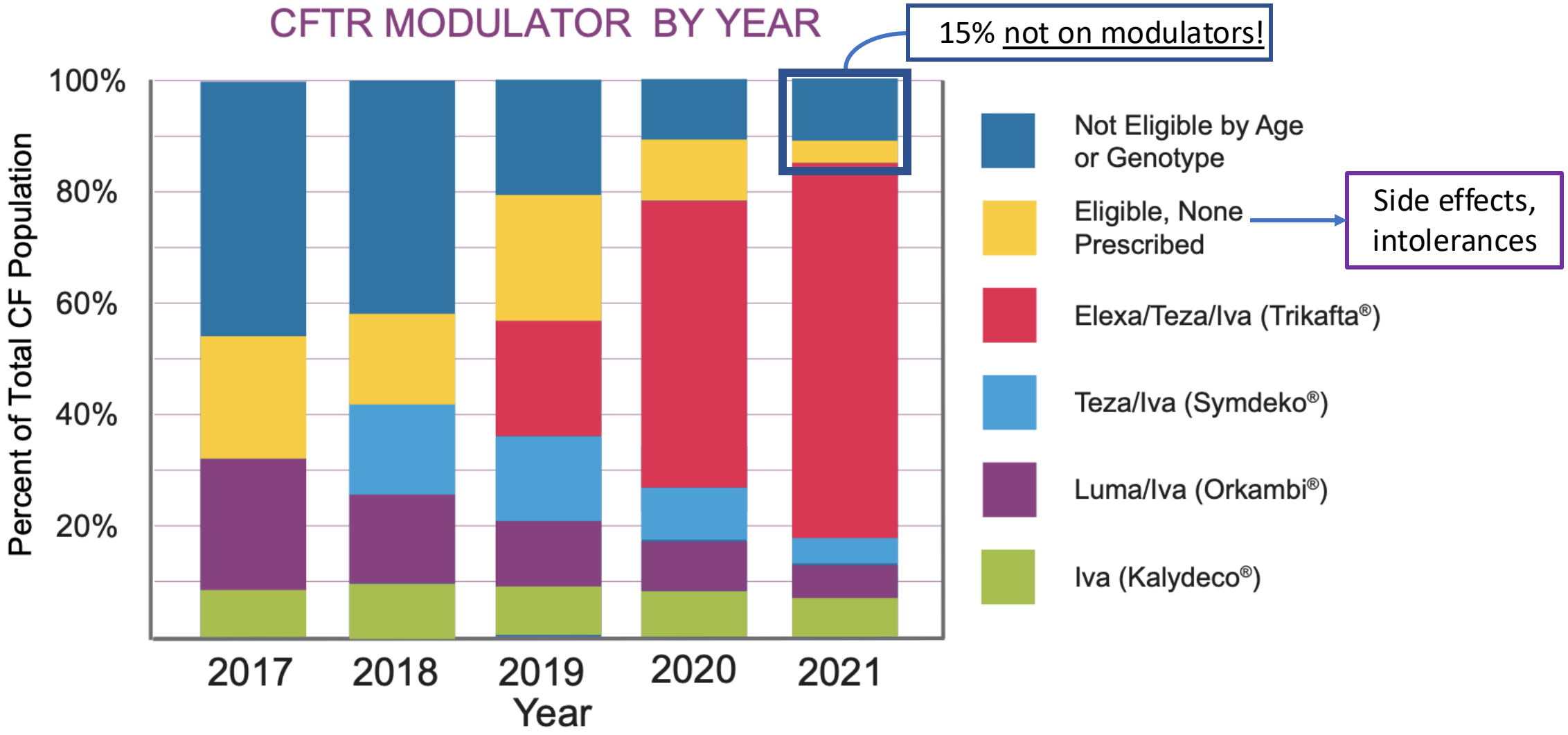
Not all CF patients eligible for modulators



Not all CF patients eligible for modulators

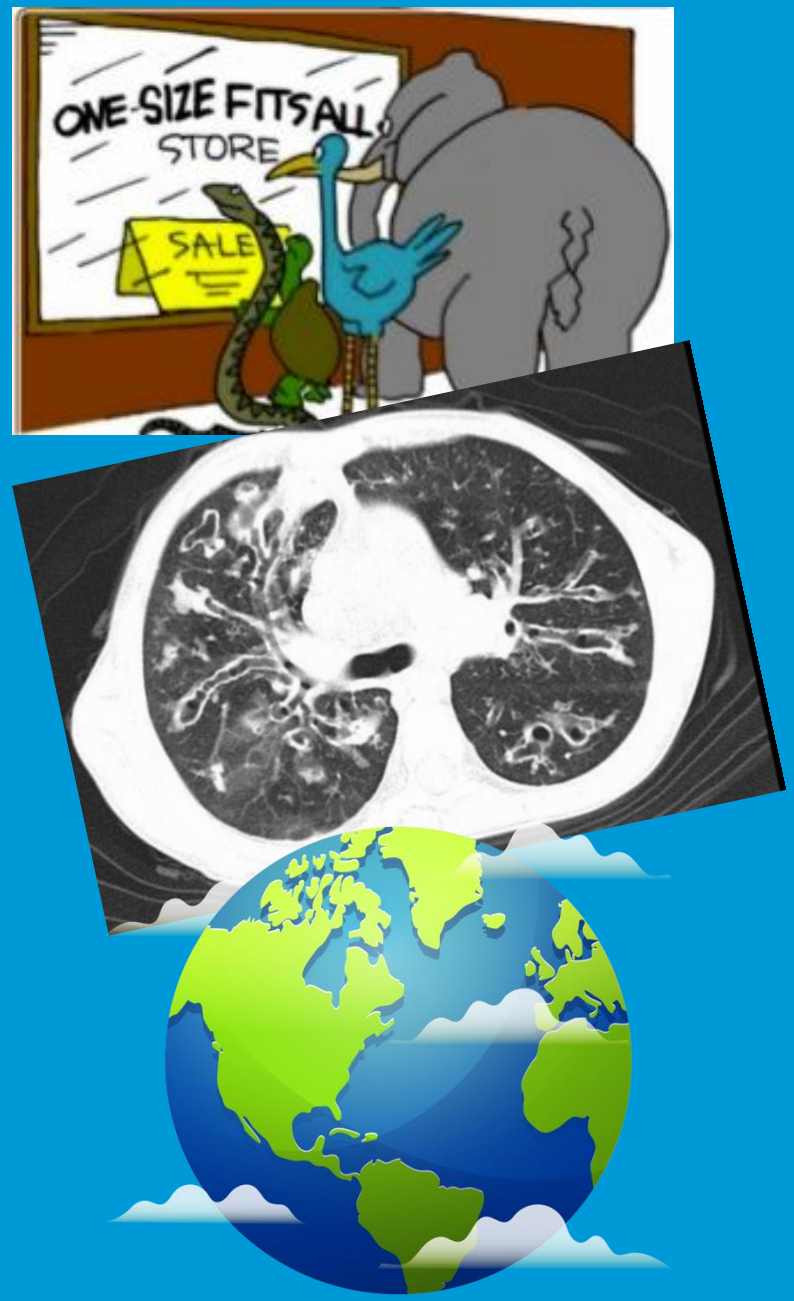


Not all CF patients eligible for modulators

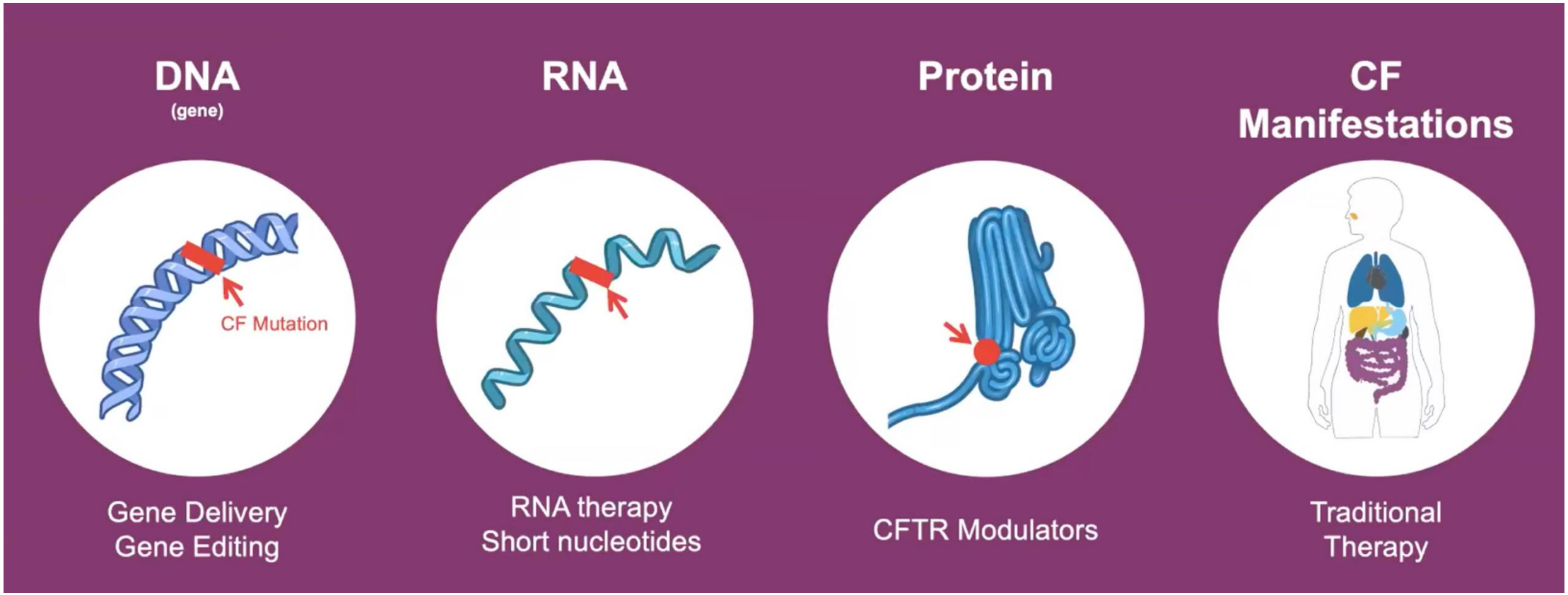


We are still not done!

- 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

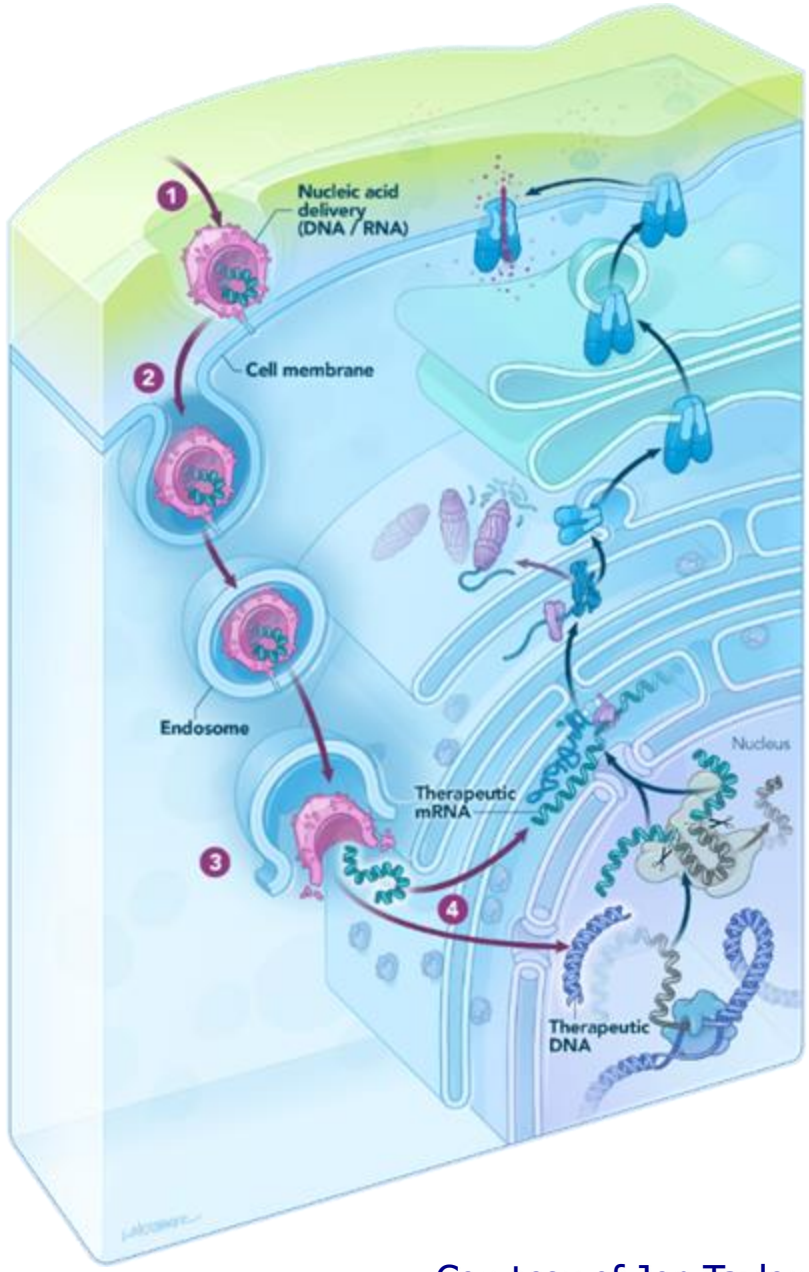


Therapeutic Approach to CF



Goal of Gene-Based Therapies

Reprogram the cell to make functional CFTR protein by providing the correct instructions



Courtesy of Jen Taylor-Cousar

REPAIR
CFTR PROTEIN

RESTORE
CFTR PROTEIN

FIX OR REPLACE
CFTR GENE

CFTR Modulators (Vertex, Abbvie)

mRNA delivery via lipoprotein particle

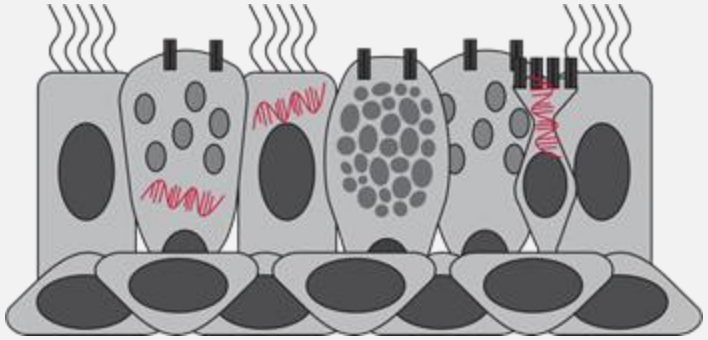
Adeno-associated virus vector
Lenti-virus vector
CRISPR/Cas9, ZFNs, TALENs)

Future of CF Therapeutics

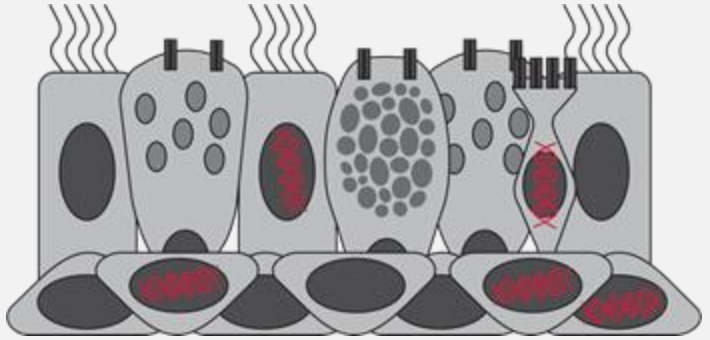
Courtesy of CFF

GENE-BASED THERAPIES FOR CF

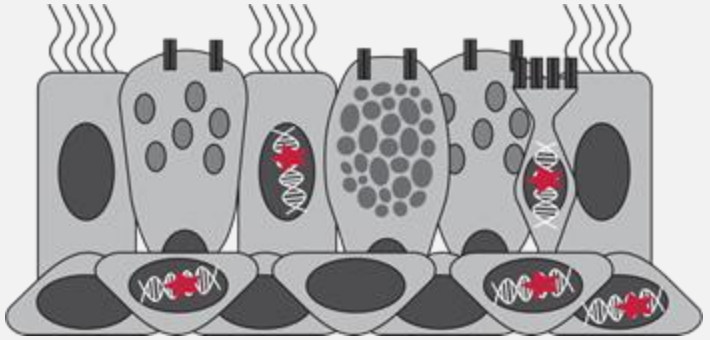
mRNA THERAPY



GENE THERAPY

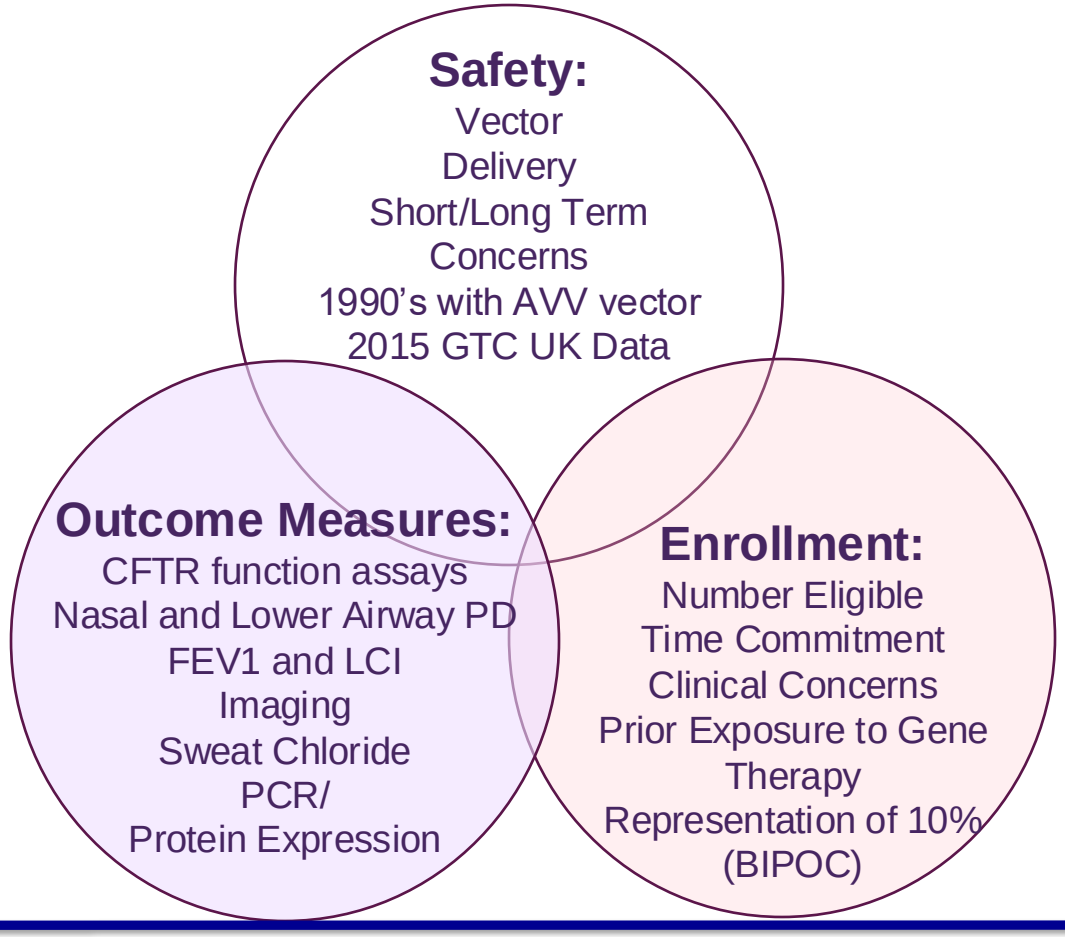


GENE EDITING



Slide courtesy of Martin Mense, Hillary Valley and Jennifer Taylor-Cousar

Challenges Faced by CF Community when designing Gene-Based Therapies



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 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

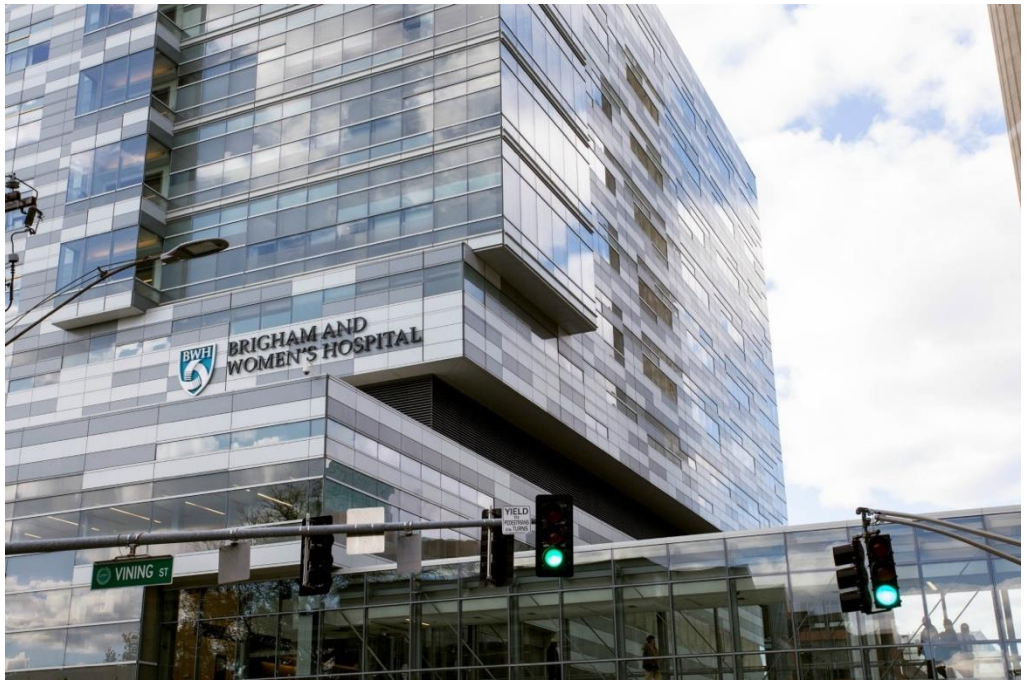
Question #2

- 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

Thank you!

Boston Children's Hospital



Brigham and Women's Hospital

Adult Cystic Fibrosis Center